

FDA Briefing Document

NDA 206321

Liraglutide Injection, 3 mg

Sponsor: Novo Nordisk

**Endocrinologic and Metabolic Drugs
Advisory Committee Meeting**

September 11, 2014

DISCLAIMER

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the new drug application (NDA) 206321, liraglutide, 3mg for injection, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
September 11, 2014

DRAFT POINTS FOR DISCUSSION

1. Please comment on whether you believe that the sponsor has provided adequate evidence to establish the efficacy of liraglutide 3 mg for chronic weight management.
2. Discuss the safety profile of liraglutide. In your discussion, please consider the following, including your level of concern for the contribution of liraglutide to these potential risks:
 - a. Neoplasms, including medullary thyroid carcinoma
 - b. Gallbladder-related events
 - c. Pancreatitis
 - d. Cardiovascular safety
 - e. Psychiatric events, including suicidality
 - f. Any other safety concerns
3. Discuss the adequacy of the safety database for liraglutide 3 mg for chronic weight management, given the extent of clinical trial and post-marketing experience with liraglutide for diabetes with doses up to 1.8 mg.
 - a. To what extent can the experience with liraglutide for diabetes be extrapolated to support the safety profile of liraglutide 3 mg for chronic weight management, given the different patient populations and doses?
 - b. There is an ongoing cardiovascular outcomes trial to assess the CV risk of liraglutide in type 2 diabetes. The maximum dose of liraglutide in this trial is 1.8 mg. Discuss whether this trial would be sufficient to characterize the CV risk of liraglutide 3 mg for weight management.
4. Considering the currently available data and the proposed Risk Evaluation and Mitigation Strategy (REMS), do you believe that the overall benefit-risk assessment of liraglutide 3 mg is favorable to support its approval for chronic weight management in individuals with a BMI 30 kg/m² or greater, or 27 kg/m² or greater with weight-related comorbidities?

Clinical Briefing Document
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
11 September 2014

New Drug Application 206321
Product: Liraglutide (Saxenda)
Sponsor: Novo Nordisk
Clinical Reviewer: Julie Golden, M.D.

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1 Executive Summary

Liraglutide is a selective glucagon-like peptide-1 (GLP-1) receptor agonist that was approved in January 2010 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (tradename: Victoza). The maximum approved dose for the T2DM indication is 1.8 mg daily, administered as a subcutaneous injection.

Because liraglutide was found to cause thyroid C-cell tumors in rodents – with unknown relevance for medullary thyroid carcinoma (MTC) in humans – liraglutide was approved with a boxed warning and a Risk Evaluation and Mitigation Strategy (REMS) that includes a communication plan. Furthermore, acute pancreatitis has been reported in clinical trials and in spontaneous post-marketing reports. This risk is also part of the REMS communication plan. Both risks are included in the Warnings and Precautions section of the Victoza label, as are risks of serious hypoglycemia, renal impairment, hypersensitivity, and the lack of macrovascular outcomes data.

Novo Nordisk (“sponsor”, “applicant”) has now submitted new data in support of a 3 mg daily dose of liraglutide for a chronic weight management indication in patients with a body mass index (BMI) 30 kg/m² (obese) or greater, or 27 kg/m² (overweight) or greater in the presence of at least one weight-related co-morbidity. The 3 mg daily dose was selected based on the results of the dose-ranging phase 2 trial 1807, which evaluated the weight change after 20 and 52 weeks of liraglutide 1.2, 1.8, 2.4, and 3 mg as compared to placebo and open-label orlistat. This trial (1807) and four phase 3 clinical trials, with a total of 5922 patients, constitute the weight management application. In addition, a phase 1 clinical pharmacology trial in 49 obese individuals was conducted.

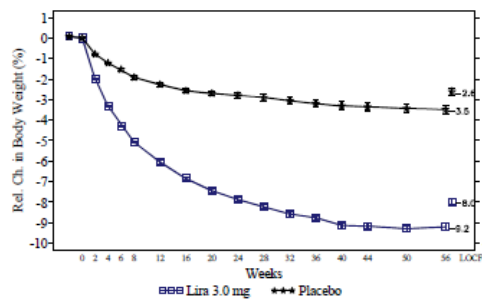
1.1 Efficacy Summary

The clinical review of efficacy is based on the sponsor’s primary analysis using last observation carried forward (LOCF) of on-treatment values only to impute missing values. The reader is referred to Dr. Bradley McEvoy’s (FDA Office of Biostatistics) review for alternative analyses.

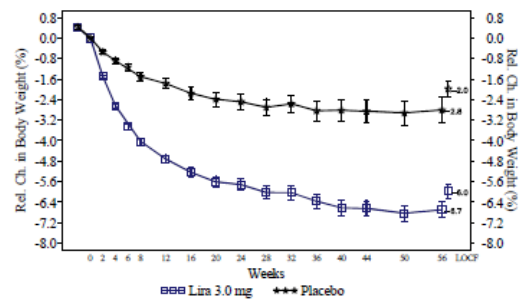
Figure 1 and Figure 2 describe the weight loss in the liraglutide 3 mg and placebo groups over time and the treatment differences for weight change from baseline, respectively. Results from the individual phase 3 56-week trials (1839, 1922, and 1923), the phase 3 32-week sleep apnea trial (3970), and the phase 2 52-week dose ranging trial (1807), and the trials combined are presented. Trial 1839 is the largest, and therefore drives the overall result in the pooled analyses.

Figure 1. Percent Body Weight Change, Weight Management Trials

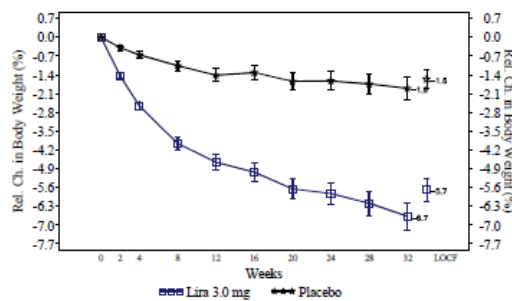
Trial 1839 (Lira 3.0 N=2437; pbo, N=1225)



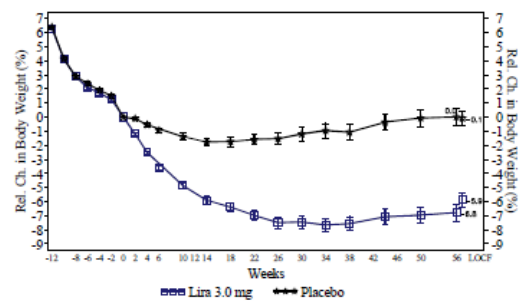
Trial 1922 (Lira 3.0 N=412; pbo, N=211)



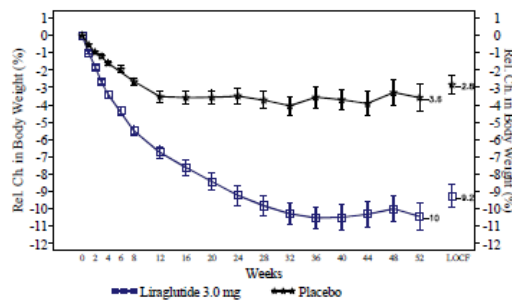
Trial 3970 (Lira 3.0 N=180; pbo, N=179)



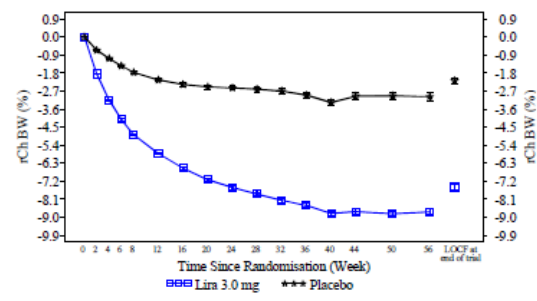
Trial 1923 (Lira 3.0 N=207; pbo, N=206)



Trial 1807 (Lira 3.0 N=92; pbo, N=98)

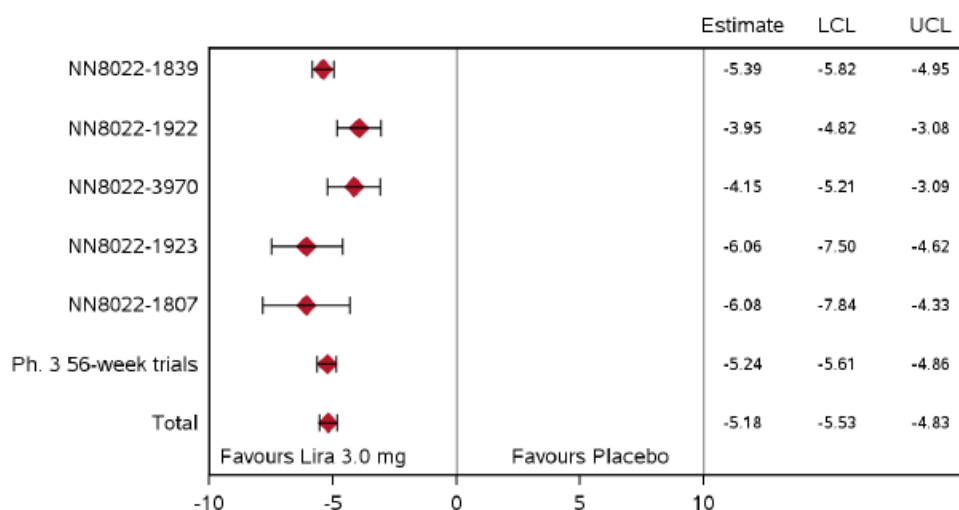


All trials (Lira 3.0 N=3301; pbo, N=1890)



Source: Summary of Clinical Efficacy, Figure 3-1

Figure 2. Treatment Differences for Fasting Percent Body Weight Change, Weight Management Trials



Data are LS means with 95% CI for the FAS with LOCF. P-value for interaction: 0.0196
Source: Summary of Clinical Efficacy, Figure 3-3

Using the primary LOCF analysis, liraglutide met the 5% mean placebo-subtracted difference in weight loss criterion described in the FDA draft weight management guidance¹ in the largest of the three phase 3 trials and in the pooled analyses.

Heterogeneity in the results was likely due to differences in study designs and patient populations:

The placebo-subtracted weight loss in the liraglutide groups was smaller in both trial 1922, which studied obese and overweight patients with T2DM for 56 weeks, and trial 3970, which studied obese patients with obstructive sleep apnea for 32 weeks, than in the other phase 2 and 3 trials. In addition to the listed co-morbidities, both trial 1922 and 3970 had higher proportions of men than the other trials, and patients in trial 3970 on average had a higher baseline body weight than other trials.

By contrast, trials 1807 and 1923 resulted in a higher placebo-subtracted mean weight loss in the liraglutide group than the overall result. On average, baseline body weight was lower in these trials than in other trials. Trial 1807, a dose-ranging trial conducted entirely in European countries, was originally 20 weeks; patients could elect to continue for the extension phase, remaining in their randomized treatment groups up to 52 weeks. Trial 1923 randomized only those patients who achieved a 5% or greater weight loss in a low-calorie diet run-in period. These two trials (1807 and 1923) therefore

¹ FDA Draft Guidance for Industry: Developing Products for Weight Management.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf>

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included a patient population perhaps not fully representative of the population that would ultimately be prescribed liraglutide for chronic weight management.

The categorical analyses, comparing the proportion of patients considered “5% responders” (defined as losing at least 5% baseline body weight by the end of the trial) and “10% responders” (losing more than 10% body weight by the end of the trial) in the liraglutide-treatment group to the placebo-treatment group are shown in Table 1 and Table 2. These analyses impute missing data with LOCF.

Table 1. Proportion of Patients Achieving at Least Five Percent Weight Loss, Weight Management Trials

	1839	1922	1923	3970	1807	Ph 3 56-wk trials	All trials
Lira 3 mg (%)	63.5	49.8	50.7	46.4	78.1	60.7	60.3
Placebo (%)	26.6	13.5	21.3	18.1	29.7	24.4	24.4

Source: ISE, Appendix 6.3, Tables 72 and 79

Table 2. Proportion of Patients Achieving More Than Ten Percent Weight Loss, Weight Management Trials

	1839	1922	1923	3970	1807	Ph 3 56-wk trials	All trials
Lira 3 mg (%)	32.8	22.9	27.4	22.4	35.9	30.9	31.2
Placebo (%)	10.1	4.2	6.8	1.5	9.7	9.0	8.7

Source: ISE, Appendix 6.3, Tables 90 and 97

A statistically significantly greater proportion of patients treated with liraglutide 3 mg compared with those treated with placebo achieved at least 5 and 10% weight loss from baseline at the end of the trial in all 5 trials (note that in trial 1923, this weight loss was in addition to the weight lost during the run-in period). In addition, all trials met the categorical efficacy standard (proportion of 5% responders in active-treatment group is at least 35% and approximately twice the proportion in the placebo-treatment group) as outlined in the FDA draft weight management guidance.¹

As would be expected, liraglutide was associated with improvements in glycemic parameters in patients with and without diabetes. Decreases in blood pressure and modest improvements in lipid parameters were generally observed.

1.2 Safety Summary

The safety profile of liraglutide up to doses of 1.8 mg daily has been characterized in the diabetes treatment program and in the post-marketing experience. This experience helped guide the clinical review for liraglutide 3 mg daily for chronic weight management. In contrast to what was done in the diabetes programs, the weight management trials included: (1) the use of placebo in all trials instead of active comparators, (2) longer duration controlled trials, (3) a higher dose, (4) a different

patient population (patients with overweight and obesity, with and without T2DM), and (5) an independent blinded adjudication of certain adverse events of interest.

The safety assessment of liraglutide was focused on concerns related to GLP-1 receptor activation (e.g., pancreatitis, neoplasms, heart rate increases, gastrointestinal symptoms) as well as concerns specific to a weight management product (e.g., gallstones, cardiovascular events, psychiatric events); see below for further details. Immunogenicity, hypoglycemia, and post-marketing reports related to liver and renal safety are also addressed in the review.

- **Pancreatitis:** Adverse events of pancreatitis in the liraglutide T2DM program and post-marketing reports of acute pancreatitis associated with liraglutide and other GLP-1-based therapies led to enhanced scrutiny of pancreatitis events during the weight management clinical program. In phase 3 trials 1839, 1922, and 3970, all suspected cases of pancreatitis were prospectively adjudicated. In trial 1923, suspected cases of pancreatitis were adjudicated *post hoc*. In trial 1807, events were not adjudicated. In the liraglutide-treatment group, 7 (0.2%) patients had an event of pancreatitis confirmed by the external event adjudication committee (EAC), compared to 1 patient (0.1%) treated with placebo. Two of the liraglutide cases and the 1 placebo case were associated with cholelithiasis. The majority of the adverse events (AEs) confirmed by the EAC as acute pancreatitis in the liraglutide group were serious and / or severe, whereas the event in the placebo-treated group was not reported as serious or severe. In addition, the one AE reported as acute pancreatitis in trial 1807 (not adjudicated) in a patient treated with liraglutide 3 mg, was reported as serious and severe. Two additional cases of acute pancreatitis in patients treated with liraglutide 3 mg have been confirmed in the ongoing (randomized) extension of trial 1839.
- **Gallbladder and biliary tree related adverse events:** Gallbladder-related events are currently not an identified labeled adverse reaction for Victoza. In the weight management program, the proportion of patients with acute gallstone events, including cholelithiasis, cholecystitis, bile duct obstruction, and biliary colic, was higher in the liraglutide-treated arm (2.3%) as compared to the placebo-treated arm (0.9%). More events in the liraglutide group were serious and / or led to withdrawal. No obvious dose-response or exposure-response to gallstone events could be identified. Gallstone events were seen more frequently in subgroups that lost greater weight, although the imbalance not in favor of liraglutide was still observed when adjusting for weight loss (using 5-10% and greater than 10% weight loss subgroup cut-offs).
- **Neoplasms:** Rodent carcinogenicity studies demonstrated an increase in thyroid C-cell tumors with liraglutide. Victoza was approved with a REMS to educate prescribers about the theoretical risk of medullary thyroid carcinoma. Risk for pancreatic cancer is an additional concern with GLP-1-based therapies, including

liraglutide. Neoplasms were adjudicated in the four phase 3 weight management trials.

Overall, adjudicated malignancies occurred at a similar rate in liraglutide- and placebo-treated groups. A numerical imbalance favoring placebo was noted for breast cancer.

During the main treatment period, 5 and 1 adjudicated thyroid neoplasm events were reported in the liraglutide and placebo groups, respectively. In the liraglutide group there were 3 cases of papillary thyroid carcinoma ('malignant' category) ranging in size from 1.35 to 1.6 centimeters based on ultrasound or pathology (1 case with size unspecified), 1 case of papillary microcarcinoma ('pre-malignant' category), and 1 case of follicular adenoma ('benign' category). In the placebo group there was 1 case of medullary thyroid carcinoma. In addition, 1 case of papillary microcarcinoma (3 mm, adjudicated as 'malignant') was reported in a liraglutide-treated patient in an ongoing extension trial. One case of C-cell hyperplasia was reported in a patient treated with liraglutide in the weight management program (with papillary thyroid microcarcinoma); this patient had elevated calcitonin values prior to trial enrollment, suggesting that C-cell hyperplasia may have been present – but undiagnosed – prior to receiving liraglutide.

There were no reports of exocrine pancreatic cancer in the weight management program. One patient treated with liraglutide was diagnosed with multiple endocrine neoplasia Type 1 (MEN1, a genetic condition), including neuroendocrine tumor of the pancreas.

- Cardiovascular Safety: Cardiovascular (CV) risk associated with liraglutide use was addressed in the Victoza application and discussed at an Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) meeting². The Victoza application was under Agency review when the 2008 FDA guidance to evaluate CV risk in new anti-diabetic drug therapies³ was issued. Cardiovascular events in the application were not prospectively defined, collected, or adjudicated in the diabetes program. The applicant relied on a customized set of MedDRA adverse events preferred terms to assess the cardiovascular risk across the pool of phase 2 and 3 diabetes trials. In this analysis, the hazard ratio for cardiovascular risk for liraglutide versus placebo ruled out a 95% CI upper bound of 1.8 (refer to the April 2, 2009 EMDAC meeting for details). A post-marketing cardiovascular outcomes trial for Victoza is ongoing.

² Endocrinologic and Metabolic Drugs Advisory Committee April 2, 2009

³ FDA Guidance for Industry: Diabetes mellitus — Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf>

As with the diabetes trials, the liraglutide trials for weight management were not powered or designed to rule out a pre-specified degree of cardiovascular risk. However, the sponsor instituted an adjudication program (prospective: weight management trials 1839, 1922, 3970; *post hoc*: weight management trials 1807 and 1923 and completed phase 2 and 3 diabetes trials) in order to assess MACE in a set of pre-specified meta-analyses. In the primary on-treatment analysis of the weight management trials, based on 17 events, the estimated hazard ratio for the primary endpoint of time to first MACE (non-fatal MI, non-fatal stroke, and CV-death) for liraglutide versus comparators was 0.40 (95% CI: 0.15; 1.05). Point estimates for the hazard ratios of the MACE components were consistent with the composite. An on-study analysis (19 events), and an analysis that combined events from weight management and T2DM trials (66 events), were consistent with the primary analysis.

Liraglutide is associated with an increase in resting heart rate (HR), on average 2 to 3 beats per minute (bpm) compared to placebo when assessed at study visits in clinical trials, both in the diabetes and the weight management programs. However, with continuous HR monitoring in a clinical pharmacology trial, a 4 to 9 bpm increase from placebo was detected, depending on the time of day, without convincing evidence of dose-dependency. In the weight management pool, more patients treated with liraglutide as compared to placebo had changes from baseline of more than 10, 15, and 20 bpm. Six percent of liraglutide-treated patients as compared to 4% of placebo-treated patients had maximum HR of at least 100 bpm; 0.9% versus 0.3%, respectively, had HR values over 100 bpm reported on two consecutive visits.

- **Psychiatric Disorders:** Psychiatric safety is an important part of any centrally acting obesity drug safety evaluation. In the liraglutide development program, psychiatric safety was monitored by adverse events as well as prospectively administered depression and suicidality questionnaires, as recommended by FDA. A predefined psychiatric AE search did not demonstrate an imbalance of events overall; however, a dose-response for psychiatric events was noted in the phase 2 dose-ranging trial. Additionally, although results from the depression and suicidality questionnaires did not suggest an effect of liraglutide on the severity of depression symptoms or an increase in suicidal thinking, 5 patients treated with liraglutide (versus none treated with placebo) reported AEs of suicidality in the weight management program (in trials with approximately 2:1 randomization). To date, 1 additional patient treated with liraglutide has reported suicidal ideation in an ongoing weight management trial.
- **Gastrointestinal Symptoms:** Nausea, vomiting, and diarrhea are three of the most commonly reported AEs with liraglutide, and are dose-related. In the post-marketing setting, renal failure as a result of dehydration due to these symptoms has been reported. In the weight management program, almost 40% of patients treated with liraglutide experienced nausea, and over 15% experienced vomiting, versus approximately 14% and 4%, respectively, of patients treated with placebo.

Diarrhea was reported approximately twice as frequently in the liraglutide 3 mg group (21%) as compared to the placebo group (10%). More nausea and vomiting AEs were moderate or severe, serious, or led to withdrawal with liraglutide versus placebo. Nausea and vomiting were reported at a comparable frequency in patients who were and were not 5% weight loss responders, suggesting these symptoms were not entirely responsible for weight loss with liraglutide.

2 GLP-1 Receptor Agonism and Liraglutide

The glucagon-like peptide-1 (GLP-1) receptor is a G-protein-coupled receptor on beta cells of the pancreas, the activation of which increases insulin secretion in response to elevated blood glucose concentrations and suppresses glucagon secretion. GLP-1, the endogenous ligand, has a very short half-life due to inactivation by dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidase (NEP); therefore, longer-acting GLP-1 receptor agonists that are more stable to degradation have been developed as treatments for type 2 diabetes (liraglutide is metabolized by DPP-4 and NEP, although at a much slower rate than GLP-1). Liraglutide was approved in the United States in 2010 as Victoza at doses up to 1.8 mg for treatment of type 2 diabetes mellitus (T2DM).

Clinical trials of liraglutide in patients with T2DM demonstrated beneficial effects on weight. In addition to their effects on insulin secretion, GLP-1 and its analogs have also been shown to slow gastric emptying,^{4,5} although notably, liraglutide demonstrated no overall effect on gastric emptying over 5 hours in a phase 1 clinical pharmacology trial conducted as part of the weight management program. A centrally mediated mode of action of liraglutide on weight loss has been posited.⁶

Liraglutide has also been shown to increase heart rate in humans and cause c-cell tumors in rodents.⁴ The relationship of liraglutide to pancreatitis or pancreatic or thyroid tumors in humans has been speculated, but remains controversial.^{7,8,9,10,11} This

⁴ Victoza (liraglutide) prescribing information.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf

⁵ Byetta (exenatide) prescribing information.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf

⁶ Sisley S, et al. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. *J Clin Invest.* 2014; 124(6): 2456-63.

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

⁸ Butler AE, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* 2013; 62(7): 2595-604.

⁹ Gier B, et al. Glucagon like peptide-1 receptor expression in the human thyroid gland. *J Clin Endocrinol Metab.* 2012; 97: 121-31.

¹⁰ Pyke C and Knudsen LB. The glucagon-like peptide-1 receptor – or not? *Endocrinology.* 2013; 154(1): 4-8.

¹¹ Pyke C, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology.* 2014; 155(4): 1280-90.

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review focuses on liraglutide clinical trial data for weight loss efficacy as well as for human safety.

3 General Discussion of Endpoint

As described in the FDA draft guidance for developing weight management drugs,¹ weight change has historically been the endpoint of interest in clinical trials for the development of obesity drugs. Among individuals with overweight or obesity, weight is an easily measured surrogate for body adiposity, and long-term weight loss in the range of 5 to 10% is associated with improved glycemic control, blood pressure, and lipid parameters.¹²

It is presumed that salutary changes in cardiovascular and metabolic risk factors will translate into cardiovascular (CV) benefit, such as reductions in the incidence of myocardial infarction and stroke. However, the results of two recent CV outcomes trials raise concern regarding the CV benefit of weight loss drugs.

The Sibutramine Cardiovascular Outcomes Trial (SCOUT), the subject of an FDA advisory committee meeting in 2010, demonstrated that sibutramine was associated with an increase in the relative risk for major adverse CV events (non-fatal myocardial infarction, non-fatal stroke, CV death, or resuscitated cardiac arrest) in a population of individuals at high CV risk [HR 1.16 (95% CI 1.03, 1.31)].¹³ The results from this trial led to sibutramine being removed from the U.S. market.

The Look AHEAD (Action for Health in Diabetes) trial¹⁴ was a randomized controlled trial in over 5000 patients with T2DM comparing an intensive lifestyle intervention (including weight loss) to standard-of-care for a follow-up of 10 years. The trial was stopped early (9.6 years) for futility of the composite primary outcome (first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalized angina); HR 0.95 (95% CI 0.83, 1.09). Weight loss was greater in the intervention group (8.6% at 1 year, 6.0% at study end) as compared to the control group (0.7% at 1 year, 3.5% at study end).

These findings raise the concern that a pharmacological effect on weight loss may not provide enough assurance of a CV benefit to offset a CV safety issue (such as increased heart rate) associated with a weight loss drug. The CV safety of liraglutide is discussed further in section 7.5.7.

¹² Van Gaal LF, et al. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int J Obes Relat Metab Disord* 1997 Mar; 21 Suppl 1: S5-9.

¹³ James WPT, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; 363:905-17.

¹⁴ The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369: 145-54.

4 Clinical Pharmacology

Please see Dr. Jaya Vaidnayathan's (FDA clinical pharmacology) memorandum for a discussion of the comparison of the pharmacokinetics of the liraglutide 1.8 mg dose in the T2DM patient population to the 3 mg dose in the obese patient population. This section will briefly summarize clinical issues surrounding dose- and exposure-response. Within the review, analyses of liraglutide dose and exposure with respect to several AEs of interest are presented in the relevant safety sections.

Liraglutide 3 mg generally resulted in higher exposure than liraglutide 1.8 mg in obese and overweight patients and the exposure increased in a dose-proportional manner. An exposure-response analysis was conducted, based on population pharmacokinetic data from phase 2 trial 1807 and phase 3 trials 1839 and 1922. See Table 3 for median exposures and mean weight loss by dose and glycemic status; note that the reported results from patients with T2DM were from a single trial, 1922, in the weight management program (i.e., not from the Victoza diabetes program).

In population PK analyses, sex and body weight were the main covariates for liraglutide dose-normalized exposure: exposure decreased with increasing body weight and was 24% lower in males than in females. Age, race, ethnicity, glycemic status, and dose were found not to be relevant covariates for dose-normalized exposure.

Table 3. Model-Predicted Median Exposures and Mean Weight Loss at Tested Doses of Liraglutide, Weight Management Program

Dose (mg)	Glycaemic status	Median exposure (AUC, nM*h)	Mean absolute body weight change (%)	Mean placebo corrected body weight change (%)	Increments in mean body weight change from lower dose level (%)	Proportion of subjects with 5% weight loss (%)	Proportion of subjects with 10% weight loss (%)
Placebo	Non-diabetic ^a	0	-2.9	0	-	29	10
1.2	Non-diabetic ^a	347	-5.67	-2.77	-2.77	54	17
1.8	Non-diabetic ^a	520	-6.98	-4.08	-1.31	62	24
2.4	Non-diabetic ^a	693	-7.95	-5.05	-0.97	67	31
3	Non-diabetic ^a	867	-8.65	-5.75	-0.70	71	37
Placebo	Type 2 diabetes	0	-2.02	0	-	20	9
1.8	Type 2 diabetes	390	-4.95	-2.93	-2.93	43	15
3	Type 2 diabetes	650	-6.55	-4.52	-1.60	53	24

Model was based on data from trial 1807, 1839 and 1922. ^aNormoglycaemic plus pre-diabetes subjects,

Source: Population PK Modeling Report, Table 6

The sponsor conducted the phase 2 dose-ranging trial 1807 to establish the dose-response relationship of four doses of liraglutide and placebo on weight loss. In the first 20 weeks of this trial (time point of the primary analysis) there was a significantly

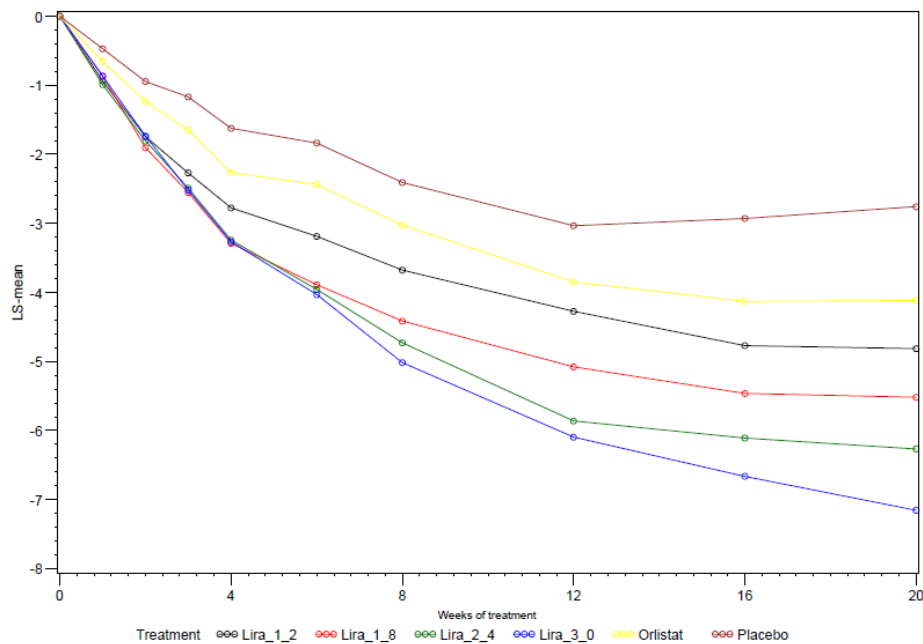
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greater dose-dependent mean weight loss in the groups treated with liraglutide compared with placebo, ranging from 4.8 kg (liraglutide 1.2 mg) to 7.2 kg (liraglutide 3 mg). Figure 3 illustrates the weight change by dose over time. Efficacy results from the extension period of trial 1807 out to 52 weeks are discussed further in section 6.3.1.1.

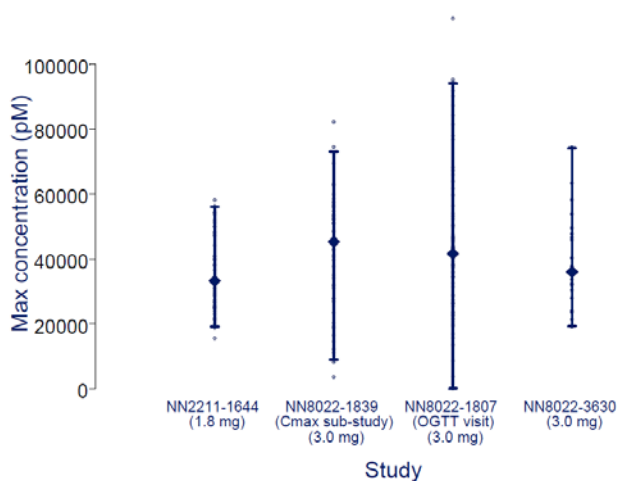
Figure 3. Plot of LS Mean Change in Body Weight versus Time, ITT, LOCF; Trial 1807



Source: Clinical Trial Report NN8022-1807, Date 8 Feb 2010, Figure 14.2.7

Liraglutide was not found to have a signal for QTc prolongation in a thorough QTc trial conducted in healthy individuals administered up to liraglutide 1.8 mg (submitted as part of the Victoza NDA, trial 1644). In order to support extrapolation of those results to the weight management program at the liraglutide 3 mg dose, exposure results (C_{max}) obtained following liraglutide 1.8 mg in the thorough QTc trial were compared with exposures (C_{max}) following liraglutide 3 mg in weight management trials 1839 (phase 3), 1807 (phase 2) and 3630 (phase 1 clinical pharmacology). Exposures were found to be largely overlapping (Figure 4); this finding supports the acceptability of the thorough QTc trial previously conducted for the weight management indication.

Figure 4. Maximum Liraglutide Concentrations from Trials 1644, 1839, 1807, and 3630



Data are individual C_{max} values with medians and 2.5-97.5% percentiles.

Source: Population PK Modeling Report, Figure 5

5 Liraglutide Clinical Program

5.1 Weight Management Program

The liraglutide program was designed to conform to the February 2007 FDA draft guidance for developing weight management drugs.¹ Key program design issues addressed in the draft guidance include:

- Sample size of the phase 3 program for safety: the draft guidance states that approximately 3,000 patients should be randomized to active drug and no fewer than 1,500 patients should be randomized to placebo for 1 year of treatment.
- Primary efficacy endpoints: efficacy should be assessed by analyses of both mean and categorical changes in body weight, with a clinically significant weight loss considered to be 5%.

As noted in the guidance, improvements in blood pressure, lipids, glycemia, or other weight-related biomarkers commensurate with the degree of weight lost are expected in patients treated with an effective weight management product, and changes in common weight-related comorbidities should be factored into the efficacy assessment of investigational weight management products. Notably, if approved, liraglutide will be the first weight management product that has previously been approved to treat a weight-related co-morbidity (T2DM, Victoza).

In response to safety concerns raised with Victoza, including medullary thyroid carcinoma [MTC], pancreatic cancer, pancreatitis, and CV risk (see section 2), the sponsor undertook a process of blinded independent adverse event adjudication for

certain adverse events of interest in the weight management program. The methodology and results of this evaluation are presented in section 7, Safety.

Other adverse events are of particular interest for weight management products. For example, since the issuance of the draft weight management guidance, the Division has requested that specific psychiatric screening and monitoring be incorporated in all phase 2 and 3 trials in centrally-acting obesity therapies. The evaluation of psychiatric adverse events and questionnaires are discussed in section 7.5.8.

The clinical development program to evaluate the efficacy of liraglutide for weight management included one phase 2 dose-finding trial (trial 1807) and four phase 3 trials (trials 1839, 1922, 3970 and 1923), conducted worldwide and involving 5922 overweight and obese patients with or without T2DM. In addition, one clinical pharmacology trial (trial 3630) with liraglutide in obese patients without T2DM assessed effects on appetite, energy metabolism, and glycemia.

5.1.1 Overview of the Trials

The single phase 2 trial in the weight management program was **trial 1807**, a dose-ranging trial that compared the effect of four doses of liraglutide with placebo and orlistat, and investigated long-term safety.

The phase 3 program included:

- **Trial 1839**, a 56-week trial that evaluated weight loss of liraglutide 3 mg as compared to placebo; an ongoing 104-week extension in patients with pre-diabetes evaluating delay or prevention of diabetes was not included in the NDA, and will not be discussed in this review (with the exception of some limited safety data)
- **Trial 1922**, a 56-week trial in patients with T2DM that evaluated weight loss with the 3 mg and 1.8 mg doses of liraglutide compared to placebo
- **Trial 1923**, a 56-week trial that compared the effect of liraglutide 3 mg versus placebo on maintaining a run-in weight loss of at least 5% (after 4 to 12 weeks of a 1200 to 1400 kcal/d diet)
- **Trial 3970**, a 32-week trial in obese patients with moderate to severe obstructive sleep apnea (OSA) to compare the effect of liraglutide 3 mg versus placebo on reducing the severity of OSA (assessed by the apnea-hypopnea index)

These trials will be discussed in more depth in the relevant sections of this review.

5.1.2 Summary of Patient Population

Table 4 enumerates demographics and baseline characteristics of the patient populations across all five phase 2 and 3 trials. Mean BMI ranged from 34 to 39 kg/m². Patients had a wide range of BMIs (25.7 to 77.2 kg/m²) and body weights (60.1 to 244.9 kg).

In the trials conducted in patients without T2DM or OSA (1839, 1923 and 1807), most participants (76 to 81%) were women, as is common in weight management trials. However, in trial 1922 (patients with T2DM), an equal proportion of men and women were included, and in trial 3970 (patients with OSA), most participants were men (72%).

Most patients were within the age range 18 to 65 years. Fewer than 2% were older than 75 years. Participants in trial 1922 (with T2DM) were on average older (mean 55 years), with 19% at least 65 years of age.

Most patients were white (85%), 10% were black or African American, and 3% were Asian. Ten percent were of Hispanic or Latino ethnicity. In the US trial population, which comprised approximately 50% of the total population, the percentages were 79% white, 18% black or African American, 1% Asian, and 11% Hispanic or Latino ethnicity. Trial 1807 was conducted exclusively in Europe and almost all patients in that trial were white (99%).

More patients in trial 1922 (with T2DM) had comorbidities of hypertension (69%) or dyslipidemia (67%) than those in trial 1839 (35% and 29%, respectively). Across trials, most of the patients with hypertension or dyslipidemia were on medications to treat these conditions. Nine percent of patients had a history of CV disease at screening.

Table 4. Demographics and Baseline Characteristics for Patients in the Phase 2 and 3 Weight Management Trials

	Trial 1807 N=469 ^a	Trial 1839 N=3723	Trial 1922 N=844	Trial 3970 N=355 ^b	Trial 1923 N=422	Combined N=5813
Mean (SD) age, yrs	45.9 (10.5)	45.1 (12.0)	54.9 (10.6)	48.5 (9.7)	46.2 (11.5)	46.9 (12.0)
Age ≥ 65 yrs, n (%)	2 (<0.1)	204 (5.5)	158 (18.7)	0	21 (5.0)	384 (6.6)
Sex, n (%) female	356 (75.9)	2921 (78.5)	419 (49.6)	98 (27.6)	343 (81.3)	4137 (71.2)
Race, n (%)						
White	462 (98.5)	3161 (84.9)	703 (83.3)	264 (74.4)	355 (84.1)	4945 (85.1)
Black	5 (1.1)	355 (9.5)	98 (11.6)	66 (18.6)	56 (13.3)	580 (10.0)
Ethnicity, n (%) Hispanic	— ^c	393 (10.6)	87 (10.3) ^c	43 (12.1)	28 (6.6)	551 (9.5)
Mean (SD) body weight, kg	97.5 (13.0)	106.3 (21.4)	105.9 (21.5)	117.9 (24.4)	99.6 (21.0)	105.7 (21.4)
Mean (SD) BMI, kg/m ²	34.4 (2.8)	38.3 (6.4)	37.1 (6.7)	39.2 (6.9)	35.6 (5.9)	37.7 (6.3)
BMI ≥ 40 kg/m ² , n (%)	3 (0.6)	1236 (33.2)	251 (29.7)	127 (35.8)	88 (20.9)	1705 (29.3)

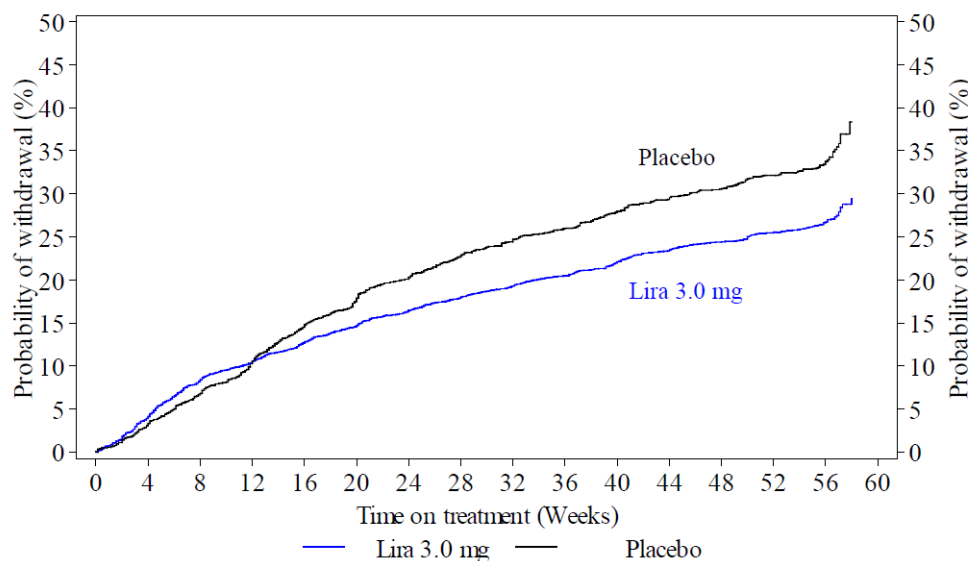
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Glycemic status						
T2DM, n (%)	0	0	844 (100)	0	0	844 (14.5)
Pre-diabetes, n (%)	249 (53.1)	2279 (61.2)	0	229 (64.5)	272 (64.5)	3029 (52.1)
Co-morbidities						
Dyslipidemia, n (%) ^d	58 (12.4)	1096 (29.4)	562 (66.6)	120 (33.8)	124 (29.4)	1959 (33.7)
Hypertension, n (%) ^e	106 (22.6)	1295 (34.8)	585 (69.3)	150 (42.3)	130 (30.8)	2266 (39.0)
Cardiovascular disease history						
MedDRA search terms ^f	14 (3.0)	321 (8.6)	126 (14.9)	21 (5.9)	41 (9.7)	523 (9.0)
Prespecified CRF ^g	–	1473 (39.5)	596 (70.4)	157 (43.7)	–	2221 (45.1)
a Not including patients randomized to orlistat (N=95) b An additional 4 patients were randomized but not exposed in 3970 c Ethnicity data were not collected in 1807 or at French sites in 1922 (N=3) d LDL-C ≥ 160 mg/dL or TG ≥ 150 mg/dL or HDL-C < 40 mg/dL (M) / < 50 mg/dL (F) e SBP ≥ 140 mmHg or DBP ≥ 90 mmHg f Based on SMOs ischemic heart disease, cardiac failure, central nervous system hemorrhages, cerebrovascular conditions, embolic and thrombotic events g Includes hypertension; not collected in 1923 or 1807						

Source: Summary of Clinical Efficacy, Table 3-2

In the first 12 weeks of the trials, liraglutide-treated patients were more likely to withdraw from the trials than placebo-treated patients, primarily as a result of gastrointestinal AEs (see figure below and Figure 35). After 12 weeks of treatment, placebo-treated patients were more likely to withdraw. Towards the end of the trials there was an increased probability of withdrawal, likely due to patients leaving the trials after end of the treatment period and not entering the non-treatment follow-up periods. Exposure and disposition will be discussed further in the efficacy discussion of the individual trials and in the safety review (section 7).

Figure 5. Time to Discontinuation, Weight Management Pool



Source: ISS, Figure 1-2

5.2 Diabetes Program and Various Pools

The Victoza clinical development program included 20 controlled phase 2 and 3 trials (including extensions) of up to 104 weeks duration as well as one uncontrolled trial and four uncontrolled trial extensions.

Additional clinical development programs with liraglutide treatment arms have included insulin degludec and semaglutide for T2DM, which included liraglutide as active comparator in one trial each at doses up to 1.8 mg/day. Additionally, a fixed combination of insulin degludec and liraglutide in T2DM (IDegLira) was conducted with doses of liraglutide up to 1.8 mg daily. This program included two controlled phase 3 trials, including one extension.

As of 02 Jul 2013, 7037 patients were exposed to liraglutide in the different T2DM programs across the 24 randomized controlled phase 2 and 3 clinical trials (excluding uncontrolled trials and extensions). The majority of the liraglutide-treated patients in the T2DM program (Victoza) were exposed in trials of 26 weeks in duration or longer. Comparators included sulfonylureas, metformin, thiazolidinediones, insulin, GLP-1 agonists, DPP-4 inhibitors, and placebo.

An overview of the phase 2 and 3 controlled trials in T2DM where liraglutide treatment has been included, and how the trials are grouped in the various pools (including T2DM and weight management), is described in the following figure:

Figure 6. Liraglutide Phase 2 and 3 Trials, Weight Management and Diabetes Pools

Weight management pool	Supplementary AE pool I	Supplementary AE pool II
Liraglutide 3.0 mg for weight management (NN8022)		
Phase 2 and 3 trials Trial 1839, 1922, 3970, 1923, 1807, 1807-ext-1, and 1807-ext-2	5 trials: Duration: 32-56 weeks; N=5813 Lira total: 3872 subjects; 3372.7 PYE Placebo: 1941 subjects; 1600.9 PYE	29 trials Duration: 2-104 weeks N=17622 Lira Total: 10909 subjects 8444.7 PYE Placebo/ comparator: 5713 subjects 4117.3 PYE
Liraglutide for T2DM (NN2211)		
Phase 2 and 3 uncontrolled trials and extensions Trials 1842 and 1842-ext-1, 1797-ext, 1797-ext-2, 1860-ext-2		
Phase 2 and 3 controlled trials Trial 1310, 1332, 1333, 1334, 1436, 1499, 1571, 1572, 1572-ext, 1573, 1573-ext-1, 1573-ext-2, 1573-ext-3, 1573-ext-4, 1574, 1697, 1700, 1700-ext, 1701, 1701-ext, 1796, 1797, 1799, 1860, 1860-ext-1, 2072, 3924, 3925		24 trials Duration 2-104 weeks N=10714 Lira total: 7037 subjects 5072.0 PYE Placebo/ comparator: 3677 subjects 2444.9 PYE
Semaglutide (NN9535)		
1 Phase 2 controlled trial: Trial 1821		
IDegLira (NN9068)		
2 Phase 3 controlled trials: Trials 3697, 3697-ext, 3912		
Degludec (NN1250)		
1 Phase 3 controlled trial: Trial 3948		

Source: Supplementary AE Report, Figure 1-1

6 Efficacy

6.1 Proposed Indication

The applicant's proposed indication (including limitations of use), as taken verbatim from the submission, is as follows:

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/m² or greater (obese), or

- *27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea*

Limitations of Use

- *In clinical trials of Saxenda, there were more cases of pancreatitis with Saxenda than with comparators. Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis has been observed in patients treated with liraglutide marketed as Victoza. Saxenda has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Saxenda.*
- *The effects of Saxenda on cardiovascular morbidity and mortality has not been established.*
- *The safety and effectiveness of Saxenda in combination with other prescription and over the counter drugs intended for weight loss has not been established.*

6.2 Methods

The efficacy review addresses the results of the five phase 2 and 3 trials in the weight management NDA. Each clinical trial report was reviewed individually, with key primary and secondary outcomes reviewed, in addition to relevant subgroups. Dr. Bradley McEvoy conducted a separate statistics review and addressed the impact of pertinent limitations, such as missing data.

The efficacy evaluation in all trials was based on a full analysis set population, defined as all randomized patients exposed to at least one dose of trial product and with at least one post-baseline assessment of body weight, or of any efficacy endpoint for trials 1839, 1922, and 3970. All the statistical analyses in the efficacy evaluation were performed using last observation carried forward (LOCF), using on-treatment values only, for imputation of missing data.

Reviewer comment: Historically, LOCF has been used for the primary analysis of weight loss drugs;^{1,15,16} however, the limitations of this approach are acknowledged, particularly with the relatively high proportion of premature discontinuations in weight loss drug trials. See Dr. McEvoy's review for further information.

Trials 1839, 1922, and 1923 each had three co-primary confirmatory weight-related endpoints that were tested in a hierarchical manner (see Table 5). Trial 1807 had two

¹⁵ Xenical (orlistat) prescribing information.

¹⁶ Belviq (lorcaserin) prescribing information.

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co-primary weight-related endpoints at weeks 20 and 52. For trial 3970 in obese patients with moderate or severe OSA, mean and categorical changes in body weight from baseline to week 32 were secondary endpoints. The primary endpoint of trial 3970 was change in the apnea-hypopnea index (AHI) after 32 weeks.

Table 5. Key Efficacy Endpoints Related to Body Weight by Weight Management Trial

Trial ID	1st Co-primary endpoint	2nd Co-primary endpoint	3rd Co-primary endpoint
1839 (at 56 wks)	Change in body weight from baseline (% , kg)	Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight (5% responders)	Proportion of patients achieving $> 10\%$ reduction of baseline body weight (10% responders)
1922 (at 56 wks)	Change in body weight from baseline (% , kg)	Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight (5% responders)	Proportion of patients achieving $\geq 10\%$ reduction of baseline body weight (10% responders)
1923 (at 56 wks)	Change in body weight from baseline (% , kg)	Proportion of patients that maintained $\geq 5\%$ reduction in initial body weight achieved during the low calorie diet run-in period	Proportion of patients achieving $> 10\%$ reduction of baseline body weight (10% responders)
1807 (at 52 wks ^a)	Change in body weight from baseline (% , kg)	Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight (5% responders)	-
Trial ID	Key secondary endpoints related to body weight		
3970 (at 32 wks)	Change in body weight from baseline (% , kg)	Proportion of patients achieving $\geq 5\%$ reduction of baseline body weight (5% responders)	Proportion of patients achieving $> 10\%$ reduction of baseline body weight (10% responders)

^a The primary analysis for trial 1807 was conducted at 20 weeks (see section 4); however, for the purposes of evaluating the long-term efficacy of the dose range, the 52-week analysis is primarily presented in section 6.3.1.

Source: Clinical overview, Table 4-1

There was no pre-specified method for controlling Type I error for the secondary endpoints in the individual weight management trials. Nominal p-values or 95% confidence intervals may be provided for descriptive purposes.

6.3 Individual Weight Management Trials

Because of the differing study designs in the five phase 2 and 3 trials, each trial's study design, baseline characteristics, disposition, and efficacy results will be summarized separately.

6.3.1 Trial 1807

This trial was conducted as a phase 2 20-week dose-ranging trial with an 84-week extension (total: 104 weeks). The NDA includes a study report for the 20-week study duration, an interim analysis at week 52, and a report of the extension phase. For the first 52 weeks of the trial, patients remained in their randomized groups; therefore, the

efficacy analysis will focus on the 52-week data to be consistent with the FDA draft weight management guidance.¹ Furthermore, because of the open-label nature of the second 52-weeks and the changing doses (patients treated with liraglutide or placebo were initially treated with liraglutide 2.4 mg, but were switched to treatment with liraglutide 3 mg), efficacy data for the full 104 weeks are not presented.

For the main trial, 564 obese patients without T2DM were randomized with equal allocation 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. The placebo arm was further subdivided into four arms with different injection volumes corresponding to the different doses of liraglutide. For the first 20 weeks, the trial was conducted as a double-blind trial; both investigator and patient knew the dose of trial drug, but not whether it was active (liraglutide) or placebo. An open-label orlistat arm was included as an active comparator.

After 20 weeks, patients could choose to enroll in the extension phase of the trial. From 20 to 52 weeks, patients and investigators remained blinded to liraglutide/placebo treatment but the sponsor was unblinded.

After the 52-week study period, patients entered 4 weeks of unblinded dose escalation, followed by 48 weeks of open-label treatment, and a post-trial follow-up visit. After 52 weeks, all patients treated with liraglutide or placebo in the main trial and extension period were initially treated with liraglutide 2.4 mg in the open-label extension period, but were all gradually changed to treatment with liraglutide 3 mg following review of the results of the 52-week interim analysis. Patients treated with orlistat in the main trial continued taking only orlistat during the extension period.

The primary objective in the first 20 weeks of this trial was to investigate the weight loss efficacy of liraglutide. The secondary objectives included establishing the dose-response of the four doses of liraglutide, comparing the weight-lowering effect of liraglutide to orlistat, and investigating the effects of liraglutide on body composition, cardiovascular risk factors, and glucose metabolism.

Demographics and baseline characteristics are summarized in Table 4, and were generally well-matched between treatment groups.

Disposition is summarized for the different phases of this trial in Table 6. All of the 564 randomized patients were exposed to treatment. A total of 472 exposed patients (83.7%) completed the 20-week trial.

A total of 398 patients were enrolled in the extension period of the trial (70.6% of those originally randomized and 84.3% of 20-week completers). Of these, 66 were exposed to placebo, 67 to orlistat, and between 59 and 72 to liraglutide. A total of 356 patients

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completed the trial up to week 52 (63.1% of those originally randomized and 89.4% of those who entered the extension).

In total, there were 134 withdrawals from baseline to week 52; 47% of these withdrawals (63 of 134) occurred in the first 14 weeks of the trial. From baseline to week 52, 37 patients (3 in the placebo-treated group, 4 in the orlistat-treated group, and between 5 and 12 in liraglutide-treated groups) were withdrawn because of reported AEs.

Table 6. Patient Disposition, Trial 1807 and Extension

	Placebo	Lira 1.2 mg	Lira 1.8 mg	Lira 2.4 mg	Lira 3 mg	Orlistat
Number Randomized	98	95	90	93	93	95
Completed 20 wks	79	85	74	73	82	79
Withdrawn from 20 wks	19	10	16	20	11	16
Adverse events	3	4	5	9	5	3
Non-compliance	3	2	2	3	2	2
Ineffective	2	1	1	0	0	1
Other	11	3	8	8	4	10
Enrolled in the extension	67	68	59	65	72	67
Completed 52 wks	62	61	55	58	65	55
Withdrawn from 52 wks*	24	17	20	27	18	28
Adverse events	3	5	6	12	7	3
Non-compliance	3	2	3	3	2	3
Ineffective	4	1	2	1	0	1
Other	14	9	9	1	9	21
Completed 104 wks	47	46	38	45	47	45
Withdrawn from 104 wks**	39	32	37	40	36	38
Adverse events	6	8	12	13	9	3
Non-compliance	4	4	5	4	7	5
Ineffective	5	3	6	2	0	2
Other	24	17	14	21	20	28
* Includes withdrawals 0-20 wks						
** Includes withdrawals 0-52 wks						

Source: Synopses NN8022-1807 and NN8022-1807 extension

6.3.1.1 Results

There was a significantly greater mean weight loss (in kg) in the groups treated with liraglutide 1.8, 2.4, and 3 mg compared with placebo (all $p < 0.001$) at week 52.

Treatment with liraglutide 2.4 and 3 mg was associated with a statistically significantly greater mean weight loss compared to orlistat (both $p < 0.05$). As seen in Figure 7, weight changes appeared reach a plateau in all treatment groups by weeks 32 to 36. As

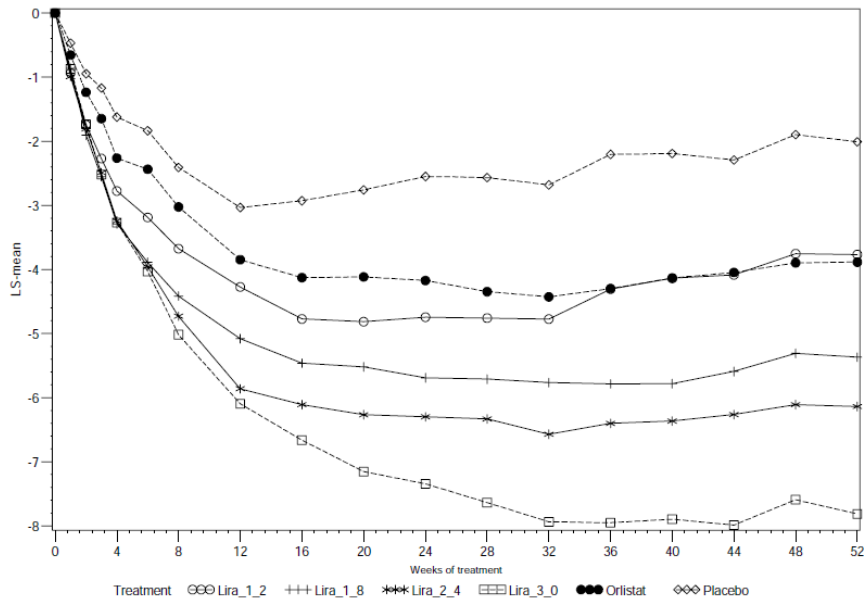
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seen in Figure 7, Table 7, and Table 8, mean weight loss with liraglutide increased with increasing doses.

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



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

Table 7. Summary of Change in Body Weight (kg), 20- and 52-Week Analyses, Trial 1807

	Placebo N=98	Lira 1.2 mg N=94	Lira 1.8 mg N=90	Lira 2.4 mg N=92	Lira 3 mg N=92	Orlistat N=95
Baseline						
Mean (SD)	97.3 (12.3)	96.4 (13.4)	98.0 (12.5)	98.4 (13.1)	97.5 (13.8)	96.0 (11.7)
Median	95.5	95.4	97.5	98.9	96.5	93.7
Min, Max	74.5, 141.3	70.2, 141.2	74.1, 138.5	69.2, 130.0	75.3, 132.0	72.7, 134.8
Week 20 (completers)						
N	79	85	74	73	82	79
Mean (SD)	-3.4 (3.4)	-5.5 (3.3)	-6.7 (5.1)	-7.4 (4.6)	-8.1 (4.5)	-4.9 (4.2)
Median	-3.2	-5.6	-5.8	-6.8	-7.1	-4.7
Min, Max	-13.5, 3.2	-13.6, 5.8	-10.0, 6.5	-18.2, 2.4	-26.2, 3.1	-21.0, 3.1
Week 52 (completers)						
N	62	61	55	58	65	55
Mean (SD)	-3.4 (5.5)	-5.0 (5.5)	-8.1 (7.2)	-8.2 (7.5)	-9.8 (5.8)	-6.4 (6.3)
Median	-2.7	-5.5	-7.0	-7.8	-8.7	-5.6
Min, Max	-18.2, 6.5	-19.2, 10.8	-33.9, 5.6	-29.2, 7.1	-31.3, -1.1	-33.4, 5.5
Week 52 (LOCF)						
N	98	94	90	92	92	95
Mean (SD)	-2.7 (4.9)	-4.6 (4.9)	-6.2 (6.5)	-7.0 (6.9)	-8.9 (6.4)	-4.7 (5.9)
Median	-1.8	-4.2	-5.2	-6.0	-7.5	-4.1
Min, Max	-18.2, 6.5	-19.2, 10.8	-33.9, 5.6	-29.2, 7.1	-31.4, 3.1	-33.4, 5.5

Source: NN8022-1807-ext Clinical Trial Report, Table 11-4

Table 8. ANCOVA of Change in Body Weight (kg) after 52 Weeks of Treatment, Trial 1807

Treatment	N	Estimated LSM		
Lira 3 mg	92	-7.81		
Lira 2.4 mg	92	-6.14		
Lira 1.8 mg	90	-5.37		
Lira 1.2 mg	94	-3.77		
Orlistat*	95	-3.89		
Placebo	98	-2.01		
	Estimated Treatment Differences	95% CI	p-value	Superiority
Lira 3 – Pbo	-5.82	(-7.95, -3.68)	0.0000	Yes
Lira 2.4 – Pbo	-4.14	(-6.25, -2.02)	0.0000	Yes
Lira 1.8 – Pbo	-3.36	(-5.48, -1.23)	0.0005	Yes
Lira 1.2 – Pbo	-1.76	(-3.87, 0.35)	0.1322	No
Lira 3 – Orlistat*	-3.80	(-6.01, -1.59)	0.0001	Yes
Lira 2.4 – Orlistat*	-2.21	(-4.40, -0.02)	0.0468	Yes
Lira 1.8 – Orlistat*	-1.47	(-3.67, 0.73)	0.2946	No
Lira 1.2 – Orlistat*	0.17	(-2.01, 2.35)	0.9990	No
* Orlistat was administered open-label				

Source: NN8022-1807-ext Clinical Trial Report, Table 11-5

Consistent with the results above, Table 9 demonstrates that the proportion of patients achieving 5% and 10% weight loss generally increased in a liraglutide dose-dependent fashion (the liraglutide 1.8 and 2.4 mg doses had similar mean numerical results). More patients lost at least 5% of baseline weight with liraglutide 1.8 mg to 3 mg compared with placebo (all $p < 0.001$). More patients in the liraglutide 3 mg group lost greater than 5% of baseline weight compared with those in the open-label orlistat group ($p < 0.001$).

Table 9. Proportion of Five and Ten Percent Body Weight Loss Responders at 52 Weeks, Trial 1807

	Placebo N=98	Lira 1.2 mg N=94	Lira 1.8 mg N=90	Lira 2.4 mg N=92	Lira 3 mg N=92	Orlistat N=95
Week 52 (completers)						
N	62	61	55	58	65	55
> 5% weight loss responders, %	37.1	54.1	69.1	67.2	81.6	61.8
> 10% weight loss responders, %	14.5	23.0	38.2	37.9	46.2	21.8
Week 52 (LOCF)						
N	98	94	90	92	92	95
> 5% weight loss responders, %	27.5	45.8	53.4*	53.2*	75.0*†	45.3
> 10% weight loss responders, %	10.2	18.1	26.7	29.3	37.0	15.8
* Superiority to placebo, $p < 0.001$						
† Superiority to open-label orlistat, $p < 0.001$						

Source: NN8022-1807-ext Clinical Trial Report, Table 11-8

6.3.1.1.1 Body Composition Substudy

A subset of patients in the phase 2 weight management trial 1807 had body composition measured by dual energy X-ray absorptiometry (DEXA) at baseline and week 20. All patients at selected sites in Belgium, Czech Republic, Denmark, Finland, Netherlands, Spain, and Sweden had the option to participate in the substudy until the required number of patients had been obtained (planned number 102; 17 patients per treatment arm).

Nominally significant findings between liraglutide and placebo or orlistat were not observed for most of the endpoints. Liraglutide and placebo were associated with mean reductions in whole body fat, whole body fat percentage, and lean body mass.

At week 20, mean whole body fat mass was reduced between 5.0 and 6.9 kg with liraglutide treatment compared to baseline (no apparent dose effect); in the placebo group the mean reduction was 4.4 kg and in the orlistat group the mean reduction was 4.9 kg. The mean whole body fat percentage reduction with liraglutide treatment ranged from 2.3 to 3.8% (no apparent dose effect), compared to a mean reduction of 2.5% with placebo and 3.6% with orlistat.

At week 20, mean lean body mass was reduced between 0.5 to 1.5 kg with liraglutide treatment compared to baseline (no apparent dose effect); in the placebo group the mean reduction was 0.6 kg. Whole body lean mass increased by a mean 0.3 kg from baseline to week 20 in the orlistat treatment group.

The percentage of body weight lost due to fat ranged from 75 to 92% of the total weight reduction in the liraglutide-treated groups, compared with approximately 88% in the placebo-treated group.

6.3.2 Trial 1839

This trial was a randomized, double-blind, placebo-controlled, parallel-group, multinational trial with obese (BMI 30 kg/m² or greater) patients or overweight (BMI 27 kg/m² or greater) patients with co-morbidities (treated or untreated hypertension or dyslipidemia). Patients with diabetes at screening were not eligible. Patients were randomized in a 2:1 manner to receive either liraglutide 3 mg or placebo; the randomization was stratified based on pre-diabetes status at screening (based on fasting plasma glucose [FPG], oral glucose tolerance test [OGTT], or HbA1c) and BMI at baseline (above or below 30 kg/m²). Patients classified at screening as having pre-diabetes were randomized to 160 weeks of treatment, followed by a 12-week off-drug/placebo observational follow-up period. Patients classified as not having pre-diabetes were randomized to 56 weeks of treatment, followed by a 12-week re-randomized treatment period, and a 2-week follow-up period. In the re-randomized period, patients without pre-diabetes who were treated with liraglutide 3 mg during the main treatment phase

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were re-randomized in a 1:1 manner to either continue treatment with liraglutide 3 mg or to switch to placebo.

Results from the first 56 weeks of treatment (all patients, with and without pre-diabetes) and the 12-week re-randomized period (patients with pre-diabetes only) were reviewed. The first 56 weeks of the trial consisted of two screening visits, a 4-week dose escalation period, and a 52-week maintenance period.

Patients followed a fixed-dose escalation. The dose was gradually escalated from 0.6 mg to 3 mg with a dose level increment of 0.6 mg every 7 days. If patients did not tolerate an increase in dose during dose escalation, the investigator had the option to individualize the timing of dose escalation with a total delay of up to 7 days. All patients had to be at the target dose of 3 mg by 35 days after randomization. After reaching the target dose, dose and dosing frequency were not to be changed at any time during the treatment period.

The primary objective was to establish the efficacy of liraglutide 3 mg compared with placebo in inducing and maintaining weight loss over 56 weeks. The other primary objective, to investigate the long-term efficacy of liraglutide 3 mg in delaying the onset of T2DM in obese patients with pre-diabetes and in overweight patients with pre-diabetes and dyslipidemia and/or hypertension, is ongoing and is therefore not addressed in this review.

For all weight and glycemic efficacy endpoints, only observations prior to glycemic rescue medication in patients who develop T2DM were to be included in the analyses, as rescue medication would have confounded the subsequent measurement of these parameters.

Reviewer comment: During the 56 weeks of treatment, four patients treated with liraglutide (0.2%) and 14 patients treated with placebo (1.1%) developed T2DM. Therefore, glycemic rescue is unlikely to have impacted the results.

Secondary objectives were to investigate the long-term efficacy of liraglutide 3 mg versus placebo on blood pressure, lipids, glucose parameters, urinary albumin-to-creatinine ratio (UACR), and patient reported outcomes (PRO). None of these endpoints were adjusted for multiplicity.

Demographics and baseline characteristics are summarized in Table 4, and were generally well-matched between treatment groups.

Among the 3731 randomized patients, 2285 and 1446 were classified with and without pre-diabetes, respectively. Patient disposition by pre-diabetes status is presented in the table below. Overall, the withdrawal rate was lower with liraglutide (28.1%) than with

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placebo (35.6%), although more patients treated with liraglutide (9 to 10%) withdrew due to adverse events as compared to those treated with placebo (3 to 4%).

Table 10. Patient Disposition by Pre-Diabetes Status, Trial 1839

	With Pre-Diabetes		Without Pre-Diabetes	
	Lira 3 mg	Placebo	Lira 3 mg	Placebo
Number Randomized	1528	757	959	487
Completed 56 wks	1110 (72.6)	505 (66.7)	679 (70.8)	296 (60.8)
Withdrawn from 56 wks	418 (27.4)	252 (33.3)	280 (29.2)	191 (39.2)
Adverse events ^a	152 (9.9)	29 (3.8)	86 (9.0)	16 (3.3)
Ineffective	12 (0.8)	22 (2.9)	11 (1.1)	14 (2.9)
Non-compliance	40 (2.6)	20 (2.6)	25 (2.6)	18 (3.7)
Withdrawal criteria	172 (11.3)	147 (19.4)	122 (12.7)	114 (23.4)
Withdrawn consent	152 (9.9)	137 (18.1)	112 (11.7)	112 (23.0)
Target dose not tolerated	1 (0.1)	0	1 (0.1)	0
Pregnancy or pregnancy intent	15 (1.0)	8 (1.1)	11 (1.1)	2 (0.4)
Use of insulin, GLP1RA, or DPP4i	0	1 (0.1)	0	0
Acute pancreatitis	5 (0.3)	0	1 (0.1)	0
Psychiatric disorder	0	0	0	0
Calcitonin \geq 50 ng/L (France)	0	0	0	0
Adverse event withdrawals total	158 (10.3)	31 (4.1)	88 (9.2)	16 (3.3)
Other	42 (2.7)	34 (4.5)	36 (3.8)	29 (6.0)
Withdrawn during 56 wks but attended visit 17x	126 (8.2)	68 (9.0)	76 (7.9)	43 (8.8)
Entered re-randomization period ^b	27 (1.8)	10 (1.3)	674 (70.3)	294 (60.4)
^a Does not include: target dose not tolerated, acute pancreatitis, psychiatric disorder				
^b Patients with pre-diabetes entered the re-randomized period due to incorrect stratification				

Source: NN8022-1839 Clinical Trial Report, Table 10-2

Of those patients entering the 12-week re-randomization phase, the proportion of withdrawals were: 2.6% of patients in the lira/lira group, 2.0% of patients in the lira/placebo group, and 4.9% of patients in the placebo/placebo group.

6.3.2.1 Results

This review covers the initial 56 weeks of treatment including both patients with and without pre-diabetes, and the 12-week re-randomized period including only patients without pre-diabetes. The efficacy parameters for the initial 56 weeks of the trial are summarized for all patients and by pre-diabetes status at screening.

The tests for superiority of liraglutide 3 mg to placebo for each of the three co-primary endpoints were tested in a hierarchical manner in the order presented below. Due to the hierarchical testing procedure, superiority of liraglutide 3 mg to placebo for a given endpoint could only be confirmed if superiority was confirmed for all preceding endpoints in the hierarchy. The three co-primary endpoints were defined as:

1. Change (%) in fasting body weight from baseline to week 56
2. Proportion of patients losing 5% or greater of baseline fasting body weight at week 56 (5% responders)
3. Proportion of patients losing more than 10% of baseline fasting body weight at week 56 (10% responders)

6.3.2.1.1 Percent Change in Body Weight

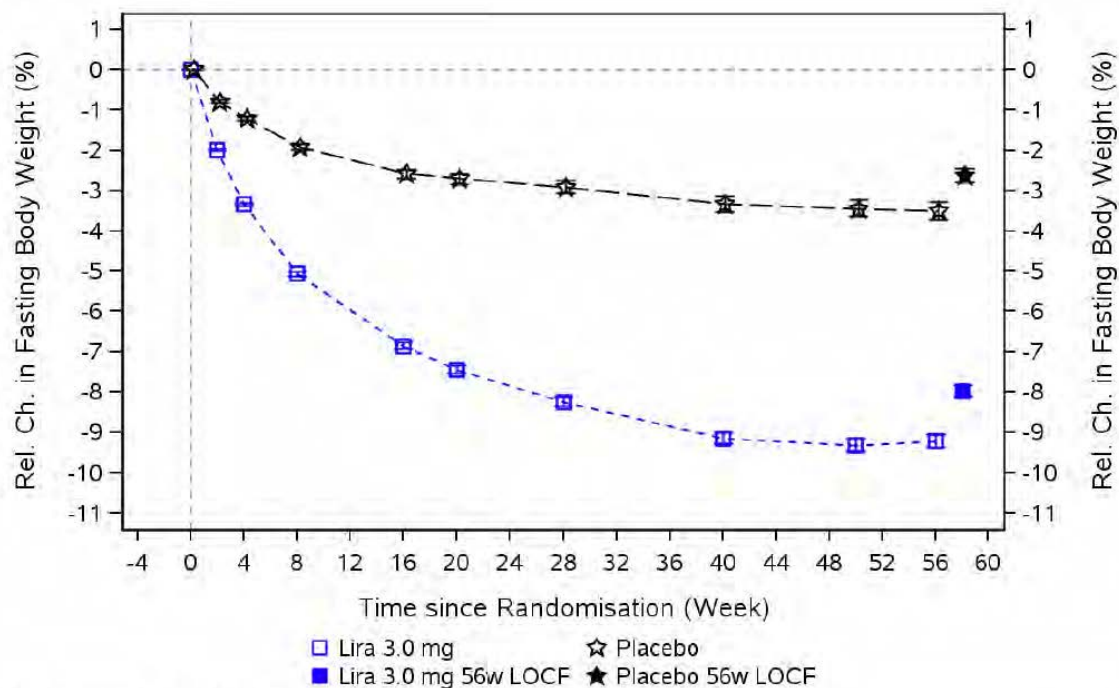
Patients treated with liraglutide 3 mg demonstrated statistically significantly greater mean weight loss at 56 weeks than patients treated with placebo, with a treatment difference at week 56 of 5.39%.

Table 11. Percent Change from Baseline in Body Weight after 56 Weeks of Treatment, LOCF, Trial 1839

Treatment	N	Baseline Mean, kg (SD)	% Change from Baseline, Wk 56
Lira 3 mg	2432	106.30 (21.23)	-7.99
Placebo	1220	106.33 (21.72)	-2.60
Between treatment difference		Difference in LS means (95% CI)	p value
Lira 3 mg vs. Placebo		-5.39 (-5.82, -4.95)	<0.0001

Source: NN8022-1839 Clinical Trial Report, Table 14.2.13

Figure 8. Percent Change from Baseline in Fasting Body Weight in the Main Treatment Period (0 to 56 Weeks), Trial 1839



FAS, observed values. Error bars: Mean +/- Standard error of the mean.
Source: NN8022-1839 Clinical Trial Report, Figure 14.2.24

The results using the LOCF imputation method for missing values are consistent with the completers' analysis:

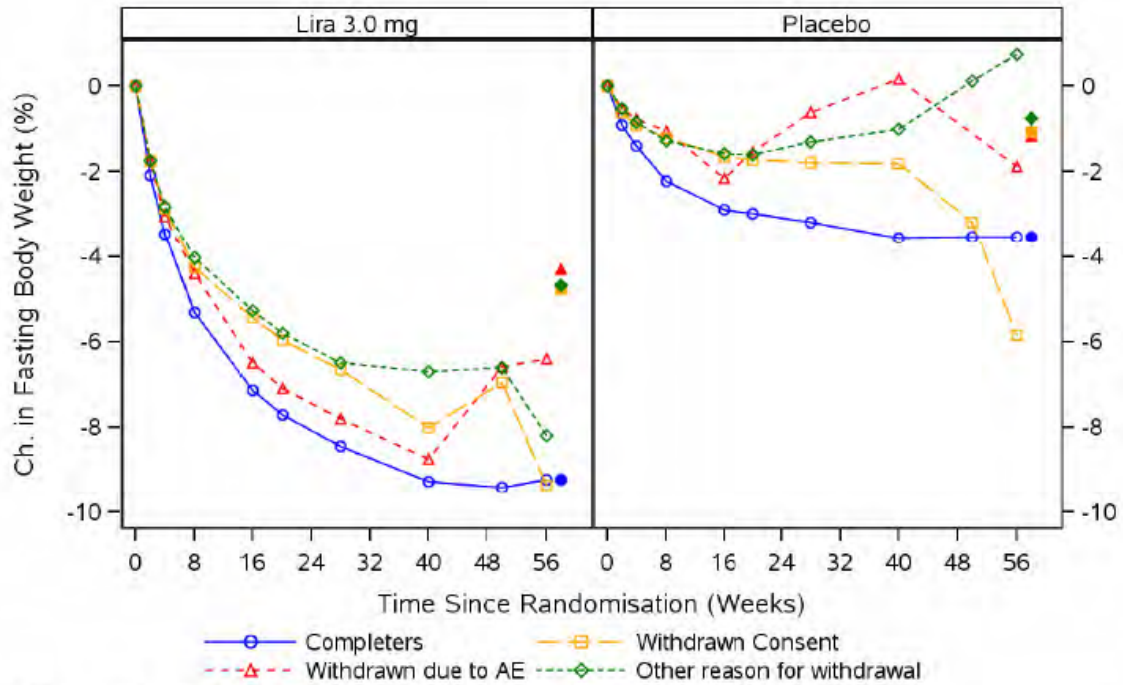
Table 12. Percent Change from Baseline after 56 Weeks of Treatment, Completers' Analysis, Trial 1839

Completers		
Treatment	N	% Change from Baseline, Wk 56
Lira 3 mg	1781	-9.22
Placebo	798	-3.53
Between treatment difference		p value
Lira 3 mg vs. Placebo		<0.0001

Source: NN8022-1839 Clinical Trial Report, Table 14.2.14

An analysis of mean percent weight change by reasons for discontinuation was conducted:

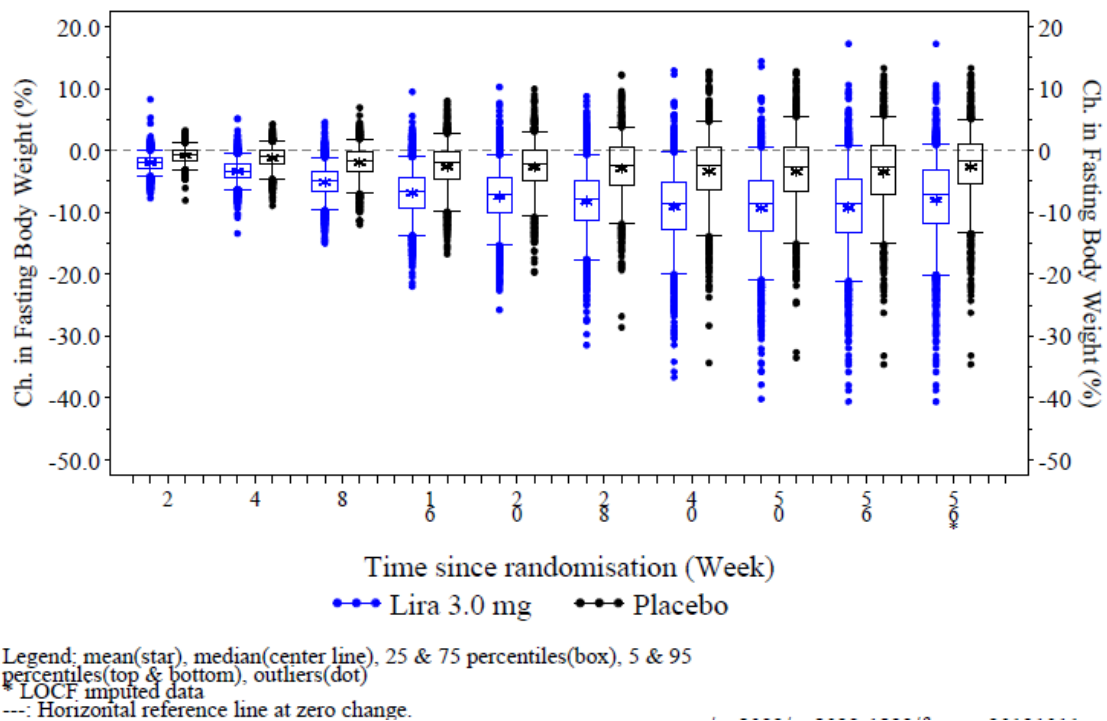
Figure 9. Percent Change from Baseline in Body Weight in the Main Treatment Period (0 to 56 Weeks) by Reason for Withdrawal, Trial 1839



Source: NN8022-1839 Clinical Trial Report, Figure 14.2.27

The following figure illustrates the percent change in body weight by treatment week as a box plot, demonstrating outliers in both treatment groups both for weight loss as well as weight gain:

Figure 10. Percent Change from Baseline in Body Weight in Main Treatment Period (0 to 56 Weeks) by Treatment Week, Trial 1839



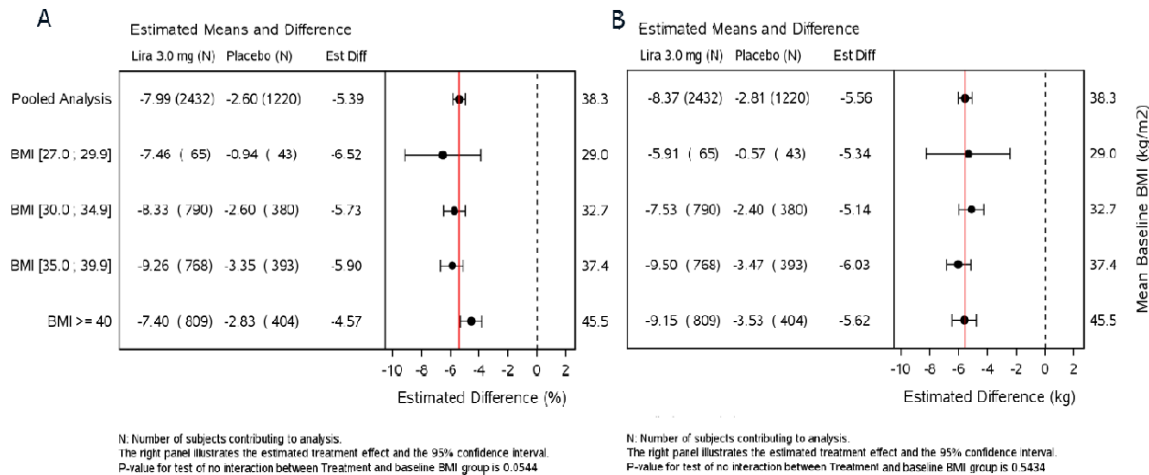
Source: NN8022-1839 Clinical Trial Report, Figure 14.2.32

6.3.2.1.1.1 Subgroups

BMI

The treatment effect of liraglutide 3 mg on absolute body weight (in kg) was similar across baseline BMI (Figure 11, panel B). This observation was reflected in an apparent decreasing effect on relative change (%) in body weight with higher BMI (interaction $p=0.05$; Figure 11, panel A).

Figure 11. Change from Baseline in Body Weight in % (A) and kg (B) after 56 Weeks of Treatment by Baseline BMI, Trial 1839



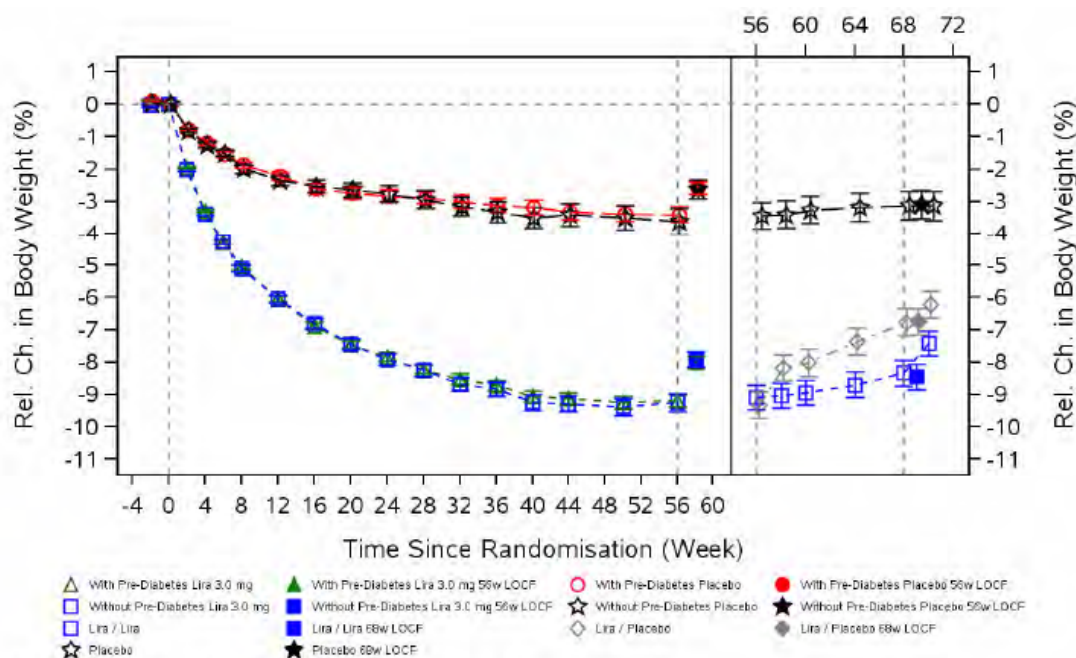
Source: NN8022-1839 Clinical Trial Report, Figure 11-5

Pre-Diabetes Status

Mean \pm SD percent weight loss was similar in patients with pre-diabetes (week 56 LOCF lira: $-8.01 \pm 6.51\%$, placebo: $-2.58 \pm 5.36\%$) and those without pre-diabetes (week 56 LOCF lira: $-7.92 \pm 6.94\%$, placebo: $-2.63 \pm 6.31\%$).

The plot below also includes the percent change in body weight in the re-randomized period (patients without pre-diabetes only). Patients who were randomized to remain on liraglutide gained a mean of 0.69% body weight over the 12-week period (week 56 to week 68) and patients re-randomized from liraglutide to placebo gained a mean of 2.91% body weight (lira/lira – lira/placebo: -2.18% , 95% CI: $-2.60, -1.75$; $p < 0.0001$). Those who remained on placebo throughout the 68 weeks gained a mean of 0.28% body weight between weeks 56 and 68.

Figure 12. Percent Change in Body Weight in the Main Treatment Period (0 to 56 Weeks) and in the Re-Randomized Treatment Period (56 to 68 Weeks) by Pre-Diabetes Status



Note: The period between weeks 68 to 70 was an off-drug follow-up period

Source: NN8022-1839 Clinical Trial Report, Figure 14.2.100

6.3.2.1.2 Five Percent Responder Analysis

A statistically significantly greater proportion of patients treated with liraglutide (63.5%) lost at least 5% of baseline body weight at week 56 compared to those treated with placebo (26.6%); see Table 13.

Table 13. Proportion of Patients Losing at Least Five Percent of Body Weight after 56 Weeks of Treatment, LOCF, Trial 1839

Treatment	N	Proportion losing at least 5%, Wk 56
Lira 3 mg	2432	63.53%
Placebo	1220	26.61%
Between treatment comparison		Treatment odds ratio (95% CI)
Lira 3 mg / Placebo		4.80 (4.12, 5.60)
		p-value
		<0.0001

Source: NN8022-1839 Clinical Trial Report, Table 14.2.66

Sensitivity analyses evaluating completers and premature withdrawal patients who are characterized as non-responders are consistent with the primary analysis.

Table 14. Proportion of Patients Losing at Least Five Percent of Body Weight after 56 Weeks of Treatment, Sensitivity Analyses, Trial 1839

Completers			
Treatment	N	Proportion losing at least 5%, Wk 56	
Lira 3 mg	1781	73.33%	
Placebo	798	35.68%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		4.96 (4.13, 5.95)	<0.0001
Premature Withdrawals Counted as Non-Responders			
Treatment	N	Proportion losing at least 5%, Wk 56	
Lira 3 mg	2432	54.32%	
Placebo	1220	23.39%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		3.89 (3.33, 4.56)	<0.0001

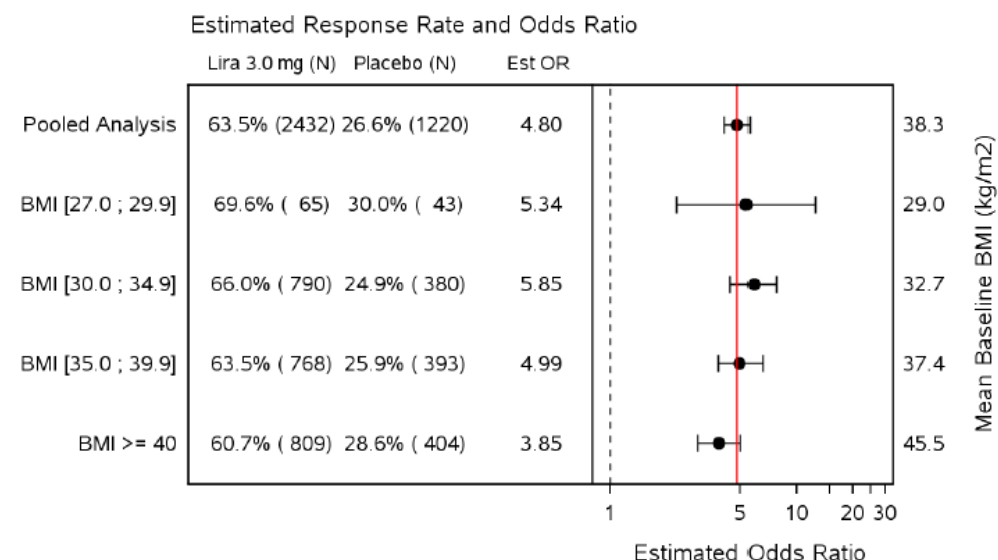
Source: NN8022-1839 Clinical Trial Report, Table 14.2.67

6.3.2.1.2.1 Subgroups

BMI

Five percent response efficacy was demonstrated in all of the BMI subgroups. As noted with the mean change difference across subgroups, the treatment effect appeared somewhat smaller with higher BMI, although the interaction p-value was 0.19. The proportion of patients treated with placebo that lost 5% or greater body weight ranged from 25 to 30% across the different BMI subgroups. The proportion of 5% responders treated with liraglutide ranged from 60 to 70%, with higher proportions in the lower BMI groups.

Figure 13. Proportion of Patients Losing Five Percent or Greater Body Weight by BMI, Trial 1839



N: Number of subjects contributing to analysis.
The right panel illustrates the estimated treatment effect and the 95% confidence interval.
P-value for test of no interaction between Treatment and baseline BMI group is 0.1867

Source: NN8022-1839 Clinical Trial Report, Figure 11-9

Pre-Diabetes Status

A similar proportion of patients with and without diabetes lost 5% body weight in both treatment groups.

Table 15. Proportion of Patients Losing at Least Five Percent Body Weight by Pre-Diabetes Status, Trial 1839

With Pre-Diabetes			
Treatment	N	Proportion losing at least 5%, Wk 56	
Lira 3 mg	1490	64.6%	
Placebo	742	26.4%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		5.09 (4.18, 6.21)	<0.0001
Without Pre-Diabetes			
Treatment	N	Proportion losing at least 5%, Wk 56	
Lira 3 mg	942	61.8%	
Placebo	478	25.8%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		4.64 (3.62, 5.96)	<0.0001
Test for interaction		0.5699	

Source: NN8022-1839 Clinical Trial Report, Table 14.2.71

6.3.2.1.3 Ten Percent Responder Analysis

A statistically significantly greater proportion of patients treated with liraglutide (33%) lost more than 10% of baseline body weight at week 56 as compared to those treated with placebo (10%); see Table 16.

Table 16. Proportion of Patients Losing More Than 10 Percent of Body Weight after 56 Weeks of Treatment, LOCF, Trial 1839

Treatment	N	Proportion more than 10%, Wk 56	
Lira 3 mg	2432	32.77%	
Placebo	1220	10.09%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		4.34 (3.54, 5.32)	<0.0001

Source: NN8022-1839 Clinical Trial Report, Table 14.2.77

As with the 5% responder analyses, sensitivity analyses were consistent with the primary analysis.

Table 17. Proportion of Patients Losing at least 10 Percent of Body Weight after 56 Weeks of Treatment, Sensitivity Analyses, Trial 1839

Completers			
Treatment	N	Proportion losing at least 10%, Wk 56	
Lira 3 mg	1781	40.71%	
Placebo	798	14.49%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		4.05 (3.25, 5.05)	<0.0001
Premature Withdrawals Counted as Non-Responders			
Treatment	N	Proportion losing at least 10%, Wk 56	
Lira 3 mg	2432	30.00%	
Placebo	1220	9.57%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		4.05 (3.29, 4.99)	<0.0001

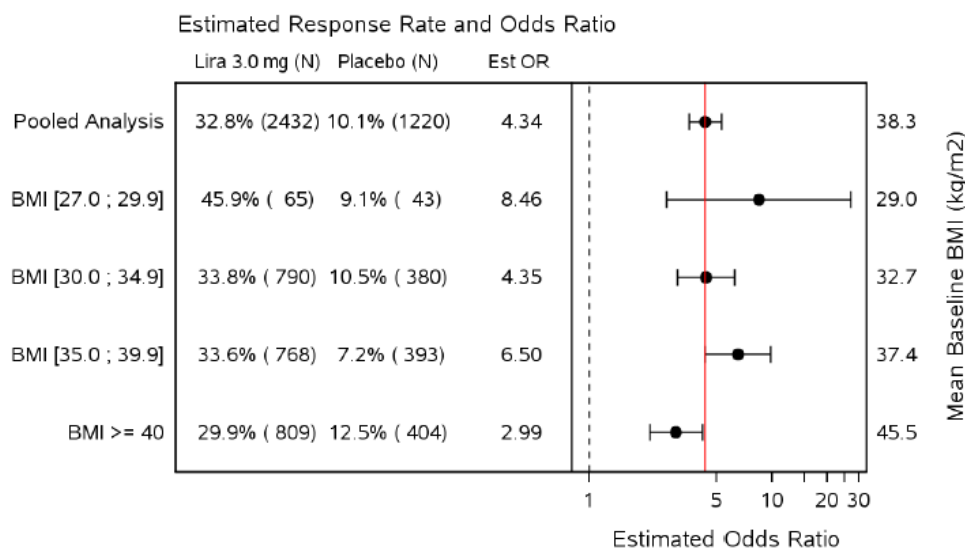
Source: NN8022-1839 Clinical Trial Report, Table 14.2.77

6.3.2.1.3.1 Subgroups

BMI

Liraglutide was superior to placebo in the 10% responder analysis in all BMI subgroups; however, there was a significant interaction between treatment effect and BMI ($p=0.02$). Similar to the other weight loss analyses by BMI, patients with the lowest baseline BMIs appeared more likely to lose 10% of body weight with liraglutide than those with the highest BMIs.

Figure 14. Proportion of Patients Losing Greater than 10 Percent Body Weight after Week 56 by BMI, Trial 1839



N: Number of subjects contributing to analysis.

The right panel illustrates the estimated treatment effect and the 95% confidence interval.

P-value for test of no interaction between Treatment and baseline BMI group is 0.0178

Source: NN8022-1839 Clinical Trial Report, Figure 11-12

Pre-Diabetes Status

A similar proportion of patients with and without diabetes lost 10% body weight in both treatment groups.

Table 18. Proportion of Patients Losing Greater than 10 Percent Body Weight after Week 56 by Pre-Diabetes Status, Trial 1839

With Pre-Diabetes			
Treatment	N	Proportion losing at least 10%, Wk 56	
Lira 3 mg	1490	32.1%	
Placebo	742	9.6%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		4.45 (3.42, 5.80)	<0.0001
Without Pre-Diabetes			
Treatment	N	Proportion losing at least 10%, Wk 56	
Lira 3 mg	942	33.8%	
Placebo	478	10.9%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		4.17 (3.03, 5.74)	<0.0001
Test for interaction		0.7604	

Source: NN8022-1839 Clinical Trial Report, Table 14.2.81

6.3.2.1.4 Secondary Endpoints

6.3.2.1.4.1 Body Composition

Baseline waist circumference (~115 cm) and BMI (~38 kg/m²) were similar between the liraglutide 3 mg and placebo randomized treatment groups.

At week 56, patients treated with liraglutide had reduced waist circumference by 8.19 cm compared to 3.94 cm in patients treated with placebo (treatment difference -4.20 cm, 95% CI: -4.68, -3.72). At baseline, patients with pre-diabetes had a larger waist circumference than patients without pre-diabetes. The overall change in waist circumference was similar in patients with and without pre-diabetes, and no statistically significant interaction between treatment and pre-diabetes status for waist circumference was observed.

At the end of the re-randomized period (week 68), waist circumference increased in all treatment groups. In patients switched from liraglutide to placebo, waist circumference increased by 1.73 cm and in those who continued liraglutide, waist circumference increased by 0.31 cm. In those who continued placebo, waist circumference increased by 0.08 cm.

At week 56, patients treated with liraglutide reduced mean BMI by 3.03 kg/m² compared with 1.01 kg/m² in patients treated with placebo (treatment difference -2.04 kg/m², 95% CI: -2.21, -1.87). At baseline, patients with pre-diabetes had slightly higher BMI than patients without pre-diabetes. The overall change in BMI was similar in patients with and without pre-diabetes, and no statistically significant interaction between treatment and pre-diabetes status was observed.

6.3.2.1.4.2 Glycemic Endpoints

At baseline, HbA1c values were similar in the liraglutide and placebo groups (5.59% versus 5.58%). At week 56, the reduction in HbA1c was statistically significantly greater with liraglutide compared with placebo.

Table 19. Change in HbA1c (%) after 56 Weeks of Treatment, Trial 1839

Treatment	N	Change in HbA1c, mean (SD), Wk 56	
Lira 3 mg	2389	-0.29	
Placebo	1209	-0.07	
Between treatment difference		Difference in LS means (95% CI)	p-value
Lira 3 mg vs. Placebo		-0.23 (-0.25, -0.21)	<0.0001

Source: NN8022-1839 Clinical Trial Report, Table 14.2.196

At baseline, patients with pre-diabetes had higher HbA1c (5.74%) compared with patients without pre-diabetes (5.33%). The treatment effect was greater in patients with pre-diabetes as compared to patients without (placebo-subtracted change in pre-

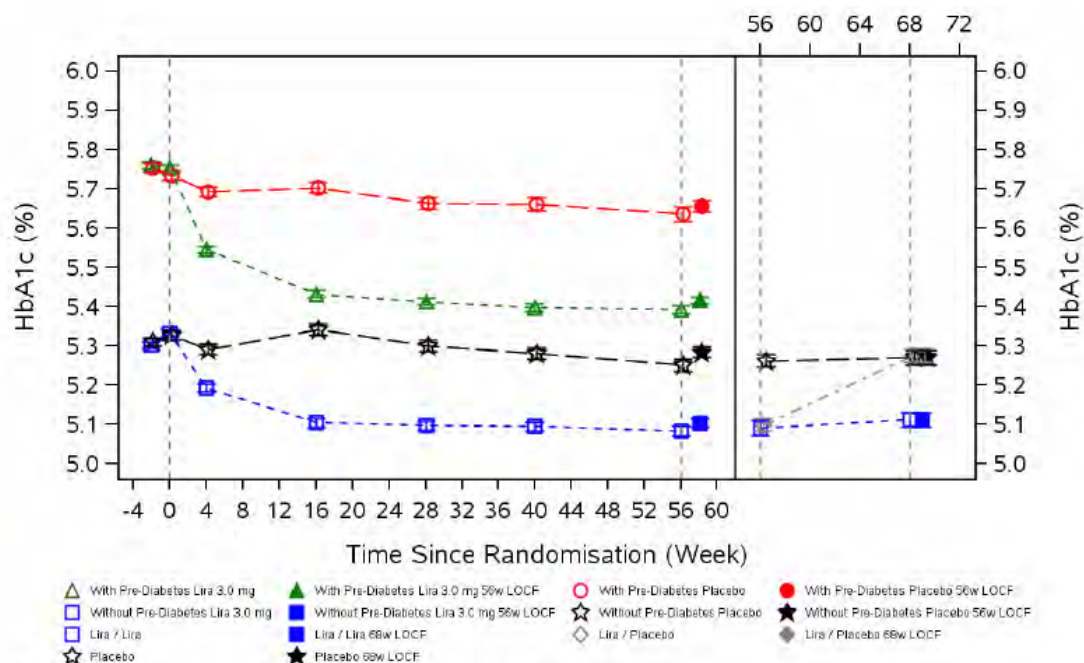
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diabetes group: -0.25% (95% CI: -0.28, -0.23); without pre-diabetes -0.19% (95% CI: -0.22, -0.16); interaction p-value: 0.0005).

Figure 15. HbA1c (%) from Baseline to Week 68, by Pre-Diabetes Status, Trial 1839



FAS, observed values. Error bars: Mean +/- Standard error of the mean.

Source: NN8022-1839 Clinical Trial Report, Figure 11-16

Baseline fasting plasma glucose in the liraglutide treatment group was 95.8 mg/dL and in the placebo treatment group, 95.4mg/dL. Change in fasting plasma glucose was greater in the liraglutide treatment group as compared to placebo.

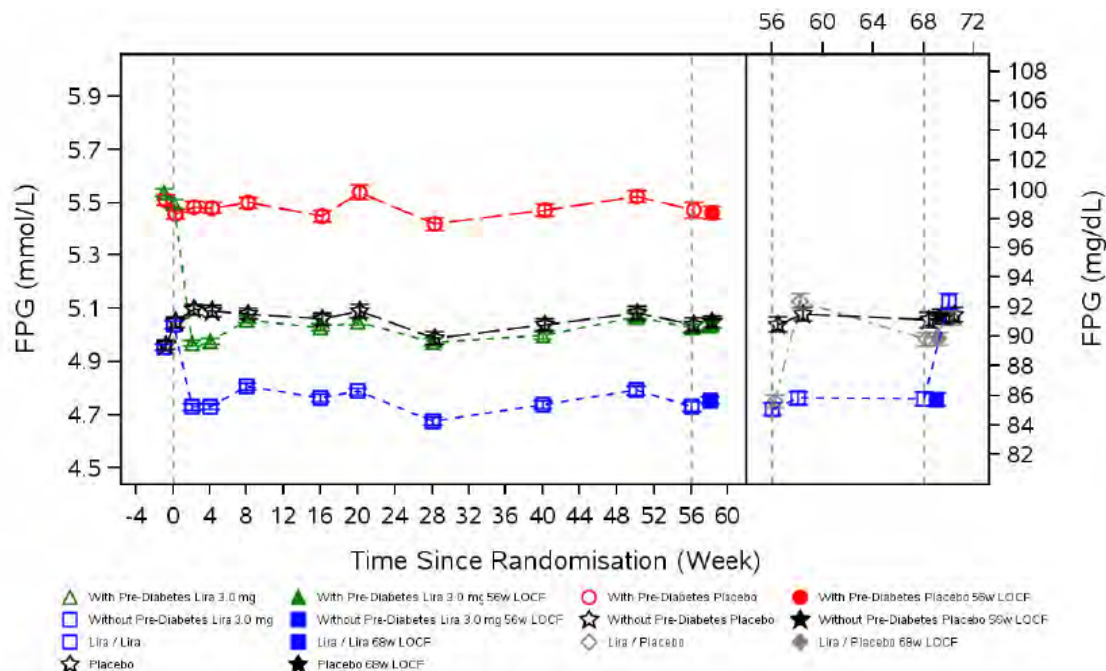
Table 20. Change in Fasting Plasma Glucose after 56 Weeks of Treatment, Trial 1839

Treatment	N	Change in FPG (mg/dL), mean (SD), Wk 56
Lira 3 mg	2432	-7.00
Placebo	1222	-0.10
Between treatment difference		Difference in LS means (95% CI)
Lira 3 mg vs. Placebo		-6.90 (-7.50, -6.31)
		p-value
		<0.0001

Source: NN8022-1839 Clinical Trial Report, Table 14.2.223

Patients treated with liraglutide 3 mg had mean decreases in FPG within the first two weeks of treatment, whereas in those treated with placebo, FPG remained relatively stable throughout the 56 weeks of treatment. The pattern was similar in patients with and without pre-diabetes, although the decreases observed in patients treated with liraglutide were more pronounced in patients with pre-diabetes than those without.

Figure 16. Fasting Plasma Glucose from Baseline to Week 68, Trial 1839



Source: NN8022-1839 Clinical Trial Report, Figure 11-18

Other glycemic markers, fasting insulin, HOMA-B, and HOMA-IR favorably improved with liraglutide, whereas there was no treatment difference seen with C-peptide.

Table 21. Summary of Fasting Glycemic Parameters, Trial 1839

	Lira 3 mg		Placebo		Lira 3 / Placebo
	Baseline	% Change	Baseline	% Change	Estimated ratio (95% CI)
Fasting insulin, $\mu\text{IU/mL}$	16.34	-12.57	16.13	-4.44	0.92 (0.88, 0.95)
Fasting C-peptide, ng/dL	2.07	-8.85	2.04	-7.89	0.99 (0.97, 1.02)
HOMA-B, %	195.06	13.67	195.00	-3.86	1.18 (1.13, 1.22)
HOMA-IR, %	3.97	-19.05	3.90	-4.54	0.85 (0.82, 0.89)

Source: NN8022-1839 Clinical Trial Report, Table 11-15

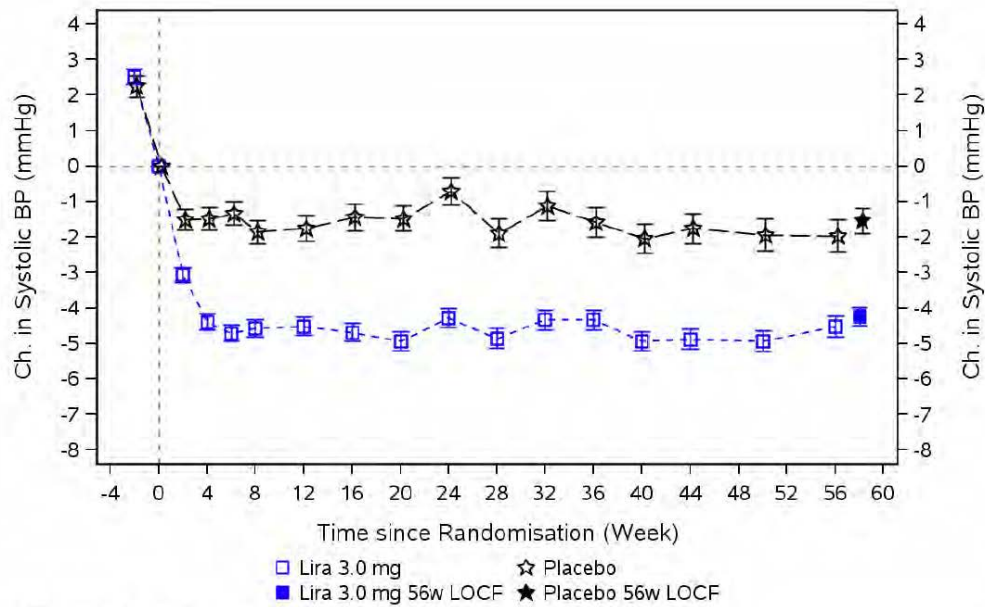
6.3.2.1.4.3 Other Cardiometabolic Parameters

Blood Pressure

At baseline, 34.7% of patients had a history of hypertension.

Mean systolic and diastolic BP were reduced from baseline throughout the treatment period for both treatment groups, with a greater effect with liraglutide for both parameters (SBP: liraglutide -4.24 mmHg, placebo -1.54 mmHg; DBP: liraglutide -2.63 mmHg, placebo -1.90 mmHg). The reduction in SBP with liraglutide occurred within the initial 4 weeks of treatment.

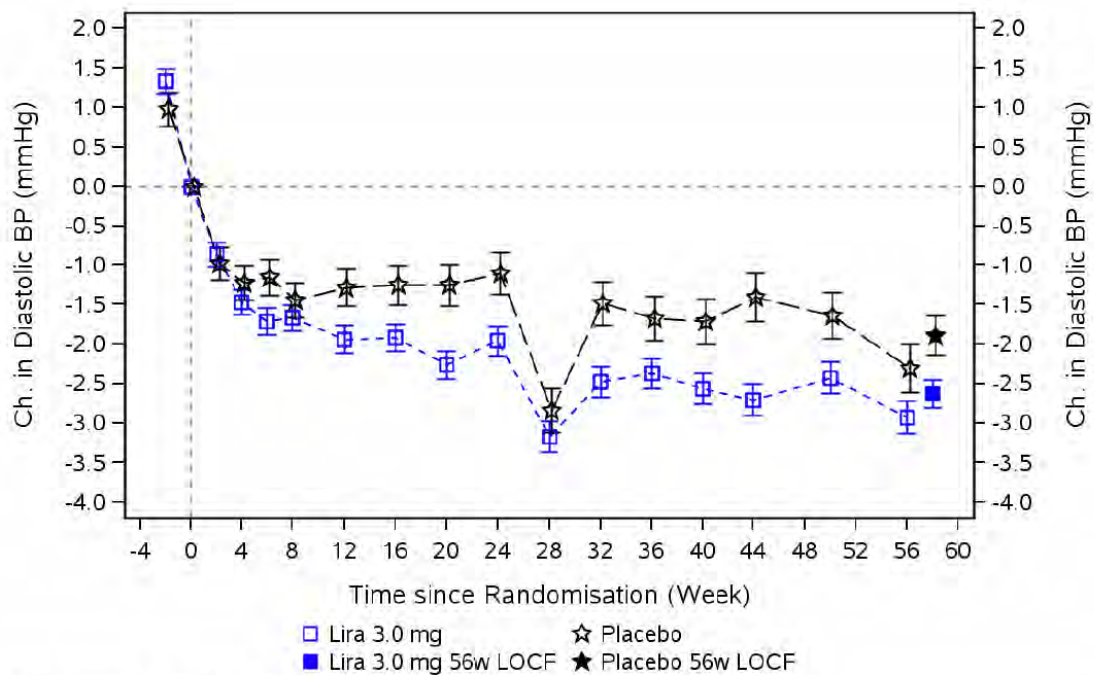
Figure 17. Change in Systolic Blood Pressure, Trial 1839



FAS, observed values. Error bars: Mean +/- Standard error of the mean.

Source: NN8022-1839 Clinical Trial Report, Figure 11-25

Figure 18. Change in Diastolic Blood Pressure, Trial 1839



FAS, observed values. Error bars: Mean +/- Standard error of the mean.

Source: NN8022-1839 Clinical Trial Report, Figure 11-27

Lipids

At baseline, 29.4% of all patients had a medical history of dyslipidemia, and 15.8% and 14.9% patients were taking lipid-lowering agents in the liraglutide 3 mg and placebo groups, respectively.

Liraglutide modestly improved all fasting lipid profile parameters compared with placebo, see Table 22.

Table 22. Summary of Lipid Profile Parameters, Trial 1839

	Liraglutide 3 mg N=2437		Placebo N=1225	
	Baseline	% Change from BL	Baseline	% Change from BL
HDL-C, mg/dL	51.36	2.28*	50.93	0.68
LDL-C, mg/dL	111.78	-2.98*	112.30	-0.95
VLDL-C, mg/dL	25.15	-13.11*	25.75	-5.54
TG, mg/dL	126.34	-13.26*	129.27	-5.53
Total-C, mg/dL	126.34	-3.07*	129.27	-1.02

* Nominal p-value for difference from placebo < 0.05

Source: Summary of Clinical Efficacy, Table 2-6

Other Cardiovascular Biomarkers

Other biomarkers tested included hsCRP, PAI-1, adiponectin, fibrinogen, and albumin/creatinine ratio. HsCRP was reduced (hsCRP: -38% vs. -10%); week 56 PAI-1 was lower¹⁷ (12.79 vs. 16.11); and adiponectin concentrations were increased (11% vs. 3%) with liraglutide 3 mg compared with placebo, respectively, suggesting improvements in these parameters. Changes in fibrinogen and albumin/creatinine ratio in patients treated with liraglutide were not different than in those treated with placebo.

6.3.2.1.4.4 Patient Reported Outcomes

Patient reported outcomes (PRO) instruments administered in trial 1839 included IWQoL-Lite: total score and scores for all individual domains; SF-36: scores for all individual domains; TRIm-Weight: total score, weight management efficacy score, and treatment burden score. These questionnaires were administered in a subset of sites at baseline, week 28, week 56, and at the end of the re-randomized period (if applicable).

The IWQOL-Lite questionnaire assesses the quality of life in obese individuals. The questionnaire contains 31 items divided into five domains:

- Physical function

¹⁷ PAI-1 baseline data were obtained with ELISA assays (ng/mL); week 56 data were obtained with chromogenic assays (arbitrary units/mL). Changes could not be calculated due to the use of two different analytic methods at baseline and week 56.

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- Self-esteem
- Sexual life
- Public distress
- Work

The SF-36 questionnaire measures the individual overall health related to quality of life. It contains 36 items divided into eight domains:

- Physical functioning
- Role functioning
- Bodily pain
- General health
- Vitality
- Social functioning
- Role emotional
- Mental health

An increased score in both instruments is considered favorable (increases in quality of life).

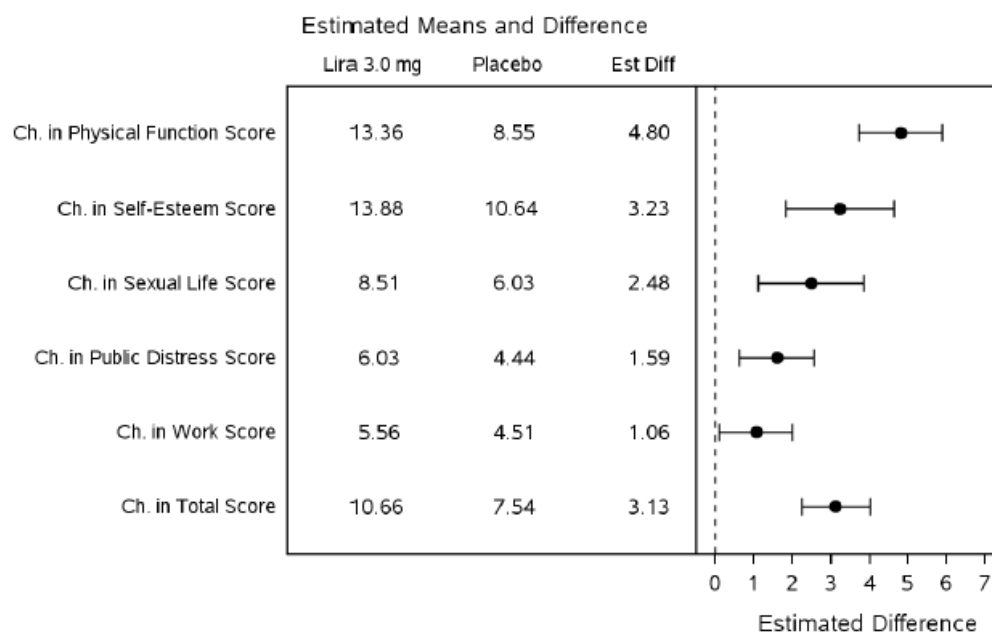
The TRIm-Weight questionnaire evaluates the overall impact and treatment satisfaction of individuals. It contains 22 items divided into five domains:

- Daily life
- Weight management
- Treatment burden
- Experience of side effects
- Psychological health

TRIm-Weight was not assessed at baseline (as it evaluates treatment satisfaction) and therefore, data are not presented as change over time. A higher score is considered favorable.

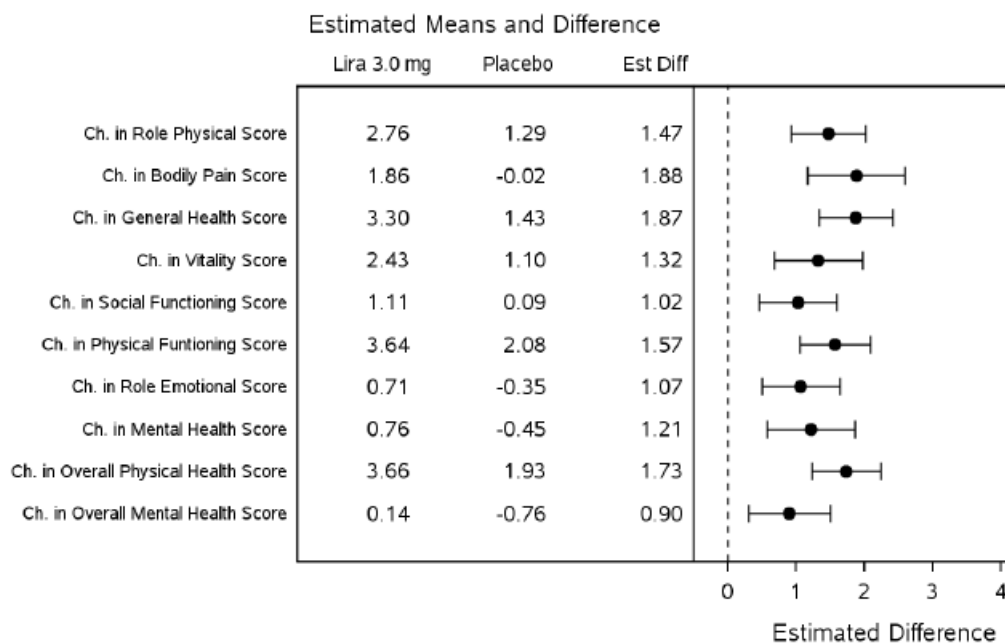
Improvements were seen in the IWQOL-Lite and SF-36 domains in liraglutide-treated patients compared to placebo, as shown in Figure 19 and Figure 20. In the TRIm-Weight PRO, improvements were reported in the total, weight management, and treatment burden scores, with a worsening seen in the experience of side effects score.

Figure 19. IWQoL, Trial 1839



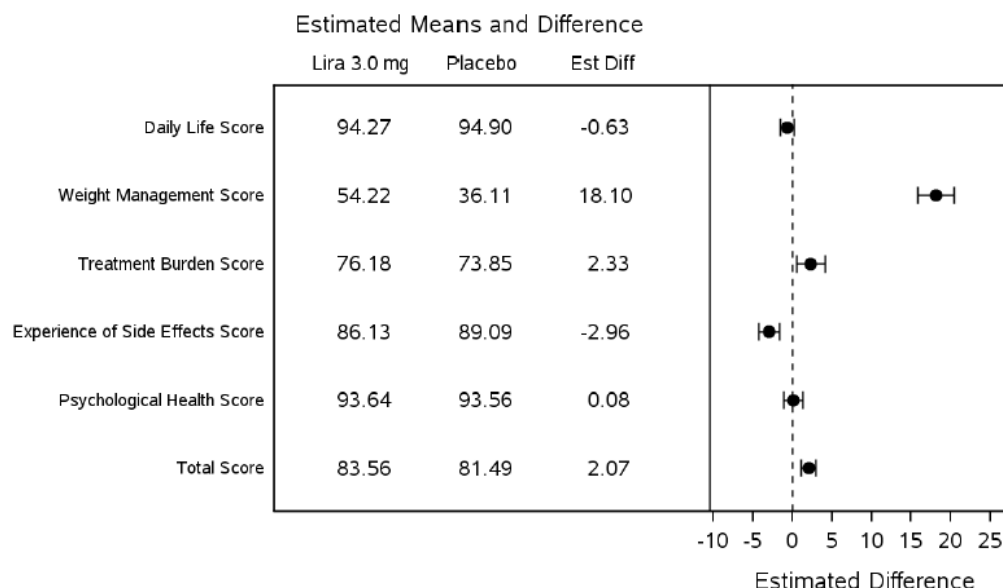
Source: NN8022-1839 Clinical Trial Report, Figure 11-40

Figure 20. SF-36, Trial 1839



Source: NN8022-1839 Clinical Trial Report, Figure 11-41

Figure 21. TRIm-Weight, Trial 1839



N: Number of subjects contributing to analysis.
Estimates are not adjusted for baseline value as the questionnaire was not filled out at baseline.

Source: NN8022-1839 Clinical Trial Report, Figure 11-42

Reviewer comment: The PRO instrument endpoints were not pre-specified nor were they adjusted for multiplicity. The sponsor did not justify or pre-specify ‘clinically meaningful’ score changes for these instruments. The Division has consulted the Study Endpoints and Labeling Development (SEALD) Team for their input regarding proposed labeling claims based on PRO instruments administered in this trial and others in the weight management program.

6.3.3 Trial 1922

This was a 56-week, randomized, double-blind, placebo-controlled, three-arm, parallel-group, multi-center, multi-national trial comparing once-daily administration of either liraglutide 1.8 mg or liraglutide 3 mg with placebo in overweight or obese patients with T2DM.

The trial consisted of a screening visit, a 2- to 4-week dose escalation period, a 52- to 54-week maintenance period, and a 12-week off-drug observational follow-up period after the last treatment.

The primary objective was to investigate the efficacy of liraglutide compared to placebo in inducing and maintaining weight loss in overweight or obese patients with T2DM after 56 weeks. Secondary objectives were to compare liraglutide and placebo regarding the effect on glycemic control, waist circumference, cardiovascular risk factors, and patient reported outcomes.

A total of 846 patients with T2DM were randomized in the trial in a 2:1:1 manner (liraglutide 3 mg, liraglutide 1.8 mg, placebo). Patients could be treated for their diabetes with diet and exercise alone or with one to three oral anti-diabetic drugs (OADs) (i.e., metformin, sulfonylurea (SU), and/or glitazone). Other inclusion criteria included HbA1c between 7% and 10% and BMI 27 kg/m² or greater.

At screening, patients treated with a SU, either as monotherapy or in combination with other oral anti-diabetic drugs, were required to reduce their SU dose by 50% or as close to 50% as possible based on dose options locally available. This was done to prevent potential hypoglycemia induced by the combination of a SU and liraglutide +/- weight loss. To limit the number of patients with early deterioration of glycemic control who would meet the fasting plasma glucose (FPG) rescue criteria early in the study (and be excluded from weight and glycemic efficacy endpoint analyses), a FPG randomization criterion of less than 220 mg/dL was included. Rescue criteria for FPG were as follows:

If self-measured FPG on three consecutive occasions exceeded the limits set below, the patient was to come in for an unscheduled FPG.

- From baseline to week 6: FPG > 270 mg/dL
- From week 7 to week 12: FPG > 240 mg/dL
- From week 13 to week 56: FPG > 200 mg/dL

If this FPG was confirmed, the background OAD was initially escalated to the maximal approved dose, followed by addition of one of the other allowed OADs.

If any of the FPG or HbA1c samples analyzed by the central laboratory exceeded the same limits or HbA1c greater than 8% week 13 to 56, the patient was to be called in for an unscheduled visit. A new FPG was to be obtained and if confirmed, the background OAD was initially escalated to the maximal approved dose, followed by addition of one of the other allowed OADs.

Patient disposition and demographics / baseline characteristics are summarized in the tables below.

Table 23. Patient Disposition, Trial 1922

	Lira 3 mg	Lira 1.8 mg	Placebo
Number Randomized	423	211	212
Completed 56 wks	324 (76.6)	164 (77.7)	140 (66.0)
Withdrawn from 56 wks	99 (23.4)	47 (22.3)	72 (34.0)
Adverse events	39 (9.2)	18 (8.5)	7 (3.3)
Ineffective	0	0	3 (1.4)
Non-compliance	12 (2.8)	8 (3.8)	13 (6.1)

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Withdrawal criteria	32 (7.6)	14 (6.6)	37 (17.5)
Withdrawn consent	27 (6.4)	10 (4.7)	28 (13.2)
Target dose not tolerated	0	0	0
Pregnancy or pregnancy intent	0	0	2 (0.9)
Use of insulin, GLP1RA, or DPP4i	0	2 (0.9)	1 (0.5)
Unacceptable hyperglycemia	5 (1.2)	2 (0.9)	9 (4.2)
Unacceptable hypoglycemia	0	0	0
Acute pancreatitis	0	0	0
Psychiatric disorder	0	0	0
Calcitonin \geq 50 ng/L (France)	0	0	0
Other	16 (3.8)	7 (3.3)	2 (5.7)
Withdrawn during 56 wks but attended visit 16x	36/99 (36.4)	12/47 (25.5)	23/72 (31.9)
Entered off-drug period	324 (76.6)	164 (77.7)	140 (66.0)
Completed 68 wks	310/324 (95.7)	154/164 (93.9)	135/140 (96.4)
Withdrawn between wk 56 and wk 68	14 (4.3)	10 (6.1)	5 (3.6)
Adverse events	1 (0.3)	1 (0.6)	0
Ineffective	1 (0.3)	0	0
Non-compliance	1 (0.3)	0	1 (0.7)
Withdrawal criteria	9 (2.8)	7 (4.3)	4 (2.9)
Withdrawn consent	3 (0.9)	4 (2.4)	2 (1.4)
Target dose not tolerated	0	0	0
Pregnancy or pregnancy intent	1 (0.3)	0	0
Use of insulin, GLP1RA, or DPP4i	6 (1.9)	3 (1.8)	2 (1.4)
Acute pancreatitis	0	0	0
Psychiatric disorder	0	1 (0.6)	0
Calcitonin \geq 50 ng/L (France)	0	0	0
Other	2 (0.6)	2 (1.2)	0

Source: NN8022-1922 Clinical Trial Report, Table 10-1

Table 24. Demographics and Baseline Characteristics, Trial 1922

	Lira 3 mg N=423	Lira 1.8 mg N=211	Placebo N=212
Age			
Yrs, mean (SD)	55.0 (10.8)	54.9 (10.7)	54.7 (9.8)
> 65 yrs, n (%)	85 (20.1)	34 (16.1)	38 (17.9)
Female sex, n (%)	203 (48.0)	103 (48.8)	115 (54.2)
Race, n (%)			
White	353 (83.5)	177 (83.9)	175 (82.5)
Black	44 (10.4)	27 (12.8)	27 (12.7)
Hispanic or Latino Ethnicity, n (%)	46 (10.9)	17 (8.1)	24 (11.3)
Weight (kg), mean (SD)	105.7 (21.9)	105.8 (21.0)	106.5 (21.3)

BMI			
kg/m ² , mean (SD)	37.1 (6.5)	37.0 (6.9)	37.4 (7.1)
> 40 kg/m ² , n (%)	124 (29.3)	65 (30.8)	63 (29.7)
Duration of diabetes (years), mean (SD)	7.54 (5.65)	7.43 (5.16)	6.71 (5.07)
HbA1c (%), mean (SD)	7.9 (0.8)	8.0 (0.8)	7.9 (0.8)
FPG (mg/dL*), mean (SD)	158.4 (34.2)	160.2 (36.0)	154.8 (32.4)
Background diabetes treatment			
Diet + exercise only	46 (11.2)	29 (14.2)	20 (9.5)
Metformin only	237 (57.5)	111 (54.4)	126 (59.7)
Metformin + glitazone	22 (5.3)	13 (6.4)	10 (4.7)
Metformin + SU	86 (20.9)	44 (21.6)	48 (21.7)
Metformin + glitazone + SU	10 (2.4)	4 (2.0)	4 (1.9)
SU only	7 (1.7)	2 (1.0)	2 (0.9)
SU + glitazone	4 (1.0)	1 (0.5)	1 (0.5)
History of CV disease, n (%)	299 (70.7)	148 (70.1)	149 (70.3)
Co-morbidities, n (%)			
Dyslipidemia	295 (69.7)	143 (67.8)	126 (59.4)
Hypertension	293 (69.3)	148 (70.1)	145 (68.4)
Both dyslipidemia + hypertension	220 (52.0)	110 (52.1)	92 (43.4)
Smoking status, n (%)			
Current	52 (12.3)	35 (16.6)	20 (9.4)
Never	231 (54.6)	108 (51.2)	118 (55.7)
Previous	140 (33.1)	68 (32.2)	74 (34.9)
* Reviewer converted from mmol/L to mg/dL			

Source: NN8022-1922 Clinical Trial Report, Table 10-2

6.3.3.1 Results

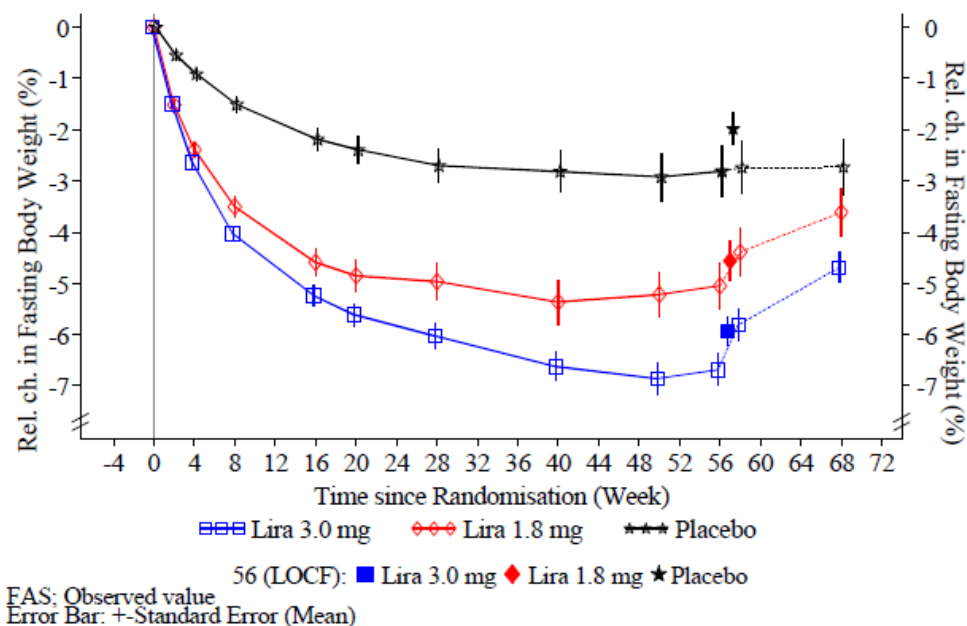
The primary endpoint consisted of three co-primary endpoint measures, evaluated by a hierarchical testing procedure.

- Change from baseline in fasting body weight at 56 weeks
- The proportion of patients losing at least 5% of baseline fasting weight at 56 weeks
- The proportion of patients losing more than 10% of baseline fasting weight at 56 weeks

6.3.3.1.1 Percent Change in Body Weight

As shown in Figure 22, fasting body weight decreased over time in a dose-dependent manner.

Figure 22. Percent Change from Baseline in Body Weight by Treatment Visit, Trial 1922



Source: NN8022-1922 Clinical Trial Report, Figure 11-1

Patients lost 5.9% (liraglutide 3 mg), 4.6% (liraglutide 1.8 mg), and 2.0% (placebo) of baseline body weight at the end of the treatment period (week 56, LOCF). Both doses of liraglutide were statistically significantly better than placebo in reducing body weight for both liraglutide 3 and 1.8 mg. Further, liraglutide 3 mg demonstrated statistically significantly greater weight loss as compared with liraglutide 1.8 mg.

Table 25. Percent Change from Baseline in Body Weight at Week 56, LOCF, Trial 1922

Treatment	N	Baseline Mean, kg (SD)	% Change from Baseline, Wk 56
Lira 3 mg	411	105.6 (21.9)	-5.93
Lira 1.8 mg	202	106.1 (21.0)	-4.58
Placebo	210	106.7 (21.2)	-1.96
Between treatment difference		Difference in LS means (95% CI)	p-value
Lira 3 mg vs. Placebo		-3.97 (-4.84, -3.11)	<0.0001
Lira 1.8 mg vs. Placebo		-2.62 (-3.63, -1.62)	<0.0001
Lira 3 mg vs. Lira 1.8 mg		-1.35 (-2.23, -0.48)	0.0024

Source: NN8022-1922 Clinical Trial Report, Tables 14.2.29 and 11-3

Reviewer comment: *These results are consistent with some weight management drugs that have been shown to have a somewhat smaller treatment effect in the*

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obese patient population with T2DM as compared with a population of obese patients without diabetes.^{18,19}

The completers' analysis was similar to the primary analysis:

Table 26. Percent Change from Baseline in Body Weight at Week 56, Completers Analysis, Trial 1922

Completers		
Treatment	N	% Change from Baseline, Wk 56
Lira 3 mg	317	-6.64
Lira 1.8 mg	157	-5.20
Placebo	116	-2.54
Between treatment difference		Difference in LS means (95% CI)
Lira 3 mg vs. Placebo		-4.10 (-5.28, -2.93)
Lira 1.8 mg vs. Placebo		-2.67 (-4.00, -1.34)
Lira 3 mg vs. Lira 1.8 mg		-1.44 (-2.49, -0.38)
		p-value

Source: NN8022-1922 Clinical Trial Report, Table 14.2.8

Patients who completed the 56-week treatment period were followed up for a 12-week off-treatment period (while continuing to receive counseling on diet and physical activity) until week 68. After being off treatment for 12 weeks, patients on average gained 2.3% in body weight in the liraglutide 3 mg group, 2.0% in the liraglutide 1.8 mg group, but remained relatively stable (-0.1%) in the placebo group.

Reviewer comment: Weight regain is to be expected after study drug discontinuation.

6.3.3.1.1.1 BMI Subgroups

There was no interaction between treatment and baseline BMI subgroup (p=0.75).

There was no apparent numeric difference in the lowest BMI category (BMI 27 to 29.9 kg/m²) between the two liraglutide doses in this exploratory analysis.

Table 27. Percent Change in Body Weight after 56 Weeks of Treatment, by BMI, Trial 1922

	BMI 27-29.9	BMI 30-34.9	BMI 35-39.9	BMI ≥ 40
Lira 3 mg	-5.10%	-5.98%	-6.19%	-6.04%
Lira 1.8 mg	-5.14%	-4.66%	-4.12%	-4.49%
Placebo	-1.10%	-2.13%	-2.15%	-1.62%

¹⁸ FDA Briefing Document for Contrave (bupropion/naltrexone) EMDAC meeting 07 Dec 2010; <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologyandMetabolicDrugsAdvisoryCommittee/UCM235671.pdf>

¹⁹ FDA Briefing Document for Zimulti (rimonabant) EMDAC meeting 13 Jun 2007; <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4306b1-fda-backgrounder.pdf>

Lira 3 mg – Placebo	-4.21% ^b	-3.79% ^a	-3.70% ^a	-4.31% ^a
Lira 1.8 mg – Placebo	-4.29% ^c	-2.60% ^e	-1.55% ^h	-2.76% ^d
Lira 3 mg – Lira 1.8 mg	0.08% ^j	-1.20% ⁱ	-2.15% ^f	-1.55% ^g
Nominal p-values: a <0.0001 b 0.0005 c 0.0015 d 0.0032 e 0.0071 f 0.0174 g 0.0564 h 0.1241 i 0.1441 j 0.9448				

Source: NN8022-1922 Clinical Trial Report, Table 14.2.9

6.3.3.1.2 Five Percent Responder Analysis

Both doses of liraglutide were significantly more likely to achieve at least 5% weight loss as compared to the placebo group. The proportion of patients randomized to liraglutide 3 mg who achieved 5% weight loss was also significantly greater than those randomized to 1.8 mg.

Table 28. Proportion of Patients Losing at Least Five Percent Body Weight after 56 Weeks of Treatment, LOCF, Trial 1922

Treatment	N	Proportion losing at least 5%, Wk 56	
Lira 3 mg	411	49.87%	
Lira 1.8 mg	202	35.04%	
Placebo	210	12.74%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		6.81 (4.34, 10.69)	<0.0001
Lira 1.8 mg / Placebo		3.69 (2.24, 6.09)	<0.0001
Lira 3 mg / Lira 1.8 mg		1.84 (1.29, 2.64)	0.0008

Source: NN8022-1922 Clinical Trial Report, Table 14.2.23

Sensitivity analyses evaluating completers and premature withdrawals characterized as non-responders were consistent with the primary analysis.

Table 29. Proportion of Patients Losing at Least Five Percent Body Weight after 56 Weeks of Treatment, Sensitivity Analyses, Trial 1922

Completers		
Treatment	N	Proportion losing at least 5%, Wk 56
Lira 3 mg	317	59.49%
Lira 1.8 mg	157	42.63%
Placebo	116	18.39%
Between treatment comparison		Treatment odds ratio (95% CI)
Lira 3 mg / Placebo		6.52 (3.86, 11.01)
Lira 1.8 mg/ Placebo		3.30 (1.86, 5.84)
Lira 3 mg / Lira 1.8 mg		1.98 (1.32, 2.97)
		p-value
		<0.0001
		<0.0001
		0.0010
Premature Withdrawals Counted as Non-Responders		
Treatment	N	Proportion losing at least 5%, Wk 56
Lira 3 mg	412	47.04%
Lira 1.8 mg	203	32.61%
Placebo	211	11.06%
Between treatment comparison		Treatment odds ratio (95% CI)
Lira 3 mg / Placebo		7.14 (4.47, 11.41)
Lira 1.8 mg/ Placebo		3.89 (2.31, 6.54)
Lira 3 mg / Lira 1.8 mg		1.84 (1.27, 2.64)
		p-value
		<0.0001
		<0.0001
		0.0011

Source: NN8022-1922 Clinical Trial Report, Table 14.2.23

6.3.3.1.3 Ten Percent Responder Analysis

The 10% responder analysis demonstrated that a statistically significantly greater proportion of patients on both doses of liraglutide lost more than 10% of body weight as compared to those treated with placebo.

Table 30. Proportion of Patients Losing More than 10 Percent of Body Weight after 56 Weeks of Treatment, LOCF, Trial 1922

Treatment	N	Proportion losing at least 10%, Wk 56
Lira 3 mg	411	22.11%
Lira 1.8 mg	202	13.31%
Placebo	210	3.85%
Between treatment comparison		Treatment odds ratio (95% CI)
Lira 3 mg / Placebo		7.10 (3.48, 14.48)
Lira 1.8 mg / Placebo		3.84 (1.75, 8.41)
Lira 3 mg / Lira 1.8 mg		1.85 (1.16, 2.95)
		p-value
		<0.0001
		0.0008
		0.0099

Source: NN8022-1922 Clinical Trial Report, Table 14.2.27

Sensitivity analyses evaluating completer and premature withdrawals characterized as non-responders were consistent with the primary analysis.

Table 31. Proportion of Patients Losing More than 10 Percent of Body Weight after 56 Weeks of Treatment, Sensitivity Analyses, Trial 1922

Completers			
Treatment	N	Proportion losing at least 10%, Wk 56	
Lira 3 mg	317	26.41%	
Lira 1.8 mg	157	15.46%	
Placebo	116	6.66%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		5.03 (2.42, 10.48)	<0.0001
Lira 1.8 mg/ Placebo		2.57 (1.13, 5.80)	0.0237
Lira 3 mg / Lira 1.8 mg		1.96 (1.18, 3.26)	0.0093
Premature Withdrawals Counted as Non-Responders			
Treatment	N	Proportion losing at least 10%, Wk 56	
Lira 3 mg	412	20.28%	
Lira 1.8 mg	203	11.60%	
Placebo	211	4.11%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		5.94 (2.99, 11.79)	<0.0001
Lira 1.8 mg/ Placebo		3.06 (1.42, 6.60)	0.0043
Lira 3 mg / Lira 1.8 mg		1.94 (1.19, 3.16)	0.0077

Source: NN8022-1922 Clinical Trial Report, Table 14.2.27

6.3.3.1.4 Secondary Endpoints – Glycemic Parameters

Because liraglutide is currently marketed in the U.S. for the treatment of T2DM at a maximum dose of 1.8 mg, the effects of liraglutide 3 mg (and 1.8 mg) on glycemic control in the T2DM patient population with overweight and obesity is of particular interest.

6.3.3.1.4.1 HbA1c

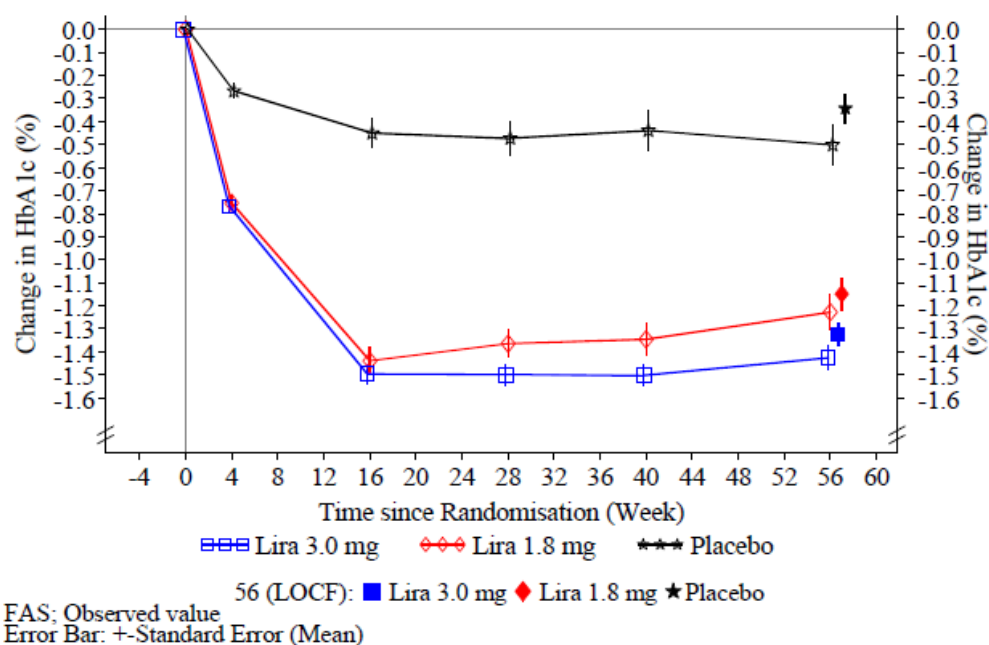
In this trial, both liraglutide 3 mg and 1.8 mg demonstrated statistically significant reduction in HbA1c at 56 weeks as compared to placebo (Table 32). During the first 16 weeks, mean HbA1c decreased in all three groups, with liraglutide groups showing more reduction than placebo. After week 16, mean HbA1c remained stable for liraglutide 3 mg and placebo, whereas a slight upward trend was observed for liraglutide 1.8 mg (Figure 23).

Table 32. Percentage Point Change in HbA1c at Week 56, LOCF, Trial 1922

Treatment	N	Baseline Mean, % (SD)	Change from Baseline, Wk 56
Lira 3 mg	402	7.9 (0.8)	-1.32
Lira 1.8 mg	195	8.0 (0.8)	-1.13
Placebo	206	7.9 (0.8)	-0.38
Between treatment difference		Difference in LS means (95% CI)	p-value
Lira 3 mg vs. Placebo		-0.93 (-1.08, -0.78)	<0.0001
Lira 1.8 mg vs. Placebo		-0.74 (-0.91, -0.57)	<0.0001
Lira 3 mg vs. Lira 1.8 mg		-0.19 (-0.34, -0.04)	0.0125

Source: NN8022-1922 Clinical Trial Report, Tables 14.2.79 and 11-25

Figure 23. Percentage Point Change in HbA1c by Treatment Week, Trial 1922



Source: NN8022-1922 Clinical Trial Report, Figure 11-6

In responder analyses evaluating the proportions of patients that achieved HbA1c values less than 7% and 6.5%, more patients treated with liraglutide achieved these targets compared to those treated with placebo.

Table 33. Proportion of Patients Achieving HbA1c Below Specific Thresholds at Week 56, Trial 1922

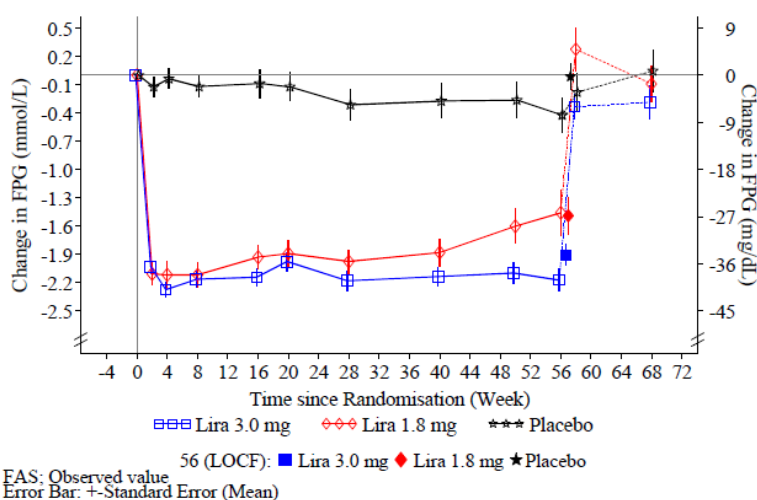
Treatment	N	Proportion with HbA1c < 7%, Wk 56	
Lira 3 mg	402	72.3%	
Lira 1.8 mg	195	69.6%	
Placebo	206	22.9%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		8.79 (5.74, 13.44)	<0.0001
Lira 1.8 mg / Placebo		7.71 (4.76, 12.51)	<0.0001
Lira 3 mg / Lira 1.8 mg		1.14 (0.76, 1.71)	0.5319
Treatment	N	Proportion with HbA1c ≤ 6.5%, Wk 56	
Lira 3 mg	402	56.7%	
Lira 1.8 mg	195	44.9%	
Placebo	206	12.0%	
Between treatment comparison		Treatment odds ratio (95% CI)	p-value
Lira 3 mg / Placebo		9.61 (6.05, 15.26)	<0.0001
Lira 1.8 mg / Placebo		5.98 (3.59, 9.97)	<0.0001
Lira 3 mg / Lira 1.8 mg		1.61 (1.10, 2.34)	0.0142

Source: NN8022-1922 Clinical Trial Report, Tables 11-27 and 11-28

6.3.3.1.4.2 Fasting Plasma Glucose

The time course for change in FPG from baseline by week is shown in Figure 24. The figure illustrates that the treatment effect is observed in the liraglutide groups in the first 4 weeks. While the FPG reduction was sustained in the liraglutide 3 mg group throughout the treatment period, the liraglutide 1.8 mg group had a slight upward trend after week 8. A modest FPG reduction was observed in the placebo group. Both liraglutide groups showed greater reductions in baseline FPG compared with the placebo group.

Figure 24. Change in Fasting Plasma Glucose by Treatment Week, Trial 1922



Source: NN8022-1922 Clinical Trial Report, Figure 11-8

6.3.3.1.4.3 Concomitant Diabetes Medications

In a dose-related fashion, compared with placebo, more liraglutide-treated patients reduced use – and fewer increased use – of oral anti-hyperglycemic agents.

Table 34. Diabetes Medication Changes, Trial 1922

	Lira 3.0 mg		Lira 1.8 mg		Placebo	
	N	(%)	N	(%)	N	(%)
Number of Subjects	412		204		211	
Drug taken at baseline						
Yes	366	(88.8)	175	(85.8)	191	(90.5)
No	46	(11.2)	29	(14.2)	20	(9.5)
Change at week 56 (LOCF)						
Increase	21	(5.1)	19	(9.3)	57	(27.0)
No Change	337	(81.8)	168	(82.4)	142	(67.3)
Decrease	54	(13.1)	17	(8.3)	12	(5.7)

N = Number of Subjects

% = Percentages are based on N

Source: NN8022-1922 Clinical Trial Report, Table 14.2.305

Reviewer comment: *These results support the glycemic efficacy of liraglutide, given that the favorable changes were seen in HbA1c and FPG despite the lesser use of OADs. However, as more patients on placebo were “rescued” for glycemic control earlier on in the trial than those of liraglutide (Table 35), the treatment effect on weight parameters could in fact be overestimated (since patients rescued earlier presumably would not have as much time for weight loss).*

Table 35. Glycemic Rescue, Trial 1922

	Lira 3 mg N=411	Lira 1.8 mg N=202	Placebo N=211
Had glycemic rescue	19 (4.6)	10 (5.0)	50 (23.7)
Number of days to rescue, mean (SD)	173.3 (63.9)	194.3 (134.1)	153.9 (73.9)

Source: B. McEvoy, FDA biostatistics (DBII)

6.3.3.1.5 Secondary Endpoints – Cardiovascular

Both liraglutide doses reduced systolic BP compared with placebo. No significant differences in diastolic BP were observed.

Table 36. Mean Changes in Blood Pressure, Trial 1922

	Lira 3 mg N=412		Lira 1.8 mg N=204		Placebo N=211	
	Baseline	Change	Baseline	Change	Baseline	Change
Systolic BP, mmHg	128.9	-2.98*	130.5	-3.07*	129.2	-0.39
Diastolic BP, mmHg	79.0	-0.99	80.1	-0.82	79.3	-0.63
* Nominal p-value for difference from placebo < 0.05						

Source: Summary of Clinical Efficacy, Table 2-8

Liraglutide 3 mg (but not 1.8 mg) improved the fasting lipid profile parameters: total cholesterol, HDL-C, VLDL-C, and triglycerides compared with placebo. Liraglutide treatment had no effect on LDL-C compared to placebo.

Table 37. Mean Percent Changes in Lipids, Trial 1922

	Lira 3 mg N=412		Lira 1.8 mg N=204		Placebo N=211	
	Baseline	% Change	Baseline	% Change	Baseline	% Change
HDL-C, mg/dL	45.2	4.70*	44.5	4.45	45.4	1.93
LDL-C, mg/dL	86.4	0.58	91.5	-3.07	85.2	5.02
VLDL-C, mg/dL	31.8	-14.10*†	33.0	-8.14	31.1	0.53
Triglycerides, mg/dL	162	-14.68*†	170	-9.45	158	0.41
Total cholesterol, mg/dL	171.0	-1.46*	178.3	-2.20	169.4	3.80
* Nominal p-value for difference from placebo < 0.05						
† Nominal p-value for difference from lira 1.8 mg < 0.05						

Source: Summary of Clinical Efficacy, Table 2-8

Both liraglutide doses reduced hsCRP compared with placebo. Liraglutide 3 mg (but not 1.8 mg) improved urinary albumin/creatinine ratio. An increase in fibrinogen was observed with liraglutide 3 mg compared to placebo, with a similar trend for liraglutide 1.8 mg.

Table 38. Mean Percent Changes in Cardiovascular Biomarkers, Trial 1922

	Lira 3 mg N=412		Lira 1.8 mg N=204		Placebo N=211	
	Baseline	% Change	Baseline	% Change	Baseline	% Change
hsCRP, mg/L	3.44	-33.51*	3.92	-33.34*	3.64	-10.45
Fibrinogen, g/L	4.13	4.54*	4.28	1.68	4.27	-3.11
Adiponectin, µg/mL	5.6	6.6	5.9	3.5	5.6	1.3
Albumin/creatinine ratio, (mg/mmol)	1.0	-18.36*	1.1	-10.79	1.0	-2.34
* Nominal p-value for difference from placebo < 0.05						

Source: Summary of Clinical Efficacy, Table 2-8

6.3.3.1.6 Secondary Endpoints – Patient Reported Outcomes

Patient Reported Outcome questionnaires were administered at baseline, week 28, and week 52 at a subset of sites. See section 6.3.2.1.4.4 for a description of the IWQoL-Lite. The Diabetes Treatment Satisfaction Questionnaire status (DTSQs) assesses the impact of treatment on patients' treatment satisfaction, including perceived frequency of hyperglycemia, perceived frequency of hypoglycemia, and satisfaction with treatment. An increased score is favorable.

Liraglutide 3 mg (but not 1.8 mg) improved patient reported outcomes (IWQoL-Lite: total and physical function scores; DTSQs: total score) compared to placebo. The IWQoL-Lite total score was driven by the treatment difference in the 'physical function' domain. No differences were found for the other four domains: 'self esteem', 'sexual life', 'public distress', and 'work'. The following results were not adjusted for multiplicity.

Table 39. Mean Changes in Patient Reported Outcomes, Trial 1922

	Lira 3.0 - Placebo		Lira 1.8 - Placebo		Lira 3.0 – Lira 1.8	
	Estimated difference and 95% CI	P-value	Estimated difference and 95% CI	P-value	Estimated difference and 95% CI	P-value
IWQoL-Lite						
Physical function	4.92 [2.12; 7.71]	0.0006	2.64 [-0.59; 5.88]	0.1089	2.27 [-0.53; 5.08]	0.1122
Self esteem	1.51 [-1.37; 4.39]	0.3030	0.01 [-3.32; 3.34]	0.9952	1.50 [-1.39; 4.39]	0.3088
Sexual life	-0.70 [-4.27; 2.88]	0.7016	-2.03 [-6.16; 2.11]	0.3360	1.33 [-2.25; 4.91]	0.4655
Public distress	1.64 [-0.61; 3.89]	0.1520	0.00 [-2.60; 2.60]	0.9986	1.64 [-0.62; 3.89]	0.1546
Work	1.54 [-0.76; 3.85]	0.1887	-1.06 [-3.73; 1.61]	0.4367	2.60 [0.29; 4.92]	0.0275
Total score	2.75 [0.57; 4.93]	0.0136	0.78 [-1.74; 3.31]	0.5424	1.96 [-0.23; 4.16]	0.0793
DTSQ						
Total score	1.44 [0.40; 2.48]	0.0066	1.14 [-0.07; 2.34]	0.0644	0.30 [-0.74; 1.35]	0.5674

Source: NN8022-1922 Clinical Trial Report, Table 11-50

6.3.4 Trial 1923

This was a multi-center, randomized, double-blind, parallel-group trial, comparing the effect of liraglutide 3 mg versus placebo on maintaining run-in weight loss of at least 5% after 56 weeks in patients without diabetes who were overweight or obese.

Patients were first treated with a low-calorie diet (total energy intake 1200-1400 kcal/day) in the run-in period lasting up to 12 weeks. Patients were provided with instruction by a nutritionist and meal replacements.

Patients who lost at least 5% of screening body weight after 4 to 12 weeks of the run-in were randomized 1:1 to receive either liraglutide 3 mg or placebo for 56 weeks. Following the end of the randomized period, there was a 12-week off-drug follow-up period. Patients who were randomized but terminated prior to completing 56 weeks of

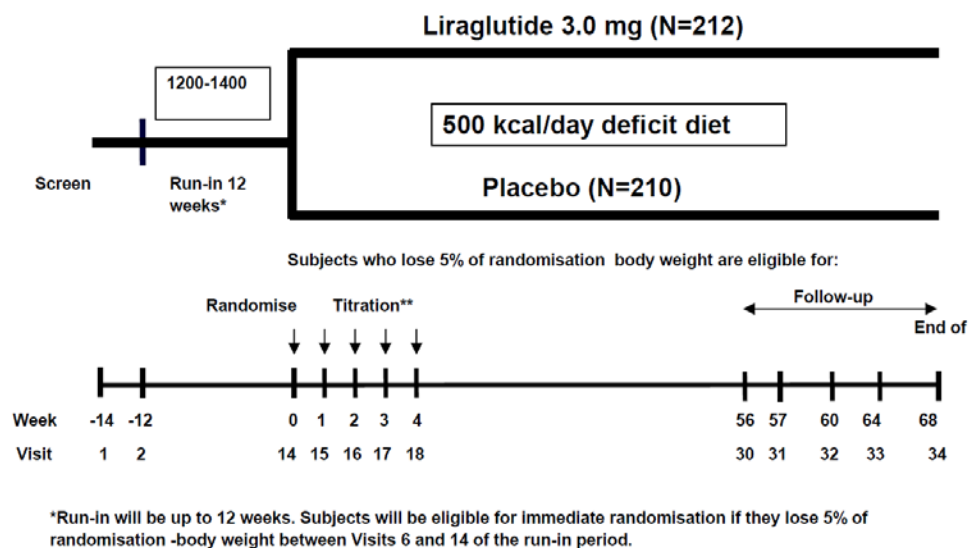
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treatment were asked to return 56 weeks after their date of randomization for a follow-up weight assessment.

Figure 25. Schematic of Study Design, Trial 1923



Source: NN8022-1923 Clinical Trial Report, Figure 9-1

The primary objectives were to compare the efficacy of liraglutide 3 mg versus placebo in maintaining run-in weight loss and to compare the efficacy of liraglutide 3 mg versus placebo in inducing weight loss beyond that achieved in run-in over 56 weeks.

Secondary efficacy objectives included the effect of liraglutide 3 mg versus placebo on weight regain and weight loss maintenance, waist circumference and BMI, parameters of glycemic control, blood pressure, and fasting lipid profile.

A total of 551 patients entered the dietary run-in, and 422 patients were randomized (76.6%).

Baseline characteristics were generally similar between treatment groups; small differences between groups in sex, race, and ethnicity are presented below.

Table 40. Demographics and Baseline Characteristics, Trial 1923

	Lira 3 mg N=212	Placebo N=210
Age		
Yrs, mean (SD)	45.9 (11.9)	46.5 (11.0)
Sex		
Female	178 (84.0)	165 (78.6)
Male	34 (16.0)	45 (21.4)

Race, n (%)		
White	170 (80.2)	185 (88.1)
Black	32 (15.1)	24 (11.4)
Other	10 (4.7)	1 (0.5)
Hispanic or Latino Ethnicity, n (%)	17 (8.0)	11 (5.2)
Weight (kg), mean (SD)		
At screening	106.7 (21.8)	105.0 (22.4)
At randomization	100.4 (20.8)	98.7 (21.2)
BMI (kg/m ²), mean (SD)		
At screening	38.2 (6.2)	37.5 (6.2)
At randomization	36.0 (5.9)	35.2 (5.9)
Co-morbidities present, n (%)	94 (44.3)	96 (45.7)
Smoker, n (%)	20 (9.4)	22 (10.5)

Source: NN8022-1923 Clinical Trial Report, Table 11-1

Patient disposition is provided in Table 41.

Table 41. Patient Disposition, Trial 1923

	Lira 3 mg	Placebo
Number Randomized	212	210
Completed 56 wks	159 (75.0)	146 (69.5)
Withdrawn from 56 wks	53 (25.0)	64 (30.5)
Adverse events	18 (8.5)	18 (8.6)
Ineffective	0	2 (1.0)
Non-compliance	8 (3.8)	5 (2.4)
Withdrawal criteria	17 (8.0)	24 (11.4)
Other	10 (4.7)	15 (7.1)
Completed 68 wks	153 (72.2)	141 (67.1)
Withdrawn from 68 wks	6 (2.8)	5 (2.4)
Non-compliance	1 (0.5)	1 (0.5)
Other	5 (2.4)	4 (1.9)

Source: NN8022-1923 Clinical Trial Report, Table 10-1

The majority of reasons provided for “other” reasons for discontinuation in both treatment groups were for “loss to follow-up”.

The following were considered withdrawal criteria:

- Target dose is not tolerated

- Pregnancy or intention of becoming pregnant
- Diagnosis of type 1 diabetes or type 2 diabetes
- Withdrawal of consent
- Acute pancreatitis

There were four pregnancies (2 on liraglutide, 2 on placebo), five patients withdrawn due to development of T2DM (all placebo), and no patients who were diagnosed with pancreatitis.

6.3.4.1 Results

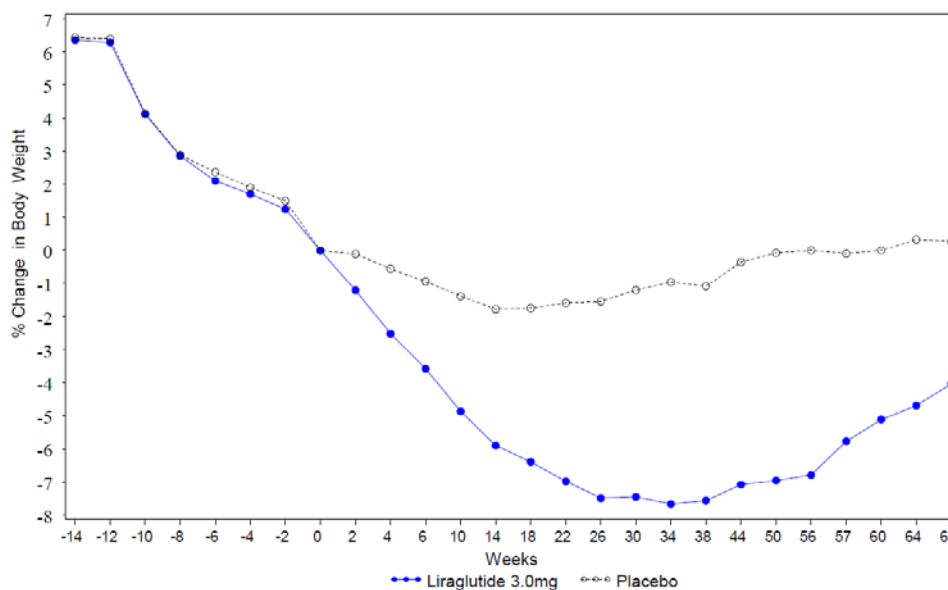
The primary endpoint consisted of three co-primary endpoint measures, evaluated by a hierarchical testing procedure.

- Percent change from randomization in fasting body weight at 56 weeks
- Percentage of patients that maintain run-in fasting weight loss after 56 weeks of treatment
- Proportion of patients losing at least 5% of randomization body weight

6.3.4.1.1 Percent Change in Body Weight

Figure 26 illustrates the percent body weight change during the trial by treatment group, from screening through the randomized treatment period, and follow-up period ending at week 68. The protocol-mandated decrease in weight was seen between weeks -12 to 0 during the run-in period. Observed mean (SD) relative and absolute weight loss during run-in for patients who were randomized was 5.95 (7.08) % and 6.3 (1.57) kg, respectively.

Figure 26. Percent Change in Body Weight, Trial 1923



Source: NN8022-1923 Clinical Trial Report, Figure 11-1

After randomization, the mean percent decrease in fasting body weight was statistically significantly greater in patients treated with liraglutide 3 mg compared to placebo at week 56 (Table 42).

Table 42. Percent Change in Body Weight at Week 56, Trial 1923

Treatment	N	% Change from Randomization (SE), Wk 56	
Lira 3 mg	194	-6.11 (0.66)	
Placebo	188	-0.05 (0.63)	
Between treatment difference		Difference in LS means (95% CI)	p-value
Lira 3 mg vs. Placebo		-6.06 (-7.50, -4.62)	<0.0001

Source: NN8022-1923 Clinical Trial Report, Table 11-4

6.3.4.1.2 Percentage of Patients who Maintained Weight Loss

A statistically significantly greater percentage of patients randomized to liraglutide maintained at least 5% weight loss after the run-in period as compared to placebo by week 56.

Table 43. Percentage of Patients Maintaining at Least Five Percent Weight Loss, Trial 1923

	Lira 3 mg		Placebo	
	N	n (%)	N	n (%)
Week 0	207	207 (100)	206	206 (100)
Week 14	192	182 (94.8)	184	125 (67.9)
Week 26	180	172 (95.6)	168	100 (59.5)
Week 38	171	156 (91.2)	159	91 (57.2)
Week 56	156	126 (80.8)	144	69 (47.9)
Week 57	159	119 (74.8)	141	70 (49.6)
Week 68	152	106 (69.7)	141	62 (44.0)
Week 56 (LOCF)	194	158 (81.4)	188	92 (48.9)
Treatment odds ratio (95% CI)	4.82 (3.01, 7.71)			
p-value	<0.0001			

Source: NN8022-1923 Clinical Trial Report, Tables 14.2.156 and 11-6

6.3.4.1.3 Five Percent Responder Analysis (from Randomization)

A statistically significantly greater proportion of patients treated with liraglutide lost 5% of randomization body weight at week 56 as compared to the proportion of patients treated with placebo.

Table 44. Proportion of Five Percent Responders from Randomization, Trial 1923

	Lira 3 mg		Placebo	
	N	n (%)	N	n (%)
Week 56 (LOCF)	194	98 (50.5)	188	41 (21.9)
Treatment odds ratio (95% CI)	3.86 (2.44, 6.09)			
p-value	<0.0001			

Source: NN8022-1923 Clinical Trial Report, Tables 11-8 and 11-9

6.3.4.1.4 Secondary Endpoints – Weight Gain

At week 56 (LOCF), 1.9% and 17.5% of patients in the liraglutide 3 mg and placebo groups, respectively, gained 5% or more of their randomization body weight ($p < 0.0001$). At week 68 (LOCF), the end of the off-treatment observational phase, the proportions of patients in each group were 9.4% and 25%, respectively.

At week 56 (LOCF) none and 2.9% of patients in the liraglutide 3 mg and placebo groups, respectively, gained 10% or more of their randomization body weight (not significant), and at week 68 (LOCF), the proportions of patients in each group were 1.9% and 3.5%, respectively.

6.3.4.1.5 Secondary Endpoints – Percent of Weight Loss Maintenance

At week 56 (LOCF) 93.2% and 70.9% of patients in the liraglutide 3 mg and placebo groups, respectively, maintained more than 50% of run-in body weight loss ($p < 0.0001$), and at week 68 (LOCF), the proportions of patients in each group were 80.5% and 59.7%.

At week 56 (LOCF), 87.4% and 54.4% of patients in the liraglutide 3 mg and placebo groups, respectively, maintained more than 75% of run-in body weight loss ($p < 0.0001$), and at week 68 (LOCF), the proportions of patients in each group were 74.8% and 49.3%.

6.3.4.1.6 Secondary Endpoints – Body Composition

Observed mean (SD) waist circumference fell during run-in from 113.51 (15.45) cm to 108.58 (15.24) cm, a 4.3% decrease for the patients who entered and completed the run-in.

Patients in the liraglutide 3 mg treatment group had greater decreases in waist circumference as compared to those in the placebo group. Estimated LS mean changes in waist circumference from randomization to week 56 were -4.36 cm and -0.86 cm, respectively, with an estimated treatment difference (ANCOVA) of -3.50 cm (95% CI -4.84, -2.15).

Observed mean (SD) BMI fell during run-in from 37.9 (6.2) kg/m² to 35.6 (5.9) kg/m², a -2.3 kg/m² (-5.9%) decrease for the patients who entered and completed the run-in.

Patients in the liraglutide 3 mg treatment group had greater decreases in BMI as compared to those in the placebo group. Estimated LS mean changes in BMI from randomization to week 56 were -1.9 kg/m^2 and $+0.15 \text{ kg/m}^2$, respectively, with an estimated treatment difference (SE) of $-2.05 (0.24) \text{ kg/m}^2$ (95% CI $-2.53, -1.57$).

6.3.4.1.7 Secondary Endpoints – Glycemic Control

Observed mean (SD) HbA1c values at the beginning and end of run-in were 5.55 (0.41) % and 5.55 (0.39) %, respectively, for patients who completed the run-in.

Patients in the liraglutide 3 mg treatment group had greater decreases in HbA1c as compared to those in the placebo group. The mean HbA1c treatment difference between liraglutide 3 mg and placebo at week 56 was -0.27% (95% CI $-0.33, -0.21$). During the 12-week off-drug follow-up period (week 56 to 68) HbA1c rose in the liraglutide group toward the mean value in the placebo group.

Observed mean FPG fell from the beginning to end of run-in from 101.8 mg/dL^{20} to 98.0 mg/dL , a mean change of -3.7% for patients who entered and completed run-in.

Patients in the liraglutide 3 mg treatment group had greater decreases in FPG as compared to those in the placebo group. Estimated LS mean changes from randomization to week 56 were approximately -9.36 mg/dL and -2.52 mg/dL for liraglutide 3 mg and placebo treatment, respectively. The mean treatment difference for liraglutide 3 mg – placebo at week 56 was approximately -6.84 mg/dL . During the 12-week off-drug follow-up period (week 56 to 68) FPG rose in the liraglutide group to the mean value in the placebo group.

Observed mean (SD) fasting insulin fell during run-in from $109.6 (69.3) \text{ pmol/L}$ to $78.0 (50.7) \text{ pmol/L}$, a mean change of -29.0% , for patients who completed the run-in.

From week 0 to week 56, the observed mean (SD) fasting plasma insulin increased by $2.8 (51.4) \text{ pmol/L}$ in the liraglutide 3 mg treated group, and increased by $16.3 (55.5) \text{ pmol/L}$ in the placebo treated group.

The mean treatment difference for liraglutide 3 mg – placebo at week 56 was approximately -13.37 pmol/L (95% CI $-24.1, -2.65$).

The homeostatic model assessment is a model used to estimate beta-cell function (HOMA- β , increased advantageous) and insulin resistance (HOMA-IR, decreased advantageous) from fasting plasma glucose and insulin. These values correlate with the

²⁰ Reviewer converted FPG from mmol/L to mg/dL.

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intravenous glucose tolerance test and hyperglycemic clamp (HOMA- β) and the euglycemic and hyperglycemic clamp (HOMA-IR).²¹

The changes in HOMA- β at week 56 were not statistically significantly different between liraglutide 3 mg and placebo treatments. Estimated LS mean (SE) HOMA- β treatment changes at week 56 were 61.4 (16.8) % and 44.4 (16.4) %, respectively, and the estimated treatment difference (liraglutide 3 mg – placebo) was 17.0 percentage points (95% CI -20.1, 54.1).

HOMA-IR fell during the run-in period, and patients randomized to liraglutide 3 mg treatment maintained that decrease throughout the treatment period, while values for the placebo group were maintained for 14 weeks before rising. The observed mean changes from randomization at week 56 were 0 and 0.6 for patients randomized to liraglutide 3 mg and placebo, respectively. The decreases in HOMA-IR for patients randomized to liraglutide 3 mg were decreased compared to those randomized to placebo. The estimated mean treatment difference for liraglutide 3 mg – placebo was -0.69 percentage points (95% CI -1.17, -0.21).

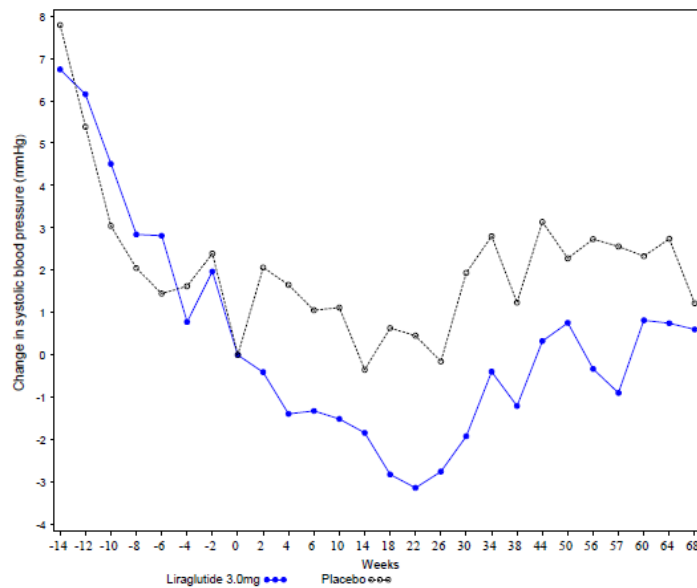
6.3.4.1.8 Secondary Endpoints – Blood Pressure

During the run-in, observed mean (SD) systolic BP decreased from 122.95 (12.69) mmHg to 117.23 (11.73) mmHg, a change of -5.7 mmHg (-4.7%), for patients who completed run-in. At randomization, observed mean (SD) SBP was 116.7 (12.6) mmHg and 117.7 (10.8) mmHg, for patients randomized to the liraglutide 3 mg and placebo groups, respectively. Patients in the placebo group maintained SBP through the end of the trial, whereas the patients in the liraglutide group decreased SBP until week 22, after which it rose towards the mean value in the placebo group (Figure 27).

At week 56, estimated mean SBP was 118.5 mmHg in the liraglutide 3 mg group compared to 121 mmHg in the placebo group, which was an increase of 1.3 and 4.0 mmHg, respectively, from randomization. The LS mean (SE) estimated treatment difference between liraglutide- and placebo-treated groups was -2.72 (1.00) mmHg (95% CI -4.69, -0.76).

²¹ Matthews DR, et al. Homeostasis model assessment: insulin resistance and β -cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; 28:412-9.

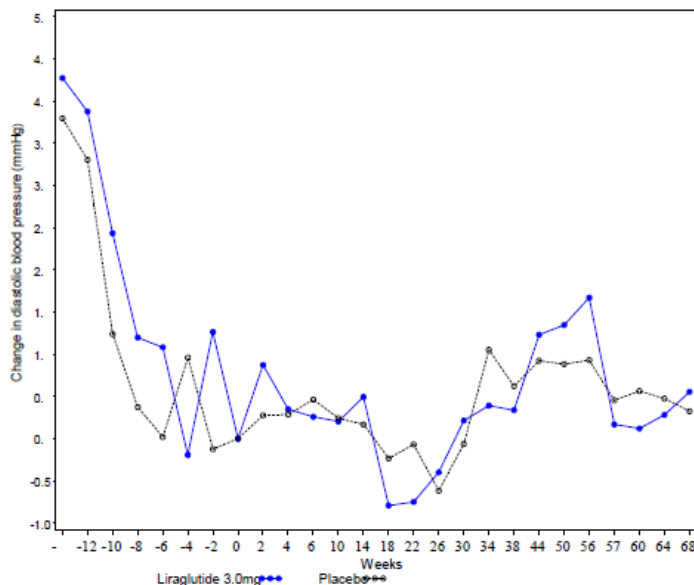
Figure 27. Change in Systolic Blood Pressure, Trial 1923



Source: NN8022-1923 Clinical Trial Report, Figure 11-11

As with SBP, diastolic BP decreased for both treatment groups during the run-in period (-3.6 mmHg); however, there was no significant difference between groups during the treatment period (Figure 28). Estimated LS mean changes in DBP from randomization to week 56 were +1.81 and +2.15 mmHg for liraglutide 3 mg and placebo groups, respectively, with an estimated mean treatment difference (SE) of -0.34 (0.71) mmHg (95% CI -1.74, 1.07).

Figure 28. Change in Diastolic Blood Pressure, Trial 1923



Source: NN8022-1923 Clinical Trial Report, Figure 11-12

6.3.4.1.9 Secondary Endpoints – Lipids

Changes in total cholesterol, LDL cholesterol, HDL cholesterol and VLDL cholesterol were modest with no statistically significant differences between groups.

6.3.5 Trial 3970

This was a 32-week trial designed to explore the effect of liraglutide on endpoints related to obstructive sleep apnea (OSA).

Reviewer comment: During the ongoing NDA review, DMEP consulted the expertise of the Division of Neurology Products (DNP) for input regarding the sponsor's study design and choice of endpoints.

Key Inclusion Criteria

- BMI ≥ 30 kg/m²
- Diagnosis of moderate or severe OSA (apnea-hypopnea index, AHI ≥ 15)
- Unwilling or unable to use continuous positive airway pressure (CPAP) or other positive airway pressure treatment ≥ 4 weeks prior to screening

Key Exclusion Criteria

- Patients on CPAP
- Type 1 or type 2 diabetes
- Use of central stimulants, hypnotics, mirtazepine, opioids, trazodone within the previous 3 months prior to screening
- Central sleep apnea

Trial duration was 36 weeks, consisting of a 2-week screening period, 4-week dose escalation period (0.6 mg starting dose increase by 0.6 mg increments every 7 days until target dose of 3.0 mg), 28-week maintenance period, and 2-week follow-up.

Polysomnography (PSG) visits occurred at screening, week 12, and week 32.

The following PSG endpoints pertinent to OSA were measured:

- AHI score
- AHI severity category (none ≤ 4.9 , mild 5.0–14.9, moderate 15.0–29.9, severe ≥ 30.0 events/hour)
- Lowest blood oxygen saturation (%)
- Percent time with blood oxygen below 80%, 85%, and 90%
- Oxygen desaturation index (ODI) $\geq 4\%$
- Wake time after sleep onset (WASO) (minutes and %)
- Percent slow wave sleep
- Sleep stage distribution (N1, N2, N3, R)
- Total sleep time
- Respiratory event related arousals (arousals per hour)

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- Proportion of supine sleep
- Period limb movement with arousal index (visit 2 only)
- Central apnea percentage (visit 2 only)
- Time in bed
- Heart rate

The following patient-reported outcomes (PRO) pertinent to OSA were measured:

- Daytime sleepiness (Epworth Sleepiness Scale),
- Health-related quality of life (Short Form 36 [SF-36] Health Survey)
- The impact of daytime sleepiness on multiple everyday activities (Functional Outcomes of Sleep Questionnaire [FOSQ])

The primary endpoint was change from baseline AHI at week 32.

Reviewer comment: DNP notes that OSA severity can be classified by AHI but the correlation between any specific improvement in AHI and clinically relevant benefit is poorly established.

Secondary endpoints pertinent to OSA included the following:

- Patients achieving OSA remission defined as AHI < 5 events/hour (yes/no) after 32 weeks of treatment
- Patients achieving 50% reduction in AHI from baseline after 32 weeks of treatment
- Patients with improved AHI severity category (none \leq 4.9, mild 5.0–14.9, moderate 15.0–29.9, severe \geq 30.0 events/hour) after 32 weeks of treatment
- Change from baseline in polysomnography measures after 32 weeks of treatment
 - Lowest blood oxygen saturation (%)
 - Percent time with blood oxygen below 80%, 85%, and 90%
 - Oxygen desaturation index (ODI) \geq 4% (events/hour)
 - WASO (minutes and %)
 - Slow wave sleep
 - Sleep stage distribution (N1, N2, N3, R)
 - Total sleep time
 - Respiratory event related arousals (RERA) (arousals per hour)
 - Proportion of supine sleep

The secondary endpoint pertinent to body weight was change in percent fasting body weight at end-of-study, with last fasting body weight imputed for missing values.

6.3.5.1 Results

A total of 359 patients were randomized, with 72% male, and 80% between the ages of 40 and 65 years. The majority, 67%, had severe sleep apnea, and the mean baseline AHI was 49 events/hour, which the sponsor reports as “highly severe”.

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Withdrawals from the trial were higher in the liraglutide as compared to the placebo group, 26% versus 21%, respectively. The difference between groups in withdrawals was related to adverse events (12.2% vs. 3.4%), primarily gastrointestinal.

6.3.5.1.1 OSA

Primary Endpoint

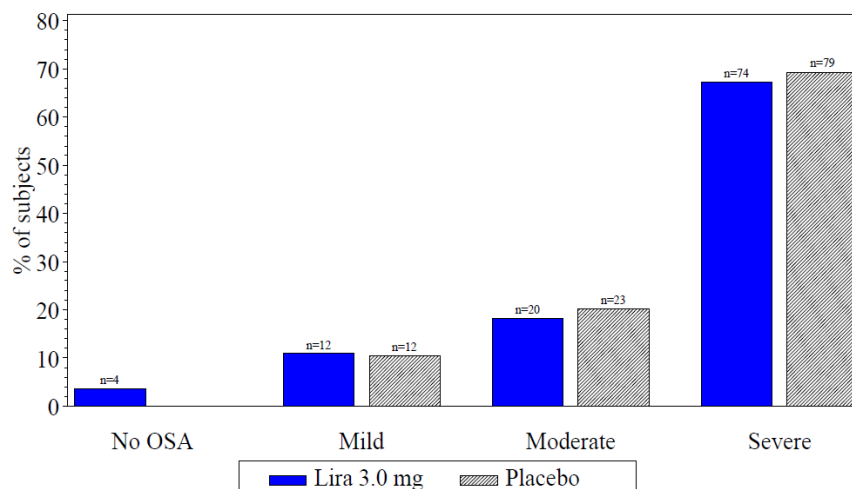
From a baseline AHI of 49 events/hour in each group, at week 32 the liraglutide arm decreased by 12 events/hour and the placebo group by 6 events/hour (p-value 0.015, LOCF imputation).

Results of this single trial were not robust to all sensitivity analyses (e.g., “completers” p-value 0.03; multiple imputation p = 0.054).

Secondary Endpoints

- OSA remission (AHI < 5 event/hours): 5.4% liraglutide vs. 1.2% placebo (p = 0.07)
- 50% reduction in AHI: 32% drug vs. 22% placebo (p = 0.05)
- Patients with improved OSA severity category (final OSA severity in patients with severe baseline OSA):

Figure 29. OSA Category at Week 32 for Patients with Severe Sleep Apnea at Baseline, Trial 3970

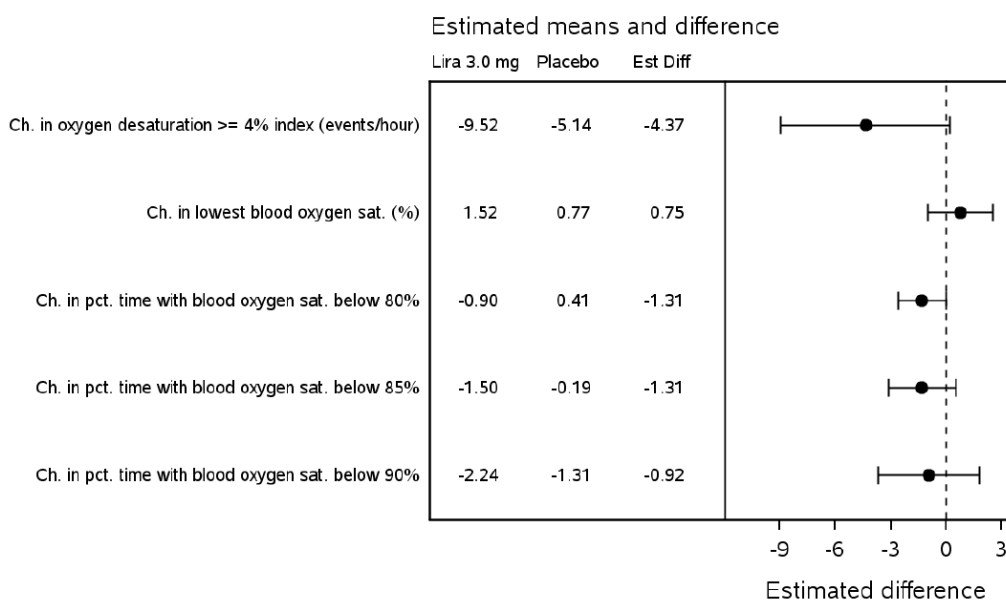


OSA: Obstructive sleep apnoea
No OSA (≤ 4.9 events/hour), Mild (5.0-14.9 events/hour), Moderate (15.0-29.9 events/hour), Severe (≥ 30.0 events/hour)
Chart includes subjects in full analysis set with post-baseline values.
Average values are based on observation carried forward (LOCF) values.

Source: NN8022-3970 Clinical Trial Report, Figure 11-4

No statistically significant differences between liraglutide and placebo were observed for any of the parameters related to blood oxygen saturation.

Figure 30. Change in Polysomnography Parameters Related to Blood Oxygen Saturation, Trial 3970

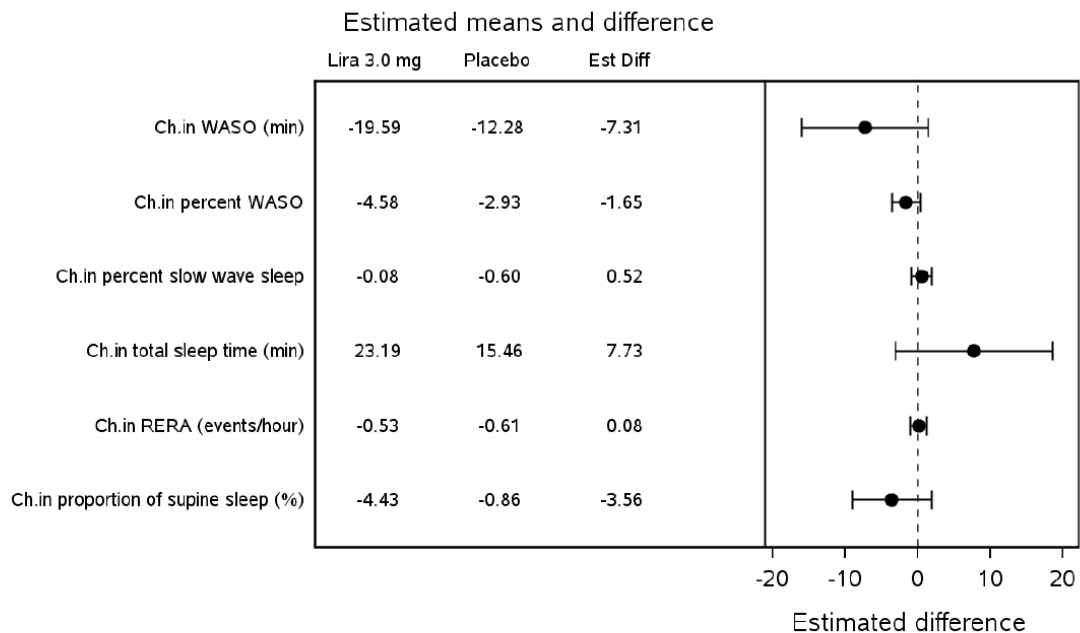


Ch.: Change
 Pct.: Percent, Sat.: Saturation

Source: NN8022-3970 Clinical Trial Report, Figure 11-5

No statistically significant differences between liraglutide and placebo were observed for any of the parameters related to sleep or sleep architecture.

Figure 31. Change in Polysomnography Parameters Related to Sleep Architecture, Trial 3970



Ch.: Change
WASO: Wake time after sleep onset, RERA: Respiratory event related arousals
Source: NN8022-3970 Clinical Trial Report, Figure 11-6

Patient Reported Outcomes were assessed with questionnaires at baseline and weeks 12 and 32.

The Epworth Sleepiness Scale (ESS) measures a patient's usual level of daytime sleepiness or average sleep propensity. It contains eight items on signs and symptoms in relation to sleep for which a patient has to indicate a chance of dozing: 0 = would never, 1 = slight chance, 2 = moderate chance, and 3 = high chance. The total score can range from 0 (low/absent propensity for daytime sleepiness) to 24 (high propensity for daytime sleepiness).

At baseline, mean total ESS scores were similar between the two treatment groups. After 32 weeks of treatment, the total ESS score decreased / improved by a similar degree in both treatment groups (-2.52 for liraglutide 3 mg and -2.33 for placebo at week 32).

The Functional Outcomes of Sleep Questionnaire (FOSQ) examines the impact of daytime sleepiness on a variety of daily activities. The questionnaire contains a total of 30 items that can be grouped into the following five domains: "general productivity", "social outcome", "activity level", "vigilance", and "intimate relationships/sexual activity". The potential range of scores for each domain ranges from 1 to 4. A low

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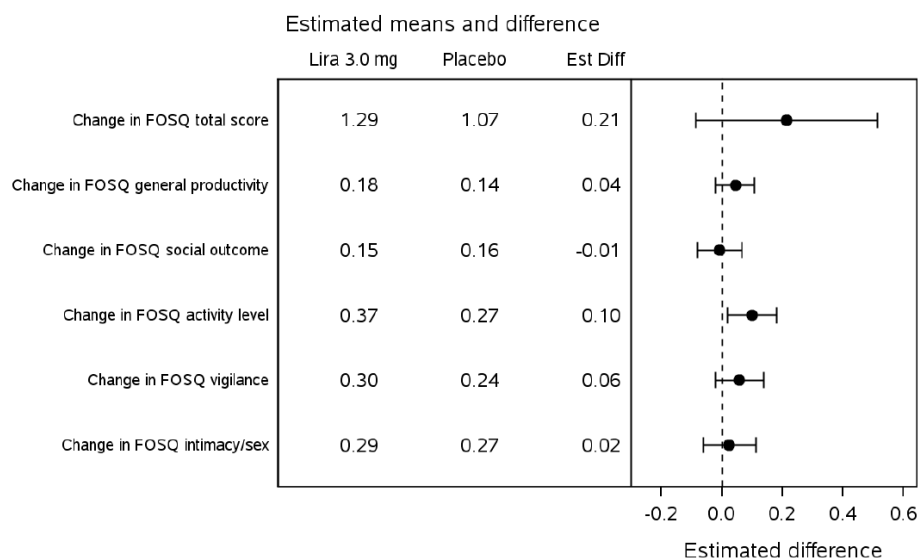
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domain/overall score indicates more functional impairment and a high score indicates less functional impairment. The SF-36 is described in section 6.3.2.1.4.4.

Most domains of the FOSQ and the SF-36 were not statistically significant.

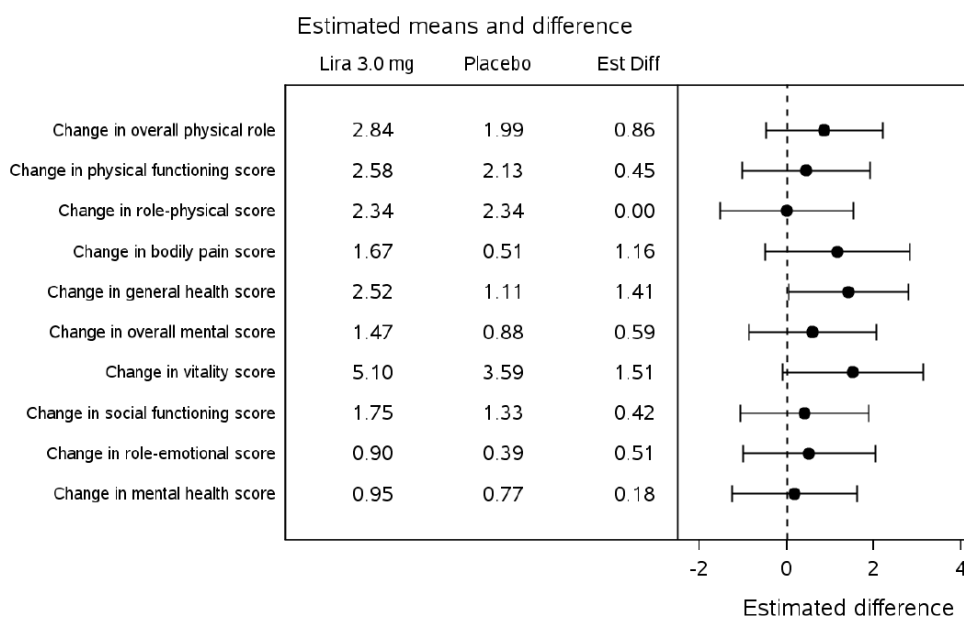
Figure 32. Change in Functional Outcomes of Sleep Questionnaire Scores, Trial 3970



FOSQ: functional outcomes of sleep questionnaire

Source: NN8022-3970 Clinical Trial Report, Figure 11-20

Figure 33. Change in SF-36 Scores, Trial 3970



Source: NN8022-3970 Clinical Trial Report, Figure 14.2.323

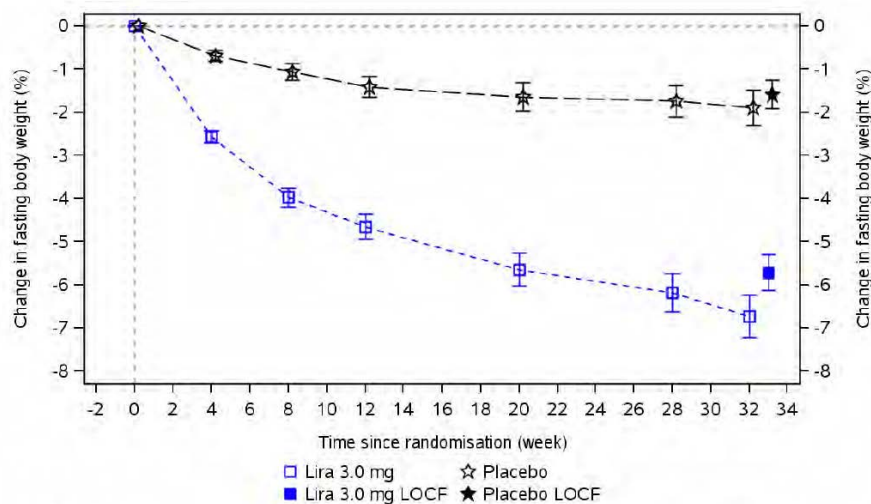
Reviewer comment: *In addition to the uncertain clinical relevance of the treatment effect in AHI change (primary endpoint), the following limitations with the OSA-related results of this trial were noted by DNP:*

- *A relatively narrow population was enrolled (moderate or severe OSA who were unable or unwilling to use CPAP)*
- *Changes in secondary endpoints, such as daytime sleepiness, nighttime sleep, and blood oxygen saturation were generally not significantly different from placebo*
- *The study was only 32 weeks duration; the changes observed in AHI at the end of the trial might not be predictive of a durable effect*

6.3.5.1.2 Body Weight

Body weight, as a secondary endpoint, was summarized descriptively. After 32 weeks, patients treated with liraglutide 3 mg had a greater mean percent body weight loss (-5.73%) than patients treated with placebo (-1.58%). The treatment difference was -4.15%.

Figure 34. Percent Change in Fasting Body Weight, Trial 3970



Means are calculated based on observed values. Means based on LOCF data are added for week 32. LOCF: Last observation carried forward.

Source: NN8022-3970 Clinical Trial Report, Figure 11-7

In the liraglutide-treated group, 46.4% of patients lost 5% of body weight or greater at week 32, as compared to 18.1% of placebo-treated patients. The proportion of 10% responders for the liraglutide and placebo treatment groups was 22.4% and 1.5%, respectively.

6.3.5.1.3 *Cardiometabolic Parameters*

At baseline, none of the patients had diabetes (exclusion criterion), but approximately two-thirds of the patients had pre-diabetes. Mean baseline HbA1c was ~5.6%. Overall, at week 32, patients treated with liraglutide had a mean change in HbA1c of -0.36 percentage points, as compared to patients treated with placebo, who had a change of -0.17 percentage points (treatment difference -0.19 percentage points [95% CI -0.25, -0.12]).

Treatment with liraglutide was associated with a reduction in systolic BP as compared to placebo (-3.74 mmHg vs. +0.38 mmHg [treatment difference -4.12; 95% CI -6.33, -1.90]). No statistically significant differences in diastolic BP, fasting lipids (HDL-C, LDL-C, VLDL-C, TG, or total cholesterol), hsCRP, or urinary albumin/creatinine ratio were observed.

Heart rate results are presented in the safety review, section 7.5.7.2.

7 Safety

The primary focus of the safety review is on the liraglutide 3 mg dose in the weight management population. The sponsor pooled the five phase 2 and 3 weight management trials to compare liraglutide 3 mg to placebo. This pooling method was agreed upon with the Agency prior to the NDA submission. Because trial 1839 was the largest, its results contributed in large part to the overall pooled results.

Individual trials were evaluated for specific adverse events (e.g., hypoglycemia in patients with T2DM (trial 1922)), or when evaluating a particular adverse event for a dose response (trials 1807 and 1922). Given the smaller sample size in these trials, the adverse events needed to be relatively common to detect a dose response.

The planned 2-year extension of trial 1839 is ongoing. It is unblinded to the sponsor, but remains blinded to trial participants and investigators. Serious adverse event (SAE) and pregnancy data were included in the safety evaluation as descriptive data with a cut-off date of 02 July 2013 in the original NDA submission and 11 Nov 2013 as of the 120-day safety update.

The T2DM trials (liraglutide doses up to 1.8 mg) were pooled to support liraglutide's safety. Of note, the diabetes pool included a variety of trial designs and durations, so there were important differences from the weight management program, including: (1) the use of active comparators, (2) shorter duration trials, (3) open-label extensions, (4) lower doses, (5) an overlapping, but not identical, patient population, and (6) the lack of adverse event adjudication (as was conducted in the majority of the weight management trials for certain adverse events of interest). Diabetes and weight management programs were combined for certain exploratory analyses, such as for cancer and cardiovascular (MACE) evaluations.

7.1 Exposure

In the phase 2 and 3 weight management pool, a total of 3872 individuals were exposed to at least one dose of liraglutide; 3384 of these to liraglutide 3 mg. A total of 2341 patients were exposed to liraglutide 3 mg for 12 months or more. Total exposure for all liraglutide doses was 3373 patient-years (PY) of exposure, of which 2974 PY were with liraglutide 3 mg. Total exposure for placebo was 1601 PY.

Table 45. Exposure, Weight Management Pool

	Lira 3 mg	Total lira	Placebo
N	3384	3872	1941
PY	2974.3	3372.7	1600.9
Exposure (yrs)			
Mean (SD)	0.88 (0.3)	0.87 (0.3)	0.82 (0.3)
Median	1.07	1.07	1.06
Min, Max	0.00, 1.22	0.00, 1.22	0.00, 1.22
N (%) ≥ 1 month exposure	3230 (95.4)	3684 (95.1)	1870 (96.3)
N (%) ≥ 2 months exposure	3082 (91.1)	3523 (91.0)	1794 (92.4)
N (%) ≥ 3 months exposure	3003 (88.7)	3427 (88.5)	1715 (88.4)
N (%) ≥ 6 months exposure	2798 (82.7)	3165 (81.7)	1524 (78.5)
N (%) ≥ 9 months exposure	2531 (74.8)	2881 (74.4)	1271 (65.5)
N (%) ≥ 12 months exposure	2341 (69.2)	2567 (66.3)	1139 (58.7)

Source: ISS, Table 1-3; Appendix 7.1, Table 4

A total of 1584 patients (liraglutide 3 mg N=1087, placebo N=497) completed the main part of trial 1839 and entered the extension phase. The following table enumerates the exposure in this phase of the trial as of the data cut-off of the 120-day safety update (11 Nov 2013):

Table 46. Exposure, Trial 1839 Ongoing Extension

	Lira 3 mg	Placebo
N	1087	497
PY	1114.8	493.6
Exposure (yrs)		
Mean (SD)	1.0 (0.3)	1.0 (0.3)
Median	1.1	1.1
Min, Max	0.0, 1.4	0.0, 1.4
N (%) ≥ 12 months exposure	1087 (100)	497 (100)
N (%) ≥ 18 months exposure	999 (91.9)	449 (90.3)
N (%) ≥ 24 months exposure	906 (83.3)	386 (77.7)

Source: 120 day safety update, Tables 1-3 and 1-6

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The following table enumerates exposure for the diabetes pool alone and in combination with the weight management pool:

Table 47. Exposure, Diabetes and Combined Pools

	Diabetes Pool		Diabetes + Weight Management Pool	
	Liraglutide	Comparator	Liraglutide	Comparator
N	7037	3677	10909	5713
PY	5072.0	2444.9	8444.7	4117.3
Exposure (yrs)				
Mean (SD)	0.72 (0.6)	0.66 (0.5)	0.77 (0.5)	0.72 (0.5)
Median	0.50	0.50	0.89	0.60
Min, Max	0.00, 3.72	0.00, 3.56	0.00, 3.72	0.00, 3.56

Source: Supplementary AE Report, Tables 1 and 2

7.2 Deaths

Deaths were infrequent in the liraglutide development programs. Overall, there did not appear to be an imbalance of deaths in the group randomized to liraglutide. Note that the incidence of deaths presented in the table below (Table 48) includes patients prior to the data cut-offs for ongoing trials, and do not include patients in the follow-up phases. Table 49 and Table 50 include additional known deaths in two liraglutide-treated patients, one from a follow-up phase, and one from the extension phase of trial 1839, as described below.

Table 48. Treatment-Emergent Deaths, Weight Management and Diabetes Programs Combined (Main Treatment Period)

	Total lira N=10909	Total comparator N=5713
Patients with Fatal AEs	11 (0.1)	9 (0.2)

Source: Supplementary AE Report, Appendix 1, Table 7

7.2.1 Clinical Pharmacology Trial

No deaths occurred in the clinical pharmacology trial 3630.

7.2.2 Weight Management Trials

In the completed phase 2 and 3 weight management trials, the proportion of patients with fatal events was less than 0.1% with liraglutide 3 mg and was 0.2% with placebo.

In addition, one additional death (cardiovascular (CV)) in a patient randomized to liraglutide 1.8 mg occurred during the follow-up period of the diabetes trial 1922, and an additional death (CV) is known to have occurred in the liraglutide 3 mg group in the ongoing extension phase of trial 1839. Both events are included separately in the table below.

Table 49. Summary of Fatal Adverse Events, Weight Management Phase 2 and 3 Trials

	Lira 3 mg	Total lira	Pbo
Completed treatment period	N=3384	N=3872	N=1941
Fatal AEs	1 (< 0.1)	1 (< 0.1)	3 (0.2)
Follow-up period	N=3384	N=3872	N=1941
Fatal AEs	0	1 (< 0.1)	0
Ongoing 1839 extension*	N=1087		N=497
Fatal AEs	1 (0.1)		0
* Prior to data cut-off			

Source: ISS, Appendix 7.2, Table 22

All deaths reported in the weight management program were adjudicated for classification as CV death or non-CV death. Of the 6 deaths sent for adjudication, 5 deaths (3 with liraglutide and 2 with placebo) were categorized as CV deaths by the EAC. Deaths categorized by the EAC as 'unknown' were regarded as CV deaths.

Table 50. Deaths, Weight Management Program

Subject Trial Days of exposure at onset	Age (years)/ Sex/ BMI (kg/m ²) ^a	PT (MedDRA)/ EAC cause of death	Causality: Investigator/ Sponsor	Relevant medical history	Description
<i>Liraglutide 1.8 mg</i>					
935011 1922-FU 391 days	53 years male 52.6	Pulmonary embolism, hypotension, acute renal failure, cerebrovascular accident, acute MI, embolism arterial, respiratory failure, embolism venous/ CV death ^b	Unlikely/ unlikely	- Morbid obesity - T2DM (2010) - hypertension - hyper-cholesterolemia - previous cardiovascular disease - cardiomegaly - bilateral pedal edema - hypoventilation syndrome - alcohol abuse	On day 435 (44 days off drug) the subject presented to the hospital with sudden difficulty in breathing, high blood pressure, hyperglycaemia and severe left leg pain. Several CT scans were performed (chest, head and abdomen) which revealed multiple bilateral, near occlusive thrombus filling all segmental pulmonary arteries bilaterally and multifocal areas considered thromboembolic infarcts in the cerebrum and the subject was diagnosed with cerebrovascular stroke and saddle pulmonary embolism. Despite receiving anticoagulant therapy and other supportive treatment, the subject decompensated and went into acute respiratory failure. The subject expired 1 day later. The events were judged to be unlikely related to trial product as judged by the investigator and sponsor
<i>Liraglutide 3.0 mg</i>					
211022 1839 235 days	50 years male 40.5	Cardiomegaly, hypertensive heart disease/ CV death	Cardiomegaly: possible/ unlikely Hypertensive heart disease: unlikely/ unlikely	- Morbid obesity - Hypertension - coronary disease - severe left ventricular systolic dysfunction - hypertensive cardiomyopathy	Subject suddenly collapsed on the street, and CPR was performed by paramedics. As the subject had pulseless electrical activity he was treated with adrenalin and intubated. After approximately 1 hour of resuscitation, death was declared.
439014 1839-ext 578 days	65 years male 33.6	Cardio respiratory arrest, ventricular fibrillation/ CV death	Possibly/ unlikely	-Hypertension -hyperlipidaemia -coronary artery disease -multiple stent replacements -sleep apnea	Subject suddenly collapsed at home and was taken to hospital in full cardiac arrest. Diagnosis was fatal acute pulmonary arrest due to ventricular fibrillation. The subject previously experienced 2 SAEs during the main treatment period; acute coronary syndrome causing syncope and coronary revascularisation, after 319 and 321 days of treatment with liraglutide 3.0 mg, respectively
<i>Placebo</i>					
125013 1923 136 days	58 years male 28.3	Cardiac failure/ CV death	Possible/ unlikely	- Hypertension - hyperlipidemia - history of alcohol abuse - smoker - family history of cardiac failure (father) and rheumatic heart disease (sister).	Approximately 4.5 months after randomisation subject had a fatal episode of heart failure. No further information is available as the family didn't agree to releasing hospital records.

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Subject Trial Days of exposure at onset	Age (years)/ Sex/ BMI (kg/m ²) ^a	PT (MedDRA)/ EAC cause of death	Causality: Investigator/ Sponsor	Relevant medical history	Description
407013 1839 114 days	51 years male 29.7	Pulmonary fibrosis/ CV death	Unlikely/ unlikely	- Hypertension - high cholesterol - pneumonia - osteoarthritis - pulmonary fibrosis	The subject passed away during hospitalisation due to worsening of pulmonary fibrosis. Despite multiple attempts no further information is obtainable.
428029 1839 111 days	59 years male 57.6	Cardio-respiratory arrest/ Non-CV death ^c	Unlikely/ unlikely	- Morbid obesity - sleep apnea/	Due to chest pain and shortness of breath the subject went to his primary care physician where he later passed out and developed asystoli. CPR was performed and subject was later intubated and treated with adrenaline and atropine. The subject was admitted to hospital and despite intensive care he rapidly deteriorated and was pronounced dead later the same day.

BMI: body mass index; CPR: cardiopulmonary resuscitation; CT: computerised axial tomography; CV: cardiovascular; EAC: event adjudication committee; FU: follow-up; MI: myocardial infarction; SAE: serious adverse event; T2DM: type 2 diabetes mellitus.

a. Age and BMI are baseline values. b. EAC: CV death due to stroke and pulmonary embolism. c. Comment from EAC: chest x-ray showed lung white out on right and partial on left. No evidence of acute MI.

Source: ISS, Table 2-30

Reviewer comments:

Given the patients' age and co-morbidities, I am unable to determine that liraglutide contributed to any of these deaths. The reports of 2 patients treated with liraglutide 3 mg who "suddenly collapsed" are noted; both of these patients had known coronary artery disease.

It is noted that an "unknown" cause of death in a patient treated with placebo, attributed by report to pulmonary fibrosis, was adjudicated as a CV death due to the lack of information. (The lack of information may result in the misclassification of events.) Another placebo-treated patient died due to "cardio-respiratory arrest" although this was adjudicated as a non-CV death due to opacification of the lungs on chest x-ray and reportedly no evidence of acute myocardial infarction.

Only one of the three liraglutide CV deaths is captured in the primary on-treatment MACE analysis (see section 7.5.7.1); one event occurred during the ongoing extension phase of trial 1839 and one event occurred during off-treatment follow-up.

7.2.3 Diabetes Pool

In the T2DM trials, an excess of death was not observed in the liraglutide treatment group as compared with placebo (0.1% versus 0.2%, respectively).

Table 51. Summary of Fatal Adverse Events, Diabetes Pool

	Total lira N=7037	Total comparator N=3677
Patients with Fatal AEs	10 (0.1)	6 (0.2)

Source: Supplementary AE Report, Appendix 1, Table 12

Table 52 lists the deaths in the T2DM programs. The asterisk [*] symbol next to the patient ID indicated that the death was previously reviewed in the Victoza NDA. Narratives for deaths from the diabetes trials not reviewed in the Victoza NDA can be found in the appendix (section 8.1).

Table 52. Fatal Adverse Events, Diabetes Pool

Treatment	Lira Dose (if applic)	Trial	Patient ID	Country	Age (yrs)	Sex	Time on Therapy (Days)	Cause of Death	EAC Adjudication
Treatment-Emergent									
Lira 1.2 + Met	1.2 mg	NN2211-1572	225011*	Germany	63	M	165	Hepatic Cirrhosis Hepatic neoplasm malignant	Non-CV death
Lira 0.6 + Met	0.6 mg	NN2211-1572	318018	Hungary	55	M	645	Pyelonephritis Renal failure acute	Non-CV death
Lira 0.6 + Met	0.6 mg	NN2211-1572	393004	India	61	M	676	Tuberculosis	Non-CV death
Lira 1.8 mg	1.8 mg	NN2211-1573	117006	US	62	F	668	Pancreatitis acute	Non-CV death
Lira	0.9 mg	NN2211-1700	09025*	Japan	63	F	36	Gastroenteritis	Non-CV death
Lira 1.8 + Met	1.8 mg	NN2211-1860	107008	Germany	50	M	12	Pancreatic carcinoma	Non-CV death
Lira 1.8 + Met	1.8 mg	NN2211-1860	452002	Croatia	65	F	401	Bile duct cancer	Non-CV death
Lira	0.9 mg	NN2211-3924	122011	Japan	68	F	168	Lung neoplasm malignant	Non-CV death
IDegLira	variable	NN9068-3697-ext	454031	South Africa	49	F	67	Death	CV death
IDegLira	variable	NN9068-3697-ext	954006	US	67	F	182	Septic shock Urinary tract infection	CV death
Glimepiride	N/A	NN2211-1573	504036*	Mexico	56	F	194	Road traffic accident	Non-CV death
OAD	N/A	NN2211-1697	689012*	Austria	67	F	77	Acute myocardial infarction	CV death
Glargine + OAD	N/A	NN2211-1697	827005*	Serbia and Montenegro	54	M	116	Acute myocardial infarction	CV death
Sitagliptin + Met	N/A	NN2211-1860	302001	Ireland	64	M	48	Cardiac arrest	CV death
Sitagliptin + Met	N/A	NN2211-1860	302017	Ireland	60	M	100	Renal cancer	Non-CV death
Sitagliptin + Met	N/A	NN2211-1860	453001	Croatia	65	M	282	Sudden cardiac death	CV death
Non-Treatment Emergent									
IDegLira	Variable	NN9068-3696-ext	457014	South Africa	47	F	287	Gunshot wound	Non-CV death

Treatment Emergent in Uncontrolled Trials/Extensions									
Exenatide+OAD / Lira 1.8	N/A / ext: 1.8 mg	NN2211-1797 ext	206008	Germany	67	F	183 exen / 17 lira	Myocardial infarction	CV death
Lira + OAD	1.8 mg	NN2211-1797 ext	485014	US	69	F	300	Cerebral infarction Pulmonary embolism	CV death
Sita+Met / Lira 1.2	N/A / ext: 1.2 mg	NN2211-1860 ext	413005	UK	55	F	385 sita / 31 lira	Renal failure acute	Non-CV death
* Death reported in the Victoza NDA									

Source: Response to FDA Request, 10 Apr 2014, Tables 3 to 5

7.3 Other Serious Adverse Events

7.3.1 Clinical Pharmacology Trial

In trial 3630, one serious adverse event (SAE) of thrombosis (blood clot in toe) was reported in a 63-year-old male patient treated with liraglutide 3 mg with a medical history of hypercholesterolemia. The blood clot was thought to be due to an infected toe.

7.3.2 Weight Management Program

Overall, there were more patients in the liraglutide groups who experienced SAEs than those in the placebo groups, primarily driven by SAEs in the hepatobiliary disorders and neoplasms system organ class (SOC). Gallbladder disorders are discussed further in section 7.5.2 and neoplasms in section 7.5.3.

The table below enumerates SAEs by SOC and selected high level group terms (HLGTs).

Table 53. Serious Adverse Events, Main Treatment Period, Weight Management Pool

	Lira 3 mg N=3384 PY=2974.3		Total lira N=3872 PY=3372.7		Placebo N=1941 PY=1600.9	
Overall System organ class High level group term	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY
Total SAEs	213 (6.3)	93	246 (6.4)	94	89 (4.6)	71
Hepatobiliary disorders	44 (1.3)	17	48 (1.2)	17	6 (0.3)	4
Gallbladder disorders	42 (1.2)	15	46 (1.2)	15	6 (0.3)	4
Hepatic and hepatobiliary disorders†	3 (<0.1)	1	3 (<0.1)	<1	0	0
Neoplasms benign, malignant and unspecified	28 (0.8)	10	31 (0.8)	9	8 (0.4)	5
Breast neoplasms malignant and unspecified‡	8 (0.2)	3	8 (0.2)	2	1 (<0.1)	<1
Infections and infestations	27 (0.8)	9	30 (0.8)	9	17 (0.9)	12
Gastrointestinal disorders	23 (0.7)	8	28 (0.7)	9	12 (0.6)	8
Gastrointestinal signs and symptoms	7 (0.2)	3	9 (0.2)	4	1 (<0.1)	<1

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Exocrine pancreas conditions*	6 (0.2)	2	6 (0.2)	2	0	0
Musculoskeletal and connective tissue disorders	21 (0.6)	8	27 (0.7)	9	8 (0.4)	5
Joint disorders	13 (0.4)	5	15 (0.4)	5	2 (0.1)	1
Injury, poisoning and procedural complications	19 (0.6)	7	20 (0.5)	7	6 (0.3)	4
Cardiac disorders	13 (0.4)	6	15 (0.4)	6	9 (0.5)	6
Renal and urinary disorders§	10 (0.3)	4	11 (0.3)	4	5 (0.3)	3
Reproductive system and breast disorders	10 (0.3)	3	11 (0.3)	3	2 (0.1)	1
Uterine, pelvic and broad ligament disorders	8 (0.2)	3	8 (0.2)	2	1 (<0.1)	<1
Respiratory, thoracic and mediastinal disorders	9 (0.3)	3	10 (0.3)	3	4 (0.2)	3
Surgical and medical procedures	9 (0.3)	3	10 (0.3)	3	5 (0.3)	4
Nervous system disorders	8 (0.2)	3	12 (0.3)	4	7 (0.4)	5
Vascular disorders	6 (0.2)	2	6 (0.2)	2	2 (0.1)	1
† Includes preferred terms hepatic cyst, hepatitis, and acute hepatitis ‡ Includes breast cancer, breast cancer in situ, and breast cancer stage III * Includes pancreatitis and acute pancreatitis § Includes 1 event of acute renal failure in the lira 3 mg group						

Source: ISS, Appendix 7.2, Table 25

SAEs have been reported for the ongoing extension phase of trial 1839; the numbers of patients and proportions are based on the numbers of patients entering the extension. Because some of the details of the serious adverse events were changed at the time of the 120-day safety update (e.g., reassigned to main portion of the trial), the SAEs provided at the time of the original NDA submission (Table 54) and the 120-day safety update (Table 55) are tabulated separately for completeness.

Table 54. Serious Adverse Events by System Organ Class and High Level Group Term or Preferred Term (Selected), Ongoing Portion of Trial 1839

	Lira 3 mg N=1087	Placebo N=497
Total SAEs	68 (6.3)	21 (4.2)
Blood and lymphatic system disorders	1 (<0.1)	0
Cardiac disorders	4 (0.4)	0
Cardiac arrhythmias	2 (0.2)	0
Coronary artery disorders	2 (0.2)	0
Endocrine disorders	0	1 (0.2)
Gastrointestinal disorders	5 (0.5)	1 (0.2)
Pancreatitis	1 (<0.1)	0
Intestinal obstruction	1 (<0.1)	0
General disorders and administration site conditions	5 (0.5)	1 (0.2)
Hepatobiliary disorders	6 (0.6)	1 (0.2)

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Gallbladder disorders	4 (0.4)	1 (0.2)
Bile duct disorders	3 (0.3)	0
Infections and infestations	10 (0.9)	5 (1.0)
Injury, poisoning and procedural complications	6 (0.6)	4 (0.8)
Investigations	1 (<0.1)	1 (0.2)
Lipase increased	1 (<0.1)	0
Metabolism and nutrition disorders	1 (<0.1)	3 (0.6)
Musculoskeletal and connective tissue disorders	9 (0.8)	2 (0.4)
Neoplasms benign, malignant and unspecified	7 (0.6)	1 (0.2)
Skin neoplasms malignant and unspecified	2 (0.2)	0
Invasive ductal breast carcinoma	1 (<0.1)	0
Adrenal adenoma	1 (<0.1)	0
Papillary thyroid cancer	1 (<0.1)	0
Bladder cancer	1 (<0.1)	0
Nervous system disorders	7 (0.6)	1 (0.2)
Central nervous system vascular disorders	2 (0.2)	0
Spinal cord and nerve root disorders	2 (0.2)	0
Dizziness	1 (<0.1)	0
Convulsion	1 (<0.1)	0
Pregnancy, puerperium and perinatal conditions	1 (<0.1)	1 (0.2)
Psychiatric disorders	4 (0.4)	1 (0.2)
Depressed mood disorders and disturbances	2 (0.2)	1 (0.2)
Suicidal and self-injurious behaviors NEC	2 (0.2)	0
Anxiety	1 (<0.1)	0
Renal and urinary disorders	4 (0.4)	2 (0.4)
Renal impairment	2 (0.2)	0
Renal failure acute	1 (<0.1)	0
Reproductive system and breast disorders	1 (<0.1)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	2 (0.2)	0
Skin and subcutaneous tissue disorders	1 (<0.1)	0
Surgical and medical procedures	5 (0.5)	2 (0.4)
Vascular disorders	2 (0.2)	0
Orthostatic hypotension	1 (<0.1)	0
Hypertension	1 (<0.1)	0

Source: ISS, Appendix 7.2, Table 30

In the 120-day safety update, which updated the findings from the ongoing extension phase of trial 1839 (updated data cut-off of 11 Nov 2013), an additional 28 events occurred in 25 patients on liraglutide and 21 events in 15 patients on placebo. This resulted in a total of 85 (7.8%) of patients on liraglutide and 34 (6.8%) of patients on placebo in the extension portion of trial 1839 experiencing at least one SAE.

Table 55. New Serious Adverse Events Not Reported in the ISS (02 Jul 2013 to 11 Nov 2013), Ongoing Portion of Trial 1839

	Lira 3 mg N=1087	Placebo N=497
New SAEs	25 (2.3)	15 (3.0)
Cardiac disorders	2 (0.2)	1 (0.2)
Atrial fibrillation	1 (0.1)	0
Cardiac tamponade	1 (0.1)	0
Endocrine disorders	0	2 (0.4)
Eye disorders	1 (0.1)	1 (0.2)
Gastrointestinal disorders	4 (0.4)	2 (0.4)
Hiatus hernia	1 (0.1)	0
Pancreatic cyst	1 (0.1)	0
Abdominal pain	1 (0.1)	0
Abdominal pain upper	1 (0.1)	0
General disorders and administration site conditions	1 (0.1)	1 (0.2)
Hepatobiliary disorders	4 (0.4)	0
Cholelithiasis	2 (0.2)	0
Cholecystitis	1 (0.1)	0
Hepatic lesion	1 (0.1)	0
Infections and infestations	3 (0.3)	0
Injury, poisoning and procedural complications	1 (0.1)	1 (0.2)
Ankle fracture	1 (0.1)	0
Metabolism and nutrition disorders	0	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (0.4)	4 (0.8)
Neoplasms benign, malignant and unspecified	1 (0.1)	0
Breast cancer metastatic	1 (0.1)	0
Nervous system disorders	2 (0.2)	3 (0.6)
Renal and urinary disorders	0	1 (0.2)
Reproductive system and breast disorders	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (0.1)	0
Skin and subcutaneous disorders	1 (0.1)	0
Social circumstances	1 (0.1)	0
Surgical and medical procedures	1 (0.1)	2 (0.4)

Source: 120-day safety update, Appendix 7.1, Table 6

7.3.3 Diabetes Pool

Overall, SAEs occurred with similar incidence in liraglutide- as compared to comparator-treated patients in the T2DM programs.

Table 56. Serious Adverse Events, Diabetes Pool

	Total lira N=7037	Comparator total N=3677
	n (%)	n (%)
SAEs	351 (5.0)	200 (5.4)
Cardiac disorders	68 (1.0)	37 (1.0)
Neoplasms benign, malignant and unspecified	54 (0.8)	21 (0.6)
Infections and infestations	50 (0.7)	20 (0.5)
Gastrointestinal disorders	39 (0.6)	14 (0.4)
Musculoskeletal and connective tissue disorders	34 (0.5)	12 (0.3)
Nervous system disorders	30 (0.4)	20 (0.5)
Injury, poisoning and procedural complications	25 (0.4)	23 (0.6)
Endocrine disorders	13 (0.2)	2 (<0.1)
Hepatobiliary disorders	12 (0.2)	8 (0.2)

Source: Supplementary AE Report, Appendix 1, Table 14

Specific SAEs of note that are imbalanced not in favor of liraglutide in the diabetes program include cardiac arrhythmias (0.2% vs. 0.1%), heart failure (<0.1% vs. 0), thyroid gland disorders (0.2% vs. <0.1%), gastrointestinal inflammatory conditions (0.1% vs. 0), gastrointestinal hemorrhages (<0.1% vs. 0), endocrine neoplasms malignant and unspecified (0.1% vs. < 0.1%). Imbalances in SAEs of interest are addressed in relevant sections of this review.

7.4 Adverse Events Associated with Discontinuation

In the weight management trials, the reason for withdrawal recorded on the end-of-trial forms included pre-specified criteria including withdrawal criteria, AEs, and other reasons. Acute pancreatitis and psychiatric disorders were specific withdrawal criteria in the liraglutide weight management trials. Patients who withdrew due to these AEs were recorded as discontinuation due to fulfillment of withdrawal criteria and not as withdrawals due to AEs. In order to capture all types of AEs leading to discontinuation in the trials, patients discontinuing due to fulfillment of withdrawal criteria of 'acute pancreatitis' and 'psychiatric disorders' were also considered as AEs leading to withdrawal.

7.4.1 Clinical Pharmacology Trial

In trial 3630, two AEs leading to withdrawal were reported during the trial. One patient treated with liraglutide 3 mg was withdrawn due to thrombosis (blood clot in a toe); this was reported as an SAE (see section 7.3.1), and one patient, randomized to placebo, was withdrawn due to a tooth infection.

7.4.2 Weight Management Program

The percentage of patients withdrawn due to AEs was higher in those randomized to liraglutide 3 mg (9.8%) than placebo (4.3%). Gastrointestinal disorders were the most common reason for AE discontinuation in the liraglutide-treated patients (6.2%), in

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contrast to placebo-treated patients (0.8%). The most common AEs by preferred term leading to withdrawal with liraglutide 3 mg were nausea (2.9%), vomiting (1.7%) and diarrhea (1.4%). Gastrointestinal AEs are discussed further in section 7.5.11.

Other AEs more frequently leading to withdrawal with liraglutide 3 mg than with placebo were (by decreasing frequency) from the SOC of 'general disorders and administration site conditions' (fatigue and asthenia), 'nervous system disorders' (headache and dizziness), 'neoplasms', and 'investigations' (lipase increased).

Six patients treated with liraglutide 3 mg withdrew due to the withdrawal criterion of acute pancreatitis; none was withdrawn due to acute pancreatitis with placebo. Pancreatitis is discussed further in section 7.5.1.

One patient treated with liraglutide 3 mg and two treated with placebo withdrew due to the withdrawal criterion of psychiatric disorders. Psychiatric disorders are discussed further in section 7.5.8.

Table 57. Adverse Events Leading to Withdrawal by System Organ Class and High Level Group Term, Weight Management Pool

	Lira 3 mg N=3384 PY=2974.3		Total lira N=3872 PY=3372.7		Placebo N=1941 PY=1600.9	
Overall System organ class High level group term	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY
Total AEs Leading to Withdrawal	331 (9.8)	168	376 (9.7)	169	83 (4.3)	72
Gastrointestinal disorders	210 (6.2)	103	235 (6.1)	102	15 (0.8)	12
Gastrointestinal signs and symptoms	156 (4.6)	72	175 (4.5)	71	10 (0.5)	7
Gastrointestinal motility and defecation conditions	74 (2.2)	26	80 (2.1)	25	3 (0.2)	2
Exocrine pancreas conditions*	7 (0.2)	2	7 (0.2)	2	0	0
General disorders and administration site conditions	40 (1.2)	14	51 (1.3)	16	14 (0.7)	10
General system disorders NEC†	22 (0.7)	8	28 (0.7)	9	4 (0.2)	2
Administration site reactions	17 (0.5)	6	22 (0.6)	7	9 (0.5)	7
Nervous system disorders	28 (0.8)	11	33 (0.9)	12	9 (0.5)	6
Neurological disorders NEC††	21 (0.6)	7	23 (0.6)	7	3 (0.2)	2
Headaches	10 (0.3)	3	14 (0.4)	4	4 (0.2)	2
Investigations	17 (0.5)	7	21 (0.5)	7	7 (0.4)	8
Gastrointestinal investigations§	12 (0.4)	5	14 (0.4)	5	3 (0.2)	2
Hepatobiliary investigations¥	2 (<0.1)	<1	2 (<0.1)	<1	3 (0.2)	3
Neoplasms benign, malignant and unspecified	15 (0.4)	5	15 (0.4)	4	7 (0.4)	4
Skin and subcutaneous tissue disorders	13 (0.4)	5	15 (0.4)	5	7 (0.4)	6

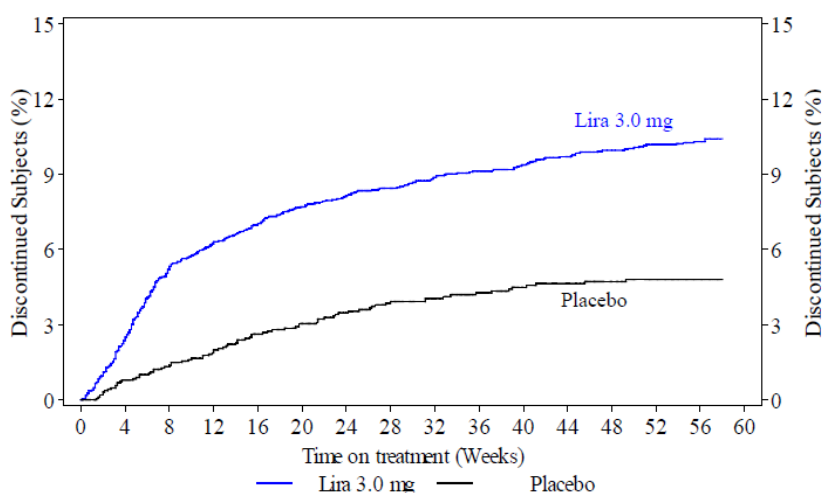
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Metabolism and nutrition disorders	11 (0.3)	4	12 (0.3)	4	5 (0.3)	3
Psychiatric disorders	9 (0.3)	4	12 (0.3)	5	11 (0.6)	7
Infections and infestations	8 (0.2)	3	10 (0.3)	3	2 (0.1)	1
Hepatobiliary disorders	8 (0.2)	3	8 (0.2)	2	1 (<0.1)	1
Gallbladder disorders	6 (0.2)	2	6 (0.2)	2	1 (<0.1)	<1
Musculoskeletal and connective tissue disorders	5 (0.1)	2	5 (0.1)	2	1 (<0.1)	<1
* Includes acute pancreatitis, pancreatic disorder, and pancreatitis † Includes fatigue, irritability, and asthenia †† Includes dizziness and dysgeusia § Includes lipase increased, amylase increased, and pancreatic enzymes increased ¥ Includes liver function test abnormal, alanine aminotransferase increased, aspartate aminotransferase increased, and transaminases increased						

Source: ISS, Appendix 7.2, Table 32

AEs leading to withdrawal were primarily reported during the initial 4 to 8 weeks of treatment (Figure 35).

Figure 35. Time to Discontinuation (Weeks) Due to Adverse Events, Weight Management Pool



Source: ISS, Figure 2-16

7.4.3 Diabetes Program

Similar to the weight management pool, more patients treated with liraglutide in the diabetes pool discontinued due to gastrointestinal disorders (specifically, nausea, vomiting, and diarrhea) as compared to those treated with placebo.

7.5 Targeted Safety Issues

7.5.1 Pancreatitis

Post-marketing reports of acute pancreatitis in GLP-1-based therapies (i.e., GLP-1 receptor agonists and DPP-4 inhibitors) have led to warnings regarding pancreatitis in

drug labeling and enhanced scrutiny of the safety of these classes of drugs.⁷ Victoza is approved with a REMS communication plan to inform prescribers about the potential risk of pancreatitis. Because GLP-1 acts on the pancreas to stimulate post-prandial insulin release, a mechanistic link to pancreatitis appears biologically plausible. Waist circumference (but not increased BMI in the referenced paper)²² and T2DM²³ have been reported to be independent risk factors for acute pancreatitis.

Patients with a history of idiopathic acute pancreatitis or chronic pancreatitis were excluded from the phase 3 trials and all suspected drugs were to be discontinued in case of suspicion of acute pancreatitis. If the diagnosis was confirmed, the patient was to be withdrawn from the trial.

7.5.1.1 Clinical Pharmacology Trial

No patients in the clinical pharmacology trial 3630 had a medical history of pancreatitis or other pancreas disorder. There were no adverse events of pancreatitis in this trial.

7.5.1.2 Weight Management Trials

In the phase 2 and 3 weight management trials, four patients (0.1%) in the liraglutide 3 mg group and three patients (0.2%) in the placebo group had a previous medical history of exocrine pancreas conditions ('pancreatic calcification', 'pancreatic cyst', 'pancreatic disorder', and 'pancreatitis chronic'). In addition, one patient (< 0.1%) treated with placebo had a history of 'pancreas divisum'.

Across the five phase 2 and 3 trials, the diagnostic criteria for acute pancreatitis were if at least two of the following three criteria were met: 1) characteristic abdominal pain, 2) amylase and/or lipase above 3× ULN and/or 3) characteristic findings on imaging of the pancreas (ultrasound, CT, MRI).

With exception of the phase 2 trial (trial 1807), which was completed prior to introduction of adjudication in the weight management program, and the first phase 3 trial (trial 1923), which was ongoing when adjudication was introduced, all suspected cases of pancreatitis were prospectively adjudicated with respect to confirmation of the diagnosis and classification as acute or chronic pancreatitis. In trial 1923, suspected cases of pancreatitis were adjudicated in a *post hoc* fashion following the same process (external, blinded evaluation) and charter as prospectively adjudicated events, to the extent possible. In trial 1807, pancreatitis was classified as a medical event of special interest (MESI) in year 2 of the extension of the trial, but events were not adjudicated.

²² Sadr-Azodi O, et al. Abdominal and total adiposity and the risk for acute pancreatitis: a population-based prospective cohort study. *Am J Gastroenterol* 2013; 108(1):133-9.

²³ Noel RA, et al. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2009; 32:834-8.

In order to identify potential events of pancreatitis not already identified by the investigator, during conduct of trials 1922, 3970, and 1839 the sponsor performed ongoing blinded searches in the clinical database for reported AEs of increased lipase/amylase with concomitant reporting of AEs of abdominal pain (occurring within a time window of +/- 30 days of the elevated lipase/amylase). Identified events were sent to a clinical research organization that performed an independent pre-evaluation and forwarded those events where pancreatitis was suspected to the external event adjudication committee (EAC) for adjudication.

In addition to adjudication, a predefined MedDRA search was performed among all AEs to identify events of pancreatitis or suspected pancreatitis using the SMQ term 'Acute pancreatitis' and HLT term 'Acute and chronic pancreatitis'. For the phase 3 trials, all events captured by the MedDRA search were adjudicated.

For the phase 2 trial, 1807, which did not include adjudication, the MedDRA search captured one event of 'pancreatitis acute'. This SAE occurred in patient 132006 (liraglutide 3 mg) on study day 299 (narrative included in Table 60).

In the phase 3 trials, a total of 26 events were sent for external adjudication (including *post hoc* adjudication for trial 1923). Of these 26, 21 were treatment-emergent and 20 occurred in the main treatment period. In the main treatment period, the proportion of patients with confirmed treatment-emergent pancreatitis was higher in those randomized to liraglutide; see the table below.

Table 58. Pancreatitis Events by EAC Category in the Main Treatment Period of the Phase 3 Weight Management Trials

	Lira 3 mg N=3291 PY=2898.6		Total lira N=3501 PY=3088.3		Placebo N=1843 PY=1527.7	
	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY
Events sent for adjudication	16 (0.5)	5.5	17 (0.5)	5.5	3 (0.2)	2.0
EAC confirmed events	7 (0.2)	2.4	7 (0.2)	2.3	1 (0.1)	0.6
Acute pancreatitis	7 (0.2)	2.4	7 (0.2)	2.3	1 (0.1)	0.6
Chronic pancreatitis	0	0	0	0	0	0

Source: ISS, Appendix 7.2, Table 181

Reviewer comment: This 4:1 adjudicated pancreatitis event rate imbalance (liraglutide vs. placebo) is very similar to the 4:1 imbalance based on AE monitoring seen in the Victoza pre-approval trials.²⁴

²⁴ Parks M and Rosebraugh C. Weighing risks and benefits of liraglutide – the FDA's review of a new antidiabetic therapy. N Engl J Med 2010; 362:774-7.

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Pancreatitis AEs were also more frequently reported as serious and severe in the liraglutide group as compared to the placebo group:

- Of the seven AEs confirmed by the EAC as acute pancreatitis in the liraglutide group, five (71%) were SAEs, whereas the one event in the placebo-treated group was not reported as serious. In addition, the one AE reported as acute pancreatitis in trial 1807 (not adjudicated), was reported as an SAE.
- Of the seven AEs confirmed as acute pancreatitis in the liraglutide group, five (71%) were reported as severe, one (14%) moderate, and one (14%) mild. The one case in the placebo-treated group was reported as mild. In addition, the one AE reported as acute pancreatitis in trial 1807 (not adjudicated), was reported as severe.

The following table describes the preferred terms sent to the EAC and subsequently confirmed as pancreatitis; note that no AEs of gastrointestinal signs and symptoms (i.e., 'abdominal pain', 'nausea', 'vomiting') were confirmed to be pancreatitis, although one AE reported as 'lipase increased' (associated with abdominal pain) was subsequently confirmed.

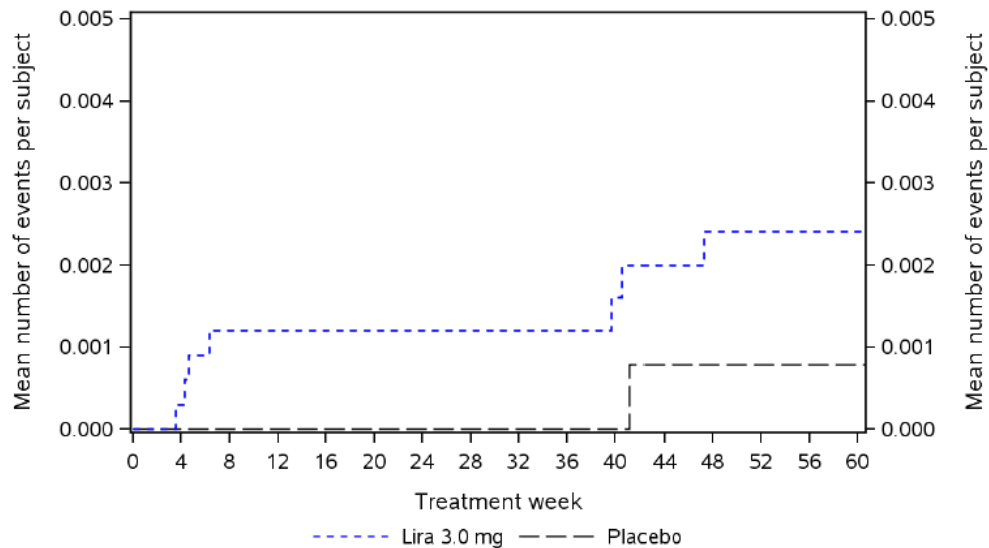
Table 59. Treatment-Emergent Adjudicated Pancreatitis or Suspicion of Pancreatitis Sent and Confirmed by System Organ Class and Preferred Term

	Lira 3 mg		Total lira		Placebo	
	Sent	Confirmed	Sent	Confirmed	Sent	Confirmed
Total	16	7 (43.8)	17	7 (41.2)	3	1 (33.3)
Gastrointestinal disorders	12	6 (50.0)	12	6 (50.0)	3	1 (33.3)
Abdominal hernia	0	0	0	0	1	0
Pancreatic disorder	1	0	1	0	1	1 (100)
Pancreatitis	1	1 (100)	1	1 (100)	0	0
Pancreatitis acute	5	5 (100)	5	5 (100)	0	0
Abdominal pain	2	0	2	0	0	0
Nausea	2	0	2	0	1	0
Vomiting	1	0	1	0	0	0
Investigations	4	1 (25.0)	5	1 (20.0)	0	0
Lipase increased	4	1 (25.0)	5	1 (20.0)	0	0

Source: ISS, Appendix 7.2, Table 178

Four of the seven events with liraglutide 3 mg occurred within the first 2 months (on days 25, 30, 32 and 44) and three of the events occurred after more than 9 months of treatment (on days 284, 299 and 331 respectively). The confirmed placebo event occurred after more than 9 months of treatment (on day 287).

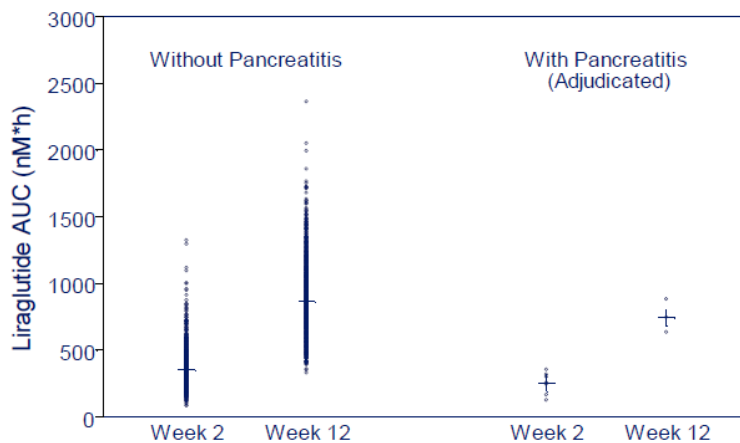
Figure 36. Mean Cumulative Event over Time Plot of Adjudicated Pancreatitis Events, Weight Management Pool



Source: ISS, Appendix 7.2, Figure 183

Liraglutide plasma exposure (based on model-derived area under the curve) at week 2 and week 12 was similar in liraglutide-treated patients with and without confirmed pancreatitis. The figure is based on patient exposure in trial 1839, which represent all 7 confirmed cases of pancreatitis with liraglutide.

Figure 37. Liraglutide Exposure in Patients with and without Pancreatitis (EAC Confirmed)



Source: ISS, Figure 2-41

Summaries of all AEs adjudicated as pancreatitis (or, for trial 1807, the one AE of pancreatitis by preferred term) are included in Table 60 below. Two of the liraglutide cases (trial 1839: patients 316022 and 132006) and the one placebo case (trial 1839: patient 214003) were associated with cholelithiasis. In comparing characteristics of

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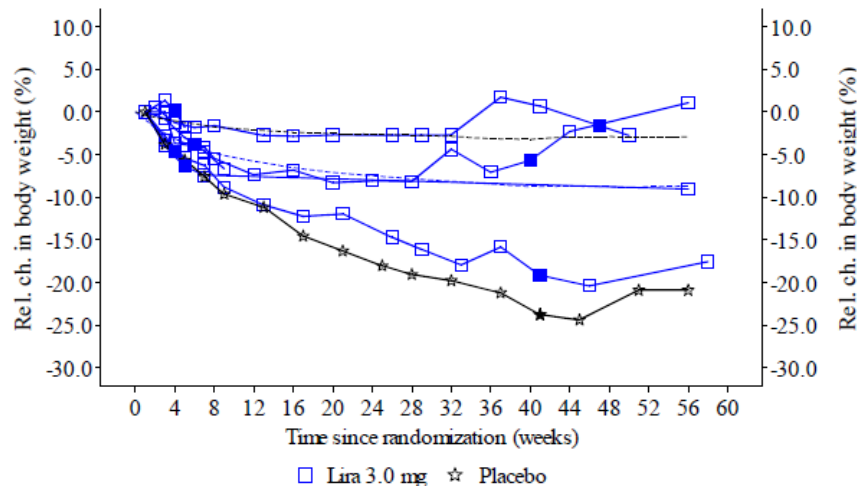
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patients with events to the overall population, mean age was similar (46.3 years), however, more patients with events tended to be male (~60%), had higher baseline BMI (44.8 kg/m²), and the majority (~85%) had pre-diabetes at baseline, but none had T2DM.

Weight loss prior to the event appeared similar in most patients with events compared to the overall population; however, 2 patients (1 on liraglutide 3 mg and 1 on placebo), who developed pancreatitis more than 9 months after initiation of treatment had greater weight losses than the overall population (20 to 25% of baseline body weight); see Figure 38.

Figure 38. Percent Change in Body Weight in Individual Patients with Adjudicated Pancreatitis Events, Weight Management Pool



Dotted lines represent mean weight curves for patients with no adjudicated pancreatitis

Solid symbols represent pancreatitis events

Source: ISS, Appendix 7.2, Figure 185

Table 60. Details of Pancreatitis Events

Subject ID/ trial ID/ Country Sex/Age/ BMI	Preferred term	Trial Period	Study day ^a / Exposure at onset/ Duration of event	Diagn. criteria fulfilled	EAC confirmed event (Y/N)	Withdrawal	SAE (Y/N)/ Severity/ Outcome	Details and medical history ^b
Treatment emergent events								
<i>Liraglutide 3.0 mg</i>								
409006/ trial 1839/ US/ M/52/62.9	Pancreatitis acute	Main	31/ 31 days/ 4 days	Abd. pain, enzymes	Yes	WC 5	Yes/ Severe/ Recovered	No history of cholelithiasis, smoking or alcohol abuse, elevated triglycerides or hypercalcaemia. No concomitant medication suspected to cause pancreatitis. Amylase at time of admission 833 U/L (ref. 28-100), lipase 690 U/L (ref. 22-51). Co-reporting of hepatitis. Ultrasound grossly normal and with no gallstones. Hospitalised for 4 days. Treatment consisted of nil per os and i.v. fluids.
461004/ trial 1839/ US/ M/51/32.7	Pancreatitis acute	Main	29/ 29 days/ 5 days	Abd. pain, enzymes	Yes	WC 5	Yes/ Severe/ Recovered	No history of cholelithiasis, smoking, alcohol abuse or hypercalcaemia. Previous history of hypertriglyceridemia, concomitantly treated with simvastatin. Amylase 447 U/L (ref. 20-112), lipase 866 U/L (ref. 0-60). No imaging performed. Subject not hospitalised due to event.
485023/ trial 1839/ US/ M/58/34.7	Pancreatitis acute	Main	43/ 43 days/ 2 days	Abd. pain, imaging	Yes	WC 5	No/ Severe/ Recovered	No history of cholelithiasis, smoking or alcohol abuse, elevated triglycerides or hypercalcaemia. No concomitant medication suspected to cause pancreatitis. Amylase 51 U/L (ref. 29-103), lipase 36 U/L (ref. 8-82.) at time of event. CT demonstrated uncomplicated acute pancreatitis involving the uncinate process (no focal fluid collection or necrosis). Was observed in hospital and discharged on the same day.
Subject ID/ trial ID/ Country Sex/Age/ BMI	Preferred term	Trial Period	Study day ^a / Exposure at onset/ Duration of event	Diagn. criteria fulfilled	EAC confirmed event (Y/N)	Withdrawal	SAE (Y/N)/ Severity/ Outcome	Details and medical history ^b
481034/ trial 1839/ US/ F/32/38.9	Pancreatitis acute	Main	24/ 24 days/ 2 days	Abd. pain, enzymes	Yes	WC 5	Yes/ Severe/ Recovered	No history of cholelithiasis, alcohol abuse or hypercalcaemia. Current smoker. No concomitant medication suspected to cause pancreatitis. Previously hypertriglyceridaemia, at time of event 179 mg/dL (ref. 35-135). Lipase at time of admission 898 U/L (ref. 23-300), the following day 244 U/L. Ultrasound normal. Was observed in hospital overnight and received i.v. fluids and pain medication.
316022/ trial 1839/ MX/ F/40/41.7	Pancreatitis	Main	283/ 283 days/ 9 days	Abd. pain, enzymes, imaging	Yes	WC 5	Yes/ Severe/ Recovered	Diagnosed with cholelithiasis at time of event. History of alcohol abuse, current smoker. Ultrasound performed on day of admission showed cholelithiasis and secondary acute pancreatitis in oedematous phase. Amylase at time of admission 712 U/L (ref. 30-118), lipase 5684 U/L (ref. 23-300). Eight days after hospitalisation laparoscopic cholecystectomy was performed. Discharged the following day.
426013/ trial 1839/ US/ F/51/48.6	Lipase increased	Main	277/ 277 days/ 15 days	Abd. pain, enzymes	Yes	Yes ^d	No/ Mild/ Recovered	No history of cholelithiasis, alcohol abuse, elevated triglycerides or hypercalcaemia. No concomitant medication suspected to cause pancreatitis. Previous smoker. Co-reporting of intermittent abdominal pain. CT scan performed after 204 days of treatment showed no acute findings. Amylase 130 U/L (ref. 20-112), lipase 213 U/L (ref. 0-60) reported after 278 days of treatment. Amylase and lipase normalised on continued treatment. No hospitalisation, early treatment consisted of antibiotics and pain medication.

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Subject ID/ trial ID/ Country Sex/Age/ BMI	Preferred term	Trial Period	Study day ^a / Exposure at onset/ Duration of event	Diagn. criteria fulfilled	EAC confirmed event (Y/N)	Withdrawal	SAE (Y/N)/ Severity/ Outcome	Details and medical history ^b
334004/ trial 1839/ RU/ M/40/54.0	Pancreatitis acute	Main	330/ 330 days/ 92 days	Abd. pain, imaging	Yes	WC 5	Yes/ Moderate/ Recovered	No history of cholelithiasis, alcohol abuse, smoking, elevated triglycerides or hypercalcaemia. No concomitant medication suspected to cause pancreatitis. Co-reporting of intermittent abdominal pain. Ultrasound performed at time of admission showed acute pancreatitis, oedematous form. 5 days later pancreas appeared normal with no focal or destructive lesions. Gastroduodenoscopy showed chronic diffuse gastritis, duodenitis and duodenogastric reflux. Amylase 8.0 mg/L (no ref.). Lipase 136 U/L (ref. 0-60 U/L) the day after discharge from hospital. Hospitalised for 12 days. Treatment consisted of i.v. fluids, spasmolytics, antibiotics, protease inhibitors and pain medication.
132006/ trial 1807/ DK/ F/42/34.2	Pancreatitis acute	Main	299/299 days/ 10 days	Abd. pain	No ^c	Yes	Yes/ Severe/ Recovered	Co-reported with cholelithiasis. No history of alcohol abuse, smoking, elevated triglycerides or hypercalcaemia. No concomitant medication suspected to cause pancreatitis. Ultrasound showed several concrements in the gallbladder. Bile ducts and pancreas presented normal. MRCP showed normal bile ducts. Blood samples revealed high levels of amylase, ALT, bilirubin and blood phosphatase upon admission (values not available). Hospitalised for 2 days. Treatment consisted of morphine, anti-emetics and fluids. Elective cholecystectomy performed 1 month later.
Subject ID/ trial ID/ Country Sex/Age/ BMI	Preferred term	Trial Period	Study day ^a / Exposure at onset/ Duration of event	Diagn. criteria fulfilled	EAC confirmed event (Y/N)	Withdrawal	SAE (Y/N)/ Severity/ Outcome	Details and medical history ^b
<i>Placebo</i>								
241003/ trial 1839/ DK/ F/55/35.5	Pancreatic disorder	Main	287/287/Unknown	Abd. pain, imaging	Yes	No	No/ Mild/ Recovered	Co-reporting of cholelithiasis at time of event. According to the medical records, the subject has a history of gall stone attacks beginning after trial start. No history of alcohol abuse, elevated triglycerides or hypercalcaemia. Current smoker. No concomitant medication suspected to cause pancreatitis. Ultrasound showed solitary gallstone and possible oedematous head of pancreas. MRCP the following day showed no focal lesions in the pancreas, but slight oedema of body of pancreas. Amylase and lipase at time of admission normal. 3 days later amylase was 319 U/L (ref. 25-120 U/L). The subject was hospitalised due to the co-reported event of 'cholelithiasis', which was rated as a SAE. Treatment consisted of observation and pain medications. Elective cholecystectomy was planned.
Events reported during follow up								
Re-randomised follow-up period – liraglutide/placebo								
363006/ trial 1839/ ZA/ F/41/36.2	Pancreatitis acute	FU	404/ 12 days after last dose of liraglutide/ 16 days	Abd. pain, enzymes	Yes	Yes	Yes/ Severe/ Recovered	No history of cholelithiasis, alcohol abuse, smoking, elevated triglycerides or hypercalcaemia. Concomitantly treated with simvastatin. Two days prior to admission: amylase 2074 IU/L (ref. 20-112 IU/L), lipase 3007 IU/L (ref. 0-60), CT scan showed non-specific basal changes with no evidence of pancreatitis, gallstones, necrosis, gastrointestinal haemorrhage or other visceral abnormalities. Hospitalised for 3 days. Treatment consisted of nil per os and i.v. fluids.

a. For EAC confirmed events, study day and exposure days are based on the EAC confirmed dates. b. Details are based on information in the case narratives from the safety database and from source documentations. c. Events from phase 2 trial 1807 were not adjudicated. d. Withdrawn due to 3 AEs ('elevated lipase', 'elevated amylase' and 'abdominal pain') and not the specific withdrawal criterion for acute pancreatitis although these AEs were diagnostic for pancreatitis

Source: ISS, Table 2-63

In addition to the above, two cases of acute pancreatitis in patients treated with liraglutide 3 mg have been confirmed in the ongoing extension of trial 1839:

Table 61. Details of EAC-Confirmed Events of Pancreatitis, Ongoing 1839 Extension

Subject ID/ trial ID/ Sex/Age/ BMI	Preferred term	Study day ^a / Duration of event	Diagn. criteria fulfilled	EAC confirmed event (Y/N)	Withdrawal	SAE (Y/N)/ Severity/ Outcome	Details and medical history ^b
Liraglutide 3.0 mg							
142003/ 1839-ext/ F/62/38.7	Gastro- enteritis	410/ Unknown	Abd. pain, enzymes	Yes	Withdrawn due to suspicion of acute pancreatitis	Y/ Unknown/ Recovered	Hyperlipidemia, no history of gallbladder disease or alcoholism. The subject reported moderate 'gastroenteritis' after 386 days of treatment. Trial drug was temporarily discontinued, whereas simvastatin and citalopram were started. Lipase level was 567 U/L (ref. range 73–393 U/L) which had decreased to normal levels one week later. The subject had trial drug reintroduced and after approximately 2½ weeks she was hospitalized due to strong upper abdominal pain and a preliminary diagnosis of pancreatitis. Lipase level upon admission was 282 U/L (ref. range 8–78 U/L), different laboratory than above. CT scan showed normal pancreas. Gastroscopy showed antrum gastritis with reflux esophagitis. Hospitalized for 3 days. Treatment consisted of i.v. fluids, spasmolytics, anti-emetics, protease inhibitors and pain medication. The subject recovered from the event. According to Atlanta classification, the pancreatitis was 'mild'. The EAC revised the onset date from 04 July 2012 (gastroenteritis reported by the investigator) to (b) (6) (b) (subject presented with signs and symptoms compatible with the diagnosis of pancreatitis (Appendix 7.2, Listing 21). Consequently, the onset date for EAC confirmed pancreatitis changed from the main part of trial 1839 to 1839-ext. The event is still listed in tables and listings for the main part of trial 1839 in the ISS – except for tables and listings of adjudicated pancreatitis events, where the event is listed for 1839-ext in this 120-day safety update.
418022/ 1839-ext/ F/48/45.1	Pancreatitis	626/ 9	Abd. pain, imaging	Yes	Withdrawn due to the event	Yes/ Moderate/ Recovered	Current smoker, medical history of hyperlipidemia, no history of gallstone disease or alcoholism. The subject developed severe abdominal pain on day 626 which was treated shortly with ciprofloxacin and metronidazole. Due to an elevated white blood count she was seen in hospital and CT scan confirmed acute pancreatitis involving the pancreatic head. These findings were subsequently confirmed with MRCP and MRI. According to Atlanta classification, the pancreatitis was 'mild'. Liver, gallbladder and biliary tree presented normal. No increased lipase activity levels were observed. The subject was hospitalized for 4 days and treated with i.v. fluids. She was considered recovered 8 days after onset of abdominal pain.

abd: abdominal; BMI: body mass index; CT: computerized axial tomography; EAC: event adjudication committee; F: female; MRCP: magnetic resonance cholangiopancreatography; SAE: serious adverse event; Y: yes; WC 5: withdrawal criteria 5 (acute pancreatitis); WD: withdrawn.

a. For EAC confirmed events, study day and exposure days are based on the EAC confirmed dates if available. b. Details are based on information in the case narratives from the safety database and from source documentations.

Source: 120-day safety update, Table 2-28

7.5.1.2.1 Amylase and Lipase

Serum amylase and lipase activity was assessed at screening, randomization, approximately once every 3 months during treatment, end-of treatment, and at follow-up in the phase 3 trials (1839, 1922, 1923, and 3970) as potential biomarkers for pancreatitis. Serum amylase or lipase activity levels 3× ULN or greater, irrespective of symptoms from the gastrointestinal tract and seriousness, were to be reported as a medical event of special interest (MESI) in the phase 3 trials, but were to lead to withdrawal from treatment only if acute pancreatitis was suspected.

The results of amylase and lipase testing from the phase 3 weight management trials are presented below: amylase elevations were rare; approximately twice as many patients treated with liraglutide had a lipase elevation $3\times$ ULN or greater as compared to patients treated with placebo.

Mean baseline serum amylase activity was similar in patients treated with liraglutide 3 mg and placebo (approximately 53 U/L). Mean serum amylase was consistently higher with liraglutide 3 mg than with placebo throughout the treatment period; the change from baseline to end-of-treatment was 7.4 U/L for patients treated with liraglutide 3 mg versus 5.5 U/L for patients treated with placebo.

Figure 39. Serum Amylase over Time, Weight Management Pool

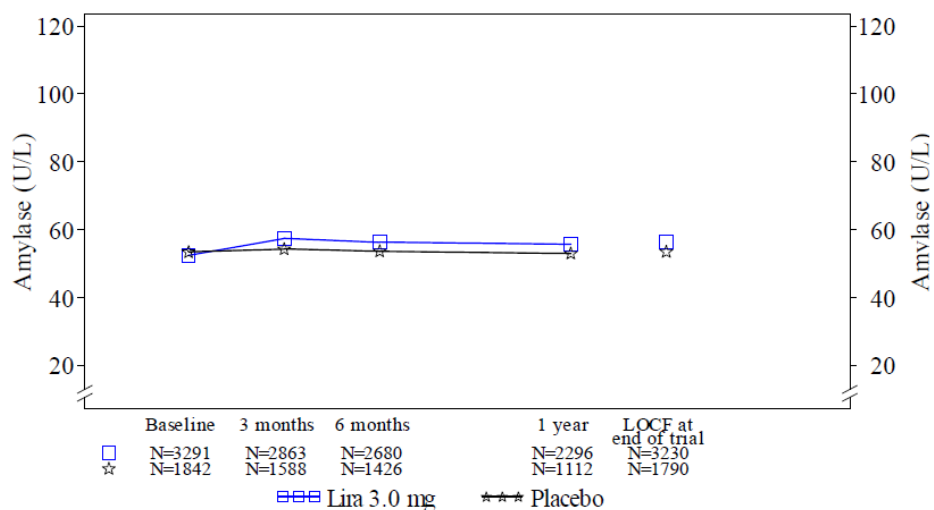


Figure is based on trials 1839, 1922, 3970 and 1923.
Note that trial 3970 is a 32 week trial.

Source: ISS, Figure 2-45

During the 1-year treatment period, more patients on liraglutide 3 mg than on placebo had an amylase value above the upper limit of normal (7.7% versus 4.9%); however, few patients (liraglutide 3 mg 0.3%, placebo 0.2%) had amylase at least $2\times$ ULN. See Table 62 for enumeration of patients with amylase at least $3\times$ ULN.

Table 62. Percentage of Patients with Amylase at Least Three Times the Upper Limit of Normal, Weight Management Phase 3 Trials

	Lira 3 mg		Placebo	
	N	n (%)	N	n (%)
Number of patients	3384		1941	
Amylase $\geq 3 \times$ ULN				
Baseline	3291	0	1842	0
3 months*	2863	0	1588	1 (<0.1)
6 months†	2680	1 (<0.1)	1426	0
1 year‡	2296	1 (<0.1)	1112	0
LOCF at end of trial§	3230	1 (<0.1)	1790	0
Any post-baseline value	2909	2 (<0.1)	1609	1 (<0.1)
Table is based on trials 1839, 1922, 3970, and 1923				
* Measurements at wk 12 (3970), wk 14 (1923), or wk 16 (1839, 1922)				
† Measurements at wk 26 (1923), wk 28 (1922, 1839), and wk 32 (3970)				
‡ Measurements at wk 56 (1839, 1922, 1923)				
§ Wk 32 for trial 3970 and wk 56 for trials 1839, 1922, and 1923				

Source: ISS, Appendix 7.5, Tables 131

Consistent with this finding, more patients reported AEs of ‘amylase increased’ in the liraglutide 3 mg group (1.4%) as compared to the placebo group (0.7%). More patients reported AEs of ‘hyperamylasemia’ in the liraglutide 3 mg group (0.2%) as compared to the placebo group (none). None of the AEs were serious.

Mean baseline serum lipase activity was similar in patients treated with liraglutide 3 mg and placebo (approximately 33 U/L). Mean serum lipase was consistently higher with liraglutide 3 mg than with placebo throughout the treatment period; the change from baseline to end-of-treatment was 11.5 U/L for patients treated with liraglutide 3 mg versus 4.9 U/L for patients treated with placebo.

Figure 40. Serum Lipase over Time, Weight Management Pool

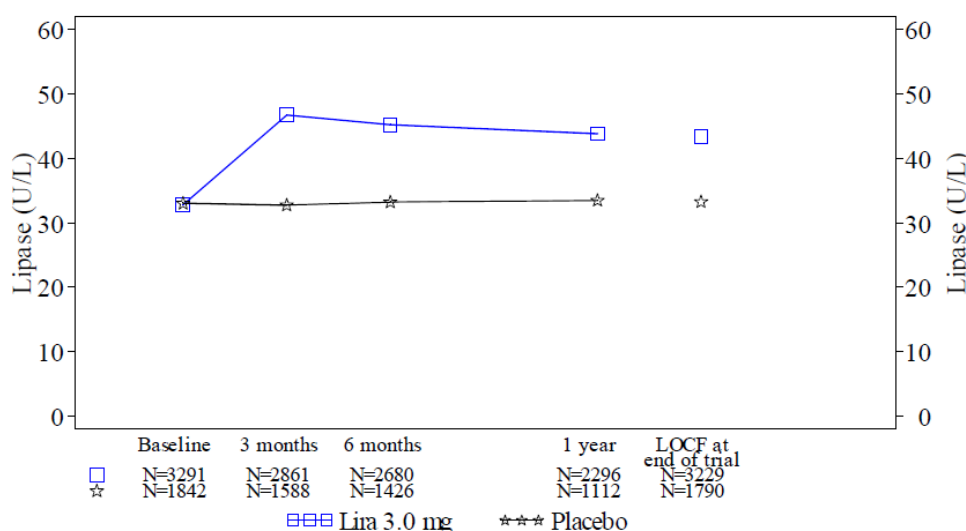


Figure is based on trials 1839, 1922, 3970 and 1923.
Note that trial 3970 is a 32 week trial.

Source: ISS, Figure 2-46

During the 1-year treatment period, more patients on liraglutide 3 mg than on placebo had a lipase value above the upper limit of normal (36.9% versus 11.7%), at least 2× ULN (5.7% vs. 2.6%), and at least 3× ULN (2.1% vs. 1.0%).

Table 63. Percentage of Patients with Lipase at Least Three Times the Upper Limit of Normal, Weight Management Phase 3 Trials

	Lira 3 mg		Placebo	
	N	n (%)	N	n (%)
Number of patients	3384		1941	
Lipase ≥ 3× ULN				
Baseline	3291	9 (0.3)	1842	7 (0.4)
3 months*	2861	24 (0.8)	1588	7 (0.4)
6 months†	2680	23 (0.9)	1426	6 (0.4)
1 year‡	2296	20 (0.9)	1112	5 (0.4)
LOCF at end of trial§	3229	27 (0.8)	1790	8 (0.4)
Any post-baseline value	2909	60 (2.1)	1609	16 (1.0)

Table is based on trials 1839, 1922, 3970, and 1923
 * Measurements at wk 12 (3970), wk 14 (1923), or wk 16 (1839, 1922)
 † Measurements at wk 26 (1923), wk 28 (1922, 1839), and wk 32 (3970)
 ‡ Measurements at wk 56 (1839, 1922, 1923)
 § Wk 32 for trial 3970 and wk 56 for trials 1839, 1922, and 1923

Source: ISS, Appendix 7.5, Tables 131 and 132

Consistent with this finding, more patients reported AEs of ‘lipase increased’ in the liraglutide 3 mg group (5.3%) as compared to the placebo group (2.2%). None of the AEs were serious. One case of lipase increased (with concomitant event of abdominal pain) was confirmed as pancreatitis by the EAC (patient 461004 in trial 1839; details in Table

60, above). Slightly more patients had AEs of hyperlipasemia in the liraglutide 3 mg group (0.1%) as compared to the placebo group (<0.1%); one event was considered an SAE for unclear reasons.

7.5.1.3 Diabetes Program

In the diabetes program, pancreatitis has been an ongoing event of interest given the post-marketing reports for the GLP-1 receptor agonists and the DPP-4 inhibitors, as well as an imbalance in the Victoza clinical program (see above). The sponsor conducted a MedDRA search to identify pancreatitis AEs in the diabetes trials; these events were not adjudicated. As seen by the listing of preferred terms, AEs of chronic pancreatitis account for some of the imbalance seen. Pancreatitis AEs were considered serious, except for two non-serious events of chronic pancreatitis reported in the liraglutide group.

Table 64. Pancreatitis or Suspicion of Pancreatitis (Predefined SMQ Search), Diabetes Pool

	Total lira N=7037	Comparator total N=3677
	n (%)	n (%)
Pancreatitis AEs	9 (0.1)	2 (<0.1)
Pancreatitis	3 (<0.1)	1 (<0.1)
Pancreatitis chronic	3 (<0.1)	0
Pancreatitis acute	2 (<0.1)	1 (<0.1)
Edematous pancreatitis	1 (<0.1)	0

Source: Supplementary AE Report, Appendix 1, Table 39

7.5.1.4 Literature Reports

Six case reports of pancreatitis associated with liraglutide were identified in a literature review.^{25,26, 27,28,29,30} One of these case reports was only available in Spanish and was therefore not reviewed;²⁷ the other five cases are summarized below.

- Lee, et al.²⁵ described the case of a 60-year-old female with T2DM treated with liraglutide 1.8 mg daily, metformin, pioglitazone, glimepiride, and insulin. The

²⁵ Lee PH, et al. Acute pancreatitis associated with liraglutide. *Ann Pharmacother*. 2011; 45:e22

²⁶ Knezevich E, et al. Liraglutide associated acute pancreatitis. *Am J Health Syst Pharm*. 2012; 69(5): 386-9.

²⁷ Artero A, et al. [Acute pancreatitis in a patient treated with liraglutide.] *Med Clin (Barc)* 2013 Oct 19; 141(8): 368-9.

²⁸ Bourezane H, et al. Late and severe acute necrotizing pancreatitis in a patient with liraglutide. *Thérapie* 2012; 67(6): 539-43.

²⁹ Famularo G, et al. Pancreatitis during treatment with liraglutide. *JOP* 2012; 13(5): 540-1.

³⁰ Nakata H, et al. Pancreatitis with pancreatic tail swelling associated with incretin-based therapies detected radiologically in two cases of diabetic patients with end-stage renal disease. *Intern Med* 2012; 51: 3045-9.

patient had been on exenatide for approximately 4 years. Twenty-three days prior to onset of symptoms, the patient's endocrinologist discontinued exenatide and prescribed liraglutide (apparently without dose titration). Of note, the patient had a history of gallstone pancreatitis 11 years prior requiring hospitalization and a cholecystectomy. There was no history of alcoholism. Other medical history included obesity, hypothyroidism, hyperlipidemia, and diabetic neuropathy. Other medications included levothyroxine, simvastatin, gabapentin, aspirin, and spironolactone as needed for edema (not taken for the last 3 weeks). The patient presented to the emergency department with a 16-hour history of mid-epigastric pain radiating to her back. Initial laboratory studies included lipase 478 U/L (8-78) and amylase 44 U/L (25-125). Triglyceride concentration was 62 mg/dL. A CT scan revealed pancreatic calcification suggestive of previous episodes of pancreatitis, but no evidence of acute inflammation or pancreatic necrosis. Upon admission, all diabetes medications were withheld with the exception of insulin. She was treated by withholding oral intake and with IV hydration. On day 3, she experienced recurrent pain, which resolved the next day. She was discharged on day 5 on all diabetes medications except liraglutide. Pancreatic enzymes were added to her regimen. Six months after discharge, the patient remained asymptomatic with no recurrence of symptoms since liraglutide was discontinued.

Reviewer comment: This case is notable for the temporal association with liraglutide initiation, as well as the fact that the event occurred after an exenatide to liraglutide switch. This case is confounded by the patient's history of gallstone pancreatitis and CT scan suggestive of chronic pancreatitis. It is unclear if liraglutide could have contributed to a chronic pancreatitis exacerbation.

- Knezevich, et al.²⁶ reported the case of a 53-year-old man with T2DM, hyperlipidemia, hypertension, peripheral neuropathy, erectile dysfunction, and obesity. He had a history of chronic alcohol use but reportedly had been abstinent for over 2 years. Medications included aspirin, metformin, simvastatin, tadalafil as needed, glimepiride, and liraglutide 1.2 mg daily. The patient's diabetes was poorly controlled, (HbA1c 14.4%), and he had previously been on exenatide (1 year prior), insulin glargine, and sitagliptin. Liraglutide was initiated approximately 2 months before presentation. He presented to the emergency department with upper abdominal pain and nausea. Serum amylase was 3963 U/L and serum lipase was greater than 15,000 U/L. Triglycerides were 149 mg/dL. A CT scan showed peripancreatic inflammation. Liraglutide and all oral medications were discontinued and he was treated with IV hydration and analgesia. He was discharged on hospital day 8, and follow-up with his endocrinologist revealed no symptoms of abdominal pain, a normal physical examination, and amylase and lipase of 140 and 617 U/L, respectively.
- Bourezane, et al.²⁸ described the case of a 63-year-old man with T2DM, obesity, hypertension, hypercholesterolemia, myocardial ischemia, and prostatic

adenomectomy, who was admitted to the hospital with a 24-hour history of mid-epigastric pain, vomiting, and diarrhea. There was no hypertriglyceridemia, gallstones, or alcohol abuse reported. Concomitant medications included: aspirin, metformin, amlodipine, rosuvastatin, disoprolol, and glicazide. Liraglutide was started 11 months prior, and had been escalated from 0.6 mg to 1.2 mg and then to 1.8 mg daily one month prior to admission. Laboratory tests on admission included lipase 2579 U/L (22-58), amylase 2514 U/L (28-100), glucose 321 mg/dL, AST 419 U/L, ALT 293 U/L, GGT 636 U/L, ALP 125 U/L, total bilirubin 2.29 mg/dL, direct bilirubin 0.79 mg/dL, and WBC 20,000/ μ L. Ultrasound showed no evidence of dilated intrahepatic or extrahepatic biliary ducts, no gallstones, and no evidence of steatosis. Abdominal CT scan showed infiltration of peripancreatic fat and presence of fluid collections, with no parenchymal pancreatic necrosis. The patient's diabetes medications were withheld and the patient was managed with insulin, bowel rest, IV hydration, and analgesics. Over 3 days, biochemical parameters improved; however, the clinical condition worsened, with aggravation of pain, anxiety and delirium, increased CRP (364 mg/L), and renal failure (creatinine 3.7 mg/dL). Repeat CT scan showed infiltration of peripancreatic fat with increased fluid collections. On day 9, the patient developed ecchymosis of the left flank, consistent with Grey-Turner's sign. On day 35, the patient developed back pain and fever. A CT scan showed a large and compressive pseudocyst, which was drained percutaneously. Retroperitoneal necrosectomy was conducted on day 62 and he was discharged on day 76 on pancreatic enzymes and insulin.

- Famularo, et al.²⁹ described the case of a 67-year-old man with T2DM, but no other relevant medical history, who presented with a 10-day history of nausea, vomiting, and epigastric pain. Five months prior to admission, liraglutide 1.2 mg daily had been added to metformin and glicazide. Laboratory data included amylase 877 U/L, lipase 653 U/L, ALT 275 U/L, AST 326 U/L, total bilirubin 2.6 mg/dL, and conjugated bilirubin 0.8 mg/dL. MRI showed a moderately enlarged and edematous pancreas and sludge in the gallbladder without biliary duct dilatation. Liraglutide was discontinued and the patient was managed with bowel rest and IV hydration. Five days after readmission he was symptom-free and enzymes returned to normal.
- Nakata, et al.³⁰ reported two cases of pancreatitis associated with use of incretin-based therapies; only of these patients was exposed to liraglutide and will be described further. This was a 75-year-old woman with T2DM and end-stage renal disease on hemodialysis. She had no history of pancreatitis, cholelithiasis, alcohol consumption, hypertriglyceridemia, or abnormal corrected calcium concentration. Because of hypoglycemia on insulin, she was switched to glicazide and vildagliptin. One month later (approximately 10 months prior to presentation), vildagliptin was switched to liraglutide 0.6 mg daily. She presented with a 3-month history of nausea. Amylase was 1649 U/L and abdominal CT showed swelling of the pancreatic tail without peripancreatic fat stranding. MRI showed no inflammatory or edematous changes. Magnetic resonance cholangiopancreatography (MRCP)

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showed no abnormalities. CA19-9 was 18.1 U/mL (normal: < 3.4). Liraglutide was discontinued, and the patient's nausea improved and pancreatic enzymes decreased.

Reviewer comment: This case is notable for nausea as the only presenting symptom, which is a common adverse event associated with liraglutide. It is unclear what led the clinicians to otherwise suspect pancreatitis in this case.

7.5.2 Gallbladder Events

Obesity and rapid weight loss are associated with an increased risk for gallstone formation.³¹ It has recently been suggested that exenatide, another GLP-1 receptor agonist, reduces cholecystokinin-induced gallbladder emptying compared with placebo in fasting healthy individuals.³²

Gallstone disorders were not identified as a safety area of concern in the T2DM program; nevertheless, gallstone disease (biliary colic or acute cholecystitis) was pre-defined as a MESI in the weight management program. Events were identified by MedDRA search and were not adjudicated.

7.5.2.1 Clinical Pharmacology Trial

No AEs related to the gallbladder were reported.

7.5.2.2 Weight Management Program

In the weight management pool, the proportion of patients with gallstone events and the rate of events were consistently higher with liraglutide 3 mg than placebo (Table 65). Approximately 75% of patients reporting events of cholelithiasis and cholecystitis had a cholecystectomy due to the events.

³¹ Stinton LM, et al. Epidemiology of gallstones. *Gastroenterol Clin North Am* 2010 Jun; 39(2): 157-69, vii.

³² Keller J, et al. Effect of exenatide on cholecystokinin-induced gallbladder emptying in fasting healthy subjects. *Regul Pept* 2012; 179(1-3):77-83.

Table 65. 'Acute Gallstone Disease' Identified by MedDRA Search, Weight Management Pool

	Lira 3 mg N=3384 PY=2974.3		Total lira N=3872 PY=3372.7		Placebo N=1941 PY=1600.9	
Overall System organ class High level group term	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY	n (%)	Rate/ 1000 PY
Acute Gallstone Disease*	79 (2.3)	31	88 (2.3)	30	17 (0.9)	12
Hepatobiliary disorders	74 (2.2)	29	80 (2.1)	27	16 (0.8)	11
Gallbladder disorders	70 (2.1)	26	75 (1.9)	25	13 (0.7)	9
Cholelithiasis	51 (1.5)	18	55 (1.4)	17	10 (0.5)	7
Cholecystitis acute	14 (0.4)	5	15 (0.4)	4	2 (0.1)	1
Cholecystitis	7 (0.2)	2	7 (0.2)	2	1 (<0.1)	1
Gallbladder disorder	2 (<0.1)	<1	2 (<0.1)	<1	0	0
Cholecystitis chronic	1 (<0.1)	<1	1 (<0.1)	<1	1 (<0.1)	<1
Bile duct disorders	6 (0.2)	2	7 (0.2)	2	3 (0.2)	2
Biliary colic	3 (<0.1)	1	4 (0.1)	1	3 (0.2)	2
Bile duct stone	2 (<0.1)	<1	2 (<0.1)	<1	0	0
Bile duct obstruction	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Hepatic and hepatobiliary disorders	1 (<0.1)	<1	1 (<0.1)	1	0	0
Hyperbilirubinemia	1 (<0.1)	<1	1 (<0.1)	1	0	0
Investigations	4 (0.1)	1	6 (0.2)	2	2 (0.1)	1
Enzyme investigations NEC	3 (<0.1)	1	4 (0.1)	1	1 (<0.1)	<1
Blood alkaline phosphatase increased	3 (<0.1)	1	4 (0.1)	1	1 (<0.1)	<1
Hepatobiliary investigations	1 (<0.1)	<1	2 (<0.1)	<1	1 (<0.1)	<1
Blood bilirubin increased	1 (<0.1)	<1	2 (<0.1)	<1	1 (<0.1)	<1
Gastrointestinal disorders	2 (<0.1)	<1	3 (<0.1)	<1	0	0
Gastrointestinal signs and symptoms	2 (<0.1)	<1	3 (<0.1)	<1	0	0
Abnormal feces	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Feces pale	1 (<0.1)	<1	2 (<0.1)	<1	0	0
* Predefined SMQ search						

Source: ISS, Appendix 7.2, Table 203

None of the events were fatal. A higher proportion of patients treated with liraglutide 3 mg had SAEs than those treated with placebo: more than half of the events reported with liraglutide 3 mg (48 of 91 events) were SAEs, whereas SAEs comprised one-third (6 of 20 events) identified with placebo. Preferred terms of SAEs reported in patients treated with liraglutide 3 mg included cholelithiasis (0.8%), cholecystitis acute (0.4%), cholecystitis (0.1%), bile duct obstruction (<0.1%), bile duct stone (<0.1%) and biliary colic (<0.1%). With placebo, SAEs of cholelithiasis (0.3%) and cholecystitis (<0.1%) were reported.

Seven patients (0.2%) treated with liraglutide were withdrawn from the trials due to events of 'acute gallstone disease' (corresponding to approximately 9% of patients with an event), whereas no patients treated with placebo were withdrawn. Events leading to withdrawal included cholelithiasis (3 patients), cholecystitis acute (2 patients), cholecystitis (1 patient), and bile duct stone (1 patient). In addition, 12 events of

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cholelithiasis and 9 events of cholecystitis led to temporary withdrawal of liraglutide 3 mg, whereas 2 events of cholelithiasis and 1 event of cholecystitis led to temporary withdrawal of placebo.

Of the 22 events of treatment-emergent cholecystitis ('cholecystitis' and 'cholecystitis acute') reported with liraglutide, 13 events were rated as severe, 8 events as moderate and 1 event was mild in severity. Cholecystectomy was performed in the majority (19 of 22 events) of the cases reported with liraglutide. The majority of cholecystectomies were elective. The action taken to trial product was 'no change' for the majority of events. A total of 9 events led to temporary withdrawal of liraglutide and 3 events led to permanent withdrawal from the trial. A total of 3 patients treated with placebo had events of cholecystitis, 2 were considered severe and 1 moderate. One event led to temporary withdrawal of placebo treatment. One event of cholecystitis with placebo was reported as an SAE.

Because gallstone disease is currently not an identified labeled adverse reaction for Victoza, one may question whether the AE identified in the weight management program could be related to dose, exposure, or magnitude of weight loss.

Biliary-related events (as assessed from preferred terms in the 'Hepatobiliary disorders' SOC) occurred too infrequently in the dose-ranging trial 1807 (52-week data) to make a determination of dose-relatedness, although the liraglutide 3 mg group appeared to have more events than the other dose groups.

Table 66. Biliary Events, Trial 1807

	Placebo N=98	Lira 1.2 N=95	Lira 1.8 N=90	Lira 2.4 N=93	Lira 3 N=93	Orlistat N=95
Cholelithiasis	0	1 (1.1)	1 (1.1)	0	2 (2.2)	1 (1.1)
Cholecystitis acute	0	0	1 (1.1)	0	1 (1.1)	0
Biliary colic	0	0	0	0	1 (1.1)	0

Source: NN8022-1807 Clinical Trial Report (Interim Trial Report), Table 14.3.1.2

In trial 1922, which evaluated both the 1.8 mg and the 3 mg dose, biliary-related events (as assessed from preferred terms in the 'Hepatobiliary disorders' SOC) were similar between the doses.

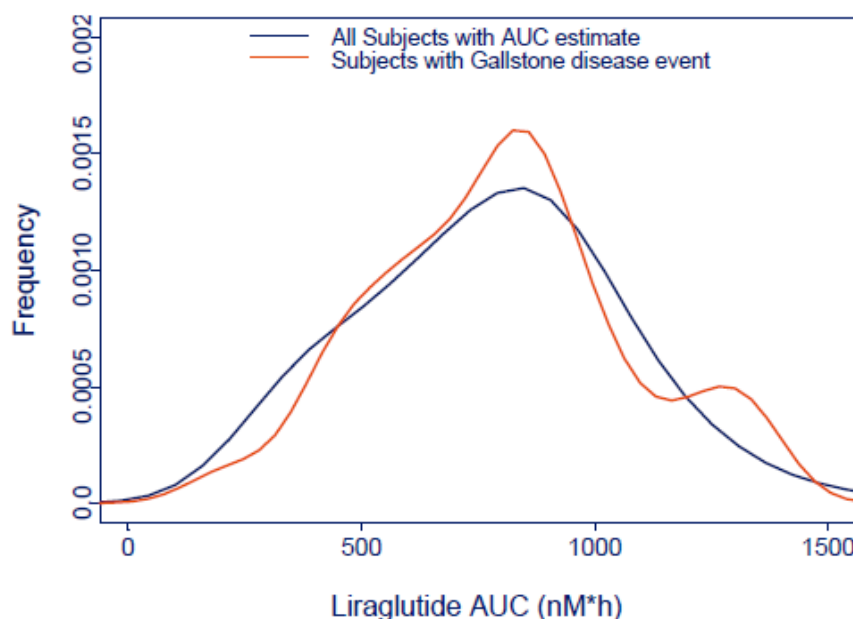
Table 67. Biliary Events, Trial 1922

	Lira 3 mg N=422	Lira 1.8 mg N=210	Placebo N=212
Gallbladder disorders	4 (0.9)	2 (1.0)	1 (0.5)
Cholelithiasis	3 (0.7)	2 (1.0)	1 (0.5)
Cholecystitis	1 (0.2)	0	0
Cholecystitis acute	1 (0.2)	0	0
Bile duct disorders	1 (0.2)	1 (0.5)	0
Bile duct obstruction	1 (0.2)	0	0
Biliary colic	0	1 (0.5)	0

Source: NN8022-1922, Table 14.3.1.15

The sponsor evaluated gallstone-related AEs by liraglutide exposure to determine if the events were possibly exposure-related. The distribution of liraglutide AUC estimates for patients with gallstone disease events in trials 1839 and 1922 was compared to the distribution of AUC estimates in the entire trial population. Most patients achieved steady-state liraglutide concentrations at the time where gallstone events occurred. Exposure was obtained as model-derived AUC estimates in liraglutide-treated patients in trials 1922 and 1839 using the last observed value either at week 2 (dose escalation) or later (at steady state) for each patient. A total of 67 patients with gallstone-related events were included. The figure below suggests similar (although not exact) distributions of liraglutide exposure in patients with and without gallstone events.

Figure 41. Distributions of Liraglutide Exposures for the Entire Population and Patients with a Gallstone Disease Event, Trials 1839 and 1922



Source: Modeling Report – Population PK and Exposure-Response Analysis, Figure 20

An additional consideration is whether the AE is associated with weight loss, which could at least partially explain the increased incidence in the liraglutide group. The proportion of patients with events and rates of events increase with degree of weight loss both with liraglutide 3 mg and placebo; however, for similar degrees of weight loss response at end-of-trial, a higher proportion of liraglutide-treated patients experienced events. As noted by the sponsor, this suggests that degree of weight loss might not explain the entire difference in acute gallstone disease AEs between treatment groups.

Reviewer comment: The potential impact of rate of weight loss, however, is not addressed in this analysis.

Table 68. AEs of Acute Gallstone Disease by Weight Loss Group, Weight Management Pool

	Lira 3 mg		Placebo	
	N	n (%)	N	n (%)
Acute gallstone disease, total	3384	79 (2.3)	1941	17 (0.9)
> 10% weight loss	1031	35 (3.4)	165	3 (1.8)
5-10% weight loss	958	27 (2.8)	297	2 (0.7)
0-5% weight loss	1020	11 (1.1)	763	5 (0.7)
Weight gain	291	3 (1.0)	665	7 (1.1)

Source: ISS, Table 2-74

7.5.2.3 Diabetes Program

A similar proportion of patients in liraglutide and placebo groups from the diabetes trials included in this NDA reported gallbladder-related AEs.

Table 69. Acute Gallstone Disease Event (Predefined SMQ Search) by Preferred Term, Diabetes Pool

	Total lira N=7037	Comparator total N=3677
	n (%)	n (%)
Gallbladder SMQ	55 (0.8)	28 (0.8)
Cholelithiasis	19 (0.3)	14 (0.4)
Blood alkaline phosphatase increased	9 (0.1)	2 (<0.1)
Biliary colic	6 (<0.1)	3 (<0.1)
Cholecystitis	4 (<0.1)	4 (0.1)
Blood bilirubin increased	3 (<0.1)	3 (<0.1)
Cholecystitis acute	3 (<0.1)	1 (<0.1)
Hyperbilirubinemia	3 (<0.1)	0
Abnormal feces	2 (<0.1)	1 (<0.1)
Bile duct stenosis	1 (<0.1)	0
Biliary tract disorder	1 (<0.1)	0

Biliary tract infection	1 (<0.1)	0
Biliary tract operation	1 (<0.1)	0
Cholangitis acute	1 (<0.1)	0
Cholecystitis infective	1 (<0.1)	0
Gallbladder disorder	1 (<0.1)	0
Hepatobiliary disease	1 (<0.1)	0
Hyperplastic cholecystopathy	1 (<0.1)	0
Jaundice	1 (<0.1)	0
Blood bilirubin abnormal	0	1 (<0.1)
Gallbladder pain	0	1 (<0.1)
Jaundice cholestatic	0	1 (<0.1)

Source: Supplementary AE Report, Appendix 1, Table 51

7.5.3 Neoplasms

Liraglutide is not genotoxic or mutagenic, however, 2-year carcinogenicity studies in mice and rats demonstrated a dose-dependent and treatment-duration-dependent increase in thyroid C-cell tumors. C-cells are calcitonin-producing parafollicular cells in the thyroid gland. The clinical relevance of the animal findings is unclear.

The most serious potential clinical consequence of an effect on thyroid C-cells, if this effect extends to humans, is medullary thyroid carcinoma (MTC), a rare form of thyroid cancer. The prognosis of MTC varies according to the type (familial, syndromic, or sporadic) and the 10-year survival has been reported to range from 43 to 88%.³³ Early diagnosis and treatment are associated with improved outcomes.³³ It is unknown precisely how survival or clinical presentation would be impacted in the setting of drug-induced MTC.

The potential risk of MTC was a major focus of the initial review of Victoza. The prescribing information for Victoza includes a boxed warning describing this potential risk, and the product was approved with a Risk Evaluation and Mitigation Strategy (REMS) consisting of a communication plan to inform prescribers about this risk. Victoza labeling includes a limitation of use that it is not recommended as first line therapy. In addition, a number of studies pertinent to MTC were established as post-marketing requirements at the time of the Victoza approval. MTC events continue to be monitored in the post-marketing setting.

Risk for pancreatic cancer has more recently emerged as a concern with GLP-1-based therapies, including liraglutide. One report observes that pancreases from organ donors with diabetes receiving incretin therapy were associated with increased mass with exocrine cell proliferation and dysplasia, and α -cell hyperplasia.⁸ However, animal, observational, and clinical trial data reviewed by FDA to date have not supported a causal association.⁷

³³ Griebeler ML, et al. Medullary thyroid carcinoma. Endocr Pract 2013; 19: 703-11.

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Neoplasms were considered MESI in the weight management development program and were prospectively adjudicated.

7.5.3.1 Clinical Pharmacology Trial

There were no neoplasms reported in this trial. One AE of elevated calcitonin was reported in a patient randomized to placebo (see section 7.5.3.2.2.1 for a discussion of calcitonin).

7.5.3.2 Weight Management Program

Using a MedDRA search of adverse events from the weight management clinical trials that include benign and malignant neoplasms, a similar proportion of patients treated with liraglutide and placebo reported a neoplasm AE (Table 70). However, approximately twice as many patients experienced serious AEs of neoplasms in the liraglutide group as compared to those treated with placebo (Table 71). The imbalance in neoplasm SAEs appears to be due to breast and colorectal neoplasms. Breast and colorectal neoplasms are described further in the discussion of the adjudicated neoplasms, below, in addition to further discussion of thyroid and pancreatic neoplasms.

Table 70. Neoplasms (predefined SMQ search), Weight Management Pool

	Lira 3 mg N=3384 n (%)	Total lira N=3872 n (%)	Placebo N=1941 n (%)
Neoplasms, SMQ search	177 (5.2)	192 (5.0)	94 (4.8)
Neoplasm SOC			
Neoplasms, benign, malignant and unspecified	105 (3.1)	112 (2.9)	60 (3.1)
Cutaneous neoplasms benign	14 (0.4)	14 (0.4)	15 (0.8)
Breast neoplasms malignant and unspecified	12 (0.4)	12 (0.3)	2 (0.1)
Endocrine neoplasms malignant and unspecified	11 (0.3)	11 (0.3)	3 (0.2)
Gastrointestinal neoplasms benign	10 (0.3)	10 (0.3)	3 (0.2)
Reproductive neoplasms female benign	7 (0.2)	10 (0.3)	10 (0.5)
Respiratory and mediastinal neoplasms malignant and unspecified	7 (0.2)	7 (0.2)	2 (0.1)
Nervous system neoplasms benign	6 (0.2)	6 (0.2)	2 (0.1)
Skin neoplasms malignant and unspecified	6 (0.2)	6 (0.2)	5 (0.3)
Soft tissue neoplasms benign	5 (0.1)	8 (0.2)	6 (0.3)
Breast neoplasms benign	4 (0.1)	4 (0.1)	0
Endocrine neoplasms benign	4 (0.1)	4 (0.1)	3 (0.2)
Miscellaneous and site unspecified neoplasms benign	4 (0.1)	4 (0.1)	3 (0.2)
Hepatic and biliary neoplasms benign	4 (0.1)	4 (0.1)	1 (<0.1)
Reproductive neoplasms male malignant and unspecified	3 (<0.1)	4 (0.1)	1 (<0.1)
Gastrointestinal neoplasms malignant and unspecified	2 (<0.1)	2 (<0.1)	0
Renal and urinary tract neoplasms malignant and unspecified	2 (<0.1)	2 (<0.1)	0
Miscellaneous and site unspecified neoplasms malignant and unspecified	1 (<0.1)	1 (<0.1)	3 (0.2)
Hepatobiliary neoplasms malignant and unspecified	1 (<0.1)	1 (<0.1)	1 (<0.1)
Plasma cell neoplasms	1 (<0.1)	1 (<0.1)	1 (<0.1)
Reproductive neoplasms female malignant and unspecified	1 (<0.1)	1 (<0.1)	1 (<0.1)
Skeletal neoplasms benign	1 (<0.1)	1 (<0.1)	1 (<0.1)
Leukemias	1 (<0.1)	1 (<0.1)	0

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Lymphomas NEC	1 (<0.1)	1 (<0.1)	0
Ocular neoplasms	1 (<0.1)	1 (<0.1)	0
Respiratory and mediastinal neoplasms benign	1 (<0.1)	1 (<0.1)	0
Metastases	0	0	1 (<0.1)
Other SOC's (Included in Neoplasm SMQ)			
Reproductive system and breast disorders	24 (0.7)	26 (0.7)	11 (0.6)
Skin and subcutaneous tissue disorders	16 (0.5)	18 (0.5)	8 (0.4)
Gastrointestinal disorders	14 (0.4)	16 (0.4)	10 (0.5)
General disorders and administration site conditions	13 (0.4)	14 (0.4)	3 (0.2)
Renal and urinary disorders	7 (0.2)	9 (0.2)	7 (0.4)
Musculoskeletal and connective tissue disorders	4 (0.1)	4 (0.1)	5 (0.3)
Congenital, familial and genetic disorders*	2 (<0.1)	3 (<0.1)	0
Endocrine disorders	2 (<0.1)	2 (<0.1)	0
Thyroid cyst	2 (<0.1)	2 (<0.1)	0
Hepatobiliary disorders	1 (<0.1)	1 (<0.1)	3 (0.2)
Infections and infestations	1 (<0.1)	1 (<0.1)	1 (<0.1)
Investigations	1 (<0.1)	1 (<0.1)	1 (<0.1)
Metabolism and nutrition disorders	0	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	0	0	1 (<0.1)

* Including one event of 'Multiple endocrine adenomatosis Type I' in a patient treated with liraglutide 3 mg

Source: ISS, Appendix 7.2, Table 254

Table 71. Serious Neoplasms (predefined SMQ search), Weight Management Pool

	Lira 3 mg N=3384 PY=2974.3		Total lira N=3872 PY=3372.7		Placebo N=1941 PY=1600.9	
	n (%)	Rate/1000PY	n (%)	Rate/1000PY	n (%)	Rate/1000PY
SAE Neoplasms, SMQ search	36 (1.1)	14	40 (1.0)	14	10 (0.5)	6
Breast						
Breast cancer	5 (0.1)	2	5 (0.1)	1	1 (<0.1)	<1
Breast cancer in situ	2 (<0.1)	<1	2 (<0.1)	<1	0	0
Breast cancer stage III	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Thyroid						
Thyroid cancer	2 (<0.1)	<1	2 (<0.1)	<1	1 (<0.1)	<1
Thyroid adenoma	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Colorectal						
Colon cancer	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Rectal cancer	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Colon adenoma	2 (<0.1)	1	2 (<0.1)	1	0	0
Colonic polyp	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Other gastrointestinal						
Carcinoid tumor of the small bowel	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Barrett's esophagus	0	0	0	0	1	<1
Hepatobiliary						
Hepatic neoplasm malignant	1 (<0.1)	<1	1 (<0.1)	<1	1 (<0.1)	<1
Gallbladder polyp	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Hepatic cyst	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Hepatic adenoma	1 (<0.1)	<1	1 (<0.1)	<1	0	0

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Hematological						
Chronic myeloid leukemia	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Lymphoma	1 (<0.1)	<1	1 (<0.1)	<1	0	0
B-cell lymphoma	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Mantle cell lymphoma stage I	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Male reproductive						
Prostate cancer	2 (<0.1)	<1	3 (<0.1)	<1	1 (<0.1)	<1
Prostate cancer recurrent	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Female reproductive						
Ovarian cancer	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Uterine leiomyoma	2 (<0.1)	<1	3 (<0.1)	<1	2 (0.1)	1
Uterine polyp	2 (<0.1)	<1	2 (<0.1)	<1	0	0
Ovarian cyst	1 (<0.1)	<1	2 (<0.1)	<1	0	0
Adnexa uteri cyst	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Endometrial hyperplasia	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Cervical dysplasia	0	0	0	0	1 (<0.1)	<1
Respiratory and mediastinal						
Laryngeal cancer	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Congenital						
Multiple endocrine adenomatosis type I	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Thyroglossal cyst	0	0	1	<1	0	0
Dermoid cyst	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Other						
Cyst	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Renal cyst	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Leiomyoma	0	0	1 (<0.1)	<1	0	0
Cholesteatoma	0	0	0	0	1 (<0.1)	<1
Hemangioma of bone	0	0	0	0	1 (<0.1)	<1

Source: ISS, Appendix 7.2, Table 258

7.5.3.2.1 Adjudicated Neoplasms

Prospective adjudication of neoplasms was implemented in the phase 3 clinical trial program after completion of trial 1923, the first of the four phase 3 trials. Prospective adjudication was utilized for trials 1839, 1922, and 3970. Neoplasms from trial 1923 were adjudicated *post hoc*. Neoplasms from phase 2 trial 1807 were not adjudicated.

There were four sources of potential events of neoplasms adjudicated by the EAC:

- Events identified by the MedDRA search for neoplasms
- Events identified by the 'MedDRA search for thyroid disorders' which were not already captured by the 'MedDRA search for neoplasms' but could potentially be confirmed as thyroid neoplasms
- More non-specific types of events not captured by any of the former (e.g., 'mass') that were either submitted as a MESI by the investigator or identified by the Novo Nordisk 'Preferred Term' search for 'missed MESI'

- Events identified by the EAC in source documents during adjudication

Events were evaluated by the EAC with regard to confirmation of the diagnosis (neoplasm: yes/no; final EAC diagnosis), malignancy status (classification of confirmed neoplasms into benign, malignant, pre-malignant/carcinoma in situ/borderline, and unclassified), staging (for malignant neoplasm), and tissue of origin/organ class. The EAC was not required to provide a reason for rejection of an event as a neoplasm, and no final diagnoses for rejected events were provided. For all confirmed neoplasms, the EAC was also to confirm the onset date.

Table 72. Classification of Neoplasm Adjudicated Events by the External Event Adjudication Committee

Event	Definitions, classifications and criteria	
Neoplasms, including thyroid neoplasms (if adjudicated as 'Neoplasm')	<p>Definitions:</p> <ul style="list-style-type: none"> - Neoplasm was defined as an abnormal growth of tissue <p>Classification:</p> <p>Neoplasms were classified according to</p> <ul style="list-style-type: none"> - tissue of origin/organ system - stage - malignancy status 	<p>Stage:</p> <ul style="list-style-type: none"> - Stage 0: <i>in situ</i> - Stage I: localised - Stage II: locally advanced - Stage III: advanced - Stage IV: metastatic - Undetermined <p>Malignancy status:</p> <ul style="list-style-type: none"> - malignant - pre-malignant/carcinoma <i>in situ</i>/borderline - benign - unclassified
Thyroid neoplasms (if adjudicated as 'Thyroid Disorder requiring thyroidectomy')	<p>Definition</p> <p>Neoplasms of the thyroid were defined as described above; medullary carcinoma of the thyroid (MTC) was defined as a distinct thyroid carcinoma, originating in the calcitonin producing parafollicular C-cells of the thyroid gland.</p> <p>Classification:</p> <p>Thyroid neoplasms were classified according to:</p> <ul style="list-style-type: none"> - type (C-cell hyperplasia, medullary microcarcinoma (carcinoma in situ), medullary carcinoma, other (please specify)) - stage (only if medullary microcarcinoma or medullary carcinoma) - malignancy status (all thyroid neoplasms) 	<p>Stage:</p> <ul style="list-style-type: none"> - Stage 0: <i>in situ</i> - Stage I: localised - Stage II: locally advanced - Stage III: advanced - Stage IV: metastatic - Undetermined <p>Malignancy status:</p> <ul style="list-style-type: none"> - malignant - pre-malignant/carcinoma <i>in situ</i>/borderline - benign - unclassified

Source: ISS, Table 2-76

Overall, 204 (6.2%) patients treated with liraglutide 3 mg had 249 events sent for adjudication; 216 (6.2%) patients treated with all doses of liraglutide had 264 events; and 113 (6.1%) patients treated with placebo had 157 events sent for adjudication.

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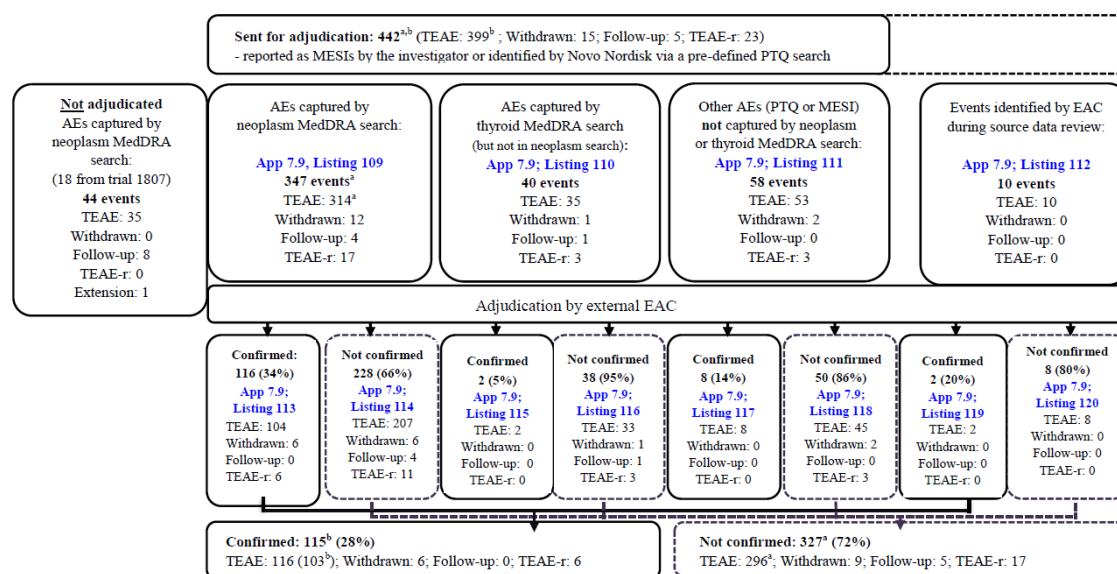
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After removal of linked events, a total of 442 events were sent for adjudication (Figure 42).

The proportions of EAC-confirmed events (of events sent for adjudication) were 28.6% and 22.2% in the liraglutide- and placebo-treated groups, respectively.

The adjudication process is summarized in the figure below, and incidences and event rates of selected EAC-confirmed neoplasms is presented in Table 73, Table 74, Table 75, and Table 76.

Figure 42. Adjudication of Neoplasm Events, Including Thyroid Neoplasms, Weight Management Pool (Excluding Trial 1807)



a. Includes 3 events with no EAC classification. b. After removal of 13 redundant linked events. TEAE: TEAEs in main period (1839) or treatment period + 7 days (1807) or + 14 days (1923, 1922 and 3970); Withdrawn: non-TEAEs (>14 days after last drug date) in withdrawn subjects; Follow-up: non-TEAEs (>14 days after last drug date) in the follow-up period (1922 and 1923); TEAE-r: AEs in re-randomised period of 1839 + 14 days; In addition there were 15 events occurring prior to treatment not summarised here

Source: ISS, Figure 2-55

After submission of the NDA, additional events from the main portion of trial 1839 were sent for adjudication and three events were confirmed by the adjudication committee. For completeness these events are included in Table 73, below.

Because events in trial 1807 were not adjudicated, this trial is not included in Table 73 (events from 1807 are included in Table 70 and Table 71, above, which include neoplasms identified in the SMQ search).

Table 73. EAC-Confirmed Neoplasms in Main Treatment Period (Selected), Weight Management Pool, Excluding Trial 1807

	Lira 3 mg N=3291		Total lira N=3501		Placebo N=1843	
	n (%)	Rate/1000PY	n (%)	Rate/1000PY	n (%)	Rate/1000PY
EAC-confirmed events	63 (1.9)	23	66 (1.9)	22	28 (1.5)	23
Malignant	26 (0.8)	9	26 (0.7)	9	12 (0.7)	9
Pre-malignant	5 (0.2)	2	5 (0.1)	2	4 (0.2)	3
Benign	32 (1.0)	11	35 (1.0)	12	14 (0.8)	10
Breast						
Malignant	7 (0.2)	3	7 (0.2)	3	1 (<0.1)	<1
Pre-malignant	3 (<0.1)	1	3 (<0.1)	<1	1 (<0.1)	<1
Benign	2 (<0.1)	<1	2 (<0.1)	<1	0	0
Colorectal						
Malignant	2 (<0.1)	<1	2 (<0.1)	<1	0	0
Benign	11 (0.3)	4	11 (0.3)	4	4 (0.2)	3
Thyroid						
Malignant	3 (<0.1)	1	3 (<0.1)	1	1 (<0.1)	<1
Pre-malignant	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Benign	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Pancreatic						
Malignant	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Skin						
Malignant	7 (0.2)	2	7 (0.2)	2	5 (0.3)	4
Pre-malignant	0	0	0	0	2 (0.1)	2
Benign	1 (0.1)	<1	1 (<0.1)	<1	1 (<0.1)	<1

Source: 120 day safety report, Appendix 7.1, Table 20

Additional adjudicated malignant neoplasms not captured in the above table include:

Table 74. EAC-Confirmed Malignant Neoplasms (Other Categories) in Main Treatment Period, Weight Management Pool, Excluding Trial 1807

	Lira 3 mg N=3291		Total lira N=3501		Placebo N=1843	
	n (%)	Rate/1000PY	n (%)	Rate/1000PY	n (%)	Rate/1000PY
Other malignant neoplasms						
Lymphomas (non-Hodgkin, Hodgkin)	2 (<0.1)	<1	2 (<0.1)	<1	0	0
Male reproductive (penile, prostate, testicular)	2 (<0.1)	<1	2 (<0.1)	<1	1 (<0.1)	<1
Bladder	1 (<0.1)	<1	1 (<0.1)	<1	1 (<0.1)	<1
Liver	1 (<0.1)	<1	1 (<0.1)	<1	1 (<0.1)	<1
Female reproductive (vaginal, cervical, ovarian)	0	0	0	0	1 (<0.1)	1
Oral	0	0	0	0	1 (<0.1)	1

Source: 120 day safety report, Appendix 7.1, Table 20

Overall, in the 12-week re-randomized portion of trial 1839 (patients without pre-diabetes only), a similar proportion of patients randomized to liraglutide and placebo experienced EAC-confirmed neoplasm AEs.

Table 75. Treatment Emergent Adjudicated Neoplasms in Re-Randomized Treatment Period (56 to 68 weeks) by EAC Category, Trial 1839

	Lira/Lira N=351		Lira/Placebo N=350		Placebo N=304	
	n (%)	Rate/1000PY	n (%)	Rate/1000PY	n (%)	Rate/1000PY
EAC-confirmed events	3 (0.9)	37	0	0	3 (1.0)	44
Malignant	2 (0.6)	25	0	0	2 (0.7)	29
Pre-malignant	0	0	0	0	1 (0.3)	15
Benign	1 (0.3)	12	0	0	0	0
Breast, Malignant	1 (0.3)	12	0	0	1 (0.3)	15
Female reproductive, Malignant	1 (0.3)	12	0	0	0	0
Male reproductive, Malignant	0	0	0	0	1 (0.3)	15
Skin, Pre-malignant	0	0	0	0	1 (0.3)	15

Source: Trial NN8022-1839 Clinical Trial Report, Table 14.3.1.137

Overall, a similar event rate was seen for EAC-confirmed neoplasms that were identified more than 2 weeks after the last dose of study drug in patients who were withdrawn; Table 76 demonstrates the distribution.

Table 76. EAC-Confirmed Neoplasms Greater than 2 Weeks after Last Dose, Weight Management Pool, Excluding Trial 1807

	Lira 3 mg N=885		Total lira N=931		Placebo N=614	
	n (%)	Rate/1000PY	n (%)	Rate/1000PY	n (%)	Rate/1000PY
EAC-confirmed events	3 (0.3)	8	3 (0.3)	8	2 (0.3)	11
Breast						
Malignant	1 (0.1)	3	1 (0.1)	3	0	0
Thyroid						
Pre-malignant	1 (0.1)	3	1 (0.1)	3	0	0
Skin						
Malignant	0	0	0	0	2 (0.3)	7
Pre-malignant	0	0	0	0	1 (0.2)	4
Female reproductive						
Malignant	1 (0.1)	3	1 (0.1)	3	0	0

Source: ISS, Table 2-78

Regarding the ongoing extension phase of trial 1839, the most updated information on neoplasm events was provided in the 120-day safety update. As of the 11 Nov 2013 data cut-off, 64 (5.9%) patients treated with liraglutide 3 mg have had 105 events sent for adjudication and 26 (5.2%) patients treated with placebo have had 38 events sent for adjudication. The overall incidence of EAC-confirmed events and selected events of interest are summarized below; note that the most prominent imbalance to date is benign colorectal lesions: 6 patients treated with liraglutide reported events versus none treated with placebo.

Table 77. Adjudicated Neoplasms by EAC Category (Selected), Ongoing 1839 Extension

	Lira 3 mg N=1087	Placebo N=497
EAC-confirmed neoplasms	17 (1.6)	7 (1.4)
Malignant	8 (0.7)	4 (0.8)
Pre-malignant	0	1 (0.2)
Benign	9 (0.8)	2 (0.4)
Breast		
Malignant	2 (0.2)	0
Thyroid		
Malignant	1 (0.1)	0
Colorectal		
Malignant	0	1 (0.2)
Benign	6 (0.6)	0
Skin		
Malignant	4 (0.4)	2 (0.4)
Pre-malignant	0	1 (0.2)

Source: 120-day safety report, Table 2-33

Other EAC-confirmed malignant neoplasms as of the data cut-off not presented in the table above are: 1 event of laryngeal cancer in the liraglutide-treated arm (0.1%) and 1 event of lymphoma in the placebo-treated arm (0.2%).

7.5.3.2.2 Thyroid

Thyroid disorders requiring thyroidectomy were considered medical events of special interest (MESI) and were subject to adjudication. If a patient underwent a thyroidectomy (partial or total) for any reason during trials in the liraglutide weight management program, pathology slides of the thyroid tissue were to be centrally reviewed in addition to the routine examination at the site level. Both the site pathology report and the central pathology report were to be reviewed by the EAC. A set of pathology slides from the pathology laboratory of the hospital where the operation was performed was to be sent centrally for a second reading by a pathologist with expertise in thyroid and C-cell pathology. The pathologist was blinded to trial treatment and site diagnosis.

Thyroid neoplasms deriving from C-cells were to be classified as C-cell hyperplasia, medullary microcarcinoma (carcinoma *in situ*), or medullary carcinoma.

Thyroid tissue sample was collected and stored from patients undergoing thyroidectomy for testing of the protein 'Rearranged during Transfection' (RET) Y1062 phosphorylation

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in the thyroid C-cells. This was only applicable if C-cell pathology was confirmed (i.e., hyperplastic or neoplastic thyroid C-cells), and if allowed by local law and if signed informed consent was obtained.

To summarize from Table 73, above, a total of 4 patients treated with liraglutide 3 mg and 1 patient treated with placebo was diagnosed with a malignant or pre-malignant thyroid neoplasm during the main period of the weight management trials. One patient treated with liraglutide was diagnosed with a pre-malignant thyroid neoplasm after withdrawal. Details of these cases are provided in Table 78. Additionally, a liraglutide-treated patient has been diagnosed with a malignant thyroid neoplasm in the ongoing trial 1839 extension. This case is described separately.

All neoplasms in the liraglutide-treated patients were of papillary or follicular origin. The single medullary thyroid carcinoma was reported in a patient treated with placebo. The single reported case of C-cell hyperplasia was reported in a liraglutide-treated patient (with papillary microcarcinoma) and was adjudicated to have an onset date prior to trial start; additional details in this case follow Table 78.

Table 78. Details on EAC Confirmed Thyroid Neoplasms, Weight Management Pool

Trial/sub- ject/age/ sex/BMI/ country	Reported term	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/ Period	Details ^b and medical history
<i>Liraglutide 3.0 mg</i>					
1839/ 284003/ 27/M/38.7/ IL	Thyroid cancer (Reported term: Worsening of papi- llary carci- noma)	Papillary thyroid carcinoma	Malignant Stage: ND ^c	212/211/ Main treatment period	A thyroid nodule was suspected at screening and ultrasound confirmed non-toxic multi-nodular goitre. 6 months later, a biopsy revealed thyroid papillary carcinoma. The subject was withdrawn from the trial. The subject underwent total thyroidectomy, started treatment with radioactive iodine and recovered with sequelae described as thyroid remnants. No relevant medical history. The subject recovered with sequelae. Calcitonin levels 1 ng/L at all visits
1839/ 414016/ 40/F/37.0/ US	Thyroid cancer (×2) (reported terms: Left nodule thyroid cancer and right nodule thyroid cancer)	Papillary thyroid carcino- mas (×2)	Malignant Stage: ND ^c	163/180 & 162/ Main treatment period	A thyroid nodule was discovered by primary care physician. Ultrasound and fine needle aspiration revealed suspicion of papillary carcinoma. A thyroidectomy was performed and pathology confirmed thyroid carcinoma (papillary and follicular variant) located to right and left lobe of the thyroid (reported and confirmed as 2 separate events of thyroid cancer). The subject underwent radioiodine ablation. Hashimoto's Thyroiditis was an additional pathological finding during thyroidectomy. No treatment was required for this condition. As a consequence of the thyroidectomy, hypothyroidism and hypoparathyroidism was later reported. The subject recovered and continued on unchanged trial medication. No relevant medical history. The subject had a total of 5 EAC confirmed events, which were linked by the EAC and appear as 2 confirmed events in summary tables. Calcitonin levels 1 ng/L at all visits
1923/ 111014/ 42/F/36.1/ US	Thyroid cancer	Papillary thyroid carci- nomas/	Malignant/ Stage I Localised	24/15/ Main treatment period	The subject had a history of hypothyroidism and family history of thyroid disease, as well as an enlarged thyroid at screening. She also had a history of thyromegaly and nodules. She withdrew from the trial, had a total thyroidectomy and had recovered at the end of the trial. The subject had a total of 2 EAC confirmed events, which were linked and appear as 1 confirmed event in summary tables.

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Trial/sub- ject/age/ sex/BMI/ country	Reported term	EAC diagnosis	EAC malig- nancy status	Inv onset, days/ EAC onset, days/ Period	Details ^b and medical history
1922/ 406003/ 58/M/48.7/ DE	Thyroid cancer	C-cell hyper- plasia	<i>In situ</i> Benign/ Stage: NA ^c	-12/-11/ Screening	Approximately 3 months after discontinuation of treatment a thyroidectomy and central lymphadenectomy were performed due to elevated calcitonin levels. A thorough histological and immunohistological processing was performed and the thyroid gland resection showed diffuse, colloid-containing micro and macrofollicular goiters on both sides with a papillary microcarcinoma 1 mm in size in the isthmus and reactive C cell hyperplasia in both thyroid gland lobes. A normally structured parathyroid gland on the left side was also detected. Due to elevated blood calcitonin level at screening the EAC assigned an onset date of the C-cell hyperplasia to prior to treatment initiation. Testing for RET oncogene was performed and no pathogenic mutations were detected in the RET gene. Medical history included T2DM, diabetic complications, arterial hypertension, dyslipidaemia and elevated calcitonin level. Calcitonin levels high (>45 ng/L) at all visits incl. baseline, except at week 56
	Lympha- denopathy	Papillary micro- carcinoma	Pre- malignant/ Stage 0/	358/358/ Main treatment period	
1922/ 109003/ 56/F/36.3/ FR	Thyroid adenoma	Follicular adenoma	Benign Stage: NA ^c	51/51/ Main treatment period	A 1.5 cm nodule was detected on left side of thyroid gland during clinical examination. The subject was withdrawn from the trial by the investigator due to the event. The subject had thyroidectomy, and the nodule was identified as benign follicular adenoma. In addition, a 0.5 mm malignant papillary microcarcinoma was noted incidentally from the removed thyroid tissue. The subject was withdrawn and recovered from both events. Calcitonin (and TSH) levels were normal at baseline and during the trial
	Papillary microcarc- inoma ^a	Papillary microcar- cinoma ^a .	Pre- malignant/ Stage 0/ <i>In situ</i>	137/137/ Withdrawn	
Placebo					
1922/ 402008/ 53/F/37.2/ DE	Thyroid carcinoma	Medullary carcinoma	Malignant/ Stage I/ Localised	23	23 days after start of trial product the subject presented with thyroid nodule. A thyroidectomy was later performed showing medullary thyroid carcinoma (MTC) of right thyroid lobe. Testing for RET oncogene was performed and no pathogenic mutations were detected in the RET gene. Calcitonin levels 18.5 ng/L at screening; 19.3ng/L at time of event. Relevant medical history included previous smoking. No relevant family history reported.

BMI: body mass index; EAC: event adjudication committee (and EAC assessment of onset day); F: female; M: male; inv: investigator assessment of onset day; PT: preferred term.

a. Please note that the event occurred after withdrawal of the subject. b. Details are based on information in the case narratives from the safety database. c. ND=Not done. Thyroid neoplasm events identified by the thyroid MedDRA search as 'Thyroid disease requiring thyroidectomy' were not evaluated by the EAC with regards to stage of neoplasm, see Section 2.1.6.2.

Source: ISS, Table 2-86

Further details regarding the malignant papillary thyroid cancers in the liraglutide-treated patients are as follows:

- Patient 284003 (liraglutide 3 mg): The biopsy report from the right hemithyroidectomy noted a tumor size of 1.35 cm, with extension of tumor beyond

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thyroid into perithyroid fatty tissue, and metastatic carcinoma in one of three regional lymph nodes was found. Left hemithyroidectomy biopsy report noted that the tumor size was 0.5 cm, with no evidence of extra-thyroidal extension, surgical margin free, and no evidence of angio-lymphatic invasion. The oncologist report concluded papillary carcinoma (papillary tumor of the thyroid gland on the right lobe with penetration to an adjacent tissue and positive margins). After radioactive iodine treatment, the thyroid scan showed remnants of thyroid in the neck with no evidence of metastasis. The patient had no reported history of radiation exposure.

- Patient 414016 (liraglutide 3 mg): A right thyroid nodule was identified during the patient's annual physical examination, which was described as 1.2 x 1.0 x 1.6 cm on ultrasound. The pathology report after thyroidectomy confirmed thyroid cancer (both papillary and follicular) with clean margins. When the total thyroidectomy was performed due to the suspicion of the right thyroid nodule, it was found that a left nodule was also cancerous (size not reported).
- Patient 111014 (liraglutide 3 mg): Thyromegaly and multinodular goiter was diagnosed in 2001; thyroid was reported to be enlarged at screening. On day 15, the patient had an ultrasound that showed multiple large nodules bilaterally; fine needle aspiration on day 23 showed papillary thyroid carcinoma. Size not reported.

As noted above, one EAC-confirmed event of C-cell hyperplasia was reported in a patient treated with liraglutide; this case was evaluated by the EAC to have onset prior to enrollment in the trial. Patient 406003 (trial 1922, treated with liraglutide 3 mg) underwent thyroidectomy for suspicion of thyroid cancer due to elevated calcitonin values.

- Patient 406003 was a 58-year-old male; baseline calcitonin was 47.5 ng/mL. Two weeks after starting liraglutide, his calcitonin value increased to 71.1 ng/mL; see the table below for calcitonin values throughout the trial.

Table 79. Patient 406003 (Trial 1922), Calcitonin Values, ng/mL

SCR	BL	7/5 2011	7/18 2011	11/1 2011	1/10 2012	2/9 2012	3/1 2012	3/29 2012	4/26 2012	6/5 2012	7/19 2012	10/9 2012
45	48	71	74	63	61	62	48	93	104	51	77	1

Source: Reviewer created from sponsor datasets

The patient had several thyroid ultrasound examinations; all were negative. T3, free T4, and TSH were within normal ranges. Trial product was discontinued permanently on June 4, 2012 due to persistent calcitonin elevations. Approximately 3 months after treatment discontinuation, thyroidectomy and lymphadenectomy were performed. Thyroid gland histopathology demonstrated diffuse, colloid-

containing micro- and macrofollicular goiters on both sides with 1 mm papillary microcarcinoma in isthmus and reactive C-cell hyperplasia in thyroid gland lobes. Due to the elevated blood calcitonin at screening, the EAC assigned onset date of C-cell hyperplasia to prior to treatment initiation. No pathogenic mutations were detected in the RET gene.

Reviewer comment: While calcitonin was clearly elevated prior to starting treatment with liraglutide and fluctuated during therapy, it appears there was a trend toward higher values on therapy (to over 100 ng/mL). Whether this is consistent with the expected natural history of C-cell hyperplasia in this patient is unknown.

C-cell hyperplasia associated with hereditary MTC (i.e., MEN2 or familial MTC) has been considered a preneoplastic lesion.³⁴ In this setting, C-cell hyperplasia may be referred to as MTC in situ. Reactive C-cell hyperplasia (not associated with MTC) has also been observed in association with other thyroid disease, including as an adjacent finding to follicular tumors.³⁴

In the extension phase of trial 1839 (as reported in the 120-day safety update), 5 events of thyroid disease requiring thyroidectomy (liraglutide 3 mg: 2 events; placebo: 3 events) were sent for adjudication. One of these events was confirmed as a thyroid neoplasm:

- Patient 216018 (trial 1839) was a 43-year-old female randomized to liraglutide 3 mg, who reported a moderate SAE of papillary thyroid cancer with onset 552 days after onset of treatment. The patient had a medical history of parathyroidectomy prior to randomization. During explorative surgery due to persisting increased level of PTH, a suspicious nodule in left thyroid lobe was identified, and a left hemithyroidectomy was performed. Histology showed a 3 mm thyroid papillary microcarcinoma, which was completely excised. The patient recovered and continued on unchanged trial medication.

Reviewer comment: This case was adjudicated as “malignant” rather than “pre-malignant”, although it was a papillary microcarcinoma. The other papillary microcarcinomas discussed above were adjudicated as “pre-malignant”.

No thyroid neoplasm events were reported in trial 1807.

7.5.3.2.2.1 Calcitonin

Because thyroid C-cells as well as MTC tumors produce calcitonin, concentrations of circulating calcitonin are useful for screening patients at risk (those with the RET proto-oncogene or a family history of MEN2 or MTC) and for predicting the aggressiveness of MTC.³³ However, although measurement of serum calcitonin in the work-up of thyroid

³⁴ Mete O and Asa SL. Precursor lesions of endocrine system neoplasms. Pathology 2013; 45(3): 316-30.

nodules might improve detection of MTC, there is controversy whether such monitoring improves patient outcomes.³⁵ The upper limit of normal for calcitonin in females is 5.0 ng/mL and in males, 8.4 ng/mL. Calcitonin values exceeding 30 to 50 ng/mL increase the likelihood of, and values exceeding 100 ng/mL are highly predictive of MTC.³⁶ The clinical relevance of smaller increases in calcitonin is unknown.

Calcitonin was measured at screening and at regular intervals in the phase 2 and 3 clinical trials in the weight management program. Post-baseline calcitonin values 20 ng/L or higher (or greater than 2× ULN and at least 50% increase from baseline in trial 1923), if confirmed by a repeat test within 4 weeks, were to be reported as a MESI ('elevated calcitonin') across the phase 3 trials. An external blinded group of thyroid experts (Calcitonin Monitoring Committee [CMC]) reviewed all these confirmed elevated calcitonin values from trials 1839, 1922, and 3970 and provided specific recommendations for further diagnostic evaluation (e.g., thyroid ultrasound, pentagastrin test, fine needle aspiration) or withdrawal according to a pre-defined algorithm. The CMC also evaluated local and central pathology reports issued in patients undergoing thyroidectomy during the trials.

Baseline calcitonin values tended to be higher in the liraglutide 3 mg treatment group than in the placebo treatment group for both female and male patients. Mean calcitonin concentrations appeared higher in the liraglutide-treated groups than the placebo-treated throughout the treatment period, and males had higher values than females.

Table 80. Calcitonin by Treatment Week and by Sex, Weight Management Pool

	Females		Males	
	Lira 3 mg N=2449	Placebo N=1374	Lira 3 mg N=935	Placebo N=567
Baseline				
Geometric mean (CV)	1.07 (100.3)	1.01 (120.5)	2.66 (120.5)	2.52 (107.5)
Min, Max	0.35, 15.5	0.35, 18.8	0.35, 68.9	0.35, 42.7
3 months*				
Geometric mean (CV)	1.11 (109.3)	1.03 (112.7)	2.75 (101.8)	2.60 (103.6)
Min, Max	0.35, 17.8	0.35, 22.5	0.35, 29.8	0.35, 31.5
6 months†				
Geometric mean (CV)	1.08 (111.0)	0.99 (101.2)	2.75 (112.4)	2.51 (135.9)
Min, Max	0.35, 23.0	0.35, 13.0	0.35, 61.1	0.35, 81.5

³⁵ Costante G, et al. Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls. *Nat Clin Pract Endocrinol Metab* 2009; 5(1): 35-44.

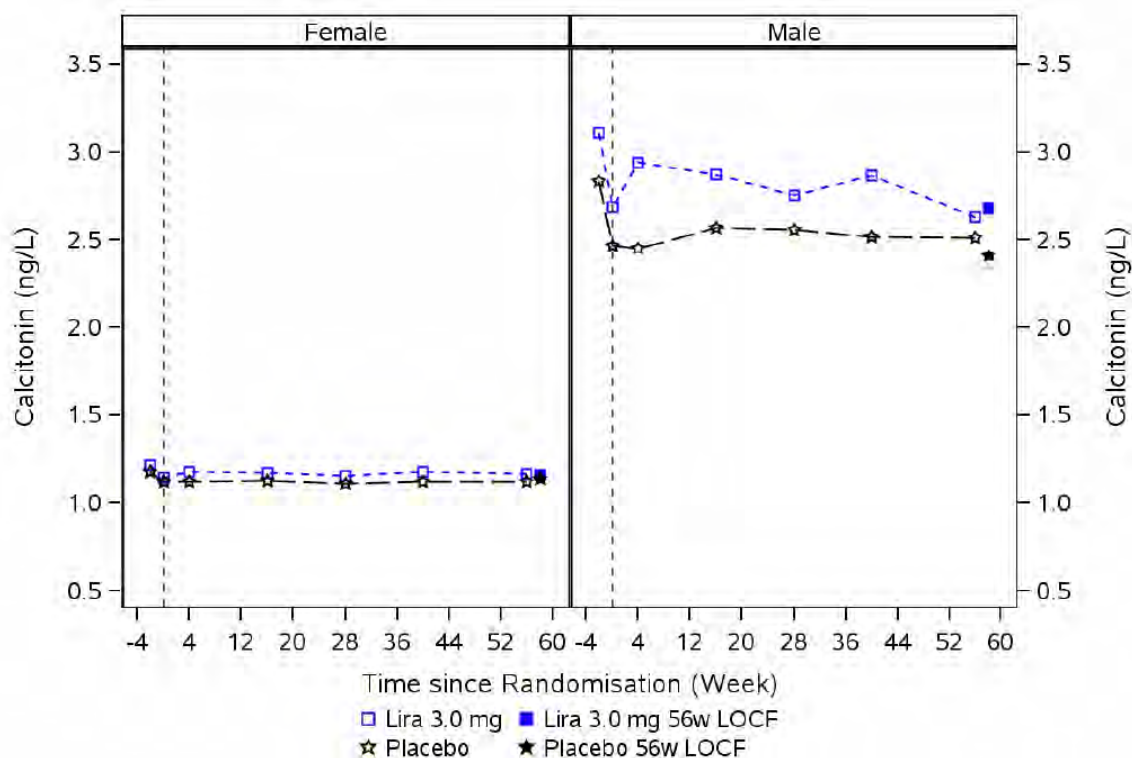
³⁶ Iacobone M, et al. Can sporadic medullary thyroid carcinoma be biochemically predicted? Prospective analysis of 66 operated patients with elevated serum calcitonin levels. *World J Surg* 2002; 26: 886-90.

1 year§				
Geometric mean (CV)	1.08 (111.2)	0.97 (107.4)	2.59 (115.5)	2.39 (94.6)
Min, Max	0.35, 26.5	0.35, 19.2	0.35, 44.1	0.35, 16.6
LOCF‡				
Geometric mean (CV)	1.08 (109.9)	1.01 (116.4)	2.62 (131.8)	2.40 (103.9)
Min, Max	0.35, 26.5	0.35, 22.5	0.35, 88.9	0.35, 30.6
Highest post-baseline value				
Geometric mean (CV)	1.19 (124.2)	1.10 (129.8)	3.47 (127.1)	3.06 (122.7)
Min, Max	0.35, 26.5	0.35, 22.5	0.35, 104.0	0.35, 81.5
* measurements at week 12 (3970, 1807), week 14 (1923), or week 16 (1839, 1922)				
† measurements at week 26 (1923), week 28 (1922, 1839), and week 32 (3970, 1807 ext 1)				
§ measurements at week 52 (1807 ext 1) and week 56 (1923, 1922, 1839)				
‡ measurements at week 32 (trial 3970), week 52 (trial 1807 ext 1), and week 56 (1839, 1922, 1923)				

Source: ISS Appendix 7.5, tables 166 and 167

The figure below from trial 1839 illustrates the sex differential, in terms of baseline values and in response to treatment.

Figure 43. Calcitonin Geometric Mean (ng/L) in the Main Treatment Period by Sex, Trial 1839



Source: Trial NN8022-1839 Clinical Trial Report, Figure 14.3.5.129

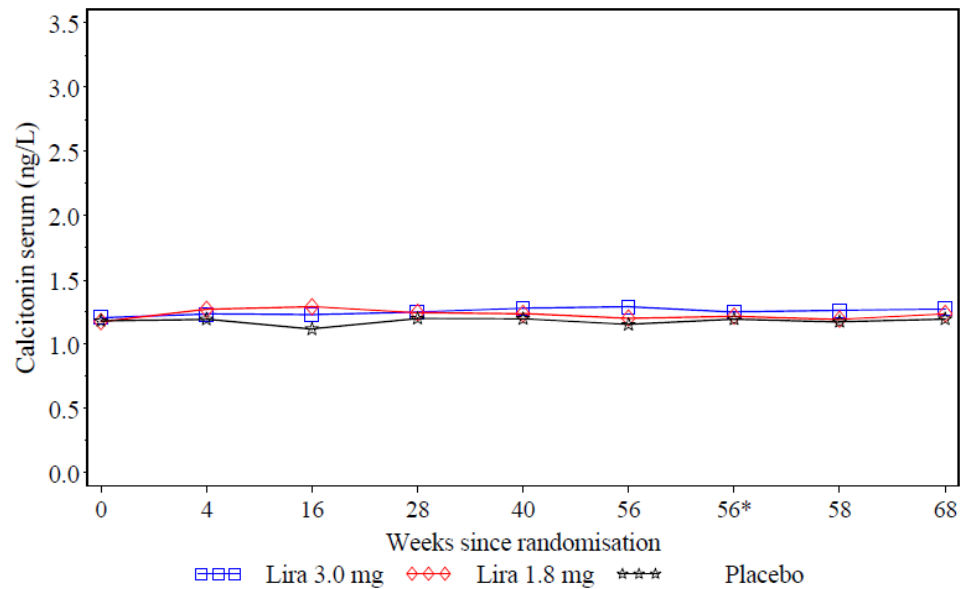
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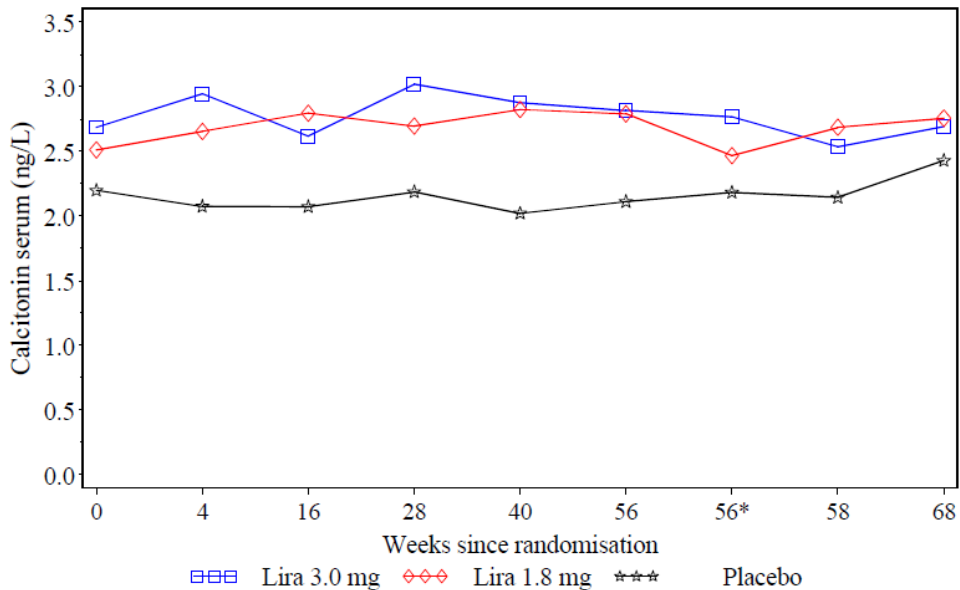
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There does not appear to be a clear dose or exposure effect on calcitonin, both based on results by dose from trial 1922 (Figure 44), as well as from an analysis of exposure-response (Figure 45).

Figure 44. Calcitonin geometric mean (ng/L) by treatment group in females (top figure) and males (bottom figure), Trial 1922



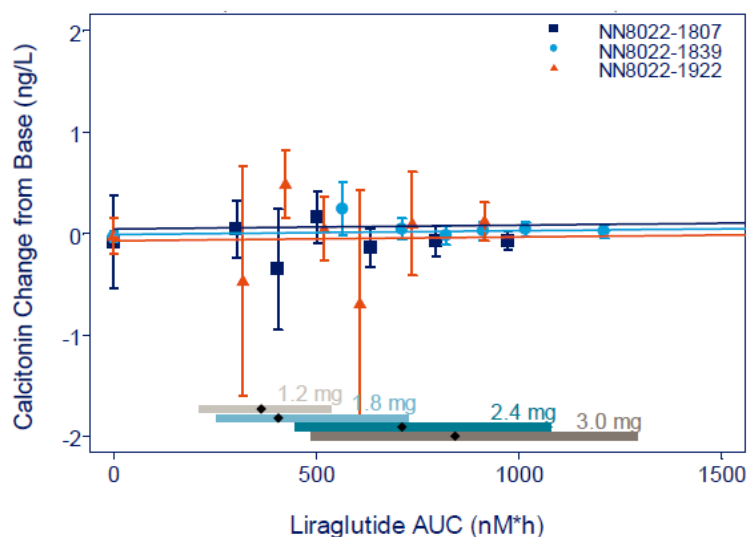
* = LOCF Week 56



* = LOCF Week 56

Source: Trial NN8022-1922 Clinical Trial Report, Figures 14.3.5.63 and 14.3.5.64

Figure 45. Change in Calcitonin versus Liraglutide Exposure, Trials 1807, 1839, and 1922



Data are mean values with 95% CI versus exposure expressed as six quantiles of AUC values (plus placebo). Lines represent covariate-adjusted model-based estimates for each trial population. Horizontal lines with diamonds represent median and 90% CI values of exposure from each dose level.

Source: ISS, Figure 2-58

There were more patients with high calcitonin values in the liraglutide 3 mg group as compared to placebo at one year / end of trial, although the incidence of calcitonin values 20 ng/L or greater, and especially 50 ng/L or greater, was low (Table 81). The proportions of patients in either group experiencing post-baseline calcitonin concentrations 20 ng/L or greater at any time during treatment was 0.47% in the liraglutide 3 mg treatment group, and 0.36% in the placebo group.

Table 81. Patients with Elevated Calcitonin Values (ng/L) at Specific Visits during Treatment, Weight Management Pool

	Lira 3 mg N=3384		Placebo N=1941	
	N	n (%)	N	n (%)
Calcitonin $\geq 1.5 \times$ ULN				
Baseline	3383	79 (2.3)	1941	45 (2.3)
3 months	2866	71 (2.5)	1596	33 (2.1)
6 months	2767	69 (2.5)	1491	29 (1.9)
1 year	2353	52 (2.2)	1170	20 (1.7)
LOCF at end of trial	3315	79 (2.4)	1878	39 (2.1)
Calcitonin $\geq 2 \times$ ULN				
Baseline	3383	31 (0.9)	1941	16 (0.8)
3 months	2866	31 (1.1)	1596	13 (0.8)
6 months	2767	26 (0.9)	1491	15 (1.0)
1 year	2353	22 (0.9)	1170	6 (0.5)

LOCF at end of trial	3315	39 (1.2)	1878	12 (0.6)
Calcitonin $\geq 3 \times$ ULN				
Baseline	3383	6 (0.2)	1941	8 (0.4)
3 months	2866	6 (0.2)	1596	4 (0.3)
6 months	2767	8 (0.3)	1491	3 (0.2)
1 year	2353	9 (0.4)	1170	1 (<0.1)
LOCF at end of trial	3315	16 (0.5)	1878	5 (0.3)
Calcitonin ≥ 20 ng/L				
Baseline	3383	15 (0.4)	1941	5 (0.3)
3 months	2866	12 (0.4)	1596	6 (0.4)
6 months	2767	9 (0.3)	1491	5 (0.3)
1 year	2353	8 (0.3)	1170	0
LOCF at end of trial	3315	16 (0.5)	1878	3 (0.2)
Calcitonin ≥ 50 ng/L				
Baseline	3383	1 (<0.1)	1941	0
3 months	2866	0	1596	0
6 months	2767	1 (<0.1)	1491	1 (<0.1)
1 year	2353	0	1170	0
LOCF at end of trial	3315	1 (<0.1)	1878	0

Source: ISS, Table 2-87

None of the liraglutide-treated patients with elevated calcitonin levels with onset at any time during treatment had events of EAC-confirmed C-cell hyperplasia or MTC. One liraglutide-treated patient had elevated calcitonin levels at screening and throughout treatment with liraglutide (45 ng/L to greater than 100 ng/L), and was later diagnosed with benign C-cell hyperplasia (described in the narrative above, patient 406003, trial 1922).

Six patients (0.15%) treated with liraglutide and one patient (0.05%) treated with placebo shifted calcitonin from less than ULN to 20 ng/L or greater during the trial.

More males treated with liraglutide 3 mg experienced persistent increases (defined as \geq ULN at all post-baseline visits) of calcitonin as compared to males treated with placebo (10 patients (1.1%) vs. 0 patients). With the exception of one patient, the rest shifted to a maximum of $1.5 \times$ ULN or less. One male in the liraglutide-treated group and one female in the placebo-treated group had persistent increases of calcitonin values to above 20 ng/L.

Table 82. Persistent Increase in Calcitonin, Weight Management Pool

	Total		Females		Males	
	Lira 3.0 mg N (%)	Placebo N (%)	Lira 3.0 mg N (%)	Placebo N (%)	Lira 3.0 mg N (%)	Placebo N (%)
Number of subjects	3384	1941	2449	1374	935	567
From < UNR to ≥ UNR	14 (0.41)	1 (0.05)	4 (0.16)	1 (0.07)	10 (1.07)	0 (0.00)
From < UNR to ≥ 1.5×UNR	0 (0.00)	1 (0.05)	0 (0.00)	1 (0.07)	0 (0.00)	0 (0.00)
From < UNR to ≥ 2×UNR	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
From < UNR to ≥ 3×UNR	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
From < UNR to ≥ 20 ng/L	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
From < UNR to ≥ 50 ng/L	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
From < 20 ng/L to ≥ 20 ng/L	1 (0.03)	1 (0.05)	0 (0.00)	1 (0.07)	1 (0.11)	0 (0.00)
From < 50 ng/L to ≥ 50 ng/L	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

N: Number of subjects, %: Percentages are based on total N

Persistent increase: Baseline calcitonin value above LLOQ and below upper limit of normal range. All scheduled post baseline calcitonin measurements above or equal to upper limit of normal range.

Table is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1

Source: ISS, Table 2-89

A search was done among all AEs to identify events of 'increased calcitonin'. This search was based on the PTs: 'blood calcitonin abnormal', 'blood calcitonin increased', 'calcitonin secretion disorder', 'ectopic calcitonin production', and 'hypercalcitoninemia'. Adjudication was not performed on these AEs. In the weight management trials, the proportion of investigator-reported AEs of increased calcitonin was higher with liraglutide 3 mg (0.8%, 9 events per 1000 PY) than placebo (0.4%, 6 events per 1000 PY). One liraglutide 3 mg treated patient had 'blood calcitonin increased' reported as an SAE (for unclear reasons):

- Patient 918004 (trial 1922) was a 41-year-old female who had a screening calcitonin value of 22.1 ng/L and a baseline value of 15.5 ng/mL and subsequently had values during the trial ranging from 16.5 to 26.5 ng/L. The patient was not hospitalized and the patient had no dose adjustment during the trial.

7.5.3.2.3 Breast

More female patients treated with liraglutide 3 mg had EAC-confirmed events of malignant, pre-malignant, and benign breast neoplasms than female patients treated with placebo. None of the male patients had a malignant or pre-malignant breast neoplasm event.

Table 83. EAC-Confirmed Breast Neoplasms in Female Patients, Weight Management Pool Excluding Trial 1807

	Lira 3 mg	Placebo
Total breast neoplasms, n	14	3
Malignant	9	2
Pre-malignant	3	1
Benign	2	0
	N=2379	N=1300
Treatment emergent, main, n (%)	12 (0.5)	2 (0.2)
Malignant	7 (0.3)	1 (0.1)
Pre-malignant	3 (0.1)	1 (0.1)
Benign	2 (0.1)	0
Treatment emergent, re-randomized (trial 1839), n	1	1
Malignant	1	1
Diagnosed after withdrawal, n	1	0
Malignant	1	0

Source: ISS, Table 2-80

Details regarding the EAC-confirmed cases are as follows:

Table 84. EAC-Confirmed Breast Neoplasms, Treatment-Emergent and Non-Treatment Emergent, Weight Management Pool

Trial/subject/ /age/sex/BMI/ Country	PT	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/ Period	Medical history	Details^a
<i>Liraglutide 3.0 mg</i>						
1922/604012/ 67/F/28.2/ IL	Breast cancer metastatic	Metastatic breast cancer	Malignant/ Stage 4: Metastatic	313/313/ Main treatment period	Breast cancer 3 years prior to event	The event was diagnosed by histology. Recurrence of breast cancer with metastatic dispersal in mediastinum, lungs bilaterally and left axilla. Family history of breast cancer (mother). Not recovered.
1923/115021/ 37/F/29.9/ US	Breast cancer	Breast cancer	Malignant/ undetermined	377/373/ Main treatment period	No relevant	Bilateral mastectomy was performed. subject was withdrawn and recovered

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Trial/subject/ age/sex/BMI/ Country	PT	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/ Period	Medical history	Details ^a
1923/102012/ 47/F/36.5/ US	Breast cancer <i>in situ</i>	Invasive breast adeno- carcinoma	Malignant/ Stage 1: Localised	249/258/ Main treatment period	No relevant	Ductal carcinoma <i>in situ</i> . Family history of breast cancer (mother and sister). Not recovered.
1839/423007/ 62/F/51.0/ US	Breast cancer	Breast cancer	Malignant/ Stage 2: Locally advanced	223/222 Main treatment period	No relevant	Ductal carcinoma confirmed by histology. Partial mastectomy was performed. Not recovered. Two additional TEAE not confirmed by adjudication (reported as 'lung neoplasm', 'pituitary tumour').
1839/458010/ 55/F/32.9/ US	Breast cancer	Breast carcinoma	Malignant/ Stage 1: Localised	343/342/ Main treatment period	Breast calcifications in 1985	Ductal carcinoma confirmed by histology. Discovered through routine mammography. Subject is recovering.
1839/459029/ 51/F/53.2/ US	Adrenal mass/ Breast cancer	Breast cancer	Malignant/ Stage 3: Advanced	37/30/ Main treatment period	No relevant	Discovered through routine mammography. Lumpectomy was performed and diagnosis was confirmed by histology. Not recovered. Two events reported ('breast cancer' and 'adrenal mass'), events linked by EAC and 'adrenal mass' selected as index event
1839/489028/ 60/F/29.6/ US	Breast cancer Breast mass	Infiltration ductal carcinoma Breast carcinoma	Malignant/ Stage 1: Localised	143/142/ Main treatment period 143/224/ Main treatment period	Hormone replacement therapy from 2002-2007	Invasive ductal carcinoma. Lumpectomy was performed and diagnosis was confirmed by histology. Second breast mass was discovered at pre-operative examination (MRI scan). Two additional events (reported as 'breast mass', 'hepatic lesion' on Day 217) were not confirmed by adjudication.
1839/439021/ 57/F/36.3/ US	Breast cancer	Breast carcinoma	Malignant/ Stage 3: Advanced	414/413/ Re-randomised period (3.0 mg)	No relevant	Invasive ductal carcinoma. Discovered through routine mammography. Lumpectomy was performed and diagnosis was confirmed by histology. No confounding factors were reported. Not recovered.
1839/223005/ 43/F/37.0/ NO	Breast cancer stage III	Breast cancer to lymph nodes	Malignant/ Stage 3: Advanced	168/193/ Withdrawn from main treatment period	No relevant	Breast cancer advancing to lymph nodes. The subject withdrew her consent 19 days prior to the event while undergoing investigations for breast cancer. Recovering

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Trial/subject/ age/sex/BMI/ Country	PT	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/ Period	Medical history	Details ^a
1839/401030/ 47/F/31.6/ US	Breast cancer <i>in situ</i>	Breast ductal carcinoma <i>in situ</i>	Pre- malignant/ Stage 0: <i>In situ</i>	153/152/ Main treatment period	Benign palpable lymph node in breast	Family history of breast cancer. Discovered through routine mammography and confirmed by biopsy of removed tissue. Not recovered.
1839/429033/ 54/F/44.2/ US	Breast cancer <i>in situ</i>	Ductal carcinoma <i>in situ</i>	Pre- malignant/ Stage 0: <i>In situ</i>	32/31/ Main treatment period	Hormone replacement therapy from 2000-2004	Family history of breast cancer. Discovered through routine mammography and confirmed by biopsy of removed tissue. Recovered.
1839/432017/ 59/F/44.5/ US	Breast cancer <i>in situ</i>	Ductal carcinoma <i>in situ</i>	Pre- malignant/ Stage 0: <i>In situ</i>	303/302/ Main treatment period	Previous breast lumpectomy, fibrocystic breast changes	Family history of colon and ovarian cancer. Discovered through screening mammography and confirmed by biopsy of removed tissue. Recovered.
1839/420023/ 56/F/32.2/ US	Fibro- adenoma of breast	Fibro- adenoma	Benign	239/238/ Main treatment period	No relevant	Fibroadenoma confirmed by histology. No surgical removal or other treatment. Not recovered.
1839/433023/ 40/F/33.8/ US	Fibro- adenoma of breast	Fibro- adenoma	Benign	16/15/ Main treatment period	No relevant	Fibroadenoma was discovered through routine mammography and confirmed by histology. No surgical removal or other treatment. Not recovered.
<i>Placebo</i>						
1839/422015/ 40/F/34.3/ US	Breast cancer	Breast cancer	Malignant/ Stage 3: Advanced	177/169/ Main treatment period	No relevant	Family history of colon cancer and brain tumour. Invasive ductal carcinoma. Discovered through screening mammography. Bilateral mastectomy performed. Not recovered.
1839/484017/ 49/F/41.2/ US	Breast cancer <i>in situ</i>	Breast ductal carcinoma <i>in situ</i>	Pre- malignant/ Stage 0: <i>In situ</i>	319/282/ Main treatment period	Benign breast tumour in 1990, breast lumpectomy in 2009	Family history of cancer. Bilateral mastectomy performed. Recovered.
1839/476006/ 62/F/39.6/ US	Breast cancer	Breast carcinoma	Malignant/ Stage 1: Localised	478/477/ Re-randomised period	Thyroid nodule and hypoechoic mass in liver	Family history of breast cancer. Lumpectomy was performed. Recovering.

BMI: body mass index; EAC: event adjudication committee (and EAC assessment of onset day); F: female; inv: investigator assessment of onset day; PT: preferred term; MRI: magnetic resonance imaging.

a. details are based on information in the case narratives from the safety database.

Source: ISS, Table 2-81

Reviewer comment: *These cases were reviewed by the Office of Hematology and Oncology Products.³⁷ The reviewer noted that the information from the case narratives and the timing of onset do not support or deny the potential role of liraglutide in cancer promotion or progression.*

In addition to the above, two treatment-emergent events were reported during year 2 of trial 1807, including one SAE of ‘breast cancer’ with liraglutide 1.8 mg/2.4 mg

³⁷ Jarow, J. (OHOP), consult for NDA 206321, dated 3 Jul 2014

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(narrative below) and one non-SAE 'intraductal papilloma of breast' with liraglutide 3 mg/2.4 mg. No events were reported in the first year of trial 1807.

- Patient 131045 (trial 1807, year 2) was a 57-year-old female who discovered an asymptomatic nodule in the left breast by auto palpation. A biopsy showed malignancy and the histology report showed a 20 mm large invasive, ductal carcinoma of the breast, receptor negative, HER2 (Herceptin) negative, malignant degree III. The patient underwent surgery and chemotherapy. Trial product was discontinued due to a decision made of the patient, the investigator, and an oncologist.

In the 120-day safety update, two EAC-confirmed malignant breast neoplasms have been reported in the ongoing extension phase of trial 1839 in patients treated with liraglutide 3 mg (2 of 820 women, 0.2%, 2 events per 1000 PY). Both events were discovered during breast cancer screening. No events have been reported with placebo (0 of 376 women).

Table 85. EAC-Confirmed Breast Neoplasms, Trial 1839 Ongoing Extension

Trial/ subject/ age/sex/BMI Country	PT	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/	Medical history	Details ^a
<i>Liraglutide 3.0 mg</i>						
1839-ext/ 134003 /58/F/ 38.2/IT	Breast cancer	Breast carcinoma	Malignant/ Stage 2: Locally advanced	757 / 756	No relevant	Discovered during breast cancer screening program (including mammography). Resection of left breast was performed and diagnosis confirmed by histology. Local spread to lymph nodes was confirmed by biopsies from sentinel lymph nodes. Additional therapy included bilateral axillary lymphadenectomy and chemotherapy. Not recovered. The trial drug was temporarily discontinued due to the event.
1839-ext/ 153009 /53/F/ 36.6/CH	Breast cancer	Breast cancer	Malignant/ Stage 1: Localized	545 / 545	No relevant	This case was described in the original NDA, ISS Module 5.3.5.3, Section 2.1.11.6. Discovered during routine mammography. Resection of left breast was performed and diagnosis was confirmed by histology. No indication of metastases to lymph nodes, lungs, liver or bones. No confounding factors were reported. Not recovered. The trial drug was discontinued permanently due to this event.

BMI: body mass index; EAC: event adjudication committee (and EAC assessment of onset day); F: female; inv: investigator assessment of onset day; PT: preferred term

a. details are based on information in the case narratives from the safety database.

Source: 120-day safety update, Table 2-35

The majority of liraglutide-treated women with EAC-confirmed events of malignant or pre-malignant breast neoplasm had a significant weight loss at the time of diagnosis (Figure 46).

Figure 46. Percent Change in Body Weight in Patients with Breast Neoplasms, Weight Management Pool

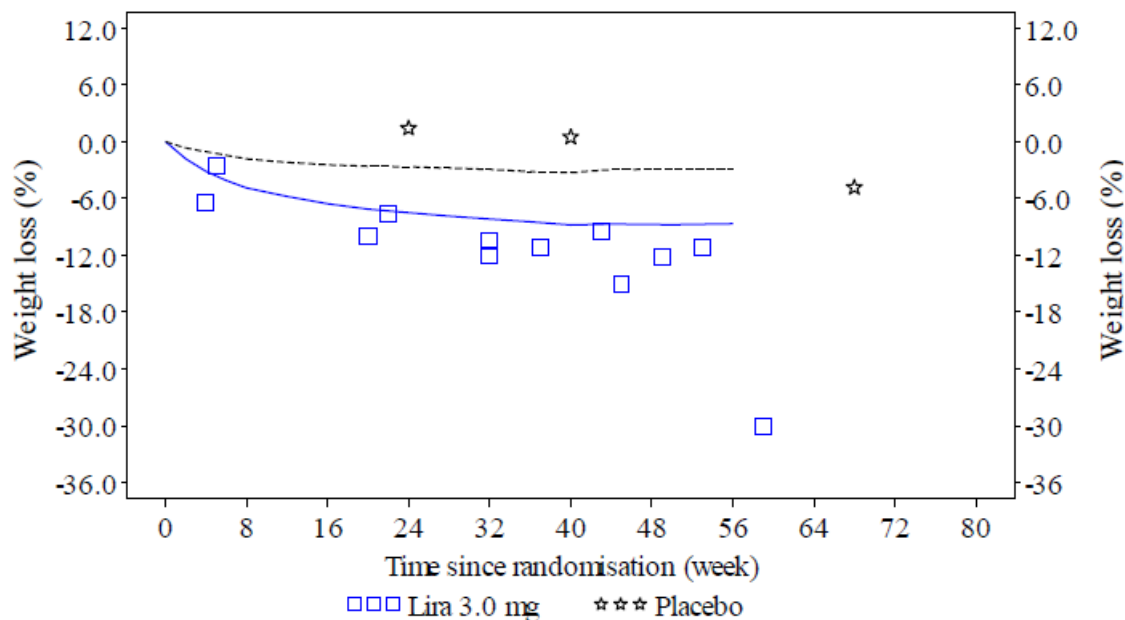


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).
Curves represent mean for subjects with no adjudicated breast neoplasms.
Events occurred during re-randomisation period of 1839 is also included.
Source: ISS, Appendix 7.2, Figure 256

Reviewer comment: *Given that most cases were detected through routine screening mammography, it is unclear whether ascertainment bias due to excess weight loss could contribute as a potential explanation for the imbalance between treatment groups in breast cancer events.*

7.5.3.2.4 Pancreas

As discussed in section 7.5.1 (pancreatitis), pancreatic safety is an ongoing area of interest with incretin mimetics. Specifically, a 2013 research publication suggested an increased incidence of pancreatic cellular changes, including exocrine cell proliferation and dysplasia and α -cell hyperplasia, in patients who had been exposed to incretin therapy (sitagliptin or exenatide) as compared to those who were not exposed.⁸ FDA, in concert with the European Medicines Agency (EMA), addressed pancreas safety with GLP-1-based therapies in a perspective published earlier this year, and noted that readjudication of clinical trial databases and evaluations of newly available nonclinical

and post-marketing clinical data that have been undertaken to date do not support a causal association at this time, although review of new data is ongoing.⁷

Pancreatitis was discussed with regard to the liraglutide clinical program in section 7.5.1.

With regard to pancreatic cancer, there were no reports of exocrine pancreatic cancer in the weight management program.

One patient was diagnosed with multiple endocrine neoplasia Type 1 (MEN1, a genetic condition) during treatment with liraglutide 3 mg in trial 1839. Adverse events of neuroendocrine tumor of the pancreas (later reclassified as MEN1), parathyroid adenomas, benign neoplasms of thyroid gland and pelvic cysts were reported during the trial and were adjudicated by the EAC:

- Patient 510010 (liraglutide 3 mg, trial 1839) was a 39-year-old female at trial enrollment. The patient was reportedly under evaluation for MEN1 and diagnosed with hyperparathyroidism prior to enrollment. By report, the patient's brother had been identified as a possible MEN syndrome patient. Relevant medical history included a benign pancreatic cyst and hemangioma in the right lobe of the liver. On trial day 70 the patient underwent an abdominal MRI that revealed cysts in the tail of the pancreas consistent with pre-study findings. In addition, the patient was diagnosed with a neuroendocrine tumor of the pancreas. Fourteen days later, a parathyroid scan was performed and suggested left-sided parathyroid adenoma. The trial product was discontinued due to this event. Following trial product discontinuation, additional investigational procedures were performed, which confirmed diagnosis of a nonfunctioning neuroendocrine pancreatic cyst and revealed multiple colloid cysts in the thyroid gland. The patient underwent a distal pancreas and spleen resection. Multiple neuroendocrine grade 1 tumors measuring 1.5 cm, 1.4 cm, 1 cm, 0.9 cm, 0.8 cm, 0.7 cm, and 0.7 cm were found. No treatment was given for the benign thyroid neoplasms. At the time of the narrative, a left-sided parathyroidectomy was planned.

At the data cut-off reported in the 120-day safety update, there were no reports of pancreatic cancer in the extension period of trial 1839.

7.5.3.2.5 Colorectum

As noted in Table 73 above, an imbalance in adjudicated colorectal neoplasms was seen in the liraglutide-treated group as compared to the placebo-treated group; most lesions were adjudicated as benign (incidence of benign colorectal neoplasms in liraglutide 3 mg and placebo-treated groups: 0.33% and 0.22%, respectively). The majority of cases were detected during routine screening colonoscopy.

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Two patients (0.06%) treated with liraglutide (and no placebo-treated patients) were reported to have malignant colorectal neoplasms; see details in Table 86.

Table 86. EAC-Confirmed Colorectal Neoplasms, Weight Management Pool

Trial/subject/ age/sex/BMI/ Country	PT	EAC diagnosis	EAC malignanc y status	Inv onset, days/ EAC onset, days/ Period	Medical history	Details ^a
<i>Liraglutide 3.0 mg</i>						
1922/402004/ 67/M/29.2/ DE	Rectal cancer	Rectal adenocarcino ma	Malignant/ Stage I	274/274/ Main treatment period	No relevant	Family history of colon carcinoma, cervix carcinoma, gastric carcinoma and bladder carcinoma
1839/143039/ 37/F/33.9/ AT	Colon cancer	Colon carcinoma	Malignant/ Stage III	33/168/ Main treatment period	No relevant	Anaemia and rectal bleeding was reported at trial start
1922/604007/ 47/M/42.2/ IL	Colon adenoma	Colon adenoma	Benign	283/283/ Main treatment period	No relevant	Diagnosed by colonoscopy followed by histology. Colonoscopy performed due to abdominal pain and change in bowel habits
1922/605004/ 64/F/33.4/ IL	Adenoma benign	Tubulo- villous adenoma	Benign	206/206/ Main treatment period	Diverticulo sis	Diagnosed during routine colonoscopy followed by histology
1922/802002/ 56/M/29.9/ TR	Colon adenoma	Colon adenoma	Benign	182/182/ Main treatment period	No relevant	Diagnosed by colonoscopy followed by histology
1922/939003/ 64/F/46.9/ US	Colon adenoma	Colon adenoma	Benign	324/324/ Main treatment period	Benign colon polyps	Diagnosed during routine colonoscopy followed by histology
1922/951001/ 56/M/31.3/ US	Colon adenoma	Tubular adenoma	Benign	387/387/ Main treatment period	Bladder cancer, intermittent diverticuliti s	Diagnosed during routine colonoscopy followed by histology
1839/123003/ 60/M/39.2/ ES	Colon adenoma	Colon adenoma	Benign	71/70/ Main treatment period	Abdominal pain since 2006	Diagnosed by colonoscopy followed by histology. Colonoscopy performed due to abdominal pain since 2006
1839/130012/ 62/F/41.9/ IT	Intestinal polyp	Adenoma	Benign	295/295/ Main treatment period	Family history of intestinal polyps	Diagnosed by colonoscopy followed by histology. Routine colonoscopy performed due to family history of intestinal polyps (father).
1839/282014/ 54/F/40.0/ IL	Colonic polyp	Colon polyp	Benign	11/10/ Main treatment period	No relevant	Diagnosed during routine colonoscopy followed by histology

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Trial/subject/ age/sex/BMI/ Country	PT	EAC diagnosis	EAC malignanc y status	Inv onset, days/ EAC onset, days/ Period	Medical history	Details ^a
1839/351011/ 51/M/29.9/ HK	Colon adenoma	Colon adenoma	Benign	345/344/ Main treatment period	No relevant	Diagnosed by colonoscopy followed by histology. Colonoscopy performed due to constipation
1839/447002/ 65/M/33.4/ US	Colon adenoma	Tubular adenoma of the colon	Benign	264/263/ Main treatment period	Diverticulo sis Benign polyp in 1999	Diagnosed during routine colonoscopy followed by histology
1922/904002/ 44/M/44.9/ US	Colon adenoma	Adenoma	Benign	406/406/ Follow-up period	Benign colon polyps, smoking	Reported during first 2 weeks of follow-up period (i.e., TEAE in tables and listings). Diagnosed during routine colonoscopy followed by histology
<i>Placebo</i>						
1839/132017/ 71/M/39.1/ IT	Colon adenoma	Colon adenoma	Benign	205/204/ Main treatment period	Polypectom y in 2010	Diagnosed during routine colonoscopy followed by histology
1839/409029/ 49/F/39.1/ US	Colon adenoma	Colon polyps	Benign	57/56/ Main treatment period	Intermittent rectal bleeding	Diagnosed by colonoscopy followed by histology. Colonoscopy showed diverticulosis and 3 tubular adenomas
1839/424003/ 62/F/43.1/ US	Colon adenoma	Colon adenoma	Benign	123/122/ Main treatment period	No relevant	Diagnosed during routine colonoscopy followed by histology
1839/445014/ 63/F/31.5/ US	Rectal polyp	Tubular adenoma	Benign	186/185/ Main treatment period	No relevant	Diagnosed during routine colonoscopy followed by histology

BMI: body mass index; EAC: event adjudication committee (and EAC assessment of onset day); F: female; M: male; inv: investigator assessment of onset day; PT: preferred term.

a. Details are based on information in the case narratives from the safety database.

Source: ISS, Table 2-83

In addition to these adjudicated events, there was one (non-adjudicated) sigmoid adenocarcinoma in a patient treated with liraglutide 2.4 mg in trial 1807 (see narrative below). There were no events of benign colorectal adenomas in trial 1807.

- Patient 133025 was a 65-year-old female with a history of heavy smoking, who participated in a program for screening for lung cancer. As part of this program she had a CT scan performed that showed liver metastases. A biopsy showed adenocarcinoma, primary tumor was determined to be adenocarcinoma of the sigmoid colon, clinical staging: T3N2M1V1, 20 of 34 lymph nodes positive, and liver metastases. The patient underwent surgery with resection of the sigmoid colon and subsequently received chemotherapy. The patient was withdrawn from the trial due to the event.

As reported in the 120-day safety update of the ongoing trial 1839, 6 EAC-confirmed benign colorectal neoplasms, all in patients treated with liraglutide 3 mg (0.6%), and 1 EAC-confirmed malignant carcinoid tumor in a patient treated with placebo (0.2%) were reported.

Table 87. EAC-Confirmed Colorectal Neoplasms, Ongoing Trial 1839 Extension

Trial/ subject/ age/sex/BMI Country	PT	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/	Medical history	Details ^a
<i>Liraglutide 3.0 mg</i>						
1839-ext/ 142018 / 42/F/40.4/ AT	Colon adenoma	Adenoma	Benign	519 / 519	No relevant	Diagnosed during routine colonoscopy followed by histology. Colonoscopy performed due to family history of colon carcinoma (mother). Recovered.
1839-ext/ 409007 / 60/M/31.4/ US	Colon adenoma	Adenoma	Benign	446 / 446	No relevant	Diagnosed during routine colonoscopy followed by histology. The adenoma was resected and no further treatment given. Recovered.
1839-ext/ 414007/ 49/M/36.4/ US	Colonic polyp	Colon adenoma	Benign	638 / 638	No further details available	No further details available
1839-ext/ 417011 / 53/M/39.2/ US	Colonic polyp	Colon adenoma	Benign	774 / 774	Personal and family history of colon polyps, irritable bowel syndrome	Discovered and removed during routine colonoscopy. Recovered.
1839-ext/ 464011 / 60/F/45.8/ US	Colonic polyp	Colon adenoma	Benign	522 / 522	Benign colon polyps in 2009	During routine colonoscopy, 10 benign (confirmed by histology) polyps were removed. Recovered.
1839-ext/ 506004 / 55/M/36.8/ CA	Colon adenoma	Colon adenoma	Benign	412 / 412	No relevant	During routine colonoscopy, a 3 mm benign (confirmed by histology) polyp in cecum was removed. Colonoscopy performed due to family history of colon carcinoma (father). Recovered.

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Trial/ subject/ age/sex/BMI Country	PT	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/	Medical history	Details ^a
<i>Placebo</i>						
1839-ext/ 106023/ 51/M/31.1/ DE	Neuro- endocrin e tumor	Carcinoid tumor	Malignant	458 / 458	Resection of colon polyp in 2011 prior to entry into the trial. Immuno- histological examination showed well differentiate d endocrine tumor	Diagnosed at follow up routine colonoscopy. Histologic examination of a rectal polyp removed showed neuroendocrine tumor. It was suggested that the lesion diagnosed in 2011 may not have been completely removed. The subject recovered and continued on unchanged trial medication.

BMI: body mass index; EAC: event adjudication committee (and EAC assessment of onset day); F: female; M: male; inv: investigator assessment of onset day; PT: preferred term.

a. Details are based on information in the case narratives from the safety database.

Source: 120 day safety update, Table 2-37

7.5.3.3 Diabetes Program

Note that neoplasms were *not* prospectively adjudicated in the diabetes trials.

A small excess of neoplasms (as identified in the MedDRA Neoplasms SMQ) was noted in the diabetes program: 3.2% in the total liraglutide groups versus 2.5% in the comparator group. Some of the excess number of events in the liraglutide group was attributable to thyroid neoplasms, a topic of active discussion at the Victoza advisory committee meeting, and discussed further below (see Table 89).

The following table demonstrates a smaller difference between treatment groups when the assessment is limited to serious AEs. Selected neoplasm SAEs of interest were presented in the table below.

Table 88. Neoplasm SAEs by Type and Preferred Term, Diabetes Pool

	Total lira N=7037	Comparator total N=3677
	n (%)	n (%)
Neoplasm SMQ, SAEs	58 (0.8)	23 (0.6)
Thyroid		
Thyroid cancer	7 (0.1)	2 (0.1)
Thyroid neoplasm	3 (<0.1)	0
Breast		
Breast cancer	4 (0.1)	1 (<0.1)
Inflammatory carcinoma of breast stage III	1 (<0.1)	0
Pancreas		
Adenocarcinoma pancreas	1 (<0.1)	0
Pancreatic carcinoma	1 (<0.1)	0
Pancreatic carcinoma stage IV	1 (<0.1)	0
Pancreatic carcinoma metastatic	0	1 (<0.1)
Colorectal		
Colon cancer	3 (<0.1)	1 (<0.1)
Rectal cancer	2 (<0.1)	0
Colon cancer stage 0	1 (<0.1)	0
Large intestine carcinoma	0	1 (<0.1)

Sources: Supplementary AE Report, Appendix 1, Table 58

Regarding thyroid neoplasms, events (serious and non-serious) identified by the MedDRA search for thyroid neoplasms were not adjudicated (in contrast to the weight management program). In controlled trials with liraglutide for T2DM, 27 patients treated with liraglutide reported 28 events of 'thyroid neoplasm' (0.4%, 6 events per 1000 PY) as compared to 4 patients with 4 events (0.1%, 2 events per 1000 PY) of comparator, and 7 liraglutide-treated patients reported 7 events of 'thyroid cancer' (<0.1%, 1 event per 1000 PY) as compared to 2 comparator-treated patients with 2 events (<0.1%, <1 event per 1000 PY); see Table 89.

Table 89. Thyroid Neoplasms, MedDRA Preferred Terms, Diabetes Pool

	Total lira N=7037	Comparator total N=3677
	n (%)	n (%)
Thyroid neoplasm	27 (0.4)	4 (0.1)
Thyroid cancer	7 (<0.1)	2 (<0.1)
Benign neoplasm of thyroid gland	2 (<0.1)	1 (<0.1)

Source: Supplementary AE Report, Appendix 1, Table 63

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The imbalance in thyroid neoplasms in the diabetes trials is consistent with the original Victoza safety review.³⁸ (There was speculation by some advisory committee members at that time that the imbalance was potentially related to increased surveillance; i.e., ascertainment bias.³⁹)

Six (of nine) cases of 'thyroid cancer' from the diabetes program reported in this NDA were reviewed in the Victoza safety review,³⁸ including one case of MTC in a patient treated with comparator (patient 770001, trial NN2211-1697), and one case of papillary cancer + MTC *in situ* in a patient treated with liraglutide 1.8 mg (patient 175008, trial NN2211-1573) who had elevated calcitonin (22.3 ng/mL) at baseline.

The three new cases are:

- Patient 224012 (trial 1572), verbatim term 'thyroid cancer', randomized to comparator (glimepiride + metformin)

This patient was reportedly diagnosed with MTC *in situ*; no further information was provided.

- Patient 117011 (trial 1573), verbatim term 'papillary thyroid carcinoma', randomized to liraglutide 1.8 mg

This was a 53-year-old female treated with liraglutide from 12 Oct 2006 to 27 Apr 2009. Medical history included thyroid nodules since 1997.

During the trial, calcitonin values ranged from < 0.7 to 1.6 ng/mL. On (b) (6) the patient was diagnosed with enlargement of the pre-existing thyroid nodules. On (b) (6) the patient had a near total thyroidectomy. Pathology reportedly demonstrated: (1) Papillary thyroid carcinoma, encapsulated follicular variant at least 2.0 cm in size; (2) Nodular thyroid hyperplasia. The patient was treated with radioiodine I-131. No change to the trial drug was taken due to the event.

- Patient 215002 (trial 1573), verbatim term 'papillary thyroid microcarcinoma', randomized to liraglutide 1.2 mg

This was a 72-year-old male patient treated with liraglutide from 16 Oct 2006. The patient was found to have elevated calcitonin at baseline (22.7 ng/L), and notably a daughter was reported to have had thyroid cancer. During the trial, calcitonin fluctuated from 17.4 to 38.4 ng/L. On 25 Oct 2006, an ultrasound of the thyroid (performed due to elevated calcitonin) showed a cystic left nodule measuring 2.1 cm. On 04 Dec 2006, ultrasound guided needle biopsy was negative for malignant

³⁸ Mahoney KM. NDA 22341 Clinical Safety Review, signed 07 Aug 2009.

³⁹ Parks M. Division Director's Memo for NDA 22341, 22 Jan 2010.

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cells. On [REDACTED] (b) (6), a left side thyroid lobectomy was performed, which showed papillary thyroid microcarcinoma 0.5 mm and several areas of C-cell hyperplasia. The patient was told that 'he was cured by the surgery performed and that he does not require radioiodine ablation'. The investigator considered this event to be due to a pre-existing condition.

Verbatim terms associated with the 'thyroid neoplasm' events are primarily thyroid nodules (see Table 90). According to the sponsor, these terms also included eight cases of benign C-cell hyperplasia (confirmed by pathological evaluation), but these patients and the clinical circumstances were not specified. Three of the cases of 'thyroid neoplasm' were reported as SAEs.

- Patient 232004 (trial 1572) was a 47-year-old female who presented with elevated blood calcitonin (value not mentioned) and a solitary right thyroid nodule after 27 days of run-in metformin therapy. Although she was randomized to liraglutide, the narrative states she never received the drug. Eight months after the elevated calcitonin and the nodule were noted, she underwent resection of the nodule, which was benign. One month postoperatively, her calcitonin value was reported as normal.
- Patient 47002 (trial 1700) was a 72-year-old male randomized to liraglutide with medical history of 'tendency of high thyroid stimulating hormone' (TSH) since September 2006. On 9 Nov 2007, a nodular lesion (13x10 mm) was discovered in the middle of the left thyroid lobe. The patient was diagnosed with left lobe thyroid tumor. A biopsy was performed; however the result was not sufficient to determine whether the tumor was benign or malignant. On 20 Dec 2007 the patient discontinued study drug. On [REDACTED] (b) (6) the patient was hospitalized and left thyroid gland was excised. The pathology results showed an "adenomatous nodule" with no evidence of malignancy.
- Patient 840006 (trial 3697) was a 60-year-old female treated with liraglutide. On study day 49, the patient was found to have discrete 1 cm nodule of left lobe. Thyroid ultrasound showed a 1 x 0.5 cm hypoechoic nodule in the anterior aspect of the left mid and lower thyroid region. Uptake thyroid scan showed a normal thyroid scan with no hot or cold nodules (nodule may have been too small to characterize). No biopsy or thyroidectomy was performed.

Table 90. Events of ‘Thyroid Neoplasm’, Diabetes Pool

Diabetes Trial	Patient ID	Treatment	Verbatim Term (Investigator)
NN2211-1334	002005	Comparator	Thyroid nodule
NN2211-1334	002006	Lira	Thyroid nodule
NN2211-1334	005011	Lira	Thyroid nodule
NN2211-1334	006017	Lira	Thyroid nodule
NN2211-1334	012006	Comparator	Thyroid nodule
NN2211-1334	014007	Lira	Thyroid nodule
NN2211-1334	020005	Lira	Thyroid nodule
NN2211-1334	022001	Lira	Thyroid nodule
NN2211-1334	026005	Comparator	Thyroid nodule
NN2211-1334	026006	Lira	Thyroid nodule
NN2211-1334	029001	Lira	Thyroid nodule
NN2211-1334	031001	Lira	Thyroid nodule
NN2211-1334	059006	Lira	Thyroid nodule
NN2211-1334	063002	Lira	Thyroid nodule
NN2211-1436	598016	Lira	Left thyroid nodule
NN2211-1572	232004	Lira	Struma uninodosa (nontoxic)
NN2211-1572	350006	Lira	Thyroid nodule
NN2211-1573	136003	Comparator	RIGHT LOWER LOBE THYROID NODULE
NN2211-1573	139003	Lira	LEFT TINY THYROID NODULE
NN2211-1573	183011	Lira	ENLARGED RIGHT AND LEFT THYROID NODULE
NN2211-1573	261006	Lira	MULTIPLE THYROID NODULES
NN2211-1574	316010	Lira	THYROID NODULES
NN2211-1700	42004	Lira	Thyroid nodule
NN2211-1700	47002	Lira	Thyroid tumour
NN2211-1797	352004	Lira	THYROID NODULE
NN2211-1860	111004	Lira	Regressive thyroid gland (one cyst, three calcificated nodes)
NN2211-1860	651008	Lira	Solitary nodule in thyroid gland
NN2211-1860	783014	Lira	THYROID NODULES
NN9068-3697-main-ext	231007	Lira	thyroid nodules
NN9068-3697-main-ext	601004	Lira	thyroid nodule
NN9068-3697-main-ext	840006	Lira	hypoechoic thyroid nodule

Source: Reviewer created from sponsor datasets

In uncontrolled trials and trial periods in the diabetes program, there was one event of ‘thyroid C-cell hyperplasia’ reported with liraglutide in trial NN2211-1842 (0.1%, 1 event per 1000 PY), one patient with one event of ‘thyroid cancer’ (0.1%, 1 event per 1000 PY) in trial NN2211-1842, and a total of eight patients with eight events of ‘thyroid neoplasm’ (0 to 1%, 0 to 12 events per 1000 PY).

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AEs of 'blood calcitonin increased' or 'blood calcitonin abnormal' were reported in 71 (1.0%) of patients treated with liraglutide and 28 (0.8%) of patients treated with comparator. In addition, one patient treated with comparator had an AE of 'hypercalcitoninemia'.

Breast, pancreatic, and colorectal cancers were similarly not adjudicated in the diabetes program, but the incidences of SAEs are listed in Table 88 (breast: liraglutide 0.1% vs. comparator <0.1%; pancreas: liraglutide <0.1% vs. comparator <0.1%; colorectal: liraglutide 0.1% vs. comparator 0.1%).

7.5.3.4 Weight and Diabetes Programs, Combined

Weight and diabetes programs are presented combined for a more robust assessment of cancer events. Some of the adverse events were able to be grouped by high level group terms, and some AEs were not summarized by higher level categories of interest, but are listed under headings grouped by the reviewer.

Note that adverse events listed as 'neoplasm' were unspecified as to whether they represented benign or malignant neoplasms. For example, as discussed in the section above, verbatim terms that mapped to 'thyroid neoplasm' included verbatim terms such as 'thyroid nodule' as well as 'thyroid tumor'.

Table 91. Treatment-Emergent Neoplasms by SMQ, System Organ Class, High Level Group Term, and Preferred Term (Selected), Weight Management and Diabetes Pool

	Total lira N=10909 PY=8444.7		Comparator total N=5713 PY=4117.3	
	n (%)	Rate / 1000 PY	n (%)	Rate / 1000 PY
Neoplasm SMQ	416 (3.8)	57	188 (3.3)	56
Neoplasm benign, malignant and unspecified SOC	233 (2.1)	31	108 (1.9)	29
Thyroid, malignant and unspecified*				
Thyroid neoplasm	32 (0.3)	4	5 (<0.1)	1
Thyroid cancer	10 (<0.1)	1	3 (<0.1)	<1
Breast neoplasms malignant and unspecified HLGT	17 (0.2)	2	3 (<0.1)	<1
Breast cancer	10 (<0.1)	1	2 (<0.1)	<1
Breast cancer in situ	4 (<0.1)	<1	1 (<0.1)	<1
Breast cancer metastatic	1 (<0.1)	<1	0	0
Breast cancer stage III	1 (<0.1)	<1	0	0
Inflammatory carcinoma of breast stage III	1 (<0.1)	<1	0	0
Pancreas, malignant*†				
Adenocarcinoma pancreas	1 (<0.1)	<1	0	0
Pancreatic carcinoma	1 (<0.1)	<1	0	0
Pancreatic carcinoma stage IV	1 (<0.1)	<1	0	0
Pancreatic carcinoma metastatic	0	0	1 (<0.1)	<1

Other gastrointestinal (malignant, benign, and unspecified)*				
Colon adenoma	11 (0.1)	1	5 (<0.1)	1
Colon cancer	4 (<0.1)	<1	1 (<0.1)	<1
Rectal cancer	3 (<0.1)	<1	0	0
Colon cancer stage 0	1 (<0.1)	<1	0	0
Colorectal carcinoma stage 0	1 (<0.1)	<1	0	0
Gastrointestinal submucosal tumor	1 (<0.1)	<1	0	0
Esophageal carcinoma	1 (<0.1)	<1	0	0
Benign colonic neoplasm	1 (<0.1)	<1	0	0
Oral fibroma	1 (<0.1)	<1	0	0
Tongue neoplasm benign	1 (<0.1)	<1	0	0
Gastric cancer	1 (<0.1)	<1	1 (<0.1)	<1
Gastrointestinal tract adenoma	1 (<0.1)	<1	1 (<0.1)	<1
Gastric cancer stage II	0	0	1 (<0.1)	<1
Large intestine carcinoma	0	0	1 (<0.1)	<1
* Reviewer headers; relevant HLGs not available				
† Note that there was also one AE of neuroendocrine tumor of the pancreas (discussed in section 7.5.3.2.4) in the weight management program that was adjudicated as MEN1.				

Source: Supplementary AE Report, Appendix 1, Table 54

Adverse events of elevated calcitonin were identified via a predefined SMQ search in the weight management and diabetes programs combined. There was a small imbalance in the liraglutide-treated group as compared to the comparator-treated group.

Table 92. Elevated Calcitonin by Preferred Term, Weight Management and Diabetes Programs Combined

	Total lira N=10909	Comparator total N=5713
AEs of Elevated Calcitonin	100 (0.9)	37 (0.6)
Blood calcitonin increased	98 (0.9)	35 (0.6)
Blood calcitonin abnormal	2 (<0.1)	0
Hypercalcitoninemia	0	2 (<0.1)

Source: Supplementary AE Report, Appendix 1, Table 66

7.5.4 Liver Events and Related Laboratory Data

7.5.4.1 Liver-Related Laboratory Data

The FDA Guidance for evaluating premarketing drug-induced liver injury⁴⁰ considers the best predictor for severe hepatotoxicity as transaminase elevation accompanied by increased serum total bilirubin, not explained by any other cause and without evidence of cholestasis (i.e., “Hy’s law”), together with an increased incidence of transaminase

⁴⁰ FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

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elevations in the overall trial population compared to control. No Hy's law cases were identified in any clinical study in the liraglutide development program.

A small imbalance of ALT elevations greater than or equal to 10 times the upper limit of normal in liraglutide-treated patients was noted in the weight management program (Table 93), so these cases were explored further. Narratives of patients with ALT values greater than 10 times the upper limit of normal treated with liraglutide 3 mg in the weight management pool follow the tables of liver parameter outliers (including patients whose high values fell outside the main treatment period window).

Table 93. Outlier Analysis of Liver Parameters, Main Treatment Period, Weight Management Pool

	Lira 3 mg N=3384	All lira N=3872	Placebo N=1941
ALT			
≥ 3x ULN	36 (1.1)	42 (1.1)	20 (1.0)
≥ 5x ULN	9 (0.3)	9 (0.2)	4 (0.2)
≥ 10x ULN	5 (0.1)	5 (0.1)	1 (0.1)
≥ 20x ULN	2 (0.1)	2 (0.1)	0
AST			
≥ 3x ULN	18 (0.5)	22 (0.6)	12 (0.6)
≥ 5x ULN	8 (0.2)	8 (0.2)	4 (0.2)
≥ 10x ULN	3 (0.1)	3 (0.1)	2 (0.1)
≥ 20x ULN	1 (<0.1)	1 (<0.1)	0
Alk Phos			
≥ 2.5x ULN	3 (0.1)	4 (0.1)	3 (0.2)
≥ 5x ULN	1 (<0.1)	1 (<0.1)	0
≥ 20x ULN	0	0	0
T. bili			
≥ 1.5x ULN	20 (0.6)	24 (0.6)	13 (0.7)
≥ 3x ULN	0	0	1 (0.1)
≥ 10x ULN	0	0	0
ALT + T. bili			
ALT > 3x ULN + T. bili > 2x ULN	0	0	0
Note: All visits after first drug exposure in the trials 1807, 1807-ext 1, 1807 ext 2, 1922, 1923, and 3970 are included. For trial 1839 all visits after the first drug exposure are included until week 56 for patients in the pre-DM strata, and until week 69 for patients in the normoglycemic strata in the lira/lira and placebo/placebo treatment arms, and until week 56 for patients in the normoglycemic strata in the lira/placebo treatment arm.			

Source: Response to FDA request dated 18 Jun 2014, Appendix 1 Table 4

Table 94. Outlier Analysis of Transaminases, Diabetes Pool

	Liraglutide N=7037	Comparator N=3677
ALT		
≥ 3x ULN	36 (0.5)	20 (0.5)
≥ 5x ULN	10 (0.1)	3 (0.1)
≥ 10x ULN	0	1 (<0.1)
≥ 20x ULN	0	0
AST		
≥ 3x ULN	28 (0.4)	11 (0.3)
≥ 5x ULN	6 (0.1)	2 (0.1)
≥ 10x ULN	0	0
≥ 20x ULN	0	0

Source: Response to FDA request dated 18 Jun 2014, Appendix 1 Table 1

The following are narratives of liraglutide-treated patients with ALT at least 10× ULN, weight management pool:

- Patient 133039 (trial 1807): This was a 40-year-old female on oral contraceptives and glucosamine. She was treated with liraglutide in trial 1807 for approximately 18 months. She had normal hepatobiliary laboratory parameters at baseline. On day 54, she complained of mild abdominal pain, and labs drawn 2 days later demonstrated ALT 955 U/L, AST 451 U/L, alkaline phosphatase 142 U/L, and normal total bilirubin. At an unscheduled visit 3 weeks later, labs were repeated and were within normal limits. She had several biliary colic AEs during the trial and underwent surgery for cholelithiasis on day 475.
- Patient 251021 (trial 1839): This was a 48-year-old white female with a history of intermittent right upper quadrant abdominal pain. Baseline medications included enalapril, simvastatin, and hydrochlorothiazide. Four days prior to the start of treatment, she presented with a serious AE of biliary colic. Her baseline labs were abnormal: ALT 436 U/L, AST 145 U/L, and alkaline phosphatase 204 U/L. She had an elective cholecystectomy on study day 52. She completed the trial on study day 529.
- Patient 251045 (trial 1839): This was a 50-year-old female with a medical history of hepatomegaly. Concomitant medications included oral contraceptives, omeprazole, and cromolyn sodium. Hepatobiliary parameters were normal at baseline. On day 30, a non-serious AE of elevated hepatic enzymes was reported (ALT 377 U/L, AST 152 U/L). Other liver parameters were normal. Repeat values over next few months demonstrated persistent elevation, although improved (ALT 87 U/L, AST 40 U/L). Abdominal ultrasound was reportedly normal. On day 205, all hepatobiliary

laboratory parameters had returned to the normal range, and remained so until study completion. She completed the trial on study day 394.

- Patient 490007 (trial 1839): This was a 36-year-old female with abnormal ALT and AST at screening and baseline (screening ALT 199 U/L, AST 76 U/L; baseline ALT 79 U/L, AST 43 U/L). Approximately 3 weeks after starting treatment with liraglutide, the patient presented with AEs of nausea, vomiting, and worsening of gastroesophageal reflux disease. At the patient's 4 week visit, she reported an AE of sinusitis and laboratory tests were drawn, which demonstrated ALT 1523 U/L and AST 911 U/L. Total bilirubin and alkaline phosphatase were within normal limits. Two weeks later, laboratory tests were repeated at an outside lab (ALT 635 U/L, AST 351 U/L, normal total bilirubin and alkaline phosphatase). The patient withdrew from the trial 4 days later due to persistent nausea and vomiting. One month after the patient discontinued drug, the laboratory values were repeated as part of the early termination study visit. The lipase and amylase enzymes were normal and the ALT and AST were continuing to improve to 444 and 250 U/L, respectively, with normal alkaline phosphatase and bilirubin. An anti-liraglutide antibody measurement was measured and the results were negative. Values normalized (below baseline) approximately 6 months after stopping the study drug. In the interim, she discontinued concomitant medications transexamic acid, oral contraceptives, esomeprazole, fexofenadine, as well as social drinking.
- Patient 241010 (trial 1839): This was a 55-year-old female on aspirin, codeine, and enalapril at baseline. Baseline ALT was slightly elevated (40 U/L). Other hepatobiliary parameters were normal. During the study, she reported several adverse events of abdominal pain, as well as nausea, diarrhea, constipation, and fatigue. Hepatobiliary parameters were normal until study day 113 (ALT 464 U/L, AST 145 U/L, alkaline phosphatase 106 U/L, lipase 70 U/L). Total bilirubin and amylase were normal. No adverse events were reported at that visit. At her next visit, laboratory data had normalized and remained so until the end of the trial (with the exception of one slight increase of ALT to 46 U/L on study day 281). She completed the trial on day 392.
- Patient 502016 (trial 1839): This was a 68-year-old female with gastroesophageal reflux disease, CV disease, and hypothyroidism on concomitant medications levothyroxine, losartan, hydrochlorothiazide, and rabeprazole. At baseline, hepatobiliary parameters were normal. She completed the trial on day 526. On day 71, she had a SAE of cholelithiasis. Trial drug was temporarily discontinued. Approximately 1 month later (still off study drug), she was treated in the ER for cholelithiasis. Two days later labs were: ALT 648 U/L, AST 341 U/L, ALP 214 mg/dL, and lipase 63 U/L. Total bilirubin and amylase were within normal limits. Trial product was reintroduced approximately 1 month later. All subsequent hepatobiliary parameters were normal.

- Patient 205007 (trial 1923): This was a 54-year-old female with hypertension and COPD. Baseline concomitant medications included: valsartan, diltiazem, and salbuterol. Baseline hepatobiliary parameters were normal. On study day 190, she had an AE for elevated liver enzyme on a routine study visit: ALT 318 U/L, AST 186 U/L, ALP 150 mg/dL, with a normal total bilirubin and amylase. Biliary colic was suspected, but not confirmed. She had normal hepatobiliary parameters thereafter and completed study drug on day 393. During the routine 7-day end of study follow-up, hepatobiliary blood tests were: ALT 536 U/L, AST 246 U/L, ALP 125 mg/dL, and normal total bilirubin and amylase. Cholelithiasis was reported 21 days after the last dose of study medication, confirmed by MRI. Labs normalized by day 477, and laparoscopic cholecystectomy was performed day 498.

Adverse events of hepatobiliary investigations were generally similar between groups:

Table 95. Adverse Events from Hepatobiliary SOC, Weight Management Pool

	Lira 3 mg N=3384	Total lira N=3872	Placebo N=1941
Hepatobiliary investigations	49 (1.4)	53 (1.4)	24 (1.2)
Alanine aminotransferase increased	24 (0.7)	25 (0.6)	14 (0.7)
Aspartate aminotransferase increased	16 (0.5)	17 (0.4)	7 (0.4)
Liver function test abnormal	9 (0.3)	9 (0.2)	4 (0.2)
Hepatic enzyme increased	8 (0.2)	9 (0.2)	3 (0.2)
Transaminases increased	3 (<0.1)	3 (<0.1)	2 (0.1)
Blood bilirubin increased	1 (<0.1)	2 (<0.1)	1 (<0.1)
Gamma-glutamyltransferase increased	0	1 (<0.1)	0

Source: ISS, Appendix 7.2, Table 425

7.5.4.2 Adverse Events of Hepatitis or Liver Injury

7.5.4.2.1 Weight Management Program

Liver events were not considered medical events of special interest and did not undergo an adjudication review process. The following table is an overall evaluation of events within the 'Hepatic and hepatobiliary disorders' HLGT.

Table 96. Liver-Related Adverse Events, Weight Management Pool

	Lira 3 mg	All lira	Placebo
Hepatic and hepatobiliary disorders	23 (0.7)	32 (0.8)	16 (0.8)
Hepatic steatosis	14 (0.4)	23 (0.6)	13 (0.7)
Hepatic lesion	2 (<0.1)	2 (<0.1)	0
Hepatic cyst	1 (<0.1)	1 (<0.1)	2 (0.1)
Hepatic mass	1 (<0.1)	1 (<0.1)	0
Hepatitis	1 (<0.1)	1 (<0.1)	0
Hepatitis acute	1 (<0.1)	1 (<0.1)	0
Hepatomegaly	1 (<0.1)	1 (<0.1)	1 (<0.1)
Liver disorder	1 (<0.1)	1 (<0.1)	0
Non-alcoholic steatohepatitis	1 (<0.1)	1 (<0.1)	0
Hepatosplenomegaly	0	0	2 (0.1)

Source: ISS, Appendix 7.2, Table 2

There were two serious adverse events of ‘hepatitis’ in the weight management program; both patients were randomized to liraglutide in trial 1839.

- Patient 295014 (preferred term: ‘hepatitis acute’) was a 54-year-old female treated from 16 Aug 2011 to 08 Dec 2011 for obesity. Medical history included nephrolithiasis, renal tuberculosis, hypothyroidism, major depression, and alcohol abuse. The patient was on treatment for about 4 months when she had an episode of severe epigastric pain. Laboratory blood tests were: ALT 672 U/L, AST 494 U/L, gamma glutamyl transferase 480 U/L, amylase 64 U/L, alkaline phosphatase 210 U/L, and total bilirubin 0.44 mg/dL. The patient was instructed to stop the use of all current medications, including the study drug (from the CRF, other ongoing medications stopped approximately at the time of the SAE included: omeprazole, fluoxetine, paracetamol (acetaminophen), carisoprodol, and dipyrrone). Three days after study drug was discontinued, gallstones were diagnosed by ultrasound; however, there was no dilatation of the biliary ducts. Laboratory blood tests demonstrated improvement (ALT 229 U/L, AST 38 U/L, Gamma GT 317 U, and alkaline phosphatase 170 U/L). No viral hepatitis serologies were performed. One month later, the patient had recovered from the event with normal liver enzymes.

Reviewer comment: *The patient did have a positive dechallenge in that liver enzymes improved off of liraglutide. This patient was not rechallenged. This is a confounded case; the patient had a history of alcohol abuse, multiple medication use including acetaminophen (of unknown dose), and gallstones. Furthermore, there was not a complete work-up (e.g., viral serologies); therefore, the potential contribution of liraglutide in this case is unclear.*

- Patient 409006 (preferred terms: ‘pancreatitis acute’ and ‘hepatitis’) was a 52-year-old male patient with a medical history of sleep apnea, increased blood pressure, gastroesophageal reflux disease, intermittent edema, and pyloroplasty. The patient

had no history of gallstones, did not drink alcohol, and only took ibuprofen for his knees as needed. Approximately one month after the patient started liraglutide, he developed abdominal pain. Amylase was 833 U/L, lipase 690 U/L, ALT 255 U/L, AST 335 U/L, and total bilirubin 1.8 mg/dL. Abdominal ultrasound was grossly normal, without gallstones. The investigator considered the hepatitis to be an inflammation of the liver due to the acute pancreatitis. Trial product was discontinued due to pancreatitis and hepatitis.

Reviewer comment: Increased liver enzymes were reported in several literature reports of pancreatitis. See section 7.5.1.4.

7.5.4.2.2 Diabetes Program

There was no signal for hepatotoxicity in the original review of Victoza (there was a slight imbalance in total bilirubin elevations of unclear significance that is included in the Victoza prescribing information).

There were three events of hepatic disease in patients treated with liraglutide in the diabetes program; all were reviewed as part of the Victoza NDA:

- Patient 225011 in trial 1572 died of hepatic cirrhosis and hepatic neoplasm
- Patient 211018 in trial 1796 had an SAE of cryptogenic cirrhosis
- Patient 514015 in trial 1573 reported SAEs of hepatic failure, hepatic encephalopathy, and micronodular cirrhosis. Autoimmune hepatitis was considered the final diagnosis.

7.5.4.3 Literature Reports

One case report describing a potential case of autoimmune hepatitis (AIH) in a patient receiving Victoza has recently been published.

- Kern, et al.⁴¹ described a young woman with T2DM and vitiligo, who presented with acute hepatitis (AST 991 U/L, ALT 1123 U/L, total bilirubin 9.5 mg/dL, INR 1.3). Other than starting liraglutide therapy 4 months prior, she reported no changes in medication therapy and no use of supplements. Liver biopsy demonstrated interface hepatitis with prominent eosinophils and rare plasma cells. The patient's liraglutide therapy was withheld but symptoms of jaundice and fatigue worsened, with persistently abnormal transaminases and liver function tests. Alpha-1-antitrypsin, ceruloplasmin, 24-hour urine copper levels, viral hepatitis serologic markers, and anti-liver-kidney-microsome-1 and F-actin antibodies were negative. A second liver biopsy revealed massive hepatic necrosis and extensive eosinophilic

⁴¹ Kern E, et al. Liraglutide-induced autoimmune hepatitis. JAMA Intern Med. 2014; 174(6): 984-7.

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infiltrate. She started oral prednisone therapy for presumed “liraglutide-induced marker-negative” autoimmune hepatitis. Six months later, the patient continued to receive prednisone without complete return of liver enzymes to the normal range.

Reviewer comment: It 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.

7.5.5 Renal Events and Related Laboratory Data

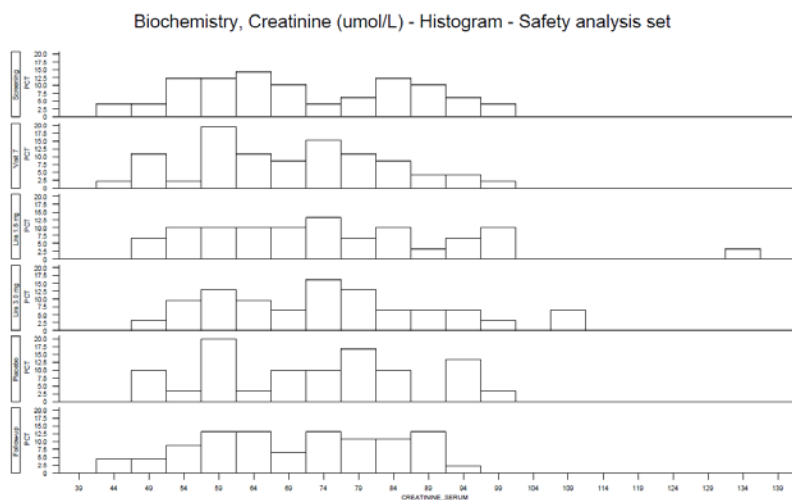
In the post-marketing setting, acute renal failure events have been identified with Victoza. According to the sponsor, these events have occurred early in treatment and have been associated with gastrointestinal symptoms such as nausea, vomiting, and diarrhea, presumably leading to a pre-renal azotemia.

7.5.5.1 Clinical Pharmacology Trial

No acute renal failure AEs were reported in this trial.

Samples for creatinine were drawn at screening, at the start of the second treatment period, at the PK sampling visits, and at follow-up. There were a few outliers for serum creatinine in the liraglutide treatment groups (not dose-dependent; liraglutide 1.8 mg shown in row 3 and liraglutide 3 mg shown in row 4):

Figure 47. Creatinine by Treatment Group / Phase of Study, Trial 3630



Source: NN8022-3630 Clinical Trial Report, Figure 14.3.5.15

There were no elevations in creatinine that were reported as AEs.

7.5.5.2 Weight Management Program

7.5.5.2.1 Adverse Events

The sponsor identified acute renal failure events using a prespecified MedDRA search. The incidence of events was similar in the treatment groups; note that adverse events specifically of 'renal failure' or 'renal failure acute' were rare. None of the events that occurred in patients treated with liraglutide 3 mg were fatal; one event with liraglutide 3 mg ('renal failure acute') was an SAE (narrative presented below). There were more patients treated with liraglutide who had AEs of 'blood creatinine increased' and 'glomerular filtration rate decreased'.

Table 97. Acute Renal Failure (predefined SMQ search) by System Organ Class and Preferred Term, Weight Management Pool

	Lira 3 mg N=3384 PY=2974.3		Total lira N=3872 PY=3372.7		Placebo N=1941 PY=1600.9	
	n (%)	Rate/1000PY	n (%)	Rate/1000PY	n (%)	Rate/1000PY
Acute Renal Failure AEs	18 (0.5)	8	21 (0.5)	8	8 (0.4)	6
Investigations	14 (0.4)	6	15 (0.4)	6	2 (0.1)	1
Blood creatinine increased	12 (0.4)	4	13 (0.3)	4	1 (<0.1)	<1
Glomerular filtration rate decreased	3 (<0.1)	1	3 (<0.1)	<1	0	0
Blood urea increased	2 (<0.1)	1	2 (<0.1)	<1	0	0
Protein urine present	0	0	0	0	1 (<0.1)	<1
Renal and urinary disorders	4 (0.1)	1	6 (0.2)	2	7 (0.4)	4
Renal failure	1 (<0.1)	<1	1 (<0.1)	<1	1 (<0.1)	<1
Renal failure acute	1 (<0.1)	<1	1 (<0.1)	<1	2 (0.1)	1
Renal impairment	1 (<0.1)	<1	2 (<0.1)	<1	1 (<0.1)	<1
Nephritis	1 (<0.1)	<1	1 (<0.1)	<1	0	0
Albuminuria	0	0	1 (<0.1)	<1	3 (0.2)	2

Source: ISS, Appendix 7.2, Table 318

Details on the two events reported as renal failure that occurred in patients treated with liraglutide 3 mg are in the following table.

Table 98. Adverse Events of Renal Failure in Patients Treated with Liraglutide, Weight Management Pool

Trial/subject ID/ /age/sex/BMI/ treatment/ Country	PT (outcome)	SAE (Y/N) / Subject withdrawn (Y/N) / Severity	Time to onset (days)	Medical history ^a	Details ^a
<i>Liraglutide 3.0 mg</i>					
1839/510002/64/F /47.1/3.0 mg/CA	Renal failure acute Recovered	Y/ N/ Severe	49	Chronic renal failure with chronic elevated levels of creatinine and urea, hypertension, cardiomegaly, myocardial infarction, pulmonary hypertension	After a few weeks on trial drug, serum creatinine levels were found to be worsening with a value of 220 umol/L. The subject complained about nausea vomiting and diarrhoea since starting study drug. 48 days after starting trial drug the subject presented with serum creatinine of 515 umol/l and hypotension and was diagnosed with acute renal failure. Study drug was temporarily withdrawn and the subject was treated with intravenous fluids for re-hydration. The subject recovered and liraglutide 3.0 mg was reintroduced after 6 days off drug. Lab findings include increased serum urea, amylase and creatinine. Concomitantly treated with ACE-inhibitor and thiazide diuretics.
1922/909005/73/F /32.2/3.0 mg/US	Renal failure Recovered	N/ N/ Mild	112	Diabetes mellitus, diabetic neuropathy	Subject presented with elevated creatinine level (1.59 mg/dL; ref range 0.4–1.20 mg/dL) after being on treatment for 112 days (creatinine level normal at screening and baseline). No symptoms or complaints at time of event. Repeat test was performed and the creatinine level was 1.33 mg/dL. No treatment was given for the event and the dose of study drug was not changed. Two months after the event, creatinine level returned to normal. Urine albumin-to-creatinine ratio was normal throughout the trial. No GI AEs were associated with the renal failure. Lab findings included increased serum urea and creatinine.

ACE-inhibitor: angiotensin-converting-enzyme inhibitor; BMI: body mass index; F: female; GI AE: gastrointestinal adverse event; PT: preferred term; SAE: serious adverse event; Y: yes, N: no.

a. Details are based on information in the case narratives from the safety database.

Reviewer note: Follow-up creatinine values in patient 510002 ranged from 1 to 1.3 mg/dL

Source: ISS, table 2-97

To explore whether there is a dose-relationship with AEs related to acute renal failure, an evaluation of the SMQ preferred terms was conducted in trial 1922, which evaluated both the 1.8 mg and 3 mg doses in patients with T2DM. Seven patients in this trial experienced at least one AE identified by the acute renal failure SMQ; five patients treated with liraglutide 3 mg (1.2%) and two patients treated with liraglutide 1.8 mg (1.0%). There was only one renal failure AE in the dose-ranging phase 2 trial 1807 (renal impairment in a patient randomized to liraglutide 2.4 mg), so dose-relatedness could not be assessed.

In addition to the acute renal failure and related AEs, an SAE of 'renal infarct' was reported in a 40-year-old female patient treated with liraglutide (ID 339004, trial 1839)

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with a history of obesity, chronic gastritis, and osteochondritis, and previous tobacco use. She presented with hematuria. A left nephrectomy was performed due to presumed tumor; however, pathology examination did not reveal a tumor, but did demonstrate renal infarction. The patient was discontinued due to the event.

In the ongoing 1839 extension, four patients treated with liraglutide and two patients treated with placebo reported SAEs from the 'Renal and urinary disorders' SOC (preferred terms not necessarily within the acute renal failure SMQ). All events in the liraglutide group, including those related to renal failure or impairment, were related to nephrolithiasis. All but one patient had a medical history of nephrolithiasis.

Table 99. Serious Adverse Events from Renal and Urinary Disorders SOC, Ongoing 1839 Extension

Trial / pt ID / age / sex	PT	Outcome	SAE / withdrawn / severity	Time to onset (days)	Medical history	Comments
Liraglutide 3 mg						
1839 / 216018 / 45 / F	Renal failure acute	Recovered	Y / N / Severe	544	Renal calculi Hypocalcemia	Both AEs in setting of nephrolithiasis
	Renal impairment	Not recovered	Y / Y ^a / Moderate	610		
1839 / 138014 / 58 / M	Renal impairment	Recovering	Y / N / Mild	495	Pre-existing altered renal function due to kidney stones	AE in setting of nephrolithiasis Patient stopped taking drug ~1 mo later at which time renal function improved
1839 / 106003 / 41 / F	Nephrolithiasis	Recovered	Y / N / Severe	603	Hypertension Nephrolithiasis	
1839 / 260013 / 33 / F	Nephrolithiasis	Recovered	Y / N / Severe	567	No relevant medical history	
Placebo						
1839 / 203024 / 60 / M	Oliguria	Recovered	Y / N / Moderate	391	Chronic renal failure	
1839 / 476015 / 68 / M	Nephrolithiasis	Recovered	Y / Y / Severe	464	Pre-diabetes Hypertension Nephrolithiasis	
a Patient stopped taking study drug 7 days before onset of event						

Source: ISS, Table 2-98; case narratives for patients 216018 and 138014

7.5.5.2.2 Serum Creatinine and Estimated Glomerular Filtration Rate

In the phase 2 and 3 clinical trials, blood samples for creatinine were drawn at screening, at baseline, at regular intervals during the trial, at end-of-treatment and at follow-up. Glomerular filtration rate was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.⁴²

As noted in Table 97 above, there were more patients in the liraglutide-treated groups with AEs of investigations related to the kidney, including blood creatinine increased. A review of the creatinine values in the 12 liraglutide-treated patients with AEs of blood creatinine increased showed that most of these patients returned to or close to their baseline creatinine values while remaining on treatment.

An outlier analysis did not demonstrate an imbalance in elevations from baseline between groups.

Table 100. Proportion of Patients with at Least One Elevation in Serum Creatinine, Weight Management Pool

	Lira 3 mg N=3384	All lira N=3872	Placebo N=1941
≥ 1.5x baseline	41 (1.2)	46 (1.2)	31 (1.6)
≥ 3x baseline	1 (<0.1)	1 (<0.1)	0

Source: Response to FDA request dated 11 Jun 2014, Appendix 1, Table 4

The one patient (ID 510002) treated with liraglutide who had an elevation in serum creatinine greater than three times baseline also had an AE of acute renal failure; see Table 98 above for a description of this event.

Estimated glomerular filtration rate demonstrated a mean decrease from baseline in both treatment groups with an increase thereafter; see the following figure.

⁴² Levey AS, et al. A New Equation to Estimate Glomerular Filtration Rate. [Ann Intern Med. 2009; 150:604-612.](#)

Figure 48. Change in Estimated Glomerular Filtration Rate (CKD-EPI Equation), Weight Management Pool

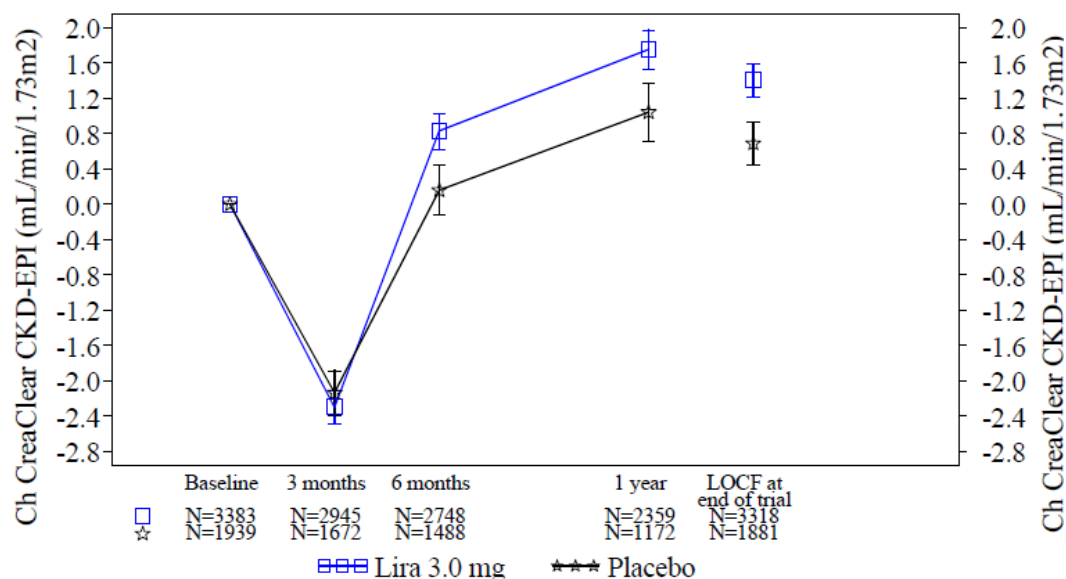


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.

Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

Source: ISS, Appendix 7.5, Figure 56

7.5.5.3 Diabetes Program

As demonstrated in the table below, an excess number of events of renal failure were not seen in the diabetes program. Four events (less than 0.1%) in the liraglutide group and 3 events (less than 0.1%) in the comparator group were considered serious.

Table 101. Acute Renal Failure (predefined SMQ search) by System Organ Class and Preferred Term, Diabetes Pool

	Total lira N=7037	Comparator total N=3677
Acute renal failure (predefined SMQ search) AEs	79 (1.1)	49 (1.3)
Investigations	36 (0.5)	19 (0.5)
Blood creatinine increased	18 (0.3)	12 (0.3)
Blood urea increased	15 (0.2)	10 (0.3)
Protein urine present	8 (0.1)	2 (<0.1)
Glomerular filtration rate decreased	1 (<0.1)	0
Renal and urinary disorders	43 (0.6)	30 (0.8)
Proteinuria	30 (0.4)	15 (0.4)
Renal impairment	6 (<0.1)	3 (<0.1)
Renal failure	3 (<0.1)	3 (<0.1)
Renal failure acute	2 (<0.1)	5 (0.1)
Albuminuria	2 (<0.1)	4 (0.1)

Renal tubular necrosis	0	1 (<0.1)
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Source: Supplementary AE Report, Appendix 1, Table 75

7.5.5.4 Literature Reports

Two recent literature reports regarding liraglutide and acute kidney injury include a case of acute interstitial nephritis⁴³ and a case of acute tubular necrosis.⁴⁴

- Gariani, et al.⁴³ described an 83-year-old man with T2DM and chronic diabetic nephropathy, who presented with acute renal failure (creatinine 9.3 mg/dL from baseline of 2.1 mg/dL with leg edema and basal fine crackles on lung auscultation), after switching from exenatide to liraglutide. Kidney biopsy showed diffuse tubulointerstitial infiltration with numerous eosinophils in addition to features of diabetic nephropathy. The patient was diagnosed with acute interstitial nephritis (AIN); investigations excluded infection or underlying immunologic disease. The patient received steroids, transient dialysis, and liraglutide therapy was discontinued. A progressive improvement in kidney function was observed, with serum creatinine decreasing to 3.6 mg/dL. The authors concluded that the AIN was likely due to liraglutide (perhaps immune-mediated) with a possible cross-reaction to exenatide.
- Kaakeh, et al.⁴⁴ described the case of a 53-year-old woman with a history of asthma, anemia, microalbuminuria, T2DM, hyperlipidemia, obesity, diabetic retinopathy, hypertension, and sarcoidosis, who presented with acute renal failure (serum creatinine 22.8 mg/dL from a baseline of 1 mg/dL one month earlier, and BUN 150 mg/dL). One month prior to presentation, her endocrinologist discontinued acarbose and started liraglutide 1.8 mg/day. Four days before this hospital admission, the patient was seen by her primary care physician when she reported nausea for 4 weeks and had many episodes of vomiting and diarrhea over the past week. At that visit she had an 8.9 kg weight loss from baseline. The patient followed up with her physician 3 days later (1 day before admission) and underwent laboratory testing, which demonstrated the results shown above. Her physician prescribed promethazine hydrochloride and dicyclomine hydrochloride for her symptoms. Other concomitant medications included glipizide, fexofenadine, spironolactone, triamterene-hydrochlorothiazide, simvastatin, azathioprine, quinapril, pioglitazone, gemfibrozil, montelukast, aspirin, calcitriol, calcium with vitamin D, fish oil, and fluticasone-salmeterol and ipratropium inhalers. The patient also had started ciprofloxacin 1 day before hospital admission (after serum creatinine and BUN laboratory tests were performed). The patient was treated with intravenous hydration, hemodialysis, and prednisone. Renal biopsy revealed patchy acute tubular necrosis, moderate and nonspecific acute interstitial nephritis, and no

⁴³ Gariani K, et al. Acute interstitial nephritis after treatment with liraglutide. *Am J Kidney Dis.* 2014; 63(2): 346-8.

⁴⁴ Kaakeh Y, et al. Liraglutide-induced acute kidney injury. *Pharmacotherapy.* 2012; 32(1): e7-11.

glomerular immune complexes or sarcoid nodules. It was also noted that the patient's amylase and lipase concentrations were elevated on admission (she did not have abdominal pain).

The authors concluded that the acute tubular necrosis that occurred within several weeks of starting liraglutide (without dose titration) in a patient on an ACE-inhibitor could reasonably be attributed to liraglutide due to marked volume depletion, possibly in part due to pancreatitis.

Reviewer comment: This case is consistent with post-marketing reports described in Victoza labeling (some cases were reported in patients without known underlying renal disease, and a majority occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration).

7.5.6 Immunogenicity

As liraglutide is a peptide product, there is potential risk of immunogenicity. Reviewers from FDA's Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) provided consults for DMEP on Victoza immunogenicity, including (1) a pre-approval review of anti-drug antibodies (ADA), as well as (2) recommendations for monitoring during the planned post-marketing cardiovascular outcomes trial.

In DPARP's initial consultation, it was noted that in pooled phase 3 trials nearly 10% of patients who received liraglutide formed ADA, of which approximately 50% cross-reacted with native GLP-1 and approximately 10% demonstrated neutralizing activity in a cell-based assay.⁴⁵ Although ADA formation, GLP-1 cross-reactivity, and the presence of neutralizing ADA did not appear to impact efficacy as measured by HbA1c, there were concerns about assay validity, which were only partially addressed by delaying sample collection (dataset was incomplete).⁴⁵ Liraglutide immunogenicity (anti-drug antibodies, adverse events) is being monitored in a subset of patients in the post-marketing CVOT, as recommended by the DPARP consultant.

The Victoza label includes the following information regarding immunogenicity:

- Under Warnings and Precautions, it is noted that, *There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with Victoza.*
- The immunogenicity section of Adverse Reactions includes the following information (summarized):

Approximately 50-70% of Victoza-treated patients in the five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of ADA at the end

⁴⁵ Porter, B. (DPARP), consult for NDA 22341, dated 7 May 2010

of treatment. Low titers were detected in 8.6% of patients. Cross-reacting ADA to native GLP-1 occurred in 4.8 to 6.9% of patients. The potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 1 to 2.3% of patients.

Among Victoza-treated patients who developed ADA, the most common category of AEs was infections, which occurred among 40% of these patients compared to 36%, 34%, and 35% of antibody-negative Victoza-treated, placebo-treated, and active-control-treated patients, respectively. The specific infections which occurred with greater frequency among Victoza-treated antibody-positive patients were primarily non-serious upper respiratory tract infections.

Antibody formation was not associated with reduced efficacy of Victoza when comparing mean HbA1c of all antibody-positive and all antibody-negative patients. However, the three patients with the highest titers of ADA had no reduction in HbA1c with Victoza treatment.

A composite of AEs potentially related to immunogenicity (e.g., urticaria, angioedema) occurred among 0.8% of Victoza-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events. Patients who developed ADA were not more likely to develop immunogenicity events than those who did not develop ADA.

- Injection site reactions were reported in approximately 2% of Victoza-treated patients in the clinical trials.

In the nonclinical studies supporting the Victoza NDA, it was noted that liraglutide caused fibrosarcomas at or near the injection site of male mice using a 0.6 mg/mL concentration, which is 10-fold lower than the concentration of liraglutide in Victoza (6 mg/mL). The human relevance is unknown.

In the weight management program, 'Immunogenicity related AEs' were considered a safety area of interest for liraglutide. The sponsor considered AEs of allergic reactions, injection site reactions, immune complex disease, and the development of anti-liraglutide antibodies to be medical events of special interest.

7.5.6.1 Allergic Reactions

A predefined search was based on the SMQs and preferred terms presented in the following table.

Table 102. MedDRA Terms Used in the Allergic Reactions Search

SMQs (narrow scope)	Preferred terms
Anaphylactic reaction	Documented hypersensitivity to administered drug
Anaphylactic/anaphylactoid shock conditions	Type II hypersensitivity
Angioedema	Type IV Hypersensitivity reaction
Severe cutaneous adverse reactions	
Asthma/bronchospasm	

SMQ: standardised MedDRA query.

Source: ISS, Table 2-100

No specific guidance was provided to the investigator as to how to determine if an event was allergic or not. Events were not adjudicated.

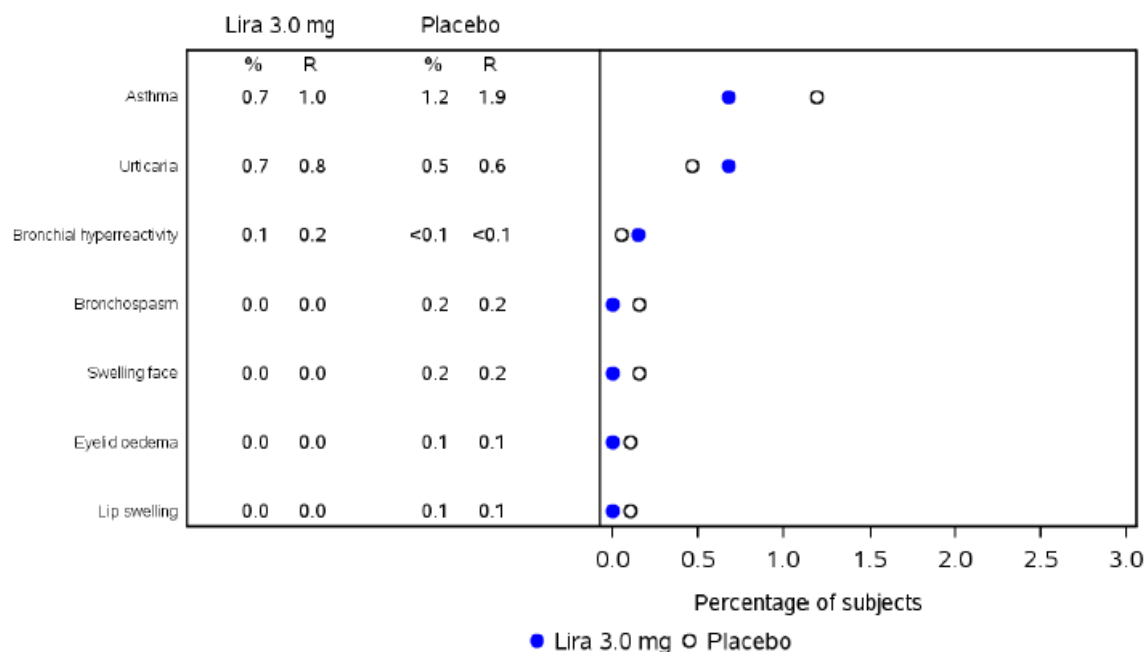
7.5.6.1.1 Weight Management

Upon suspicion of acute severe hypersensitivity in trials 1839, 1922, and 3970, a sample for drug-specific IgE antibodies was to be drawn and analyzed. Tryptase measurement was recommended in trial 1839. (No samples for tryptase measurement were actually taken.)

The percentage of patients with allergic reactions as identified by MedDRA search was similar between patients treated with liraglutide 3 mg (2.0%) and placebo (2.4%). None of the AEs under the allergic reactions search were fatal. The frequency of allergic reaction SAEs were: liraglutide 3 mg (0.1%) and placebo (0.2%). SAEs reported included: anaphylactic reaction, asthma, oropharyngeal swelling, and circulatory collapse⁴⁶ with liraglutide 3 mg; asthma with liraglutide 1.8 mg; and asthma, bronchospasm, and angioedema with placebo. Five patients were withdrawn due to allergic reaction AEs. Four patients treated with liraglutide 3 mg withdrew due to five events including face edema, Type IV hypersensitivity reaction, and three events of urticaria in two patients. Two events of urticaria led to withdrawal of one patient treated with placebo. The most frequently reported allergic events were asthma and urticaria (Figure 49).

⁴⁶ 'Circulatory collapse' AEs did not appear to be due to allergic reactions.

Figure 49. Most Common Allergic Reactions Identified by MedDRA Search, Weight Management Pool



%: Percentage of subjects experiencing at least one event, R: event rate per 100 exposure years.

Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.

Source: ISS, Figure 2-68

Two anaphylactic reactions (one SAE and one non-serious event) were reported in two patients treated with liraglutide 3 mg at trial day 235 and 289, respectively (patients 415017 and 512016 in trial 1839). The patient who experienced an SAE had a medical history of intermittent anaphylaxis to unknown cause and allergic reactions. Both patients continued with liraglutide treatment. In addition, one SAE of anaphylactic reaction was reported during the second year of trial 1807 (patient 161033, liraglutide 3 mg). According to the report, the anaphylactic shock was due to administration of Arthrotec (diclofenac/ misoprostol), which the patient had started on the same day. The patient was withdrawn from the trial due to the event. Anti-liraglutide antibodies were not detected in any of the patients with anaphylactic reactions.

A total of three events of angioedema were reported by two patients treated with liraglutide 3 mg and one event was reported in a patient treated with placebo (see narrative for the liraglutide-treated patient with two events, below). The event reported with placebo was reported as a moderate SAE, the events reported with liraglutide 3 mg were non-SAEs and mild in severity.

- Patient 353031 (trial 3970) was a 43-year-old male treated with liraglutide 3 mg. On day 81, mild angioedema of lips was reported; on day 90, mild angioedema of lips and left eyelid was reported. These events were considered “possibly” related to treatment, although the patient remained on treatment.

7.5.6.1.2 Diabetes

In the diabetes trials, overall, adverse events (1.1%) and SAEs (<0.1%) were observed with similar incidence in both arms. However, certain AEs were seen more frequently with liraglutide, including urticaria and angioedema, and various other AEs of swelling or edema. Only one AE reportedly led to withdrawal: urticaria in a patient treated with liraglutide. One patient treated with liraglutide had Stevens-Johnson syndrome reportedly caused by carbamazepine on trial day 230. There was no change to trial product due to the event and the patient completed the trial.

Table 103. Allergic Reactions by MedDRA SMQ, Diabetes Pool

	Total lira N=7037	Comparator total N=3677
Allergic reaction SMQ	77 (1.1)	39 (1.1)
Angioedema and urticaria	33 (0.5)	10 (0.3)
Urticaria	28 (0.4)	8 (0.2)
Angioedema	4 (<0.1)	0
Swelling face	2 (<0.1)	1 (<0.1)
Bronchial disorders (excl neoplasms)	31 (0.4)	21 (0.6)
Asthma	29 (0.4)	17 (0.5)
Bronchial hyperreactivity	1 (<0.1)	2 (<0.1)
Bronchospasm	1 (<0.1)	2 (<0.1)
Others		
Pharyngeal edema	2 (<0.1)	0
Edema mouth	2 (<0.1)	0
Anaphylactic reaction	1 (<0.1)	1 (<0.1)
Stevens-Johnson syndrome	1 (<0.1)	0
Face edema	1 (<0.1)	0
Lip swelling	1 (<0.1)	0
Eyelid edema	1 (<0.1)	1 (<0.1)
Dermatitis bullous	1 (<0.1)	2 (<0.1)
Circulatory collapse	1 (<0.1)	2 (<0.1)

Source: Supplementary AE Report, Appendix 1, Table 81

7.5.6.2 Injection Site Reactions

The sponsor conducted a search of pre-defined terms related to injection site reactions using the MedDRA high level terms (HLT) listed below.

Table 104. MedDRA Terms Used in the Injection Site Reactions Search

HLTs	
Administration site reactions NEC	Lipodystrophies
Application and instillation site reactions	Injection site reactions
Infusion site reactions	

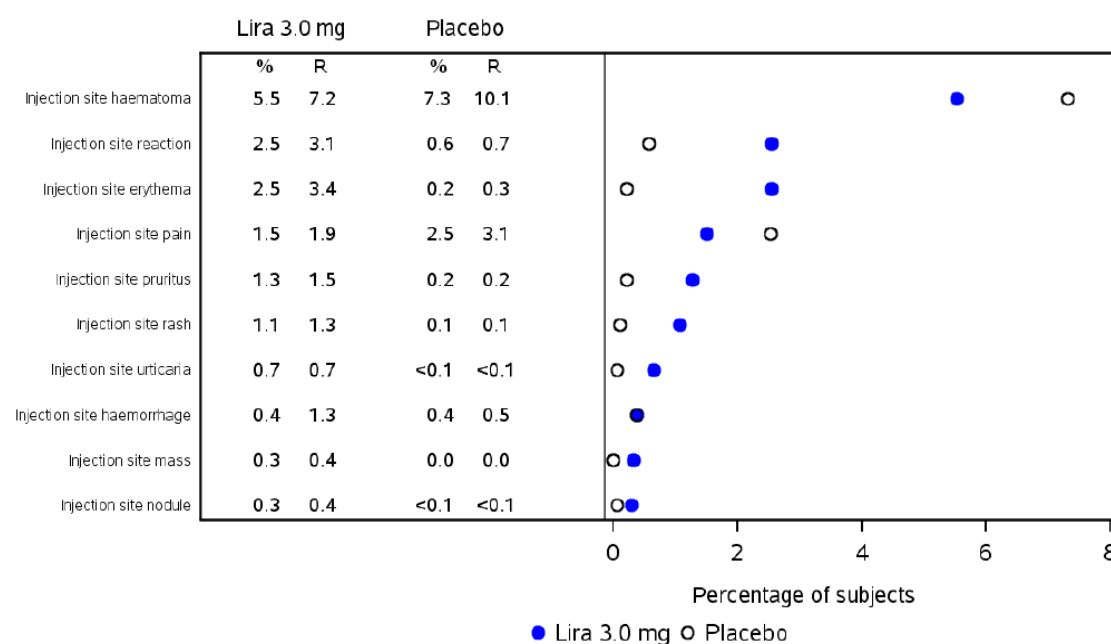
HLT: high level term.

Source: ISS, Table 2-102

Overall, the proportion of patients with injection site reactions was higher with liraglutide 3 mg (13.9%) than with placebo (10.5%). No events were reported as SAEs, although three events, all in patients treated with liraglutide 3 mg, were reported as severe, two events of injection site pain and one event of injection site urticaria. The proportion of patients withdrawn due to injection site reactions was similar with liraglutide 3 mg and placebo (0.5% each). Three events in 2 patients treated with liraglutide 3 mg led to dose reduction, and 9 patients treated with liraglutide 3 mg and 3 patients treated with placebo experienced events that led to temporary withdrawal.

Figure 50, below, illustrates the most common injection site reaction AEs by preferred term in the weight management trials (liraglutide 3 mg versus placebo).

Figure 50. Injection Site Reactions Identified by MedDRA Search, Weight Management Pool



%: Percentage of subjects experiencing at least one event, R: event rate per 100 exposure years.

Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.

Source: ISS, Figure 2-70

Reviewer comment: The adverse events more common with liraglutide (injection site reaction, erythema, pruritus, rash, urticaria) are also those that seem more likely to be

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due to a localized immune reaction (rather than mechanical injury; e.g., injection site hematoma).

The tables below demonstrate the incidence of injection site reactions by dose in trials 1807 and 1922, respectively. The results in trial 1807 suggest a dose response; the finding is not as pronounced in the diabetes trial 1922 (although the majority of events are due to hematoma).

Table 105. Injection Site Reactions (Predefined SMQ Search) by Preferred Term, Trial 1807 (up to 52 weeks)

	Placebo N=98	Lira 1.2 mg N=95	Lira 1.8 mg N=90	Lira 2.4 mg N=93	Lira 3 mg N=93
Injection site reaction AEs	2 (2.0)	8 (8.4)	8 (8.9)	11 (11.8)	13 (14.0)
Injection site irritation	0	1 (1.1)	1 (1.1)	1 (1.1)	3 (3.2)
Injection site hematoma	0	1 (1.1)	2 (2.2)	2 (2.2)	2 (2.2)
Injection site pain	1 (1.0)	0	1 (1.1)	1 (1.1)	2 (2.2)
Injection site dermatitis	0	0	1 (1.1)	0	1 (1.1)
Injection site discomfort	0	0	0	1 (1.1)	1 (1.1)
Injection site erythema	0	1 (1.1)	0	1 (1.1)	1 (1.1)
Injection site rash	0	2 (2.1)	0	1 (1.1)	1 (1.1)
Injection site reaction	1 (1.0)	0	1 (1.1)	2 (2.2)	1 (1.1)
Injection site urticaria	0	0	0	0	1 (1.1)
Injection site extravasation	0	0	0	1 (1.1)	0
Injection site hypersensitivity	0	2 (2.1)	0	0	0
Injection site inflammation	0	2 (2.1)	0	0	0
Injection site pruritus	0	1 (1.1)	0	1 (1.1)	0
Vessel puncture site hematoma	0	0	1 (1.1)	0	0
Lipodystrophy acquired	0	0	0	1 (1.1)	0

Source: ISS, Appendix 7.7, Table 37

Table 106. Injection Site Reactions (Predefined SMQ Search) by Preferred Term, Trial 1922

	Placebo N=212	Lira 1.8 mg N=210	Lira 3 mg N=422
Injection site reaction AEs	18 (8.5)	17 (8.1)	39 (9.2)
Injection site hematoma	12 (5.7)	4 (1.9)	19 (4.5)
Injection site reaction	0	4 (1.9)	5 (1.2)
Injection site pain	4 (1.9)	0	5 (1.2)
Injection site erythema	0	3 (1.4)	4 (0.9)
Injection site rash	0	1 (0.5)	3 (0.7)
Injection site induration	0	0	2 (0.5)
Injection site inflammation	0	0	2 (0.5)
Injection site urticaria	0	0	2 (0.5)
Application site hematoma	1 (0.5)	0	2 (0.5)
Lipohypertrophy	1 (0.5)	0	2 (0.5)

Injection site pruritus	0	4 (1.9)	1 (0.2)
Injection site hemorrhage	0	1 (0.5)	1 (0.2)
Injection site vesicles	0	0	1 (0.2)
Vessel puncture site hematoma	0	0	1 (0.2)
Injection site hypersensitivity	0	1 (0.5)	0
Injection site warmth	0	1 (0.5)	0
Vessel puncture site reaction	0	1 (0.5)	0

Source: NN8022-1922 Clinical Trial Report, Table 14.3.1.109

7.5.6.3 Immune Complex Disease

The following terms were used to identify potential AEs of immune complex disease.

Table 107. MedDRA Terms Used in the Immune Complex Disease Search

SMQs (narrow scope)	Preferred terms
Systemic lupus erythematosus	Serum sickness
Vasculitis	Serum sickness-like reaction
Guillain-Barre syndrome	Cryoglobulin urine present
	Cryoglobulins
	Cryoglobulinuria
	Acute interstitial pneumonitis
	Granulomatous pneumonitis
	Pneumonitis
	Fibrillary glomerulonephritis
	Glomerulonephritis
	Glomerulonephritis acute
	Glomerulonephritis chronic
	Glomerulonephritis membranoproliferative
	Glomerulonephritis membranous
	Glomerulonephritis minimal lesion
	Glomerulonephritis proliferative
	Glomerulonephritis rapidly progressive
	Immunotactoid glomerulonephritis
	Mesangioproliferative glomerulonephritis
	Immune complex level increased
	Type III immune complex mediated reaction

SMQ: standardised MedDRA query.

Source: ISS, Table 2-104

In the weight management program, immune complex disease was identified in 1 patient treated with liraglutide 3 mg and in 4 patients treated with placebo. The event in the liraglutide group (patient 414009, trial 1839) was 'chronic pigmented purpura'. The event was non-serious and mild, co-reported with 'solar lentigo' in a patient with a medical history of eczema and petechial patches and on concomitant medications prednisone and sildenafil. The patient continued on medication and was reported as 'not recovered'.

7.5.6.4 Immune-Mediated AEs

The potential for immune-mediated AEs has been raised in two recent published case reports. A case of autoimmune hepatitis⁴¹ is discussed in section 7.5.4.3, and a case of

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interstitial nephritis⁴³ is discussed in section 7.5.5.4. The role of liraglutide, and specifically whether or not the AEs were in fact immune-mediated, is somewhat speculative, but was suggested in both literature reports. There was an additional literature report²⁵ discussed in section 7.5.1.4 (pancreatitis). This case report (which notably, did have confounding factors) did not raise immunity as a potential cause for the pancreatitis. However, it is noted that this case (as with the case of interstitial nephritis⁴³) reported a recent switch from exenatide to liraglutide.

7.5.6.5 Anti-Drug Antibodies

Blood samples for assessment of antibody formation were collected in trials 1807, 1839, 1922, and 1923. Antibody-positive samples were further characterized for neutralizing effects and cross-reactivity against GLP-1. Blood samples for anti-liraglutide antibodies were drawn at screening or baseline and at follow-up after trial product discontinuation.

Overall, of the liraglutide-treated patients in the phase 2 and 3 weight management trials who were tested for anti-liraglutide antibodies, 2.3 to 2.5% developed antibodies. Antibody titers were presented as percent bound / total (%B/T); the highest value was 11.71. The majority of positive anti-liraglutide antibody tests were based on samples taken after treatment discontinuation and after a wash-out period.

Table 108. Anti-Liraglutide Antibodies, Weight Management Trials

	Lira 3 mg N=1684	Total lira N=2172
Positive anti-liraglutide antibody*	42 (2.5)	49 (2.3)
Positive cross-reacting effect	8 (0.5)	9 (0.4)
Positive neutralizing effect	18 (1.1)	18 (0.8)
Table is based on trials 1839, 1922, 1923, 1807, 1807-ext-1 and 1807-ext2 Pre-diabetic subjects from trial 1839 are not part of this table. * These values could not be reproduced by this reviewer (lira 3 mg: n=43; total lira: n=50)		

Source: ISS, Table 2-105

No AEs related to antibody development have been reported to date, and the proportion of patients reporting AEs were similar for patients with and without ADA (anti-drug antibodies).

Table 109. Adverse Events with Liraglutide by ADA Status, Weight Management Pool

	ADA		No ADA	
	Lira 3 mg N=43	Total lira N=50	Lira 3 mg N=3165	Total lira N=3646
Total AEs	41 (95.3)	48 (96.0)	2919 (92.2)	3363 (92.2)

Source: ISS, Table 2-106

Figure 51. Most Frequent System Organ Class Terms by Antibody Status, Weight Management Pool

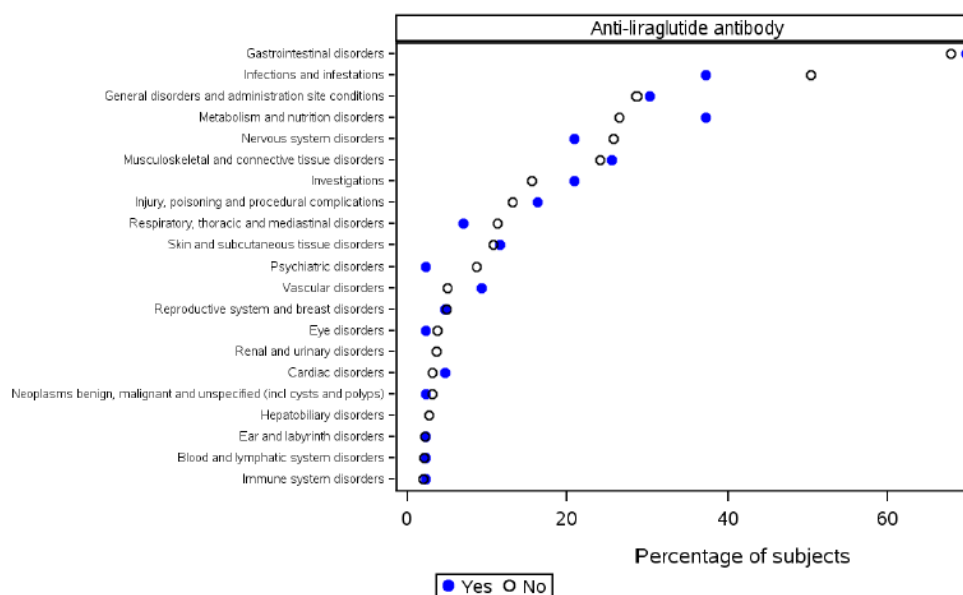


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Source: ISS, Appendix 7.2, Figure 575

Reviewer comment: *An imbalance was noted in the SOC, 'Metabolism and nutrition disorders'. An exploration of the SOC was conducted; AEs in patients with antibodies in this SOC that were related to glucose metabolism appeared to be due to 'hypoglycemia' (not shown in Figure 52).*

Figure 52. Most Frequent Preferred Terms by Antibody Status, Weight Management Pool

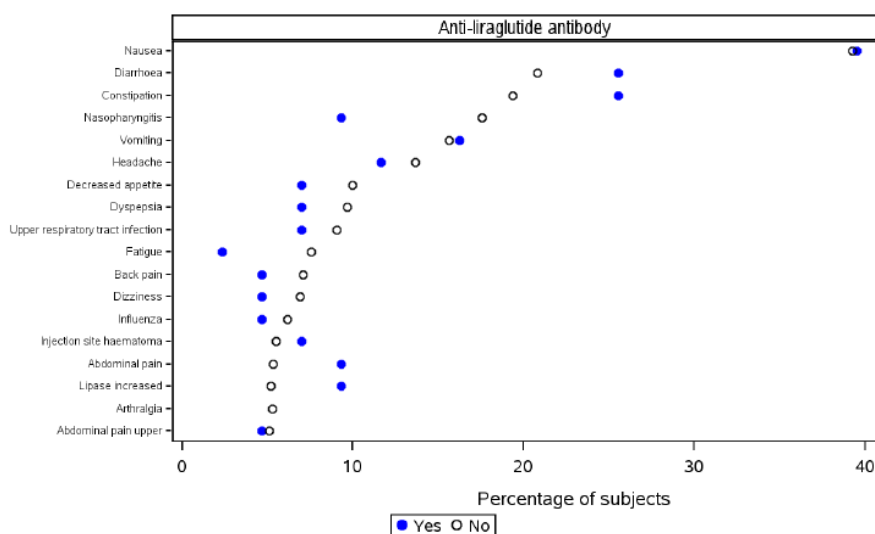


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Source: ISS, Appendix 7.2, Figure 576

An additional question with the development of ADA is whether they impact liraglutide efficacy. This was explored in trial 1839:

Table 110. Changes in Body Weight and HbA1c from Baseline to Week 56 by Anti-Liraglutide Antibody Status, Trial 1839

	Subjects with Positive Antibodies			Subjects without Positive Antibodies		
	N	n	Mean	N	n	Mean
Change from baseline in Fasting Body Weight (%)	21	21	-9.4	1372	1326	-6.9
Change from baseline in HbA1c (%)	21	21	-0.3	1372	1281	-0.2

N: Number of subjects, n: Number of subjects with non-missing change
Missing values for change in HbA1c and change in fasting body weight are imputed using last observation carried forward.
Subjects with positive antibodies in the main trial or at visit 18 are considered to have positive antibodies. All subjects in SAS were not sampled for antibodies in the main trial (samples were only collected for subjects withdrawing in the main part of the trial), and subjects entering the re-randomised treatment period were scheduled to sample antibodies at visit 18.

Source: NN8022-1839 Clinical Trial Report, Table 12-70

Reviewer comment: ADA do not appear to be associated with loss of efficacy. The numerical reductions in weight, HbA1c, and potential increased incidence of hypoglycemia (discussed above) are noted in patients with positive ADA, but the numbers of patients with ADA were small.

Four patients treated with liraglutide 3 mg developed ADA with both a cross-reacting effect to GLP-1 and a neutralizing effect to liraglutide; all four patients were in trial 1923. Three out of the four patients gained weight during the randomized period (all would be considered “non-responders”) and all four patients had either no change or an increase in HbA1c.

Table 111. Patients with Positive Cross-Reacting and Neutralizing Antibodies, Weight and Glycemic Change, Weight Management Trials

Trial / Patient ID	Week	Anti-lira Ab (%B/T)	Cross-reacting effect	Neutralizing effect	Change in		
					Body weight (kg) / (%)	FPG (mg/dL*)	HbA1c (%)
1923 / 103009	57	5.56	Positive	Positive	3.70 / 2.76	3.6	0.30
1923 / 107033	57	8.18	Positive	Positive	-4.10 / -4.05	-12.6	0.10
1923 / 109009	57	2.81	Positive	Positive	5.08 / 4.04	16.2	0.70
1923 / 110015	57	2.35	Positive	Positive	6.99 / 5.55	1.8	0.00

* Reviewer converted from mmol/L to mg/dL

Source: ISS, Appendix 7.9, Table 57

Reviewer comment: In theory, if there were antibodies to both endogenous GLP-1 and liraglutide, a clinical (neutralizing) effect might be more evident than if only one was positive. Aside from nausea, no AE was reported in more than one patient. There were no SAEs reported in these patients.

7.5.7 Cardiovascular Safety

In 2008, FDA published a guidance regarding CV risk assessment in drugs to treat T2DM,³ a patient population with many similar and overlapping characteristics to the population with obesity. Specifically, the guidance states that drug development programs should include a proposal to rule out excess CV risk such that the upper-bound of the 95% confidence interval for the estimated risk ratio of major adverse cardiovascular events (MACE) between drug and comparator is less than 1.8 prior to approval and less than 1.3 post-approval.

Because of the sibutramine (see section 3) and diabetes drugs experiences, in March 2012 the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened to discuss and vote on a CV risk assessment approach for weight loss drugs analogous to that of diabetes drugs. EMDAC voted 17 to 6 to require pre-approval assessments to exclude some degree of CV risk for all weight loss drugs, even in the absence of a CV signal or theoretical risk. For drugs with a signal for potential CV harm, FDA determined that a certain degree of excess CV risk should be ruled out through conduct of a dedicated CVOT prior to market approval. However, to date, FDA has not established a policy for CV risk assessment for drugs being developed for chronic weight management.

At the time of its approval for diabetes, liraglutide (Victoza) was “caught in the middle” of the newly-formulated guidance, given that its clinical development program for diabetes was completed prior to the guidance. Nevertheless, a meta-analysis of the phase 2 and 3 trials met the pre-approval standard for diabetes drugs (1.8). Utilizing a customized set of MedDRA preferred terms for an assessment of major adverse cardiovascular events (MACE), the hazard ratio for liraglutide versus placebo was 0.72 (95% CI 0.30, 1.74). A post-marketing requirement for the post-approval standard is being addressed with a CVOT, currently ongoing.

The liraglutide trials for weight management were not powered or designed to rule out a pre-specified degree of cardiovascular risk. Therefore, the sponsor has undertaken a series of analyses to assess CV risk in the obesity and diabetes patient populations.

In addition to MACE analyses, an assessment of vital signs and adverse events related to the known increases in heart rate associated with liraglutide use are presented in section 7.5.7.2. Hypotension and heart failure-related events are presented in sections 7.5.7.3 and 7.5.7.4, respectively.

Blood pressure and lipid changes were reported in section 6 (efficacy) for the individual trials. Only a small proportion of patients in the 56-week phase 3 liraglutide trials reported changes in concomitant blood pressure medication (increase: lira 3.3%, placebo 5.2%; decrease: lira 5.4%, placebo 3.4%) or lipid-altering medication (increase: lira 2.1%, placebo 3.3%; decrease: lira 1.4%, placebo 0.9%).

7.5.7.1 Major Adverse Cardiovascular Events

Meta-analyses of adjudicated MACE collected in the liraglutide weight management and diabetes programs were conducted to support the assessment of CV safety.

Prospective adjudication of MACE was implemented for the phase 3 liraglutide in weight management trials (1839, 1922, 3970), and a similar process was set up for the liraglutide in weight management phase 3 trial 1923, which was ongoing at the time the decision was made to prospectively adjudicate MACE in phase 3.

Post hoc adjudication was conducted for all trials in which MACE were not prospectively adjudicated, including all completed and Victoza trials, the weight management phase 2 dose-finding trial (1807), and the semaglutide phase 2 dose-finding trial (NN9535-1821). MACE in those trials were identified by broad pre-specified standardized MedDRA (SMQ) searches.

Adjudication of all serious and non-serious AEs were performed by the blinded external event adjudication committee (EAC). All deaths were adjudicated and categorized as either 'CV death', 'non-CV death', or 'death due to unknown cause'. Events deemed 'definitely' or 'likely' MACE, as well as all deaths reported as 'death due to unknown cause' were considered confirmed MACE.

The primary analysis was an analysis of on-treatment events from the weight management program (trials 1807, 1839, 1922, 1923, and 3970). The sponsor also conducted an on-study (including patients off treatment) analysis. The weight management analyses do *not* include the adjudicated events from the ongoing 1839 extension, during which one EAC-confirmed CV death in a liraglutide-treated patient has been reported to date (see section 7.2.2).

The sponsor also conducted supportive meta-analyses from T2DM programs (the liraglutide [Victoza] program and the semaglutide program in which liraglutide was used as a comparator). The T2DM meta-analysis included all intermediate and long-term trials (phase 2 and 3) in programs for T2DM that included one or more treatment arms with liraglutide and with database lock prior to 02 Jul 2013. Trials where insulin degludec was part of the treatment were not included.

Table 112. Development Programs Included in the Cardiovascular Meta-Analyses

	WM	T2DM	combined WM & T2DM
NN8022: Liraglutide in weight management	Yes	No	Yes
NN2211: Liraglutide in type 2 diabetes (Victoza®)	No	Yes	Yes
NN9535: Semaglutide in type 2 diabetes	No	Yes	Yes
NN9068: Fixed combination of liraglutide and insulin degludec in type 2 diabetes (IDegLira)	No	No	No
NN1250: Insulin degludec	No	No	No

Yes = included, No = excluded

Source: CV Meta-Analysis Report, Table 1-1

MACE was defined as a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

7.5.7.1.1 Weight Management Analysis

The primary analysis⁴⁷ evaluated first occurrence of MACE on treatment. Patients not experiencing an event in the treatment period or within 30 days after last dose were censored at last treatment date plus 30 days.

The number of patients and the patient-years of exposure for liraglutide and comparator (placebo plus orlistat) and adjudicated MACE in the weight management on-treatment analysis are shown in the following table.

Table 113. Adjudicated MACE, Weight Management Pool

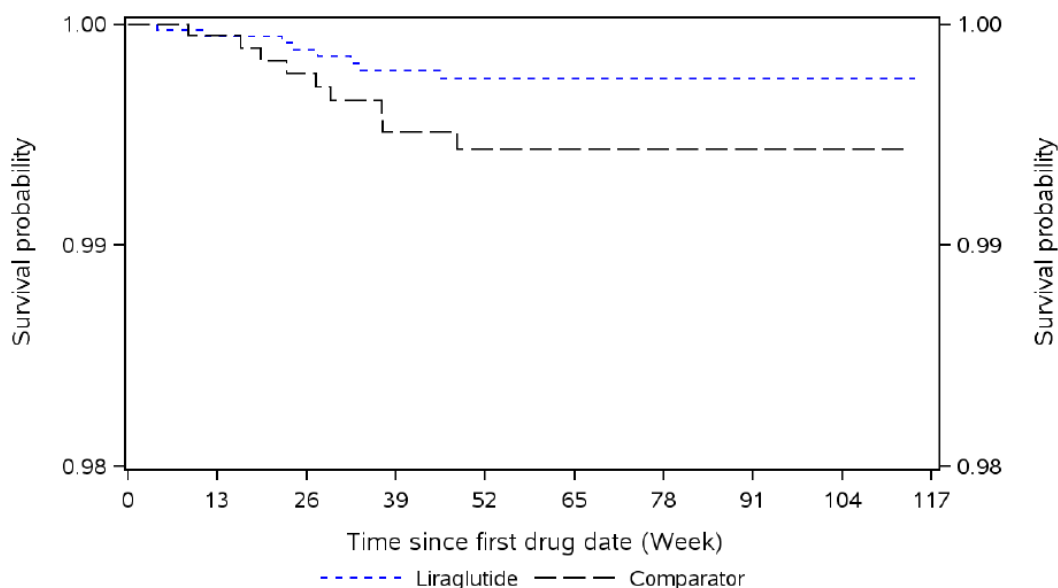
	Liraglutide N=3872 3982.5 PY		Comparator N=2036 1958.3 PY	
	n (%)	Events/1000 PY	n (%)	Events/1000 PY
Events sent for adjudication	63 (1.6)	18.6	34 (1.7)	19.4
EAC confirmed events	8 (0.2)	2.0	9 (0.4)	4.6
Non-fatal myocardial infarction	5 (0.1)	1.3	5 (0.3)	2.6
Non-fatal stroke	2 (0.1)	0.5	2 (0.1)	1.0
Cardiovascular death	1 (<0.1)	0.3	2 (0.1)	1.0

Source: CV Meta-analysis Report, Table 6-1

The estimated hazard ratio for the primary endpoint of time to first MACE for liraglutide (8 events) versus comparators (9 events) was 0.40 (95% CI: 0.15; 1.05); the Kaplan-Meier plot is shown below. Point estimates for the hazard ratios of the MACE components were consistent with the composite, as shown in Figure 54.

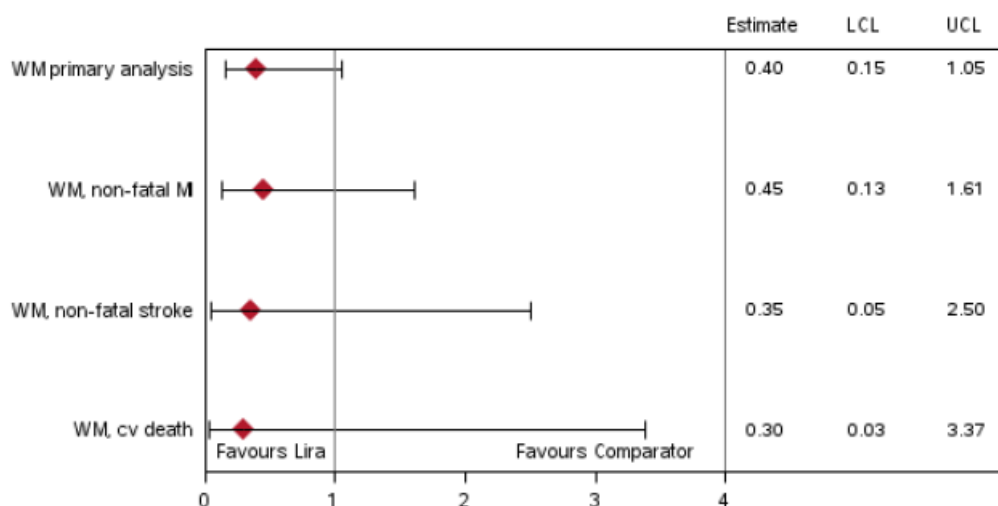
⁴⁷ Note that this review will present main primary and secondary analysis results. See the memorandum from Dr. Rongmei Zhang (Office of Biostatistics, Division of Biometrics 7) for information regarding statistical methodology. A number of sensitivity analyses conducted by the sponsor were consistent with the main analyses.

Figure 53. Time to First MACE, Weight Management Pool



Source: CV Meta-analysis Report, Figure 6-1

Figure 54. Estimated Hazard Ratios for MACE Composite and MACE Components, Weight Management Pool



Source: CV Meta-analysis Report, Figure 6-2

When the off-drug follow-up period was included in a sensitivity analysis, three additional EAC-confirmed MACE for patients treated with liraglutide were reported, including 1 patient who had 2 MACE events (nonfatal stroke, followed by cardiovascular death). No new EAC-confirmed MACE in patients treated with comparator were reported. The hazard ratio (95% CI) for this “on-study” analysis is 0.49 (0.20, 1.23).

7.5.7.1.2 Combined Weight Management and Diabetes Analyses

The sponsor conducted a number of analyses evaluating MACE in the T2DM program. This section is focused on the analyses that combine the weight management and T2DM pools.

The overall incidence rate of confirmed MACE in the combined weight management and T2DM on treatment analysis was lower with liraglutide (34 events) than with comparators (32 events), with a hazard ratio of 0.56 (95% CI: 0.34, 0.93).

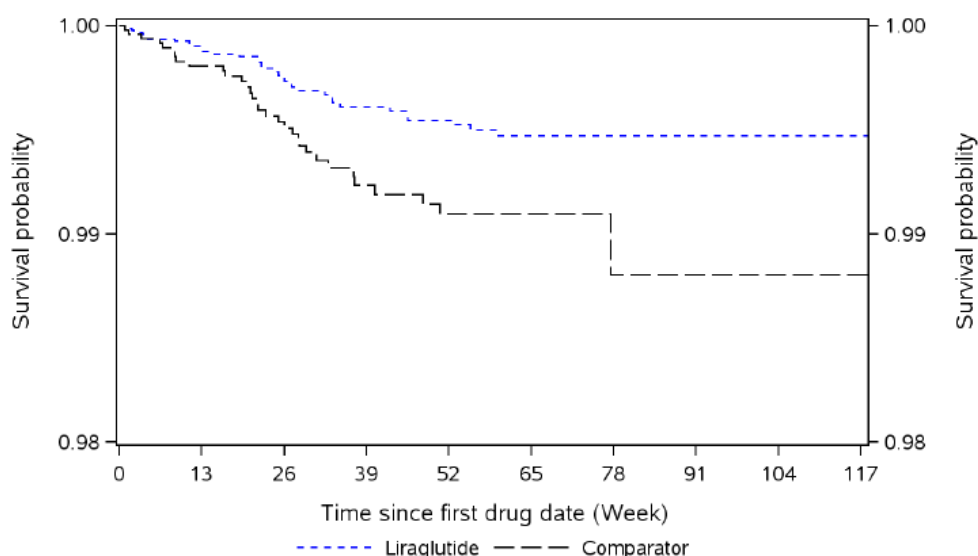
Table 114. Adjudicated MACE, Weight Management and Diabetes Pools, Combined

	Liraglutide N=9383 8312.3 PY		Comparator N=4784 4039.7 PY	
	n (%)	Events/1000 PY	n (%)	Events/1000 PY
Events sent for adjudication	202 (2.2)	29	109 (2.3)	35
EAC confirmed events	34 (0.4)	4	32 (0.7)	9
Non-fatal myocardial infarction	22 (0.2)	3	19 (0.4)	5
Non-fatal stroke	11 (0.1)	1	9 (0.2)	3
Cardiovascular death	1 (<0.1)	<1	7 (0.2)	2

Source: CV Meta-analysis Report, Appendix 1, Table 15

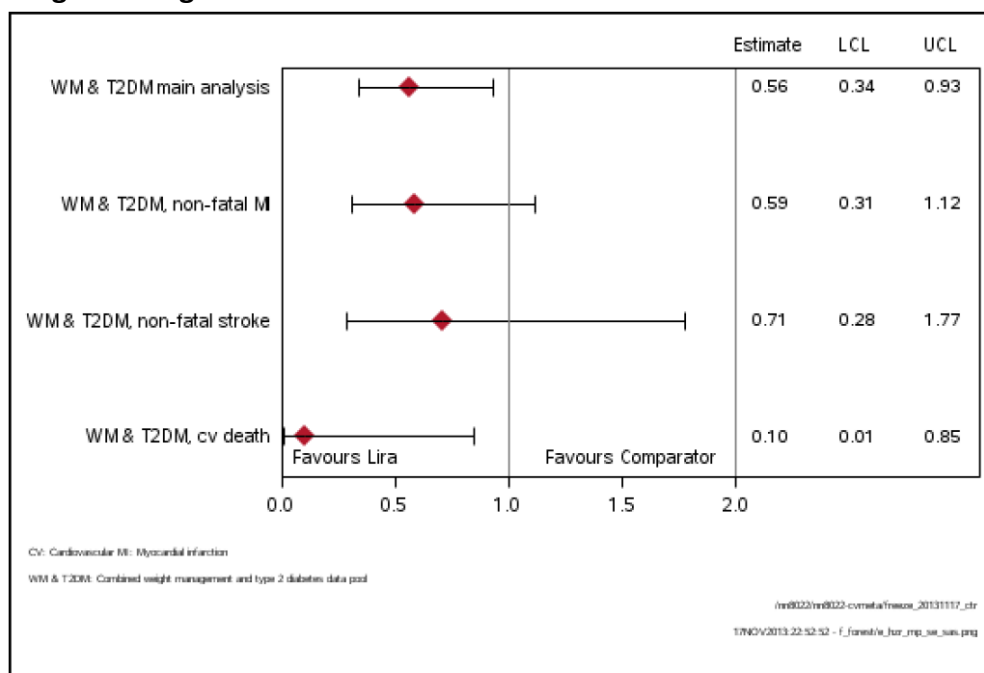
See Figure 55 for a Kaplan-Meier plot of the time to first MACE in the combined weight management and diabetes programs on-treatment analysis population, and Figure 56 for a plot of the main analysis of the MACE composite and the individual components.

Figure 55. Time to First MACE, Combined Weight Management and Type 2 Diabetes Pool



Source: CV Meta-analysis Report, Figure 6-5

Figure 56. Estimated Hazard Ratios for MACE Composite and MACE Components, Weight Management + Diabetes Pools



Source: CV Meta-analysis Report, Appendix 1, Figure 78

7.5.7.1.3 Other Endpoints

Events adjudicated as ‘unstable angina pectoris’ and ‘transient ischemic attack’ were not included as MACE in the analyses. There were 4 adjudicated events of ‘transient ischemic attack’ with liraglutide (0.10%) and 1 with placebo (0.05%) in the weight management on-treatment analysis population. There were no confirmed events of ‘unstable angina pectoris’. In the diabetes trials, the proportion of patients with these events was similar between liraglutide (events combined n=16, 0.29%; unstable angina pectoris n=11, 0.20%; transient ischemic attack n=5, 0.09%) and comparator (events combined n=8, 0.29%; unstable angina pectoris n=6, 0.22%; transient ischemic attack n=2, 0.07%).

7.5.7.2 Increased Heart Rate and Arrhythmias

7.5.7.2.1 Heart Rate

As noted in the Victoza label, mean increases from baseline in heart rate (HR) of 2 to 3 beats per minute (bpm) were observed with liraglutide compared to placebo in the T2DM program. Although the clinical consequences of drug-induced increases in HR in the setting of unchanged or decreased blood pressure are largely unknown, it remains a safety concern and theoretically could increase patients’ risk for cardio- or cerebrovascular events. Of interest in the obesity program is whether there is an increased effect seen with the 3 mg dose, and whether the obese patient population

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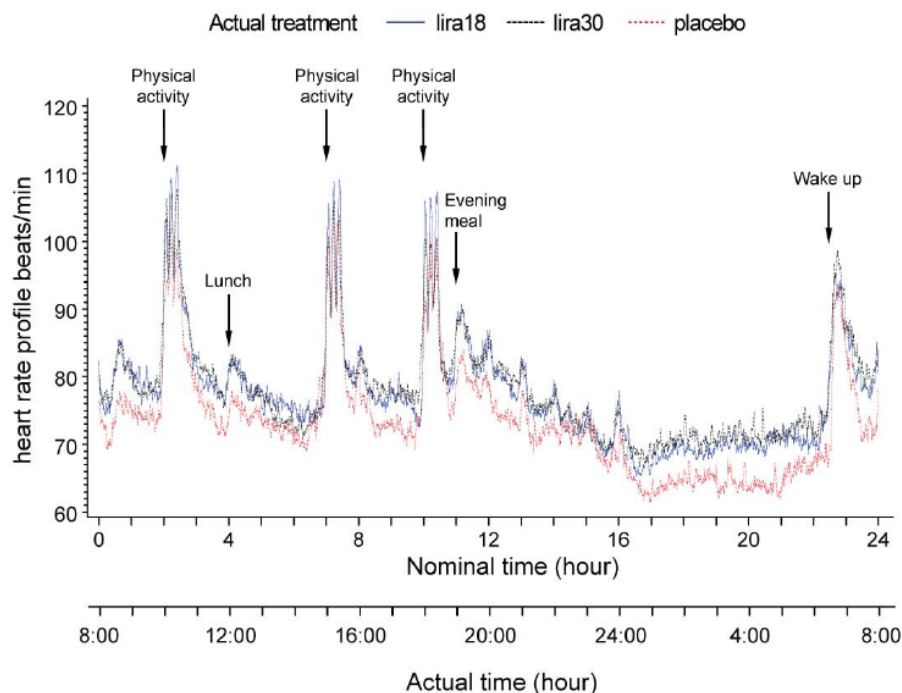
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has a different susceptibility to HR increases as compared to the patient population with T2DM.

In the clinical pharmacology trial, the effects of liraglutide on HR were investigated by 24-hour continuous HR monitoring. Obese patients without diabetes were randomized into liraglutide 3 mg (N=32), liraglutide 1.8 mg (N=30), and placebo (N=32) groups over two 5-week treatment periods in a crossover trial design. HR was continuously recorded during a 24-hour respiratory chamber stay at the end of each of the two treatment periods.

Both liraglutide 1.8 and 3 mg were associated with an increased mean HR as compared to placebo (6 to 7 bpm) throughout the 24-hour period; see Figure 57 and Table 115. The increase was more pronounced during nighttime than during daytime (daytime: 4.3 to 4.6 bpm, sleeping: 7.0 to 8.9 bpm, lowest physical activity: 5.9 to 9.0 bpm).

Figure 57. Mean HR Profile during 24-hr Respiratory Chamber by Treatment, Trial 3630



Source: NN8022-3630 Clinical Trial Report, Figure 12-1

Table 115. Heart Rate during 24-hr Respiratory Chamber by Treatment, Trial 3630

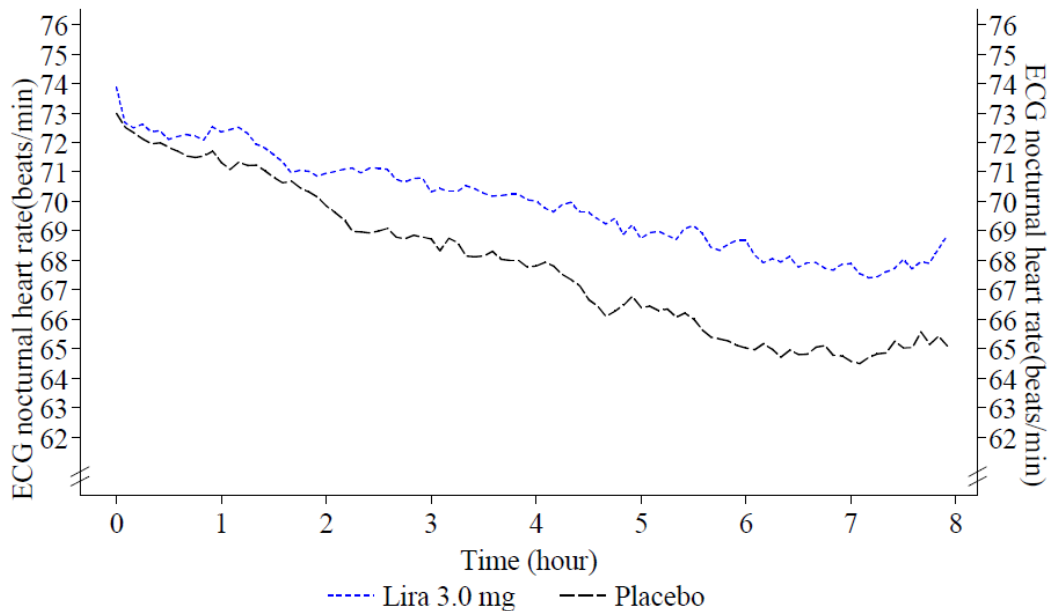
	Estimated LS Mean			Estimated Difference (95% CI)		
	Lira 3mg	Lira 1.8mg	Pbo	3mg vs Pbo	1.8mg vs Pbo	3mg vs 1.8mg
24-hr HR, bpm	78.20	77.26	71.59	6.61 (4.02, 9.19)	5.67 (3.20, 8.13)	0.94 (-1.63, 3.52)
9-hr daytime HR, bpm	80.23	80.59	75.95	4.28 (0.98, 7.57)	4.63 (1.40, 7.87)	-0.36 (-3.70, 2.98)
3-hr sleeping HR, bpm	72.45	70.56	63.52	8.93 (6.56, 11.30)	7.04 (4.82, 9.25)	1.89 (-0.46, 4.25)
3-hr lowest spont phys activity HR, bpm	72.62	69.59	63.66	8.96 (6.53, 11.38)	5.93 (3.46, 8.40)	3.02 (0.69, 5.36)

Source: NN8022-3630 Clinical Trial Report, Table 12-6

Reviewer comment: The HR increases over the 24-hour monitoring with both doses of liraglutide compared to placebo in this study are considerably higher than what was described in the diabetes program or in the resting HR assessments in the weight management program (see below), which suggests that “resting” HR might not be sensitive enough to capture the full liraglutide HR effect.

Overnight HR was also obtained during polysomnography testing in trial 3970 (in obese patients with moderate or severe obstructive sleep apnea). A decline in HR (calculated as the 8th hour mean – 1st hour mean) was observed during the night in both treatment groups, but less so with liraglutide 3 mg than placebo (liraglutide: baseline -8 beats/min, week 12 -4 beats/min, week 32 -4.5 beats/min; placebo approximately -7 beats/min at all visits).

Figure 58. ECG Nocturnal HR during Polysomnography after 32 Weeks of Treatment, Trial 3970



ECG nocturnal heart rate is part of the polysomnography assessment. Profiles are shown for the first 8 hours of recording corresponding to the normal time in bed for PSG assessments.

Source: NN8022-3970 Clinical Trial Report, Figure 12-12

In the phase 2 and 3 trials, resting HR was measured at the majority of visits, approximately once monthly. Liraglutide consistently demonstrated an increase in HR as compared to placebo (Figure 59). Increases were seen within the first 2 weeks (during the titration phase), and consistently remained elevated as compared to placebo throughout the trial duration. In the 5 weight management trials pooled, the estimated treatment difference between liraglutide 3 mg and placebo in mean resting HR at end-of-treatment was 2.49 bpm (95% CI: 2.02, 2.97); Figure 60 presents the pooled and by trial (range: 1 to 5 bpm) treatment differences.

Figure 59. Mean Change in Resting Heart Rate by Visit, Weight Management Pool

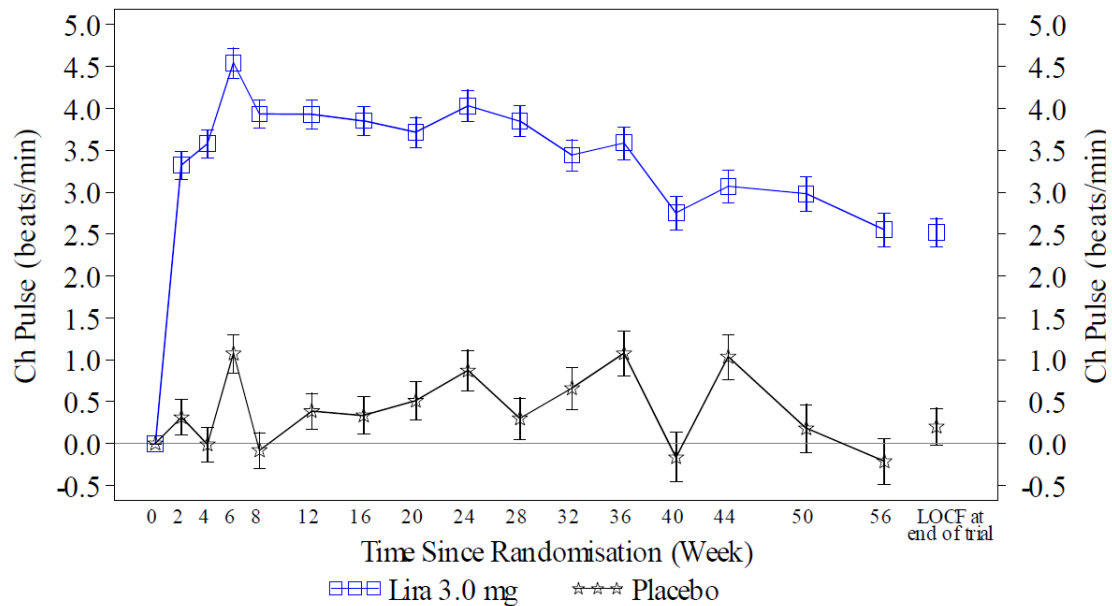
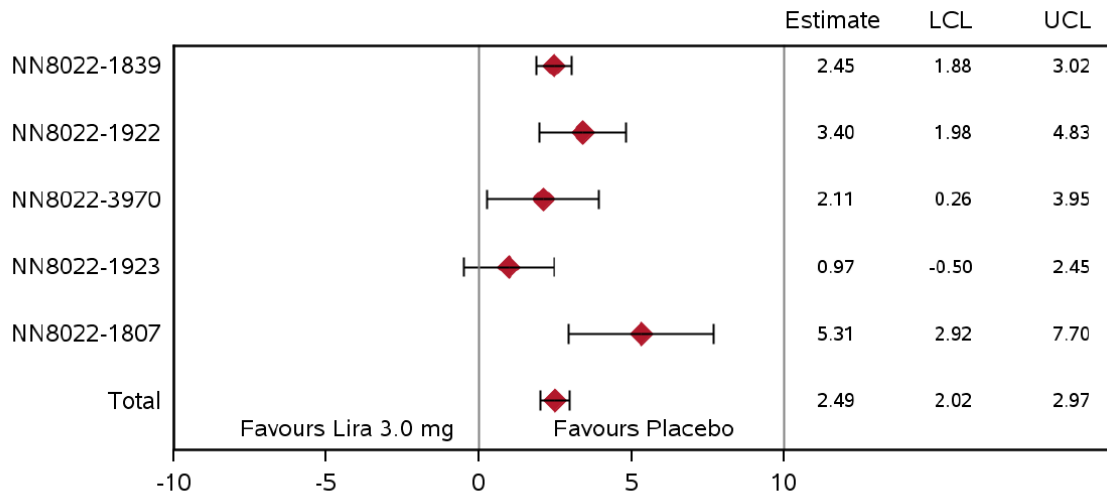


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).
Source: ISS, Figure 2-35

Figure 60. Mean Change in Resting Heart Rate at End-of-Treatment, by Trial and Pooled



P-value for interaction: 0.0256.
LCL: Lower 95% confidence limit, UCL: Upper 95% confidence limit

Source: ISS, Figure 2-34

Mean changes in HR at the end of the trial as measured by central electrocardiogram assessments were consistent with these findings: liraglutide 3 mg: 3.2 bpm, placebo: -0.4 bpm.

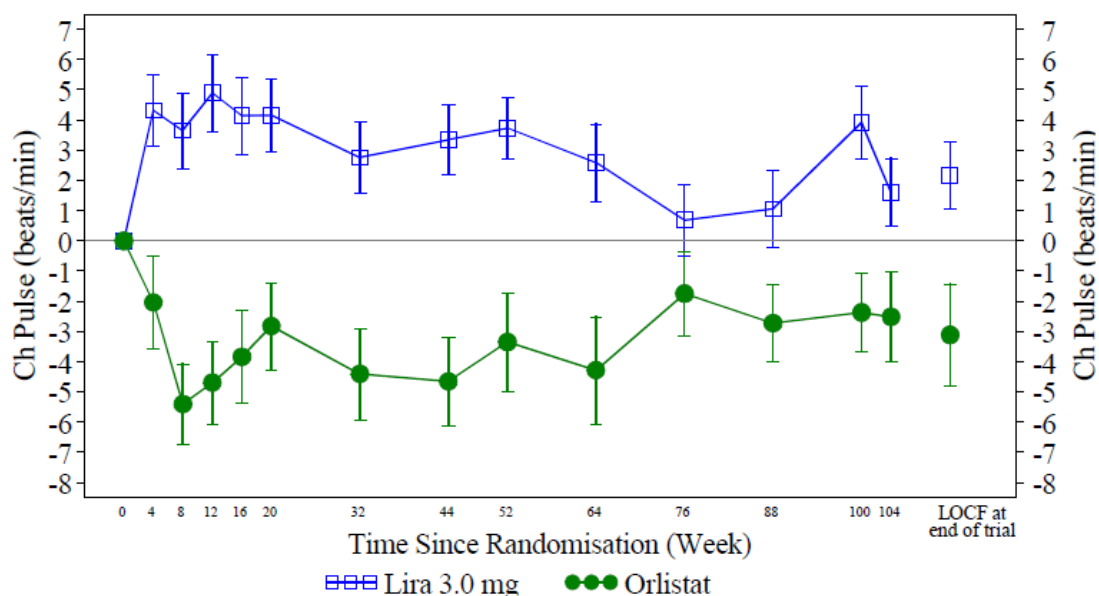
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The following figure illustrates that an increase in HR with liraglutide 3 mg persists through 2 years of treatment, as compared to orlistat treatment.

Figure 61. Mean Change in Heart Rate by Visit, Trial 1807 (Weeks 0 to 104)



Data from trial 1807 for subjects randomised to liraglutide 3.0 mg or orlistat and treated in 1807-ext-2.

Source: ISS Appendix 7.7, Figure 154

Consistent with the increase in mean resting HR, categorical increases in resting HR (in the categories > 0, 5, 10, 15 or 20 bpm) during treatment and at end-of-treatment were generally observed in a higher proportion of patients treated with liraglutide compared to those treated with placebo.

Table 116. Maximum HR and HR Change, Weight Management Pool

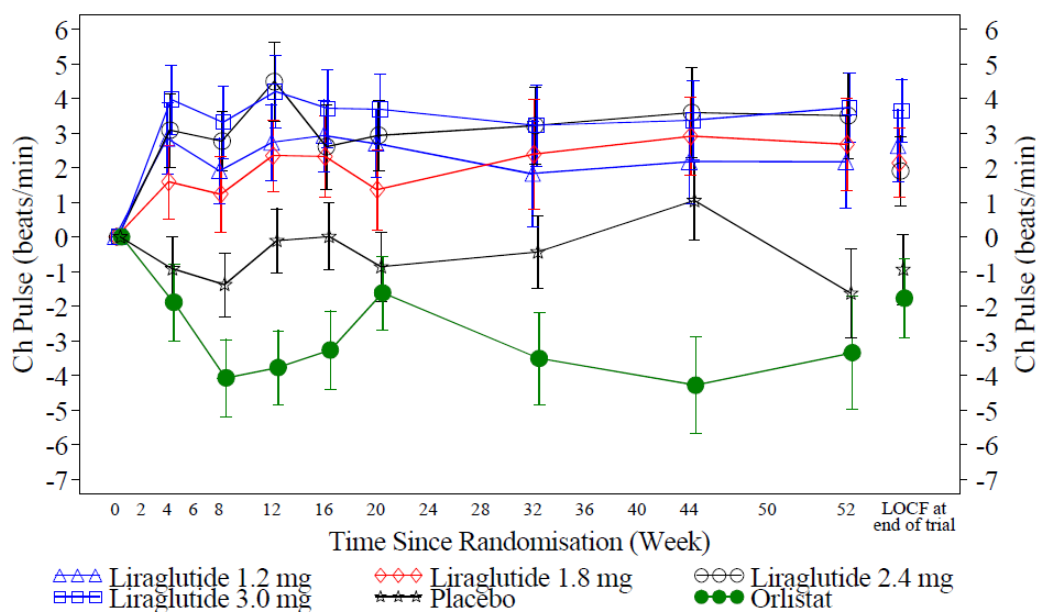
	Lira 3 mg N=3384 n (%)	Placebo N=1941 n (%)
Change from baseline to max > 0 bpm	3065 (90.6)	1665 (85.8)
Change from baseline to max > 5 bpm	2723 (80.5)	1355 (69.8)
Change from baseline to max > 10 bpm	2056 (60.8)	907 (46.7)
Change from baseline to max > 15 bpm	1364 (40.3)	512 (26.4)
Change from baseline to max > 20 bpm	662 (19.6)	215 (11.1)
Max HR ≥ 80 bpm	2560 (75.7)	1164 (60.0)
Max HR ≥ 90 bpm	928 (27.4)	337 (17.4)
Max HR ≥ 100 bpm	195 (5.8)	78 (4.0)
Change > 0 bpm at ≥ 2 consecutive visits	2598 (76.8)	1272 (65.5)

Change > 5 bpm at ≥ 2 consecutive visits	1997 (59.0)	830 (42.8)
Change > 10 bpm at ≥ 2 consecutive visits	1151 (34.0)	371 (19.1)
Change > 15 bpm at ≥ 2 consecutive visits	538 (15.9)	139 (7.2)
Change > 20 bpm at ≥ 2 consecutive visits	167 (4.9)	33 (1.7)
HR > 80 bpm at ≥ 2 consecutive visits	1240 (36.6)	447 (23.0)
HR > 90 bpm at ≥ 2 consecutive visits	248 (7.3)	77 (4.0)
HR > 100 bpm at ≥ 2 consecutive visits	31 (0.9)	5 (0.3)

Source: ISS, Tables 2-54, 2-55, and 2-56

There was no clear indication of a liraglutide dose-response, based on a within-dose comparison of change in mean resting HR at end of treatment in the 2 trials that included lower doses of liraglutide. Mean change in HR by liraglutide dose in trials 1807 and 1922 is illustrated in Figure 62 and Figure 63, respectively.

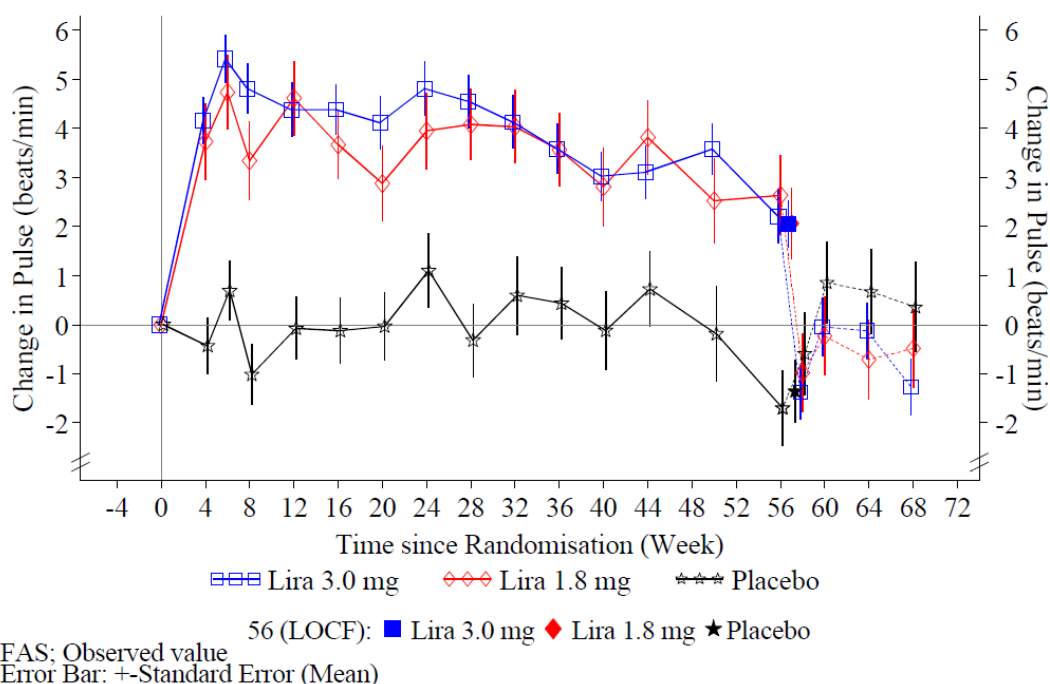
Figure 62. Mean Change in Heart Rate by Visit, Trial 1807 (Weeks 0 to 52)



Note: LOCF includes weeks 0-104, based on 65 patients randomized to lira 3 mg and entering year 2

Source: ISS, Appendix 7.7, Figure 140

Figure 63. Mean Change in Heart Rate by Visit, Trial 1922



Source: NN8022-1922 Clinical Trial Report, Figure 12-14

In trial 1922 (Figure 63, above), the estimated treatment difference between liraglutide 3 mg and placebo at week 56 was 3.40 bpm, and between liraglutide 1.8 mg and placebo was 3.70 bpm, with no significant difference between liraglutide 1.8 and 3 mg observed.

Categorical HR cutoffs demonstrated consistent findings. The proportion of patients with various categories of HR increase was higher in the liraglutide-treated groups than placebo and in general, the proportions were similar between liraglutide groups (Table 117).

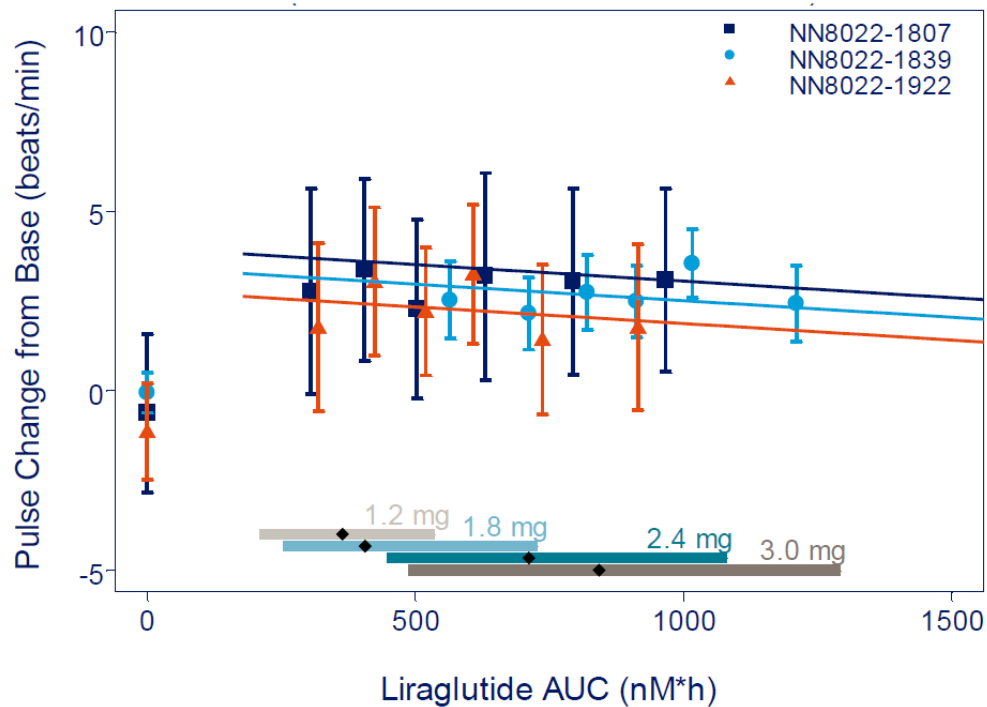
Table 117. Categories for HR Increase from Baseline until Week 56, Trial 1922

Change from baseline to week 56	Lira 3 mg N=422 n (%)	Lira 1.8 mg N=210 n (%)	Placebo N=212 n (%)
> 0 bpm	374 (88.6)	180 (85.7)	169 (79.7)
> 5 bpm	337 (79.9)	157 (74.8)	136 (64.2)
> 10 bpm	256 (60.7)	127 (60.5)	85 (40.1)
> 15 bpm	171 (40.5)	77 (36.7)	50 (23.6)
> 20 bpm	77 (18.2)	38 (18.1)	19 (9.0)

Source: NN8022-1922 Clinical Trial Report, Table 14.3.6.6

The lack of a dose-response was supported by the lack of an exposure-response relationship based on population PK samples from trials 1839, 1922, and 1807:

Figure 64. Resting HR Change versus Liraglutide Exposure (Steady-State AUC), Trials 1839, 1922, and 1807



Data are mean values with 95%CI versus exposure expressed as six quartiles of AUC values (plus placebo). Lines represent covariate-adjusted model-based estimates for each trial population over the obtained exposure range. Horizontal lines with diamonds represent median and 90% CI values of exposure from each dose level.

Source: ISS, Figure 2-37

There was no significant interaction for change in HR in the assessment of the following subgroups: sex, age (< 65 yrs vs. ≥ 65 yrs), race, Hispanic ethnicity, baseline BMI, baseline weight, and glycemic status (diabetes, pre-diabetes, normoglycemia). A treatment effect for HR was observed regardless of whether a patient was a 5% responder or not (Figure 65).

Figure 65. Change in Heart Rate by Visit in 5% Weight Loss Non-Responders (Top) and Responders (Bottom)

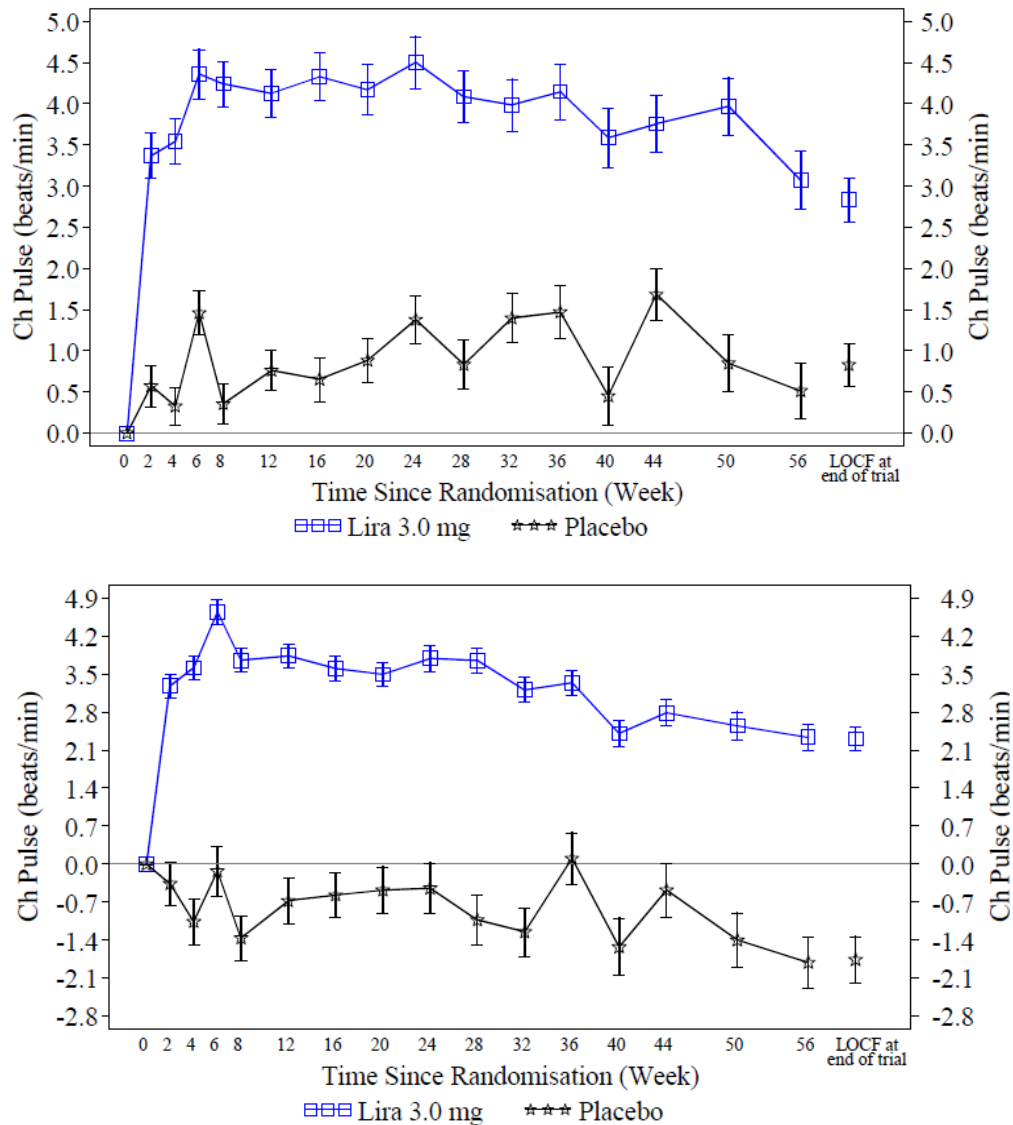


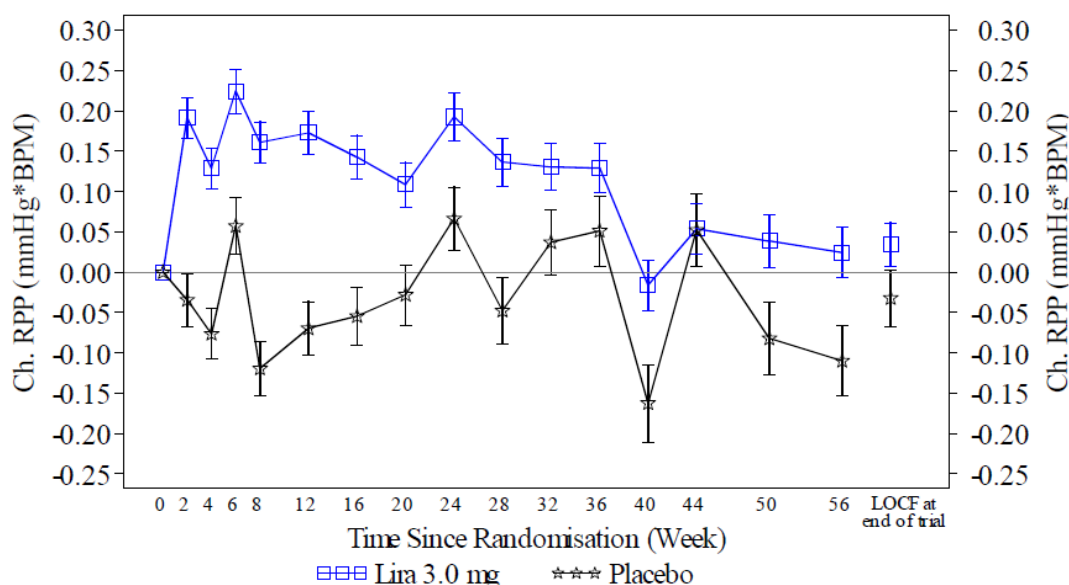
Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

Source: ISS, Appendix 7.4, Figures 186 and 187

Rate-Pressure Product

The rate-pressure product (RPP) is the product of heart rate (bpm) and systolic blood pressure (mmHg), and is an estimate of myocardial oxygen demand. RPP was increased in the liraglutide-treated group as compared to the placebo-treated group throughout the trials.

Figure 66. Change in Rate-Pressure Product by Visit, Weight Management Pool



Source: ISS, Figure 2-39

7.5.7.2.2 Adverse Events of Cardiac Arrhythmia

The sponsor conducted a pre-defined MedDRA search to identify events potentially related to cardiac arrhythmia, based on the following SMQs. Of note, GLP-1 receptors have been localized to the sinoatrial node of monkey and human cardiac tissues; however, the AV-node, other atrial and ventricular myocytes, the HIS-purkinje system, smooth muscle cells, and endothelial cells did not show GLP-1 receptor staining in normal monkey heart.¹¹

Table 118. MedDRA Terms Used in the Cardiac Arrhythmia Search

SMQs	
Arrhythmia related investigations, signs and symptoms	Cardiac arrhythmia terms, nonspecific
Bradyarrhythmia terms, nonspecific	Supraventricular tachyarrhythmias
Conduction defects	Tachyarrhythmia terms, nonspecific
Disorders of sinus node function	Ventricular tachyarrhythmias

SMQ: standardised MedDRA query.

Source: ISS, Table 2-42

Main Treatment Phase

The MedDRA search for 'cardiac arrhythmia' identified a total of 132 treatment-emergent events reported in 113 patients treated with liraglutide 3 mg (3.3%) and 64 events in 58 patients treated with placebo (3.0%). Table 119 presents the incidence of the individual preferred terms in treatment groups.

Consistent with the finding of increased heart rate was an increased incidence of AE reports of tachycardia in the liraglutide group (0.6%) as compared to placebo (0.1%).

‘Cardiac conduction disorders’ (MedDRA high level term) were reported by a higher proportion of patients treated with liraglutide 3 mg (n=11, 0.3%) than with placebo (none); the events included ‘atrioventricular block first degree’ (7 events in 6 patients), ‘bundle branch block right’ (4 events in 4 patients), and ‘bundle branch block left’ (2 events in 2 patients). All ‘cardiac conduction disorder’ events were non-serious and reported as mild or moderate by the investigator, and none of them led to withdrawal.

None of the adverse events of ‘electrocardiogram QT prolonged’ were considered SAEs. All QT prolongation events were considered of mild severity. No dose adjustments were made.

Table 119. ‘Cardiac Arrhythmia’ Search (Selected Preferred Terms), Weight Management Pool

	Lira 3 mg N=3384	All lira N=3872	Placebo N=1941
Cardiac arrhythmia AEs	113 (3.3)	135 (3.5)	58 (3.0)
Palpitations	25 (0.7)	32 (0.8)	18 (0.9)
Syncope	21 (0.6)	26 (0.7)	9 (0.5)
Tachycardia	19 (0.6)	20 (0.5)	2 (0.1)
Atrial fibrillation	9 (0.3)	9 (0.2)	5 (0.3)
Atrioventricular block first degree	6 (0.2)	8 (0.2)	0
Heart rate increased	5 (0.1)	5 (0.1)	2 (0.1)
Bundle branch block right	4 (0.1)	4 (0.1)	0
Supraventricular extrasystoles	4 (0.1)	4 (0.1)	0
Electrocardiogram QT prolonged	2 (<0.1)	2 (<0.1)	1 (<0.1)
Bundle branch block left	2 (<0.1)	2 (<0.1)	0
Heart rate irregular	2 (<0.1)	2 (<0.1)	0
Loss of consciousness	2 (<0.1)	2 (<0.1)	0

Source: ISS, Appendix 7.2, Table 137

Cardiac arrhythmia SAEs reported in patients treated with liraglutide 3 mg were ‘tachycardia’ (1 event), ‘supraventricular tachycardia’ (1 event), ‘atrial fibrillation’ (1 event), ‘sinus arrest’ (1 event), and ‘syncope’ (2 events). SAEs reported in patients treated with placebo were ‘atrial fibrillation’ (1 event), ‘cardiorespiratory arrest’ (1 event), and ‘palpitations’ (1 event). SAEs related to tachycardia and sinus arrest are as follows:

- Patient 232008 was a 61-year-old male randomized to liraglutide 3 mg in trial 1839. Medical history included asthma, pulmonary hypertension, hypertension, and pulmonary embolism. A pulmonary endarterectomy for ‘worsening pulmonary function’ was performed approximately 9 months into the trial. The patient was started on bisoprolol for coronary artery disease. One week after discharge from

the hospital, the patient reported rapid heartbeat or pounding, which was reported as tachycardia (**reviewer comment: the patient appears to have been off drug for approximately 3 weeks at the time of this AE**). This event was reported as serious because it was temporal to the embolectomy procedure. Five days later, liraglutide was restarted. Bisoprolol dose was doubled 1 week later. Prednisolone was prescribed due to a small amount of pericardial fluid. During a follow-up hospitalization, an ECG demonstrated prolonged PQ and during tachycardia, the P wave disappeared. Liraglutide was temporarily stopped, but the AE did not abate after stopping drug; liraglutide was restarted 3 days later. The heart rate normalized approximately 2 months later. Bisoprolol was discontinued.

Reviewer comment: Tachycardia appears to have been related to the embolectomy and / or the pericardial effusion.

- Patient 532007 was a 52-year-old female randomized to liraglutide 3 mg in trial 1839. Medical history included hypertension, hypercholesterolemia, and insulin resistance. The patient was hospitalized for supraventricular tachycardia on study day 110 (sinus rhythm with runs of SVT at rates of 180 bpm). Chest x-ray was normal. Troponin I was slightly elevated at 0.1 µg/L, but no other evidence of myocardial infarction was seen. The patient was treated with electrical cardioversion and sotalol. Liraglutide was temporarily discontinued for the event, but titrated back to the 3 mg dose after 2 weeks. The event did not reappear after liraglutide reintroduction.
- Patient 323017 was a 51-year-old female randomized to liraglutide 3 mg in trial 3970. Medical history included severe OSA, uvulectomy, tonsillectomy, deviated septum, and inferior turbinate hypertrophy. On trial day 205, the patient was hospitalized for pre-planned elective surgery related to her sleep apnea (septoplasty and reduction of inferior turbinates). After discharge (day 208) she could not swallow or eat due to severe post-operative swelling. She was hospitalized on trial day 213 for dehydration. During hospitalization, she experienced episodes of significant sinus pauses during sleep and was noted to have worsening sleep apnea due to oropharyngeal swelling. A pacemaker was inserted on trial day 21.

Trial 1839 Extension Phase

In the extension phase of trial 1839, 3 patients experienced 4 SAEs in the 'cardiac arrhythmia' HLG by the data cut-off as reported in the 120-day safety update. All SAEs occurred in patients treated with liraglutide 3 mg: 'atrial fibrillation' (2 events in 2 patients) and 'cardio-respiratory arrest' and 'ventricular fibrillation' (2 events in 1 patient). The SAEs of cardio-respiratory arrest and ventricular fibrillation in patient 439014 led to death (details in section 7.2.2).

7.5.7.3 Hypotension

Liraglutide is associated with blood pressure decreases, as described in section 6 (efficacy results). It has been speculated that GLP-1 receptor agonists may exert blood pressure lowering effects via natriuresis and/or vasodilatory action.^{48,49,50}

Absolute numbers were very small, but more patients treated with liraglutide than placebo reported an AE of 'hypotension' (0.7% vs. 0.3%), 'orthostatic hypotension' (0.3% vs. 0.2%), or 'blood pressure decreased' (0.1% vs. 0) during the treatment period.

All treatment-emergent AEs related to blood pressure were non-serious, except one SAE of 'circulatory collapse' reported after 136 days of treatment with liraglutide 3 mg:

- Patient 141023 (trial 1839) was a 65-year-old female had circulatory collapse after having diarrhea (non-serious event) the day before. The patient sustained a fall resulting in a head wound which led to hospitalization. The event of circulatory collapse was of moderate severity. The patient recovered with no change in trial medication.

In addition, a non-serious 'circulatory collapse' event was reported after 35 days of treatment with liraglutide 3 mg (patient 312007, trial 1922). The event was mild and lasted 1 day. The patient recovered with no change in trial medication.

One SAE of orthostatic hypotension was reported in a patient treated with liraglutide 3 mg in the ongoing extension portion of trial 1839:

- Patient 203031 (trial 1839) was a 57-year-old-male who reported mild orthostatic hypotension on day 351. According to the investigator this was related to a chronic condition due to concomitant treatment with a beta-blocking agent.

Consistent with the blood pressure results (section 6) and the slight increase in reported AEs of hypotension in patients treated with liraglutide, more patients treated with liraglutide than placebo had at least one SBP measurement less than 90 mmHg (2.5% vs. 0.7%), less than 85 mmHg (0.8% vs. 0.1%), and less than 80 mmHg (0.1% vs. 0).

More patients treated with liraglutide 3 mg than placebo experienced persistent decrease (at least two consecutive visits) of SBP. Few patients had persistent SBP values below 90 mmHg during the treatment period (2.5% vs. 0.7%, for liraglutide 3 mg and

⁴⁸ Kim M, et al. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med.* 2013; 19(5): 567-75.

⁴⁹ Gutzwiller JP, et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab.* 2004; 89(6): 3055-61.

⁵⁰ Ussher JR and Drucker DJ. Cardiovascular actions of incretin-based therapies. *Circ Res.* 2014; 114(11): 1788-803.

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placebo, respectively) and no patient in either group had a persistent decrease in SBP below 85 mmHg. Of the patients with persistent SBP below 90 mmHg, none reported events of 'syncope'. Few patients reported AEs of dizziness, including postural dizziness (4 patients, all on liraglutide 3 mg), fatigue (liraglutide 3 mg: 3 patients; placebo: 1 patient), and pre-syncope (liraglutide 3 mg: 1 patient).

7.5.7.4 Heart Failure

A predefined MedDRA search for heart failure and events potentially related to heart failure was performed among all reported AEs based on the MedDRA SMQ 'Cardiac failure'.

The heart failure SMQ search identified 58 events in 55 patients (1.6%) treated with liraglutide 3 mg and 51 events in 48 patients (2.5%) treated with placebo. The imbalance between liraglutide and placebo (in favor of liraglutide) is driven by a greater incidence of peripheral edema in the placebo treatment group.

Table 120. Heart Failure AEs, Weight Management Pool

	Lira 3 mg N=3384	All lira N=3872	Placebo N=1941
Heart failure SMQ AEs	55 (1.6)	64 (1.7)	48 (2.5)
Peripheral edema	47 (1.4)	55 (1.4)	43 (2.2)
Edema	4 (0.1)	5 (0.1)	2 (0.1)
Pulmonary congestion	2 (<0.1)	2 (<0.1)	2 (0.1)
Cardiomegaly	1 (<0.1)	1 (<0.1)	0
Diastolic dysfunction	1 (<0.1)	1 (<0.1)	1 (<0.1)
Cardiac failure	0	0	1 (<0.1)

Source: ISS, Appendix 7.2, Table 122

Heart failure events requiring hospitalization were adjudicated in trials 1839, 1922 and 3970. In trial 1923, events of heart-failure identified via the pre-defined SMQ search were adjudicated *post hoc*.

One treatment-emergent event was confirmed by the EAC as heart failure. This occurred in a patient treated with liraglutide 3 mg. Note that this event was not captured in the above MedDRA search because the preferred term 'cardiomyopathy' is not included in the SMQ.

- Patient 302004 (trial 1922, liraglutide 3 mg) was a 45-year-old female hospitalized for severe 'cardiomyopathy' (PT) during the first 2 weeks of the follow-up period (day 390). The patient had a medical history of peripartum cardiomyopathy (in 2005). She reportedly had an abnormal ECG at screening suggestive of previous cardiomyopathy. Five days after discontinuation of treatment with the trial drug, the patient presented with dyspnea at rest and was hospitalized with cardiomyopathy of unclear etiology. No acute myocardial infarction or arrhythmia

was present. Echocardiogram showed diffuse, severe left ventricle systolic impairment, LV ejection fraction 20-25%, severe left cavity dilation, dilated left atrium, mild mitral regurgitation, and good right ventricular systolic function. Coronary angiogram was normal. She was treated with diuretics, ACE-inhibitors, beta-blockers, and oxygen, and was reported as recovering.

As of the cut-off date for the extension phase of trial 1839, there were no AEs of heart failure or related to heart failure that qualified for adjudication.

7.5.8 Psychiatric Events

The assessment of mood disorders and suicidality is a standard part of the safety review for any obesity drug with a centrally acting mechanism.^{51,52,53,54} FDA has recommended that sponsors screen for psychiatric disorders and include questionnaires (PHQ-9 and C-SSRS, described further below) to assess depression and suicidal ideation or behavior in phase 2 and 3 clinical trials of obesity drugs.

In the liraglutide phase 3 weight management program, patients with severe past or present psychiatric disorders were not eligible for enrollment. Exclusion criteria included:

- History of major depressive disorder within the last 2 years
- Patient Health Questionnaire 9 (PHQ-9) score ≥ 15 (indicative of at least moderately severe depression) at screening or baseline
- History of other severe psychiatric disorders, e.g., schizophrenia, bipolar disorder
- Any lifetime history of a suicide attempt
- History of any suicidal behavior in the last month prior to randomization
- Any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) in the last month prior to randomization

The mental health questionnaires PHQ-9 and C-SSRS were used in all phase 3 weight management trials. The questionnaires were administered at all visits in trials 1839, 1922, 3970 and 1923 (except week -1 in trial 3970 and the dose-titration visits in 1923). Mental health questionnaires were not used in the clinical pharmacology trial 3630 and the phase 2 trial 1807.

During the phase 3 trials, a patient was to be referred to a Mental Health Professional (MHP) if he/she had a PHQ-9 score 10 or greater (indicative of moderate depression) or any suicidal behavior or any suicidal ideation of type 4 (active suicidal ideation with

⁵¹ Egan A. FDA Clinical Review of NDA 21888 (rimonabant), EMDAC 13 Jun 2007.

⁵² Golden J. FDA Clinical Review of NDA 22529 (lorcaserin), EMDAC 16 Sep 2010 and 10 May 2012.

⁵³ Roberts M. FDA Clinical Review of NDA 22580 (phentermine/topiramate), EMDAC 15 July 2010 and 22 Dec 2012.

⁵⁴ Craig E. FDA Clinical review of NDA 200063 (naltrexone/bupropion), EMDAC 7 Dec 2010.

some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) on the C-SSRS. Enrolled patients were to be withdrawn from the trials if they developed a psychiatric disorder that could not be adequately treated with psycho- and/or pharmacotherapy. Furthermore, a referral to a MHP was also to be made if in the opinion of the investigator it was necessary for the safety of the patient.

The PHQ-9 is a 9-item depression subscale of the self-administered patient health questionnaire (mental disorder instrument for use in primary care).⁵⁵ The patient rates the frequency of the following 9 items on the scale from 0 (not at all) to 3 (nearly every day) in the last 2 weeks:

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other people could have noticed, or the opposite – being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or hurting yourself in some way

The total score ranges from 0 to 27. Total scores of 0–4 represent no to minimal depression, total scores of 5–9 represent mild depression, total scores of 10–14 represent moderate depression, total scores of 15–19 represent moderately severe depression, and total scores of 20–27 represent severe depression.

Major depression is diagnosed if 5 or more of the 9 criteria have been present at least “more than half the days” in the past 2 weeks and one of the symptoms is depressed mood or anhedonia.

The symptom criterion in Question 9, “thoughts that you would be better off dead or hurting yourself in some way,” counts if present at all, regardless of duration.

Before making a final diagnosis, the clinician is expected to rule out physical causes of depression, normal bereavement, and history of a manic episode.⁵⁵

⁵⁵ Kroenke K, et al. The PHQ-9 – validity of a brief depression severity measure. J Gen Intern Med. 2001; 16: 606-13.

The C-SSRS is a standardized assessment to quantify the severity of suicidal ideation and behavior.⁵⁶ The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of the ideation, and 6 questions addressing suicidal behavior. The following categories were used in order to classify the events:

- Suicidal ideation:
 1. Wish to be dead (passive)
 2. Non-specific active suicidal thoughts (no method, intent, or plan)
 3. Active suicidal ideation with any methods (not plan) without intent to act
 4. Active suicidal ideation with some intent to act, without specific plan
 5. Active suicidal ideation with specific plan and intent
- Suicidal behavior:
 1. Completed suicide
 2. Actual suicide attempt
 3. Interrupted suicidal attempt
 4. Aborted suicide attempt
 5. Preparatory acts or behavior towards making a suicidal attempt
- Non-suicidal self-injurious behavior

7.5.8.1 Adverse Events

At baseline, 9.5% of patients in the weight management pool had a medical history of depression and 7% of patients had a history of anxiety. No patient had a history of suicide attempt or suicidal behavior based on the suicide and self-injury SMQ.

Table 121. Baseline Psychiatric Disorders, Weight Management Pool

	Lira 3 mg N=3384	Total lira N=3872	Placebo N=1941
Depression SMQ	309 (9.1)	346 (8.9)	206 (10.6)
Suicide SMQ	0	0	0
Anxiety*	243 (7.2)	258 (6.7)	151 (7.8)
* Includes high level terms 'anxiety symptoms' and 'anxiety disorders NEC'			

Source: ISS, Appendix 7.1, Table 21

A predefined MedDRA search was performed among all AEs to identify all reported events of psychiatric disorders during the trials. The search was based on the SOC 'psychiatric disorders', and included all primary and secondary preferred terms within the SOC.

⁵⁶ Posner K, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Amer J Psych.* 2011; 168: 1266-77.

Although overall, the AEs in the predefined psychiatric SMQ were similar between groups, there were individual AEs within the psychiatric disorders SOC that demonstrated some imbalances. High level group terms (HLGTs) within the SOC are shown in Table 122 and most common PTs in the SMQ are shown in Figure 67. These analyses suggest that sleep disorders, and specifically, insomnia, may be associated with liraglutide treatment.

None of the events were fatal. The proportions of patients with SAEs identified in the MedDRA search for psychiatric disorders were low and similar with liraglutide 3 mg and placebo (Table 122). In patients treated with liraglutide 3 mg, 5 SAEs in 4 patients were: 'anxiety', 'panic attack', 'depression suicidal' (see narrative in section 7.5.8.1.1, below) and 2 events of 'sleep apnea syndrome'. 'Anxiety' and 'nightmare' were reported as SAEs by 2 patients treated with placebo.

The most frequent reasons for withdrawal due to a psychiatric AE in patients treated with liraglutide 3 mg were depression (4 patients vs. 2 patients on placebo) and irritability (3 patients vs. none on placebo). One patient treated with liraglutide 3 mg was withdrawn due to suicidal ideation (see narrative in section 7.5.8.1.1, below).

Small imbalances in anxiety (2.0% vs. 1.6%) and depression (1.8% vs. 1.6%) were noted in the weight management program of uncertain significance.

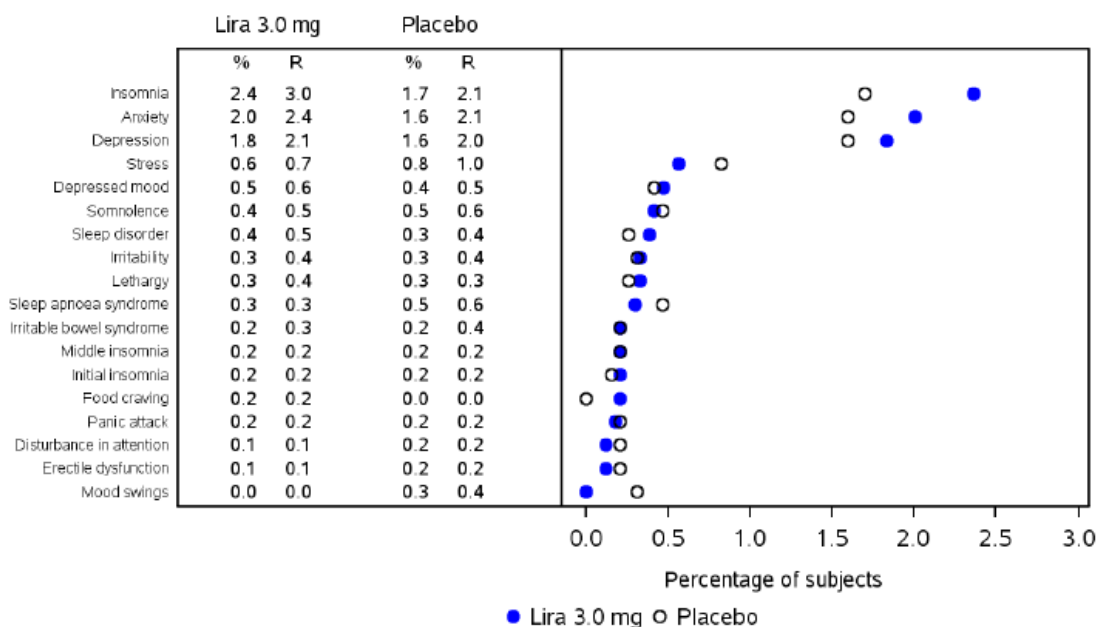
Table 122. Psychiatric Disorders, Weight Management Pool

	Lira 3 mg N=3384	Total lira N=3872	Placebo N=1941
Psychiatric SMQ	366 (10.8)	414 (10.7)	197 (10.1)
Serious	4 (0.1)	4 (0.1)	2 (0.1)
Severe	8 (0.2)	9 (0.2)	13 (0.7)
AE leading to withdrawal	14 (0.4)	18 (0.5)	13 (0.7)
Outcome: not recovered	105 (3.1)	118 (3.0)	55 (2.8)
Psychiatric disorders SOC	292 (8.6)	332 (8.6)	156 (8.0)
Sleep disorders and disturbances	112 (3.3)	124 (3.2)	49 (2.5)
Anxiety disorders and symptoms	100 (3.0)	111 (2.9)	60 (3.1)
Depressed mood disorders and disturbances	83 (2.5)	96 (2.5)	46 (2.4)
Mood disorders and disturbances NEC	8 (0.2)	9 (0.2)	12 (0.6)
Changes in physical activity	6 (0.2)	7 (0.2)	1 (<0.1)
Adjustment disorders	5 (0.1)	6 (0.2)	3 (0.2)
Cognitive and attention disorders and disturbances	3 (<0.1)	3 (<0.1)	1 (<0.1)
Eating disorders and disturbances	3 (<0.1)	5 (0.1)	1 (<0.1)

Sexual dysfunctions	3 (<0.1)	3 (<0.1)	3 (0.2)
Suicidal and self-injurious behaviors NEC	3 (<0.1)	3 (<0.1)	0
Manic and bipolar mood disorders	2 (<0.1)	2 (<0.1)	0
Communication disorders	1 (<0.1)	1 (<0.1)	1 (<0.1)
Deliria	1 (<0.1)	1 (<0.1)	3 (0.2)
Personality disorders and disturbances in behavior	1 (<0.1)	1 (<0.1)	1 (<0.1)
Psychiatric disorders NEC	1 (<0.1)	2 (<0.1)	0
Disturbances in thinking and perception	0	0	1 (<0.1)

Source: ISS, Appendix 7.2, Tables 371 and 372

Figure 67. Most Common Preferred Terms in Psychiatric Disorders SMQ, Weight Management Pool



%: Percentage of subjects experiencing at least one event, R: event rate per 100 exposure years.

Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.

Source: ISS, Appendix 7.2, Figure 373

7.5.8.1.1 Suicidality

In the main treatment portion of the weight management trials, 5 treatment-emergent suicidality AEs were reported by 5 patients treated with liraglutide 3 mg and none with placebo; a sixth patient reported suicidal ideation during the extension phase of 1839. Three of these events occurring in the main treatment period were captured in the AE reporting in Table 122, above ('Suicidal and self-injurious behaviors NEC' HLGT). A fourth patient reported an SAE of a suicidal attempt; for unclear reasons this was not captured in the main part of the trial, but rather in the extension phase of 1839 (although it occurred on day 113). A fifth patient reported an SAE of 'depression suicidal' (which is categorized under the 'Depressed mood disorders and disturbances' HLGT). The narratives follow.

- Patient 486024 (trial 1839): This was a 28-year-old female with no prior history of psychiatric disorder. Approximately 6 months into the treatment, the patient presented with depression. The patient's family reported that the depression had been evident for the last couple of months, whereas the patient felt it only over the last few weeks. The patient was not interested in daily activities and emotionally labile. The patient had misused Vicodin to "take away the pain". Three weeks later, the patient reported that she had had two fleeting suicidal thoughts. No action was taken towards making a suicide attempt. The patient's PHQ-9 score at that time was 17 (moderately severe depression). The drug was discontinued. The investigator was unsure if the patient had recovered after treatment discontinuation. Two months later, the site contacted the patient for a post-study follow-up and she stated that she was diagnosed with mild depression and the depressed mood continued intermittently.
- Patient 338009 (trial 1839): This was a 42-year-old female with no reported history of mental illness who had a 1-day AE of suicidal ideation on day 16 of the trial. The AE was reported as mild and 'possibly' related to study drug. On the C-SSRS, the patient reported 'wish to be dead' and 'active suicidal ideation with any methods (not plan) without intent to act' (type 3), at week 4. She recovered and remained in the trial with no change to her dose. No further psychiatric AEs were reported.
- Patient 435014 (trial 1839): This was a 41-year-old female with a history of situational depression who had a 1-day AE of suicidal ideation on day 327 of the trial. The AE was reported as mild and 'unlikely' related to study drug. On the C-SSRS the patient reported 'wish to be dead' at screening and at week 50. She recovered and remained in the trial with no change to her dose. She also had an AE of mild worsening depression reported on day 327 and moderate chronic anxiety reported on day 388, neither of which she had recovered from by report.
- Patient 410022 (trial 1839): This was a 42-year-old female with a medical history of depression who reported a suicide attempt on day 113 of treatment. She was hospitalized after taking an overdose of an unknown medication with suicidal ideation following an argument with her mother. The patient reported situational depression (family issues and work-related stress) and that she had made a poor choice. By report, she was grateful that her suicide attempt did not succeed. She continued to receive psychological counseling for her suicidal ideations. Eight months later, the patient experienced depression, which was not considered a separate event by the investigator. She was on leave from work due to mental health issues. At that time the patient denied suicidal thoughts or plans and was reportedly better away from work stress. She was treated with aripiprazole, clonazepam, and bupropion. Four months later, the patient discontinued trial product due to the psychiatrist's recommendation and 5 months later reportedly recovered from her suicidal ideations, although major depressive disorder was ongoing and considered a chronic condition.

- Patient 344003 (trial 3970) was a 36-year-old female with a medical history that included intermittent anxiety and depression during the previous 13 years and an unconfirmed instance of suicide attempt. SAEs of anxiety and depression suicidal (i.e., depression with suicidal ideation) were reported on day 203. Both events were classified as severe. The patient was voluntarily hospitalized in a psychiatric unit due to these SAEs that reportedly resulted from an event in the patient's on-going divorce proceedings. During hospitalization, the patient was treated with individual and group therapy and pharmacologic agents. The patient continued using prescription medication for the diagnosed anxiety and depression. The trial product dosage remained unchanged and the patient did not withdraw from the trial due to these events. Both of these events had outcomes of 'not recovered'.

In addition, an event was reported in the ongoing 1839 extension, in a patient treated with liraglutide 3 mg:

- Patient 503014 (trial 1839-ext) was a 49-year-old male who presented with suicidal ideation following the death of his father. The patient was sent to the emergency room for evaluation, but was not hospitalized. The patient found his father dead on the roof of the house, was very close to him, and felt a great amount of guilt. Treatment included Wellbutrin and Rivotril. No action was taken to trial product due to the event and the patient recovered approximately 1½ months later.

In the diabetes (Victoza) program, one patient treated with liraglutide 1.2 mg reported 2 events of suicidal ideation (details below), and one patient treated with comparator reported a suicide attempt.

- Patient 189008 (trial 1573): This was a 42-year-old female with a history of bipolar disorder, anxiety, and depression who presented with SAEs of suicidal thoughts on days 132 and 505. No change was made to the trial medication.

In addition to the above, one patient treated with liraglutide 3 mg reported non-specific suicidal behavior on the suicidality questionnaire, the C-SSRS. No AE was reported. Details are provided in section 7.5.8.2.2.

7.5.8.1.2 Insomnia

As shown in Figure 67, there was a small imbalance in the proportion of patients reporting insomnia with liraglutide (2.4%) versus placebo (1.7%). The imbalance in insomnia was primarily seen in the first 3 months of the treatment period (liraglutide 3 mg 1.4%, placebo 0.8%), and then the incidence was similar between groups over subsequent time periods; the following plot of time to onset of new insomnia events generally supports this finding:

Figure 68. Cumulative Event over Time Plot of Insomnia, Weight Management Pool

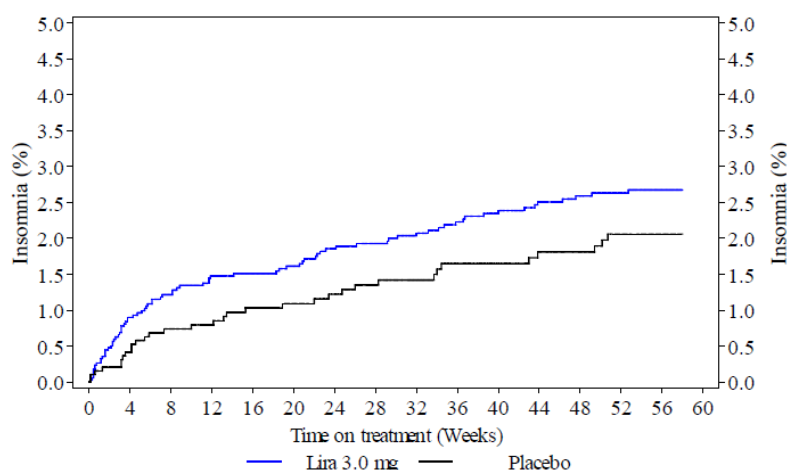


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial 3970 is a 32 week trial.

Source: ISS, Appendix 7.2, Figure 384

The use of hypnotics and sedatives (primarily promethazine, benzodiazepine derivatives, and melatonin) in the weight management trials was similar between groups (liraglutide: 0.6 to 1.2%, placebo: 0.6 to 1.1%), although a slightly higher proportion of patients in the liraglutide- as compared to the placebo-treated group took benzodiazepine-related drugs (e.g., zolpidem) (1.2% vs. 0.8%) and hypnotics and sedatives categorized as 'other' (e.g., scopolamine) (0.4% vs. 0.2%).

7.5.8.1.3 Dose Relationship

The results from trial 1807 suggested a liraglutide dose effect for psychiatric disorders overall (liraglutide 2.4 mg and 3 mg), although sleep-, anxiety-, and depression-related terms that compose the respective HLGs were not strongly dose-related. Preferred terms within the psychiatric disorders SOC and SMQ reflect a variety of adverse events, and do not point toward any one particular diagnosis.

Table 123. Psychiatric AEs by Dose, Trial 1807

	Placebo	Lira 1.2	Lira 1.8	Lira 2.4	Lira 3	Orlistat
Psychiatric SMQ	6 (6.1)	4 (4.2)	7 (7.8)	12 (12.9)	17 (18.3)	7 (7.4)
Psychiatric disorders SOC	6 (6.1)	3 (3.2)	5 (5.6)	11 (11.8)	12 (12.9)	7 (7.4)
Sleep disorders	3 (3.1)	0	0	2 (2.2)	5 (5.4)	3 (3.2)
Anxiety disorders and symptoms	3 (3.1)	1 (1.1)	1 (1.1)	4 (4.3)	4 (4.3)	1 (1.1)
Depressed mood disorders and disturbances	0	1 (1.1)	2 (2.2)	4 (4.3)	2 (2.2)	1 (1.1)
Other SOC						
Irritability	0	0	0	0	2 (2.2)	0
Memory impairment	0	0	0	0	2 (2.2)	0

Source: ISS, Appendix 7.7, Table 38

7.5.8.2 Mental Health Questionnaires

7.5.8.2.1 PHQ-9

At baseline, the mean PHQ-9 total scores for depression were similar between liraglutide 3 mg (2.8) and placebo (2.9).

During the treatment period, the mean PHQ-9 total scores decreased slightly (improvement), and were similar in both treatment groups. A summary of results is presented in Table 124 and Table 125.

Table 124. Overview of PHQ-9 Results During Treatment, Weight Management Pool

PHQ-9	Liraglutide 3.0 mg	Placebo
Mean scores		
Mean PHQ-9 total score at end-of-treatment	1.8	1.9
Mean PHQ-9 highest scores over treatment period	3.7	3.7
Total scores above cut-off		
≥10 at end-of-treatment (week 56 LOCF)	1.9%	1.7%
≥10 at any time during trial	6.1%	6.8%
≥15 at end-of-treatment (week 56 LOCF)	0.4%	0.4%
≥15 at any time during trial	1.1%	1.5%
≥20 at end-of-treatment (week 56 LOCF)	<0.1%	0.2%
≥20 at any time during trial	0.2%	0.4%

LOCF: last observation carried forward; PHQ-9: patient health questionnaire 9.

Source: ISS, Table 2-112

Table 125. PHQ-9 Total Scores, Shift from Baseline to Maximum, Weight Management Pool

	Lira 3.0 mg N (%)	Total lira N (%)	Placebo N (%)
Number of subjects	3291	3501	1843
Total number of subjects improving from baseline to highest score	317 (9.6)	333 (9.5)	182 (9.9)
Mild to none	231 (7.0)	244 (7.0)	132 (7.2)
Moderate to none	27 (0.8)	28 (0.8)	12 (0.7)
Moderate to mild	59 (1.8)	61 (1.7)	35 (1.9)
Moderately severe to moderate	0 (0.0)	0 (0.0)	0 (0.0)
Moderately severe to mild	0 (0.0)	0 (0.0)	1 (0.1)
Moderately severe to none	0 (0.0)	0 (0.0)	2 (0.1)
Severe to moderately severe	0 (0.0)	0 (0.0)	0 (0.0)
Severe to moderate	0 (0.0)	0 (0.0)	0 (0.0)
Severe to mild	0 (0.0)	0 (0.0)	0 (0.0)
Severe to none	0 (0.0)	0 (0.0)	0 (0.0)
Total number of subjects worsening from baseline to highest score	653 (19.8)	692 (19.8)	347 (18.8)
None to mild	483 (14.7)	509 (14.5)	251 (13.6)
None to moderate	66 (2.0)	72 (2.1)	40 (2.2)
None to moderately severe	9 (0.3)	10 (0.3)	10 (0.5)
None to severe	1 (0.0)	1 (0.0)	4 (0.2)
Mild to moderate	69 (2.1)	73 (2.1)	29 (1.6)
Mild to moderately severe	13 (0.4)	13 (0.4)	6 (0.3)
Mild to severe	2 (0.1)	2 (0.1)	2 (0.1)
Moderate to moderately severe	7 (0.2)	9 (0.3)	4 (0.2)
Moderate to severe	3 (0.1)	3 (0.1)	1 (0.1)
Moderately severe to severe	0 (0.0)	0 (0.0)	0 (0.0)
No change	2291 (69.6)	2442 (69.8)	1293 (70.2)
Missing	30 (0.9)	34 (1.0)	21 (1.1)

N: Number of subjects, %: Proportion of randomised subjects, PHQ-9: Patient health questionnaire 9
Table is based on trials 1839, 1922, 3970 and 1923.
None: PHQ-9 total score of 0-4
Mild depression: PHQ-9 total score of 5-9
Moderate depression: PHQ-9 total score of 10-14
Moderate severe depression: PHQ-9 total score of 15-19
Severe depression: PHQ-9 total score of >=20

Source: ISS, Appendix 7.6, Table 3

Four patients who reported a PHQ-9 total score of 15 or greater (corresponding to moderately severe depression or worse) during treatment had a corresponding AE of depression or depressed mood and were withdrawn from the trials; 2 patients treated with liraglutide 3 mg (scores of 18 and 20) and 2 patients treated with placebo (scores of 21 and 24).

During the treatment period, the proportion of patients who had a positive score for Question 9 ('thoughts that you would be better off dead or of hurting yourself in some way') at any time post-baseline was similar in patients treated with liraglutide 3 mg (1.8%) and placebo (2.2%). In a separate analysis of the worst Question 9 score, slightly more patients treated with liraglutide 3 mg reported these thoughts on more than half the days than patients treated with placebo:

Table 126. PHQ-9 'Question 9' Worst Post-Baseline Score, Weight Management Pool

	Lira 3.0 mg N (%)	Total lira N (%)	Placebo N (%)
Thoughts that you would be better off dead or of hurting yourself in some way			
Worst score&			
0 - Not at all	3203 (97.3)	3406 (97.3)	1786 (96.9)
1 - Several days	57 (1.7)	60 (1.7)	43 (2.3)
2 - More than half the days	7 (0.2)	8 (0.2)	1 (<0.1)
3 - Nearly every day	0 (0.0)	0 (0.0)	0 (0.0)
NA	4 (0.1)	5 (0.1)	5 (0.3)

Source: ISS, Appendix 7.6 Table 8

7.5.8.2.2 C-SSRS

C-SSRS post-baseline results are summarized in the table below.

Table 127. C-SSRS Summary, Weight Management Pool (Excluding Trial 1807)

	Lira 3 mg N=3270	Total lira N=3478	Placebo N=1832
Patients with suicidal behavior and/or ideation	22 (0.67)	22 (0.63)	14 (0.76)
Patients with suicidal ideation	21 (0.64)	21 (0.60)	14 (0.76)
1. Wish to be dead	18 (0.55)	18 (0.51)	13 (0.71)
2. Active suicidal ideation, non-specific thoughts	9 (0.27)	9 (0.26)	6 (0.33)
3. Active suicidal ideation with any methods (no plan) without intent	5 (0.15)	5 (0.14)	3 (0.16)
4. Active suicidal ideation with some intent to act, without specific plan	1 (0.03)	1 (0.03)	1 (0.05)
5. Active suicidal ideation with specific plan and intent	0	0	1 (0.05)
Patients with suicidal behavior	1 (0.03)	1 (0.03)	0
1. Completed suicide	0	0	0
2. Actual suicide attempt	0	0	0
3. Interrupted suicide	0	0	0
4. Aborted suicide attempt	0	0	0
5. Preparatory acts toward imminent suicidal behaviors	0	0	0
Patients with non-suicidal self-injurious behavior	1 (0.03)	1 (0.03)	0

Source: ISS, Appendix 7.6, Table 11

The proportions of patients with suicidal ideation were similar in the liraglutide and placebo treatment arms. The majority of these patients reported 'wish to be dead' (type 1) or 'non-specific active suicidal thoughts' (type 2). Few patients in either treatment group reported active suicidal ideation with or without intent (type 3 or 4). The one patient treated with liraglutide with type 4 suicidal ideation recorded at week 36 (patient 961008, 55-year-old male in trial 1922) had no psychiatric AEs reported and all subsequent visits (weeks 40, 44, 50, and 56) were negative for any type of suicidal ideation. In the placebo group, one patient reported 'active suicidal ideation with specific plan and intent' (type 5).

Golden, J.

Liraglutide 3 mg (Saxenda)

Clinical Review

As seen in Table 127, one patient treated with liraglutide 3 mg reported suicidal behavior on the C-SSRS.

- Patient 210005 (trial 1923) was a 54-year-old female who reported suicidal behavior at week 14, but did not define the behavior, and no other C-SSRS questions regarding specific behaviors were answered affirmatively. No further information was provided. It was noted that no psychiatric AE was recorded for this patient at any time during the trial and the suicidal behavior question and all other C-SSRS questions were answered “no” on all previous and subsequent visits (to week 44).

Patient 410022 (trial 1839) had a suicide attempt (discussed in section 7.5.8.1.1) that for unclear reasons was not captured in the C-SSRS.

7.5.9 Hypoglycemia

Liraglutide lowers fasting and postprandial glycemia in a glucose-dependent manner. The sponsor notes that in patients with T2DM, the risk of hypoglycemia at doses of liraglutide up to 1.8 mg (maximum approved dose for T2DM) is low. As reported in the Victoza label:

In the eight clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 11 Victoza-treated patients (2.3 cases per 1000 patient-years) and in two exenatide-treated patients. Of these 11 Victoza-treated patients, six patients were concomitantly using metformin and a sulfonylurea, one was concomitantly using a sulfonylurea, two were concomitantly using metformin (blood glucose values were 65 and 94 mg/dL) and two were using Victoza as monotherapy (one of these patients was undergoing an intravenous glucose tolerance test and the other was receiving insulin as treatment during a hospital stay). For these two patients on Victoza monotherapy, the insulin treatment was the likely explanation for the hypoglycemia.

In patients without diabetes, fasting hypoglycemia is uncommon. However, the sponsor notes that GLP-1 has been implicated as a mediator in reactive hypoglycemia (post-glucose load), and in hypoglycemia in patients who have had roux-en-Y gastric bypass surgery. (There was only one patient in the weight management program with a reported medical history of gastric bypass surgery, patient 460027 in trial 1839; this was a 37-year-old female who was treated with placebo.)

In the weight management trials, all hypoglycemic episodes were to be reported as AEs (definitions summarized in sections below). In trials 1839, 1922, and 3970, hypoglycemic episodes requiring third party assistance (‘severe’ hypoglycemia) were considered medical events of special interest, and required an additional form to be completed. In trials 1807 and 1923, ‘major hypoglycemic episodes’ were to be reported as SAEs. All episodes of hypoglycemia either observed by the investigator or reported spontaneously by the patients were to be recorded by the investigator and evaluated.

In addition, the patients were to be asked at each contact with the trial site whether they had had any hypoglycemic episodes since the last visit. Patients were instructed on possible symptoms of hypoglycemia.

7.5.9.1 Patients without Type 2 Diabetes

Patients without T2DM were not provided with glucometers or hypoglycemia diaries. AEs of hypoglycemia were recorded on standard AE forms. Hypoglycemia symptoms were not systemically recorded.

AEs of hypoglycemia could be captured from routine fasting plasma glucose (FPG) measures (all glucose measures 70 mg/dL or less were to be reported as an AE, irrespective of symptoms), or 'hypoglycemia' (definition not specified) during an oral glucose tolerance test (OGTT) (trials 1807 or 1839).

AEs of hypoglycemia reported outside FPG and OGTT visits were referred to as 'spontaneously reported' AEs of hypoglycemia. The reporting of events was based on symptoms alone and not supported by biochemical measurements as patients did not have a glucometer.

No AEs of hypoglycemia were reported in the clinical pharmacology trial 3630, including during the mixed meal test.

In the phase 2 and 3 trials in patients without T2DM, more patients treated with liraglutide reported 'hypoglycemia' (spontaneous and during a FPG or OGTT visit) than patients treated with placebo (Table 128). The majority of AEs of hypoglycemia were reported on the day of either an FPG or an OGTT visit. AEs of hypoglycemia reported at FPG and OGTT visits were more frequently reported in patients who were normoglycemic (either with liraglutide or placebo) compared to those who met the diagnostic criteria for pre-diabetes.

Table 128. Hypoglycemia AEs in Patients without Type 2 Diabetes, Weight Management Pool (Excluding Trial 1922)

	Lira 3 mg N=2962		Placebo N=1729	
	n (%)	Events	n (%)	Events
All patients reporting an AE of hypoglycemia	317 (10.7)		50 (2.9)	
Spontaneously reported	46 (1.6)	59	19 (1.1)	23
Reported at FPG visit	97 (3.3)	119	13 (0.8)	14
Reported at OGTT visit	206 (8.0)	283	18 (1.3)	21
Normoglycemic patients (without pre-diabetes)	N=1129		N=676	
All patients reporting an AE of hypoglycemia	157 (13.9)		27 (4.0)	
Spontaneously reported	16 (1.4)	22	6 (0.9)	6
Reported at FPG visit	54 (4.8)	65	9 (1.3)	10

Reported at OGTT visit	109 (10.9)	158	12 (2.3)	15
Patients with pre-diabetes	N=1833		N=1053	
All patients reporting an AE of hypoglycemia	160 (8.7)		23 (2.2)	
Spontaneously reported	30 (1.6)	37	13 (1.2)	17
Reported at FPG visit	43 (2.3)	54	4 (0.4)	4
Reported at OGTT visit	97 (6.2)	125	6 (0.7)	6
<p>The number of events that fulfill the criteria are the number of AEs for which there exist a plasma glucose measurement that fulfill the criteria on the same date as the patient has reported an episode.</p> <p>Spontaneously reported events are events which are not reported on the same day as a plasma glucose value.</p> <p>Note that there can be several measurements which fulfill the cut off criteria for adverse events reported on the same day as part of an OGTT.</p> <p>Note that the N presented in the table is used as a denominator for the spontaneously reported AEs only. Denominators for FPG and OGTT were the number of patients who had at least one FPG or OGTT visit, respectively.</p>				

Source: ISS, Table 2-17 and ISS Appendix 7.2, Table 607

None of the spontaneously reported AEs of hypoglycemia fulfilled the American Diabetes Association (ADA) criteria of a severe hypoglycemic episode (requiring third party assistance). The majority of spontaneously reported AEs of hypoglycemia were classified by investigator as mild or moderate in severity. Events classified as being 'severe,' defined as having considerable interference with a patient's daily life, are as follows (neither were SAEs):

- Patient 436018 (trial 1839), liraglutide 3 mg: 38-year-old female with pre-diabetes, who reported that 'she did not eat' prior to the event. The event occurred 373 days after liraglutide 3 mg initiation, the patient recovered and no other AEs were co-reported with this AE of hypoglycemia. Plasma glucose was not reported.
- Patient 122002 (trial 1807), liraglutide 1.8 mg: 42-year-old female who reported hypoglycemia after 11 days of treatment. The liraglutide dose was not changed and the patient recovered from the event. Plasma glucose was not reported.

Among those who reported at least one event of hypoglycemia, the majority reported a single AE (liraglutide 3 mg: 71%, placebo: 86%), although there were higher proportions of patients treated with liraglutide (of those who reported hypoglycemia AEs) reporting:

- Two AEs: liraglutide 3 mg: 20%, placebo: 12%
- Three AEs: liraglutide 3 mg: 6%, placebo: 2%
- More than three AEs: liraglutide 3 mg: 4%, placebo: none

None of the AEs of hypoglycemia reported at FPG visits fulfilled the ADA criteria of a severe hypoglycemic episode (requiring third party assistance). The majority of AEs of hypoglycemia reported at FPG visits (114 of 119 events) in patients treated with

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liraglutide 3 mg were associated with a glucose value between 56 mg/dL and 70 mg/dL; two events were associated with a glucose value less than 56 mg/dL (Table 129).

Table 129. Fasting Plasma Glucose Values in Patients with Hypoglycemia AEs Reported at FPG Visits, Weight Management Pool, Patients without T2DM Only (Excluding Trial 1922)

Criteria	Lira 3.0 mg			Placebo		
	N	%	E	N	%	E
All subjects						
FPG <= 3.9 mmol/L (70 mg/dL)	92	(3.1)	114	13	(0.8)	14
FPG < 3.1 mmol/L (56 mg/dL)	2	(0.1)	2	1	(0.1)	1
Normoglycaemic						
FPG <= 3.9 mmol/L (70 mg/dL)	52	(4.6)	63	9	(1.3)	10
FPG < 3.1 mmol/L (56 mg/dL)	1	(0.1)	1	1	(0.1)	1
Pre-diabetes						
FPG <= 3.9 mmol/L (70 mg/dL)	40	(2.2)	51	4	(0.4)	4
FPG < 3.1 mmol/L (56 mg/dL)	1	(0.1)	1	0	(0.0)	0

N: Number of subjects experiencing at least one episode, %: percentage of subjects experiencing at least one episode, E: Number of events

FPG: Fasting plasma glucose

The number of events which fulfill the criteria are the number of adverse events for which there exist a (fasting) plasma glucose measurement which fulfill the criteria on the same date as the subject has reported an episode. Note that events which fulfill the <3.1 mmol/L (56 mg/dL) criteria also fulfill the <=3.9 mmol/L (70 mg/dL) criteria.

Source: ISS, Table 2-21

Available information regarding the two patients with FPG less than 56 mg/dL follow:

- Patient 335026 (trial 1839, normoglycemic stratum) was a 33-year-old female who had a FPG of 20 mg/dL on trial day 286 and a concomitant AE of hypoglycemia. It is unknown whether she was symptomatic during this event. This patient reported 7 hypoglycemia AEs during the trial, including during the follow-up period when she was re-randomized to placebo and 2 weeks after she completed the trial:

Table 130. Hypoglycemia AEs, Patient 335026, Trial 1839

Treatment period	Day	Verbatim term ^a	Treatment emergent?	Action	Related?	Serious?	Severity
Lira 3 mg	197	Hypoglycemia 2.3 mmol/l [41.4 mg/dL]	Y	Dose not changed	Possibly	No	Mild
Lira 3 mg	197	Hypoglycemia 3.9 mmol/l [70.2 mg/dL]	Y	Dose not changed	Possibly	No	Mild
Lira 3 mg	286	Hypoglycemia 1.1 mmol/l [19.8 mg/dL]	Y	Dose not changed	Possibly	No	Mild
Lira 3 mg	391	Hypoglycemia 3.2 mmol/l [57.6 mg/dL]	Y	Dose not changed	Possibly	No	Mild
Lira 3 mg*	391	hypoglycemia 3.8 mmol/l [68.4 mg/dL]	Y	Dose not changed	Possibly	No	Mild
Follow-up†	477	Hypoglycemia 3.4 mmol/l [61.2 mg/dL]	Y	Not applicable	Possibly	No	Mild
Follow-up§	492	Hypoglycemia 3.4 mmol/l [61.2 mg/dL]	N	Not applicable	Possibly	No	Mild
^a glucose values included in verbatim term from investigator in mmol/l; reviewer converted to mg/dL * last day of main period (liraglutide) † during re-randomized period (placebo) § 2 wks after trial completion							

Source: Reviewer created using sponsor datasets

- Patient 417003 (trial 1839, pre-diabetes stratum): This was a 62-year-old female who reported an AE of “asymptomatic hypoglycemia” (verbatim term) on day 29, coinciding with a FPG of 43 mg/dL. All other recorded post-baseline FPG values were between 85 and 99 mg/dL.

None of the hypoglycemia AEs reported during the OGTT fulfilled the ADA criteria of ‘severe’. The proportion of patients with post-baseline OGTT plasma glucose values 70 mg/dL or less (with an AE of hypoglycemia reported) was 7.3% in the liraglutide-treated group and 1.1% in the placebo-treated group; for glucose values less than 56 mg/dL, the proportions were 2.2% and 0.1%, respectively. Hypoglycemia AEs during the OGTT visits were generally reported late in the test (90 to 120 minutes).

Table 131. Plasma Glucose Measurements in Patients with Hypoglycemia AEs Reported at OGTT, Weight Management Pool, Patients without T2DM Only (Excluding Trial 1922)

Nominal time	Criteria	Lira 3.0 mg			Placebo		
		N	%	E	N	%	E
All subjects		206	(8.0)	283	18	(1.3)	21
Total during OGTT	PG ≤ 3.9 mmol/L (70 mg/dL)	203	(7.9)	279	16	(1.2)	19
	PG < 3.1 mmol/L (56 mg/dL)	58	(2.3)	76	2	(0.1)	2
Baseline (0 min)	FPG ≤ 3.9 mmol/L (70 mg/dL)	45	(1.7)	61	2	(0.1)	2
	FPG < 3.1 mmol/L (56 mg/dL)	1	(0.0)	1	0	(0.0)	0
Total after baseline	PG ≤ 3.9 mmol/L (70 mg/dL)	188	(7.3)	264	15	(1.1)	18
	PG < 3.1 mmol/L (56 mg/dL)	57	(2.2)	75	2	(0.1)	2
10 min	PG ≤ 3.9 mmol/L (70 mg/dL)	10	(0.4)	11	0	(0.0)	0
	PG < 3.1 mmol/L (56 mg/dL)	1	(0.0)	1	0	(0.0)	0
20 min	PG ≤ 3.9 mmol/L (70 mg/dL)	3	(0.1)	6	0	(0.0)	0
	PG < 3.1 mmol/L (56 mg/dL)	0	(0.0)	0	0	(0.0)	0
30 min	PG ≤ 3.9 mmol/L (70 mg/dL)	4	(0.2)	7	1	(0.1)	1
	PG < 3.1 mmol/L (56 mg/dL)	0	(0.0)	0	0	(0.0)	0
60 min	PG ≤ 3.9 mmol/L (70 mg/dL)	34	(1.3)	52	1	(0.1)	2
	PG < 3.1 mmol/L (56 mg/dL)	7	(0.3)	11	0	(0.0)	0
90 min	PG ≤ 3.9 mmol/L (70 mg/dL)	96	(3.7)	141	5	(0.4)	6
	PG < 3.1 mmol/L (56 mg/dL)	18	(0.7)	23	1	(0.1)	1
120 min	PG ≤ 3.9 mmol/L (70 mg/dL)	149	(5.8)	208	14	(1.0)	16
	PG < 3.1 mmol/L (56 mg/dL)	43	(1.7)	56	1	(0.1)	1

N: Number of subjects experiencing at least one episode, %: percentage of subjects experiencing at least one episode, E: Number of events
The number of events which fulfil the criteria are the number of adverse events for which there exists a plasma glucose measurement which fulfil the criteria on the same date as the subject has reported an episode. Note that events which fulfil the <3.1 mmol/L (56 mg/dL) criteria also fulfill the ≤3.9 mmol/L (70 mg/dL) criteria.
The 'total after baseline' category shows all adverse events which were accompanied with at least one confirmatory measurement between 10 and 120 minutes, and the 'total during OGTT' shows all events which were accompanied with at least one confirmatory measurement between 0 and 120 minutes. FPG values measured at OGTT visit are not counted under 'Reported at FPG visit'.
Note that there can be several measurements which fulfil the ≤ 3.9 mmol/L (70 mg/dL) and <3.1 mmol/L (56 mg/dL) criteria for adverse events reported on the same day as a OGTT profile which is the reason why the number of events per time point does not add up to the total number of events reported at the same day as OGTT profiles.

Source: ISS, Table 2-23

Two patients treated with liraglutide had a plasma glucose less than 40 mg/dL recorded during the OGTT (not captured in the table above because not reported as AEs):

- Patient 121015 (trial 1807, liraglutide 3 mg) was a 60-year-old male who experienced a plasma glucose value of 37.8 mg/dL at 52 weeks (120 min of OGTT).
- Patient 151004 (trial 1807, liraglutide 1.8 mg) was a 48-year-old female who experienced a plasma glucose value of 19.8 mg/dL at 20 weeks (30 min of OGTT).

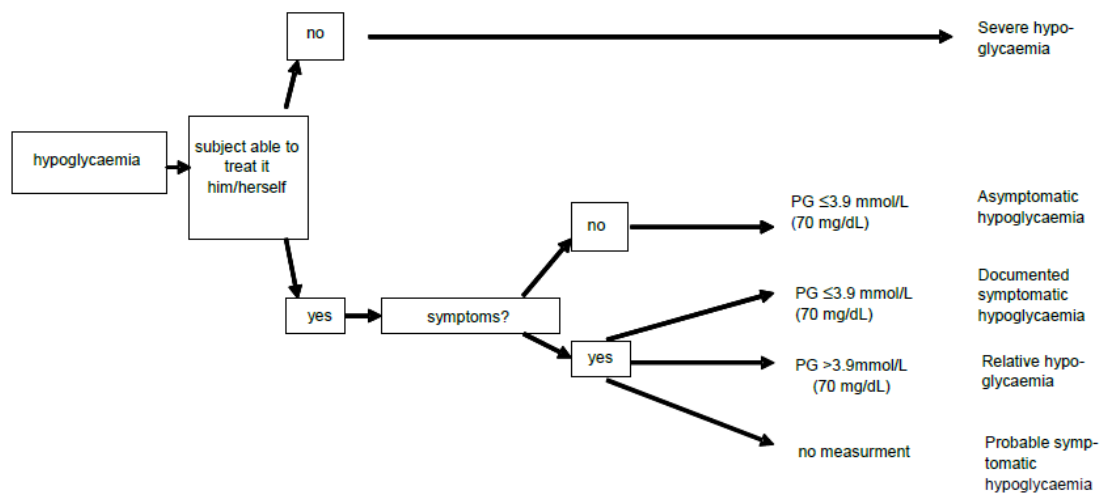
In addition to AEs coded with the PT 'hypoglycemia', the following AEs related to low glucose (PT: 'blood glucose decreased') were also reported:

- In patients without pre-diabetes :
 - Liraglutide 3 mg: 16 (1.4%) reported 28 AEs
 - Placebo: 4 (0.6%) reported 5 AEs
- In patients with pre-diabetes:
 - Liraglutide 3 mg: 12 (0.7%) reported 13 AEs
 - Placebo: 3 (0.3%) reported 3 AEs

7.5.9.2 Patients with Type 2 Diabetes

In patients with T2DM (trial 1922), dedicated hypoglycemia forms were to be completed in case of a hypoglycemic episode. Glucometers and hypoglycemia diary pages were provided to patients with T2DM along with instructions to measure glucose at any time if there was a suspicion of hyper- or hypoglycemia as well as on a regular basis. More frequent monitoring of glucose values could be instituted by the investigator as clinically indicated. Low values (see definitions below) were to be noted in the diary along with details of the event.

Figure 69. American Diabetes Association (ADA) Definition of a Hypoglycemic Episode



PG = plasma glucose.

Source: ISS, Figure 2-10

The sponsor also included a definition they refer to as 'minor' hypoglycemia, defined as any plasma glucose value less than 56 mg/dL (or full blood glucose value less than 50 mg/dL) with or without symptoms that the patient handles him or herself.

The proportions of patients with adverse events of 'hypoglycemia' by MedDRA preferred term were similar for the two liraglutide doses and higher than placebo (liraglutide 3 mg: 44.3%, liraglutide 1.8 mg: 40.0%, placebo: 27.8%). The proportions of patients with 'blood glucose decreased' were infrequent and not dose-dependent (liraglutide 3 mg: 0.7%, liraglutide 1.8 mg: 3.3%, placebo: none).

Hypoglycemic episodes by classification are presented in Table 132. These events are based on what was reported on hypoglycemia forms.

ADA-defined ‘severe’ hypoglycemia was only reported in patients concomitantly taking sulfonylureas (SUs); see further discussion below. In addition, the incidence of documented symptomatic hypoglycemia was higher in patients treated with liraglutide and placebo concomitantly on SUs versus those not on SUs (on SUs: lira 3, 43.6%; lira 1.8, 44.2%; placebo, 27.3%; not on SUs: lira 3, 15.7%; lira 1.8, 15.2%; placebo, 7.6%).

Table 132. 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

A total of 8 severe hypoglycemic episodes were reported by 5 patients, all treated with liraglutide (plus SU). One additional patient – reported below, in Table 133 – experienced a severe hypoglycemia episode during the 12-week follow-up period that was not considered treatment emergent (a second patient also had 2 episodes during the follow-up period, but as these events occurred in the first 2 weeks of discontinuing drug, they were considered treatment-emergent). None of the severe hypoglycemic episodes were reported as SAEs. All patients with severe hypoglycemic episodes continued unchanged on trial medication without dose interruption or adjustment and recovered from the events.

Table 133. Summary of Patients Reporting Severe Hypoglycemic Episodes, Trial 1922

Pt ID	Treatment	TE (Y/N)	Onset day	PG (mg/dL)	Outcome	Action	Using SU	Wk 56 HbA1c	Wk 56 % WL
702008	Lira 3mg	Y*	395	31	Recovered	NA	Y	6.5%	-2.3
		Y*	406	18	Recovered	NA	Y		
705006	Lira 3mg	N	465	38	Recovered	NA	Y	6.1%	-15.2
920003	Lira 1.8mg	Y	33	70	Recovered	No	Y	6.5%	-6.2
931011	Lira 1.8mg	Y	281	52	Recovered	No	Y	7.8%	+4.5
		Y	289	59	Recovered	No	Y		
933002	Lira 3mg	Y	21	55	Recovered	No	Y	9.3%	-7.8
		Y	343	31	Recovered	No	Y		
941001	Lira 3mg	Y	27	67	Recovered	No	Y	5.7%	-8.5
* Occurred during weeks 56-58									
TE: treatment emergent, SU: sulfonylurea, PG: plasma glucose, NA: not applicable, WL: weight loss									

Source: NN8022-1922 Clinical Trial Report, Table 12-48

Six patients had a FPG less than 56 mg/dL recorded at trial study visits, 3 patients treated with liraglutide and 3 with placebo. A summary of the patients treated with liraglutide follows:

- Patient 311004 (trial 1922, liraglutide 3 mg) was a 73-year-old male who had a FPG recorded as 34.2 mg/dL at 50 weeks, which was reported as an AE of asymptomatic hypoglycemia (severity mild, recovered). The patient also had 2 events of “mild hypoglycemia” reported on study day 3; one of the verbatim terms reported the blood sugar reading as 41 mg/dL.
- Patient 910010 (trial 1922, liraglutide 3 mg) was a 49-year-old female who had a FPG recorded as 55.9 mg/dL at 50 weeks. An AE was reported as “documented symptomatic hypoglycemia”.
- Patient 969001 (trial 1922, liraglutide 1.8 mg) was a 63-year-old male who had a FPG recorded as 43.2 mg/dL at 2 weeks (with two hypoglycemia AEs reported), and 48.6 mg/dL at a follow-up visit. The patient had multiple AEs of hypoglycemia recorded during the trial.

7.5.10 Thyroid Disorders

This section addresses non-neoplasm- and non-calcitonin-related thyroid disorders. For a discussion of thyroid neoplasms and calcitonin, see section 7.5.3.

The proportions of adverse events of ‘blood thyroid stimulating hormone decreased’ and ‘blood thyroid stimulating hormone increased’ were higher in the liraglutide 3 mg treatment group as compared with placebo. However, the proportion of AEs of ‘hypothyroidism’ was higher in the placebo-treated group as compared with liraglutide. Incidence rates of thyroid AEs relevant to this section are presented below:

Table 134. Thyroid Disease by Preferred Term (Excluding Neoplasm- and Calcitonin-Related AEs), Weight Management Pool

	Lira 3 mg N=3384	All lira N=3872	Placebo N=1941
Hypothyroidism	21 (0.6)	25 (0.6)	27 (1.4)
Blood thyroid stimulating hormone decreased	21 (0.6)	22 (0.6)	5 (0.3)
Blood thyroid stimulating hormone increased	14 (0.4)	18 (0.5)	3 (0.2)
Hyperthyroidism	7 (0.2)	7 (0.2)	2 (0.1)
Goiter	4 (0.1)	4 (0.1)	7 (0.4)
Blood thyroid stimulating hormone abnormal	3 (<0.1)	3 (<0.1)	0
Autoimmune thyroiditis	2 (<0.1)	2 (<0.1)	4 (0.2)
Thyroid cyst	2 (<0.1)	2 (<0.1)	0
Primary hypothyroidism	1 (<0.1)	1 (<0.1)	1 (<0.1)
Thyroid disorder	1 (<0.1)	1 (<0.1)	0
Thyroid function test abnormal	1 (<0.1)	1 (<0.1)	0
Thyroiditis acute	1 (<0.1)	1 (<0.1)	0
Thyroiditis chronic	1 (<0.1)	1 (<0.1)	0
Tri-iodothyronine increased	1 (<0.1)	1 (<0.1)	0
Basedow's disease	0	1 (<0.1)	1 (<0.1)
Thyroglossal cyst	0	1 (<0.1)	0
Endocrine ophthalmopathy	0	0	1 (<0.1)
Thyroid mass	0	0	1 (<0.1)

Source: ISS Appendix 7.2, Table 288

The average weight loss in patients with AEs of 'blood thyroid stimulating hormone decreased' was 11.5% with liraglutide 3 mg (N=21) and 8.7% with placebo (N=5).

Regarding thyroid stimulating hormone (TSH):

- The majority of patients had TSH values within the normal reference range at baseline, during treatment with liraglutide 3 mg, and at end-of-treatment.
- The proportion of patients with normal TSH at baseline and levels above the upper reference range at end-of-treatment was low and similar with liraglutide 3 mg (1.5%) and placebo (1.6%).
- The proportion of patients with normal TSH levels at baseline and levels below the lower reference range at end-of-treatment was higher with liraglutide 3 mg (2.6%) than with placebo (1.3%).

In the T2DM (Victoza) trials, thyroid disorders occurred at a similar incidence in liraglutide- and comparator-treated patients.

Table 135. Thyroid Disease by Preferred Term (Excluding Neoplasm- and Calcitonin-Related AEs), Diabetes Pool

	Total lira N=7037	Comparator total N=3677
Goiter	24 (0.3)	7 (0.2)
Hyperthyroidism	8 (0.1)	6 (0.2)
Thyroid cyst	8 (0.1)	2 (<0.1)
Hypothyroidism	6 (<0.1)	6 (0.2)
Autoimmune thyroiditis	4 (<0.1)	2 (<0.1)
Thyroid disorder	3 (<0.1)	0
Thyroiditis chronic	1 (<0.1)	0
Thyroxine decreased	1 (<0.1)	0
Ultrasound thyroid abnormal	1 (<0.1)	0
Thyroid pain	0	1 (<0.1)

Source: Supplementary AE Report, Appendix 1, Table 63

7.5.11 Gastrointestinal AEs

Gastrointestinal disorders are well-described side effects of liraglutide and are considered to be mediated via activation of the GLP-1 receptor. The Victoza label notes the following:

In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred at a higher incidence among Victoza-treated patients included nausea, vomiting, diarrhea, dyspepsia and constipation.

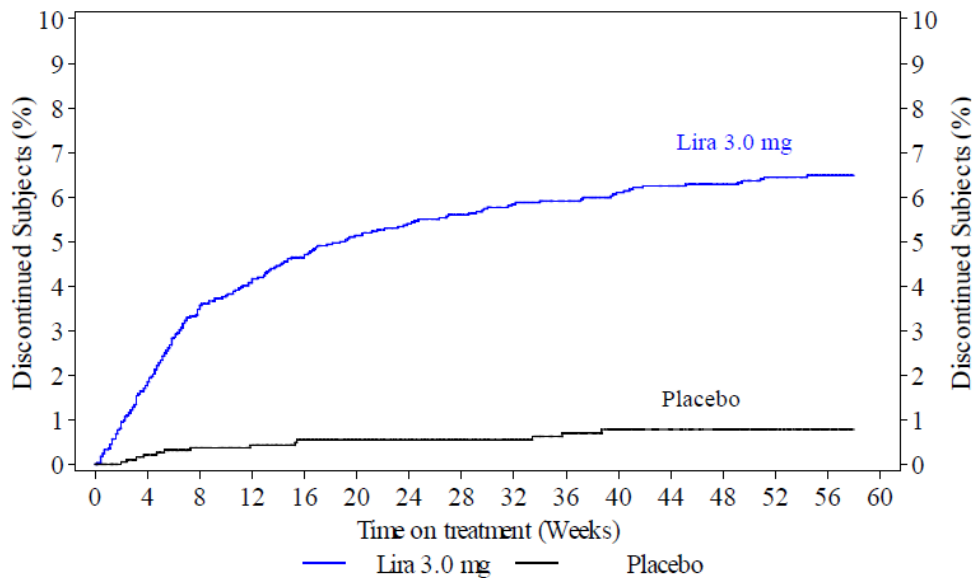
In the weight management pool, gastrointestinal disorders were more frequently reported with liraglutide (68%) as compared to placebo (39%). The gastrointestinal disorders reported most frequently in patients treated with liraglutide 3 mg were nausea (39%), diarrhea (21%), constipation (19%), vomiting (16%), and dyspepsia (10%). Nausea, vomiting, and diarrhea are discussed in more detail in the respective sections below.

The majority of the gastrointestinal disorders were mild or moderate in severity. The proportion of patients reporting severe gastrointestinal disorders was higher in those treated with liraglutide 3 mg (4.8%) than placebo (1.4%).

‘Gastrointestinal disorders’ was the SOC with most AEs leading to withdrawal. A higher proportion of patients withdrew due to gastrointestinal disorders with liraglutide 3 mg (6.2%) than with placebo (0.8%). Withdrawal due to gastrointestinal disorders mainly occurred within the first 2 to 3 months of the treatment period. The highest frequency of withdrawal due to gastrointestinal disorders was during the initial 8 weeks of treatment, which may have contributed to a decrease of patients with events over time.

However, the majority of patients with gastrointestinal events continued with treatment.

Figure 70. Time to Discontinuation due to Gastrointestinal Disorders, Weight Management Pool



Source: ISS, Figure 2-5

7.5.11.1 Nausea and Vomiting

GLP-1 slows gastric emptying in a dose-dependent fashion.⁵⁷ Therefore, nausea is an expected side effect of GLP-1 receptor agonists, and has been shown to occur with liraglutide in the T2DM population.⁴ (Although – as noted in section 2 – a phase 1 clinical pharmacology trial in obese patients did not detect a statistically significant difference in gastric emptying between liraglutide and placebo during the 5 hours tested, liraglutide did appear to decrease gastric emptying during the first hour.)

In the weight management program, almost 40% of patients treated with liraglutide experienced nausea, and over 15% experienced vomiting during the trial. By contrast, approximately 14% of patients on placebo experienced nausea and 4% experienced vomiting. Although most events were mild, more patients on liraglutide experienced moderate or severe nausea and vomiting AEs than those on placebo. Likewise, although serious AEs and AEs leading to withdrawal were infrequent occurrences, they occurred with greater frequency in patients randomized to liraglutide than placebo.

⁵⁷ Nauck MA, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 1997; 273(5 Pt 1):E981-E988

Table 136. Adverse Events of Nausea and Vomiting, Weight Management Pool

	Liraglutide 3 mg N=3384		Placebo N=1941	
	n (%)	No. of events	n (%)	No. of events
Nausea	1329 (39.3)	1946	267 (13.8)	334
Mild	1091 (32.2)	1453	225 (11.6)	272
Moderate	355 (10.5)	449	49 (2.5)	55
Severe	42 (1.2)	44	7 (0.4)	7
Vomiting	530 (15.7)	786	75 (3.9)	89
Mild	351 (10.4)	497	45 (2.3)	53
Moderate	209 (6.2)	245	29 (1.5)	33
Severe	37 (1.1)	44	3 (0.2)	3

Source: ISS Table 2-5 and Appendix 7.2, Table 38

Four patients in the main treatment period of the trials reported nausea and/or vomiting SAEs: 3 of the patients with SAEs were randomized to liraglutide 3 mg and 1 was randomized to liraglutide 2.4 mg. An additional SAE was reported in year 2 of trial 1807 (patient 102003, liraglutide 3 mg). Brief narratives of the SAEs follow:

- Patient 101012 in trial 1807 was a 44-year-old female randomized to liraglutide 3 mg on 30 Jan 2007. On 15 Aug 2007, the patient experienced an event of gallstones (non-serious), for which she had a laparoscopic cholecystectomy on (b) (6). Post-surgery, the patient was considered recovered. On (b) (6), the patient was hospitalized as she presented with post-cholecystectomy abdominal pain and vomiting, considered by the investigator to be related to retained biliary calculus. In addition, lab test workup revealed abnormal liver function (not considered an adverse event by the investigator). Treatment consisted of analgesics, antibiotics, anti-emetics and intravenous hydration. On (b) (6), the events of abdominal pain and vomiting were considered resolved. On 19 Nov 2007, the patient restarted study medication at a dose of 0.6 mg, which was increased to 3 mg.

Reviewer comment: The SAE of vomiting appears in this case to be related to cholelithiasis. See section 7.5.2.2 for a discussion of the potential relationship of liraglutide to gallbladder AEs in the weight management trials.

- Patient 102003 in trial 1807 was a 52-year-old female randomized to liraglutide 3 mg on 5 Feb 2007. On (b) (6), the patient developed chest pain associated with nausea and vomiting and was admitted for cardiac work-up/treatment. By report, troponin I was normal and stress test was negative. On 18 Feb 2008, an abdominal ultrasound showed presence of gallstones. The final diagnosis for her initial symptoms was considered to be acute cholecystitis. On (b) (6) a cholecystectomy was performed. Trial drug administration continued unchanged throughout the course of the event.

Reviewer comment: The SAEs of nausea and vomiting appear in this case to be related to cholelithiasis. See section 7.5.2.2 for a discussion of the potential relationship of liraglutide to gallbladder AEs in the weight management trials.

- Patient 103011 in trial 1807 was a 42-year-old female randomized to liraglutide 2.4 mg on 4 Apr 2007. On (b) (6), the patient experienced a sudden onset of epigastric abdominal pain, radiating to her back and several episodes of vomiting for which she was admitted to the hospital on the same day. Prior to these events the patient experienced headache and loss of vision in the left eye associated with migraine (reported as non-serious events). However, this condition passed (onset date and duration unknown). Marked epigastric tenderness was observed. An x-ray was normal and an abdominal ultrasound revealed no abnormalities. Due to a hemolyzed blood sample, there was no amylase result available. Test was not repeated. Treatment consisted of one dose of morphine. The next day, the symptoms were completely gone and the patient was discharged from hospital. An ultrasound was performed without findings. Trial drug continued unchanged throughout the course of the event.

Reviewer comment: The etiology of this event of the acute onset of two day duration abdominal pain and vomiting is not clear; there is not enough information to make a determination regarding potential pancreatitis or gallstones. Notably, symptoms abated while the patient remained on study drug.

- Patient 471018 in trial 1839 was a 36-year-old female randomized to liraglutide 3 mg on (b) (6). Medical history included obesity, cholecystectomy, rash on feet, stage 1 cervical cancer, anemia 2001, occasional swelling of lower extremities, gallstone disease in 2010, occasional headaches and occasional migraine headaches from 2010, chronic back pain and neck pain, gastric reflux, and insomnia. On (b) (6), 2 days after the patient had started on trial drug, the patient experienced nausea and severe headaches, as a worsening of previous condition, which prompted her to go to the Emergency Room where she was hospitalized. She received Toradol, Benadryl, and Reglan as a single dose, which gave her good relief of her headaches. Treatment with the trial drug was discontinued. She was discharged the following day. On 10 Oct 2011, liraglutide was reintroduced at the same (0.6 mg) dose. On 14 Oct 2011 trial drug was withdrawn permanently. On 16 Oct 2011 the patient recovered from the event of nausea.
- Patient 530011 in trial 1839 was a 50-year-old female randomized to liraglutide 3 mg on 18 Aug 2011. On 21 Aug 2011, 3 days after the patient had started on trial drug, she experienced mild nausea. On (b) (6), the patient suffered from vertigo and vomiting. It was reported that the vertigo deteriorated. Accordingly, the patient called an ambulance and was admitted. At the hospital she was treated with Maxolon intravenously. The patient recovered from vertigo, nausea, and vomiting

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events the following day and was discharged. The patient withdrew from the study.
Last dose of study medication was on 21 Aug 2011.

Reviewer comment: Although in the two cases above the patients were randomized to liraglutide 3 mg, events occurred at the titration dose of 0.6 mg.

Figure 71 illustrates that nausea and vomiting AEs were reported by the highest proportion of patients within the first 4 to 8 weeks of liraglutide treatment, primarily during the dose escalation period.

Figure 71. Percentage of Patients with Nausea (Top) and Vomiting (Bottom) by Week and Treatment, Weight Management Pool

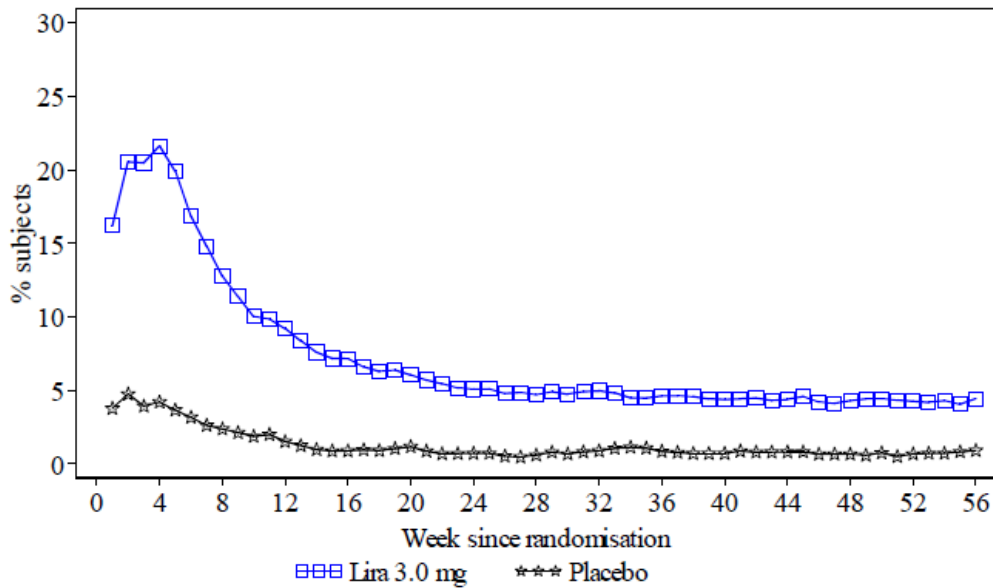


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

19NOV2013:10:56:30 -f /nn8022/nn8022-iss/freeze 20131117 ctr
perc eventsase percent nausea sas.cgm

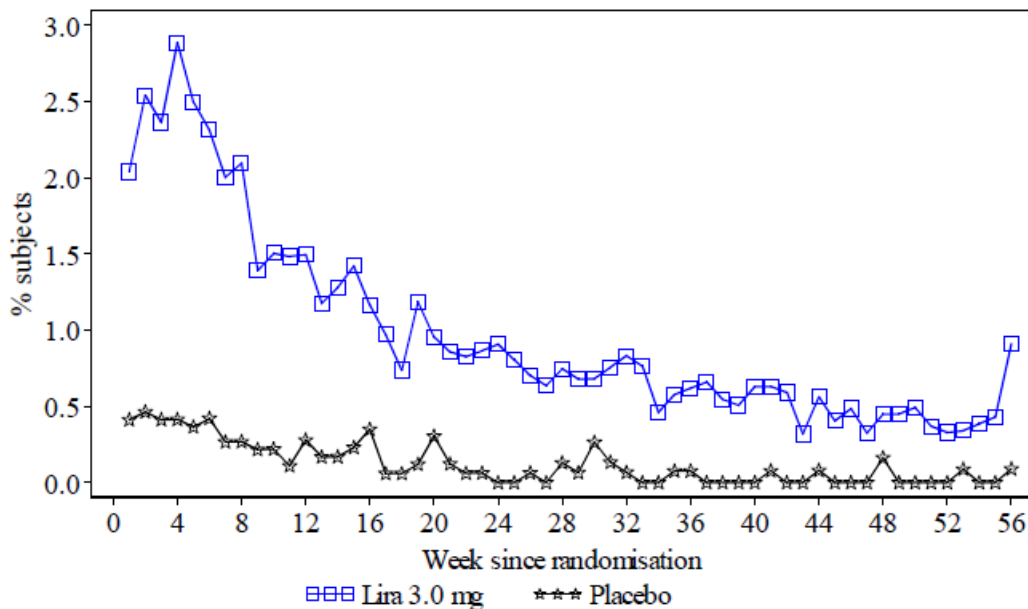


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

19NOV2013:10:56:47 -f /nn8022/nn8022-iss/freeze 20131117 ctr
perc eventsase percent vomit sas.cgm

Source: ISS, Appendix 7.2, Figures 40 and 41

The proportion of patients reporting nausea and vomiting generally increased with increasing dose of liraglutide (1.2 to 3 mg) in trials 1807 and 1922.

Table 137. Nausea and Vomiting Events by Liraglutide Dose, Trials 1807 and 1922

	Placebo	Lira 1.2 mg	Lira 1.8 mg	Lira 2.4 mg	Lira 3 mg
Trial 1807					
N	98	95	90	93	93
Nausea	7 (7.1)	23 (24.2)	29 (32.2)	35 (37.6)	46 (49.5)
Vomiting	2 (2.0)	5 (5.3)	9 (10.0)	15 (16.1)	12 (12.9)
Trial 1922					
N	212		210		422
Nausea	29 (13.7)		66 (31.4)		138 (32.7)
Vomiting	12 (5.7)		21 (10.0)		66 (15.6)

Source: ISS, Tables 2-121, 2-122; Appendix 7.7, Table 23

Nausea and vomiting were reported at a comparable frequency in patients who were and were not 5% weight loss responders, suggesting that weight loss was not entirely due to these symptoms.

Table 138. Nausea and Vomiting Events by Weight Loss Responder Status, Weight Management Pool

	Lira 3 mg	Total lira	Placebo
5% responders			
Nausea	804 (40.4)	867 (39.3)	59 (12.8)
Vomiting	316 (15.9)	343 (15.6)	18 (3.9)
Non-responders			
Nausea	483 (36.8)	564 (36.2)	204 (14.3)
Vomiting	200 (15.3)	220 (14.1)	56 (3.9)

Source: ISS, Appendix 7.2, Tables 561 and 562

7.5.11.2 Diarrhea

Overall, the preferred term 'diarrhea' was reported approximately twice as frequently in the liraglutide 3 mg group (21%) as compared to the placebo group (10%) in the weight management program.

No SAEs of diarrhea were reported in the liraglutide treatment group; one patient (<0.1%) in the placebo treatment group reported an SAE of diarrhea.

More patients treated with liraglutide withdrew from the trial due to diarrhea as compared to placebo (1.4% vs. 0). Similarly, more patients temporarily withdrew medication (1.0% vs. 0.2%) or decreased dose (0.3% vs. 0) due to diarrhea.

Diarrhea associated with liraglutide appeared to be dose-dependent:

Table 139. Diarrhea Event by Liraglutide Dose, Trials 1807 and 1922

	Placebo	Lira 1.2 mg	Lira 1.8 mg	Lira 2.4 mg	Lira 3 mg
Trial 1807					
N	98	95	90	93	93
Diarrhea	10 (10.2)	8 (8.4)	9 (10.0)	12 (12.9)	14 (15.1)
Trial 1922					
N	212		210		422
Diarrhea	27 (12.7)		37 (17.6)		108 (25.6)

Source: ISS, Tables 2-121, 2-122; Appendix 7.7, Table 23

7.5.12 Common Adverse Events

The most common AEs seen with liraglutide in the weight management clinical trials were: nausea, diarrhea, constipation, vomiting, hypoglycemia, and decreased appetite.

Table 140. Most Frequent Adverse Events (%), Weight Management Pool

	Lira 3 mg N = 3384	Placebo N = 1941
Gastrointestinal disorders		
Nausea	39.3	13.8
Diarrhea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Dyspepsia	9.6	2.7
Abdominal pain	5.4	3.1
Abdominal pain upper	5.1	2.7
Metabolism and Nutrition Disorders		
Hypoglycemia [†]	14.9	5.6
Decreased Appetite	10.0	2.3
General Disorders and Administration Site Conditions		
Injection site reactions*	9.0	1.7
Fatigue	7.5	4.6
Nervous System Disorders		
Headache	13.6	12.6
Dizziness	6.9	5.0
[†] Combined for patients with and without T2DM (see Table 128 and Table 132)		
* Excluding preferred terms reported more frequently with placebo		

Source: Proposed PI, Table 3; ISS Appendix 7.2, Table 10

7.5.13 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 treatment 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. All women who gave birth had healthy babies: 15 women treated with liraglutide and 6

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women treated with placebo. No congenital abnormalities have been observed in any of the pregnancies that have resulted in a live birth. Other outcomes are reported in the table below.

Table 141. Pregnancies, Weight Management Trials

	Liraglutide (all doses)^a N (%)	Placebo N (%)
Completed trials		
Females in safety analysis set	2763	1374
Pregnancies (% of females) ^b	31 (1.1%)	15 (1.1%)
Mean maternal age at baseline, years (min-max)	32.5 (18–43)	33.1 (24–40)
Mean BMI at baseline, kg/m ² (min-max)	38.4 (31.2–53.5)	38.4 (29.2–51.1)
Mean duration of exposure before withdrawal, days (min-max)	227.2 (33–481)	223.6 (2–455)
Mean duration of exposure since conception, days (min-max) ^c	22.2 (8–44)	28.7 (0–139)
Outcome of pregnancies^d		
Healthy children	15 (48.4%)	6 (40.0%)
Spontaneous abortion ^e	9 (29.0%)	2 (13.3%)
Elective abortion	4 (12.9%)	3 (20.0%)
Abortion	1 (3.2%)	0
Ectopic pregnancy	1 (3.2%)	2 (13.3%)
Lost to follow-up/unknown	1 (3.2%)	2 (13.3%)
Contraception^d		
Oral contraceptives	8 (25.8%)	5 (33.3%)
None ^e	13 (41.9%)	2 (13.3%)
Other	8 (25.8%)	8 (53.3%)
Unknown	2 (6.5%)	
Ongoing trial (1839-ext)		
Females in safety analysis set	820	376
Pregnancies (% of females)	5 (0.6%)	3 (0.8%)
Outcome of pregnancies^d		
Healthy child	2 (40%)	1 (33.3%)
Spontaneous abortion	1 (20%)	0
Lost to follow-up		1 (33.3%)
Awaiting follow-up	2 (40%)	1 (33.3%)

N: number of subjects; %: percentage of subjects; BMI: body mass index. The table includes reported cases as of the cut-off date 02 July 2013, updated with information from the case narratives from the safety database as of 19 November 2013 ([Appendix 7.10.2](#) and [Appendix 7.10.3](#)) and from data on file.

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a. All pregnancies were reported in subjects treated with 3.0 mg liraglutide; b. In addition, 1 pregnancy was reported in a woman who was not treated with trial product (trial 1807), this case is not included in this overview; c. The duration of exposure since conception was a conservative estimate based on available data in the safety database. For 2 subjects (Subjects 478028 and 175014, both in trial 1839), the duration of treatment since conception was '<10 days' and was changed to 9 days in the calculation; d. The percentages for the pregnancy outcomes as well as types of contraception have been estimated from the total number of pregnancies in each group; e. 1 event (in Subject 421019) could not be confirmed.

Source: ISS, Table 5-14

As reported in the 120-day safety update, 6 additional pregnancies have been reported in the extension phase of trial 1839 as of 14 Mar 2014, for a total of 14 (liraglutide: 9, placebo: 5).

Table 142. Pregnancies in Ongoing Trial 1839-Extension, as of 14 March 2014

	Liraglutide 3.0 mg	Placebo
Number of pregnancies	9	5
Pregnancy outcomes		
Healthy child	3	1
Spontaneous abortion	1 ¹⁾	
Miscarriage of partner	1 ²⁾	
Ectopic pregnancy		1
Awaiting follow-up	4 ³⁾	2
Lost to follow-up		1
Contraception		
Oral contraceptives	2	1
None	2	3
Other	4	1
Unknown	1	

1): The spontaneous abortion with liraglutide 3.0 mg was reported with the original NDA (Subject ID 413020).

2): Subject ID [351017](#), 3): Includes Subject ID [439008](#)

Note 2: 'Miscarriage of partner' was a pregnancy in the wife of a 39-year-old male patient (patient 351017). Termination of pregnancy was induced due to absence of fetal heart beat.

Note 3: 'Awaiting follow-up' in 42-year-old patient 439008: A prenatal test lab test reportedly showed a 99% risk that the fetus has Down's syndrome. Further information is pending.

Source: 120-day safety update, Table 5-1

8 APPENDIX

8.1 Narratives of Deaths from Diabetes Pool

- Patient 117006 from trial NN2211-1573 was a 64-year-old female in the liraglutide 1.8 mg treatment group. The autopsy revealed signs of acute pancreatitis which was assessed to have caused the death. This fatality was reported during the 52-week open-label period (Year 2). The patient had also been diagnosed with colon cancer on (b) (6) prior to her death on (b) (6). The outcome was listed as unknown and the dose was not changed. The patient had undergone a colonoscopy 3 days prior to death and she had received propofol, which has been associated with pancreatitis in rare cases.
- Patient 485014 from trial NN2211-1797 in the liraglutide-liraglutide group had a cerebral infarction during the first 14 weeks of the extension period after 282 days of treatment. The outcome of this event was fatal; the patient died approximately 3 weeks later.
- Patient 206008 from trial NN2211-1797 in the exenatide-liraglutide group had a myocardial infarction after 198 days of treatment during the extension period. The outcome of this event was fatal.
- Patient 413005 from trial NN2211-1860 was a 56-year-old female who initiated treatment with sitagliptin + metformin on 18 Sep 2008 and who switched to treatment with liraglutide 1.2 mg + metformin on (b) (6). The patient received treatment with sitagliptin + metformin for a total of 385 days and with liraglutide 1.2 mg + metformin for a total of 31 days. The patient had a significant medical history of chronic respiratory problems (sleep apnea, chronic hypoxia and hypoventilation syndrome) requiring non-invasive ventilation, Perthes' disease which rendered the patient wheelchair-bound and a long-term indwelling urine catheter as well as a history of depression and severe obesity (baseline BMI of 42.4 kg/m²). After switching to treatment with liraglutide 1.2 mg+metformin, the patient experienced a non-serious event of vomiting for 2 days and recovered. On 31 Oct 2009, the patient experienced a serious adverse event of gastroenteritis and on 1 Nov 2009, the patient reported a number of non-serious adverse events (abdominal pain, back pain, decubitus ulcer, and dizziness). All these events were reported as not recovered. On (b) (6), the patient had suffered from diarrhea and vomiting for a week and was admitted to hospital being severely dehydrated, hypothermic (33°C), hypotensive (blood pressure of 89/46 mmHg) and with lactic acidosis (14.8 mmol/L, normal range < 2.2 mmol/L). Septicemia was suspected due to findings of elevated white cell and neutrophil counts and a serious adverse event of sepsis was reported. The source of infection was reported to be *Staphylococcus aureus* but no blood culture was performed. The patient was treated with sodium chloride and

sodium bicarbonate intravenously, although the venous access was extremely difficult. No other treatments were initiated. The attending physician thought it inappropriate to transfer the subject to a critical care unit in view of her comorbidities, particularly the chronic respiratory problems. The patient expired on (b) (6). No autopsy was performed. Renal failure was reported as the primary cause of death and diarrhea, vomiting and septicemia were considered as contributing factors. The trial drug was continued without change throughout the course of events.

Reviewer comment: The source for the S. aureus infection is not clear (decubitus ulcer? urosepsis?), however the contribution of liraglutide to gastrointestinal symptoms leading to dehydration and renal failure appears plausible.

- Patient 107008 from trial NN2211-1860 was a 50-year-old man randomized to liraglutide 1.8 mg who initiated treatment with liraglutide + metformin on (b) (6). On (b) (6), the patient was admitted to the hospital due to acute pain in the right flank and hematuria. At the time of admission, the patient had been treated with liraglutide for approximately 1 week, and was still on the 0.6 mg dose. Computer tomography together with laboratory values led to the suspicion of a pancreatic tumor. On (b) (6), the patient was diagnosed with inoperable pancreas carcinoma classification IV B. On (b) (6) the patient was withdrawn from the trial. On (b) (6), the patient died.

Reviewer comment: It is not clear how the presenting symptoms related to the diagnosis, but I cannot ascribe the pancreatic cancer as related to liraglutide given the very brief treatment duration.

- Patient 452002 from trial NN2211-1860 was a 65-year-old female who initiated treatment with liraglutide 1.8 mg + metformin on (b) (6). The patient received treatment in the trial for a total of 401 days (all of the period on liraglutide 1.8 mg + metformin); the bile duct cancer diagnosis was established after treatment for 316 days ((b) (6)). The patient had a medical history of stenosis of ductus hepaticocholedochus and cholecystectomy with stent implant in 2006. Ten days prior to the first admission during the trial ((b) (6)), the patient had felt nausea, mild epigastric pain, had vomited several times and had icterus. On (b) (6), computerized tomography demonstrated dilatation of ductus hepaticus and stenosis of ductus hepaticus communis and extraction of the biliary endoprosthesis was done (b) (6). The patient developed 'acute cholangitis' and sepsis on (b) (6) and five days later a new endoprosthesis was inserted by endoscopic retrograde cholangio-pancreatography (ERCP). The patient recovered from the events and was discharged on (b) (6). One month later, the patient was diagnosed with adenocarcinoma of ductus hepatici communis with liver metastases. The patient was re-admitted on (b) (6) due to icterus caused by stenosis of ductus hepatici communis and dysfunction of endobiliary prosthesis. On (b) (6)

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a new prothesis was introduced, after which the patient suffered from acute cholangitis (recovered (b) (6)). On (b) (6), the patient was discharged from hospital and reported as being not recovered from the event of stenosis of ductus hepatici communis and icterus. A new ERCP was performed on (b) (6) where a new endobilliary prothesis was implanted. On (b) (6), the patient was discharged from the hospital and died on (b) (6). No autopsy was performed.

- Patient 302001 from trial NN2211-1860 was a 64-year-old male who initiated treatment with sitagliptin + metformin on (b) (6). The patient received treatment in the trial for a total of 48 days. The patient had a medical history of myocardial infarction, hypertension, dyslipidemia, gout, asthma and coronary artery bypass graft surgery. The patient died on (b) (6) due to cardiac arrest outside a hospital.
- Patient 302017 from trial NN2211-1860 was a 60-year-old male who initiated treatment with sitagliptin + metformin on (b) (6). The patient received treatment in the trial for a total of 100 days when the diagnosis of metastatic renal cell carcinoma including bone metastasis and probable lung metastasis was established (b) (6). No medical history was reported. The patient had reported gross hematuria in Oct 2008 and on 16 Dec 2008, and an expanding mass was subsequently visualized in the upper half of the left kidney. From Feb 2009 the patient was treated with palliative radiation therapy and on (b) (6), the patient died. No autopsy was performed.
- Patient 453001 from trial NN2211-1860 was a 66-year old male who initiated treatment with sitagliptin + metformin on (b) (6). The patient received treatment in the trial for a total of 282 days. No medical history was reported. On (b) (6), the patient was found dead lying in the street from sudden cardiac death. An autopsy was not performed.
- Patient 122011 from trial NN2211-3924, a 67-year-old female treated with liraglutide died due to 'lung neoplasm malignant'. The patient started to experience back pain after 158 days (~5 months) of exposure to the trial product. The first investigations (computed tomography scan and abdominal ultrasonography) revealed an adrenal tumor, left renal cyst, and a gallbladder stone. The treatment with trial product was discontinued, and the patient was hospitalized. Further investigations revealed metastatic malignant tumor of lumbar vertebral spine, thoracic vertebral compression fracture, right pulmonary mass, lymphadenopathy of mediastinum and pleural effusions on both the lungs. Lumbar vertebral mass biopsy was performed and undifferentiated carcinoma was found. Contrast head MRI and bone scintigraphy showed multiple bone metastases. The patient underwent a bronchoscopy and was diagnosed with 'epithelial anaplastic carcinoma'. The patient started on chemotherapy; however, approximately 13 weeks from the first symptom, the patient died. No autopsy was performed.

- Patient 454031 from trial NN2211-3924, a 49-year-old woman in the IDegLira group had an AE of 'death' on Day 68. Medical history included hypertension since 2003, hypercholesterolemia since (b) (6) and type 2 diabetes mellitus since 2010. The patient took the following concomitant medications: perindopril, hydrochlorthiazide, nifedipine, and simvastatin. Baseline BMI was 32.0 kg/m² and baseline blood pressure and pulse were 164/97 mmHg and 97 beats/min, respectively. During the trial, no episodes of severe hypoglycemia were reported, but the patient had reported 14 hypoglycemic episodes (five documented symptomatic and nine asymptomatic) with plasma glucose ranging from 61 to 70 mg/dL. The patient had been well the days prior to the event, with self-measured plasma glucose values within normal range. The morning self-measured plasma glucose had been normal (90 mg/dL). The patient collapsed at home in the evening. A neighbor and family member tried to resuscitate the patient unsuccessfully. An autopsy was not performed. The death was adjudicated as a cardiovascular death.
- Patient 954006 from trial NN2211-3924, a 66-year-old female treated with IDegLira, died from 'urinary tract infection' and 'septic shock' that had an onset on Day 182. The patient was hospitalized on (b) (6) (Day 182) after having fever, chills, and becoming very confused at home. She had a medical history of hypertension, hyperlipidemia, aortic stenosis, prosthetic valve placement, congestive heart failure, and hypercholesterolemia and had smoked one pack of cigarettes a day for many years. Diagnosis at admission to hospital was urinary tract infection with sepsis and mild congestive heart failure. Upon arrival, gram-negative rods were identified in urine cultures. On (b) (6), the patient died from cardiopulmonary arrest (asystole). The death was adjudicated and classified as a cardiovascular death by the EAC.
- Patient 457014 from trial NN2211-3924, a 46-year-old female treated with IDegLira, was fatally wounded in a gunshot attack on (b) (6) (Day 295, 8 days after the last confirmed dose of IDegLira). She died the same day. The last confirmed date of trial product intake was (b) (6) (the day before Visit 44). Since the family of the deceased had asked not to be contacted again, the date of the last actual intake of trial product is unknown.
- Patient 318018 from trial 2211-1572, a 55-year-old male treated with liraglutide 0.6 mg + metformin died of acute renal failure and pyelonephritis following approximately 21 months of exposure to trial drug. No further information was provided.
- Patient 393004 from trial 2211-1572, a 61-year-old male treated with liraglutide 0.6 mg + metformin died of tuberculosis following approximately 22 months of exposure to trial drug. No further information was provided.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL ASSESSMENT OF EFFICACY

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON LIRAGLUTIDE FOR WEIGHT MANAGEMENT

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory Committee,
September 11, 2014

Bradley W. McEvoy, DrPH
Mark Rothmann, PhD

Division of Biometrics II
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Document Date: August 13, 2014

1 INTRODUCTION AND BACKGROUND

Novo Nordisk (the sponsor) has submitted a new drug application (NDA) for liraglutide 3.0 mg/day as an adjunct to a reduced caloric diet and physical exercise for chronic weight management in adult patients that are overweight with co-morbidities or obese. This document summarizes the primary efficacy findings from five randomized Phase 2 and Phase 3 Trials included in the NDA. This review mainly focuses on the three Phase 3 trials (1839, 1922 and 1923) due to their weight management objective, trial duration (at least 56 weeks), and their ability to support our preferred analysis. For these trials an emphasis is placed on 1) the extent and impact of missing data, and 2) the statistical methods used to explore the potential impact of missing data.

This document is organized as follows.

- Section 2 discusses statistical considerations of two elements of the 2007 Draft FDA Guidance for weight management—efficacy benchmarks and analysis methods.
- Section 3 summarizes the individual trial designs, statistical methods, patient disposition and trial results. In Section 3.3 limitations of the sponsor’s missing data sensitivity analyses are explored and discussed. In Section 3.4 the primary prespecified analysis is shown to over-estimate the intention-to-treat (ITT) effect using our preferred analysis by a relative change of up to 15%. Our preferred approach is an ITT analysis that represents missing data on the primary endpoint using information from subjects that prematurely discontinued but returned for a primary endpoint measurement. Based on this approach (detailed in Section 3.3), subjects treated with liraglutide 3.0 mg compared to placebo, had an average excess reduction from baseline to week 56 in fasting weight of 4.8% (95% CI =4.3, 5.3) in Trial 1839 and 3.4% (95% CI =2.3, 4.5) in Trial 1922. When liraglutide was used after an initial 5% weight reduction from a low caloric diet in Trial 1923, liraglutide treated subjects lost on average an additional 5.3% (95% CI =3.8, 6.8) compared to placebo.
- Section 4 provides a brief summary of findings.

The statistical evaluation of cardiovascular events is addressed in a separate statistical review conducted by the Division of Biometrics VII.

2 Draft FDA Guidance for products for weight management: Statistical considerations

In 2007 FDA released the Draft Guidance for Industry: *Developing Products for Weight Management* that provides recommendations for the development of drugs for the indication of weight management. The content relevant to evaluating the effectiveness of liraglutide is described in the sections on efficacy benchmarks and statistical methods. Below excerpts from these sections are provided along with a discussion of statistical considerations.

Efficacy benchmarks:

Box-1. Efficacy Benchmarks (Section IV.B.3.c)

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant.
- The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

It is useful to consider the benchmarks within the context of the goal of a product for weight management: long-term reduction in fat mass with a goal of reducing morbidity and mortality. It must therefore be recognized that the effectiveness is evaluated using a surrogate endpoint. Whether the observed change in the surrogate is clinically meaningful depends, in part, on safety considerations. That is, whether the benefits outweigh the risks relies on weighting the demonstrated effectiveness of the product against its risks.

Analysis methods:

Box-2. Analysis Methods (Section VI.C)

The analysis of (percentage) weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model. The analysis should be applied to the last observation carried forward 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. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. The imputation strategy should always be prespecified and should consider the expected dropout patterns and the time-course of weight changes in the treatment groups. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. Repeated measures analyses can be used to analyze longitudinal weight measurements but should estimate the treatment effect at the final time point.

Since the publication of the Draft Guidance the Division's view and handling of missing data has evolved, which was communicated to the sponsor in a May 06, 2013 Advice letter. The letter stated while the Division was not requesting the primary analysis be modified, the Division has reconsidered the use of LOCF following the publication in 2010 of a report on missing data by the National Academy of Sciences (NAS), The "*Prevention and Treatment of Missing Data in Clinical Trials.*"

An analysis that uses the last available observation on-treatment (LAO-OT) presents unique challenges interpreting the results overall and relative to the estimate of the intention-to-treat (ITT) effect. Some of the challenges associated with the recommended analysis are:

- Part of a therapy's effect is mitigated through the ability to tolerate the therapy. Therefore, an analysis that excludes observations after discontinuing therapy likely inflates the treatment effect since subjects that go off-treatment tend to regain weight.
- The average endpoint may have limited utility for a patient making a treatment decision because it is not known (nor is it possible to know) how long they will tolerate treatment; this can only be known after starting a treatment.
- The endpoint may not be clinically relevant for subjects with limited treatment adherence (e.g., one or two months) given the long-term goals of weight management.
- The distribution of the timing of the last available on-treatment measurement can differ across treatment arms. When this occurs the comparison of on-treatment experiences across treatment arms can be time-confounded.

Based on these considerations our preferred analysis is one that estimates the intent-to-treat effect using data from all subjects at the landmark visit. Because none of the sponsor's sensitivity analyses were found to adequately estimate this quantity for reasons described in Section 3.3, we fit two different statistical models to estimate this quantity; details of these model are provided in Section 3.3.

3 Evaluation of Efficacy

3.1 Study Design and Endpoints

A summary of the study design and endpoints for the trials reviewed in this document are shown in Table 1. Additional details of the trial designs are provided in Sections 3.1.1 to 3.1.5 with primary efficacy endpoints described in Section 3.1.6. Across the Phase 3 trials the studies differed in important ways. In particular, Trial 1922 was the only study in subjects with type 2 diabetes mellitus (T2DM); Trial 1923 studied subjects after having lost 5% of their bodyweight during a 12 week low calorie diet (LCD); and Trial 3970 primary objective was not related to inducing or maintaining weight loss. In all trials subjects received diet and activity counseling.

Table 1. Summary of Trial Designs

Trial	Study population	Design	Length of study (primary landmark visit)	Primary endpoints	Treatment arm (No. randomized)
1807 (Phase 2)	Obese subjects w/o T2DM	R, DB/OL*, PG, AC, PC	104 weeks (week 20)	1. Δ in bodyweight (kg) 2. 5% responder	Lira 1.2 mg –95 Lira 1.8 mg –90 Lira 2.4 mg –93 Lira 3.0 mg –93 Placebo – 98 Orlistat –95
1839 (Phase 3)	Non-diabetic subjects that are obese or overweight with co-morbidities	R, DB, PG, PC	160 weeks (week 56)	1. Δ in bodyweight (%) 2. 5% responder 3. 10% responder	Lira 3.0 mg –2487 Placebo –1244
1922 (Phase 3)	Obese or overweight subjects with T2DM	R, DB, PG, PC	56 weeks (week 56)	1. Δ in bodyweight (%) 2. 5% responder 3. 10% responder	Lira 1.8 mg –211 Lira 3.0 mg –423 Placebo –212
1923 (Phase 3)	Obese subjects without diabetes	R, DB, PG, PC	56 weeks (week 56)	1. Δ in bodyweight (%) 2. maintain run-in bodyweight 3. 5% responder	Lira 3.0 mg –212 Placebo –210
3970 (Phase 3)	Non-diabetic, obese subjects with moderate or severe sleep apnea	R, DB, PG, PC	32 weeks (week 32)	1. Δ in AHI	Lira 3.0 mg –180 Placebo –176

Source: FDA statistical reviewer

T2DM-Type 2 diabetes mellitus; R-Randomized; DB-Double-blind; PG-Parallel group; PC-placebo controlled; AC-active controlled; OL-open-label.

* DB/OL: the active control arm was open-label, and the liraglutide and placebo arms were double-blind.

3.1.1 Trial 1807

Trial 1807 was a Phase 2, randomized, partially blinded, parallel group, placebo and active controlled dose-finding trial in non-diabetic, obese subjects. A total of 564 subjects in 19 sites in 8 European countries were randomized 1:1:1:1:1:1 to one of four liraglutide doses (1.2, 1.8, 2.4, or 3.0 mg once daily), matching liraglutide placebo, or open-label orlistat (120 mg three times daily). Randomization was stratified by gender. The treatment duration was planned for 20 weeks with an optional 84 week extension period. A total of 398 randomized subjects consented to and continued study treatment in the extension phase. After the 52 week visit subjects treated with liraglutide or placebo were initially treated with the open-label 2.4 mg dose. Subjects were subsequently switched to the 3.0 mg dose following discussion from the planned week 52 analysis.

3.1.2 Trial 1839

Trial 1839 was a randomized, double-blind, placebo controlled, parallel group trial in non-diabetic obese or overweight subjects with co-morbidities. A total of 3731 subjects in 191 sites including 69 in the US were randomized 2:1 to liraglutide 3.0 mg or placebo. Randomization was stratified by pre-diabetes status (with, or without) and BMI (≥ 30 kg/m², or < 30 kg/m²). Subjects in the pre-diabetes stratum were randomized to 160 weeks of treatment; data post 56

weeks was not included in the submission. Subjects in the stratum without pre-diabetes were randomized to 56 weeks of treatment followed by a 12 week re-randomization treatment period. Subjects randomized to liraglutide were then re-randomized 1:1 to liraglutide or placebo. Subjects that prematurely discontinued were asked to attend a follow-up visit that took place 56 weeks after their randomization date.

3.1.3 Trial 1922

Trial 1922 was a 56 week randomized, double-blind, placebo controlled, three-arm parallel group trial in obese or overweight subjects with T2DM. A total of 846 subjects in 126 sites including 67 in the US were randomized 2:1:1 to liraglutide 3.0 mg, liraglutide 1.8 mg or placebo as an add-on to their background diabetes treatment. Randomization was stratified by HbA1c ($\geq 8.5\%$, or $< 8.5\%$) and background treatment (diet and exercise or single compound oral antidiabetic treatment, or combination oral antidiabetic treatment). Subjects that prematurely discontinued were asked to attend a follow-up visit that took place 56 weeks after their randomization date.

3.1.4 Trial 1923

Trial 1923 was a 56 week randomized, double-blind, placebo controlled parallel group trial in non-diabetic obese or overweight subjects with dyslipidemia and/or hypertension. Subjects were randomized if they lost at least 5% of their bodyweight during a 12 week low calorie diet (1200–1400 kcal/day) run-in period. A total of 422 subjects in 36 sites in the US (26) and Canada (10) were randomized 1:1 to liraglutide 3.0 mg or placebo. Randomization was stratified by co-morbidity status (presence or absence of treated or untreated hypertension or dyslipidemia). Subjects that prematurely discontinued were asked to attend a follow-up visit that took place 56 weeks after their randomization date.

3.1.5 Trial 3970

Trial 3970 was a 32 week randomized, double-blind, placebo controlled parallel group trial in non-diabetic obese subjects with moderate or severe obstructive sleep apnea (OSA). The primary study objective was to evaluate whether liraglutide reduces the severity of OSA assessed by apnea-hypopnoea index (AHI). A total of 359 subjects in 40 sites in the US (35) and Canada (5) were randomized 1:1 to liraglutide 3.0 mg or placebo.

3.1.6 Efficacy Endpoints

The pre-specified primary efficacy endpoints for the individual trials are displayed in the table below. Note that for Trial 1839 the fourth primary endpoint is still being collected at the time of the NDA submission; interim results are not presented in this review. Furthermore, it is noted that the primary endpoint definition from trial protocols (fixed time-point) is not consistent with the endpoint in the primary analysis that relies on LAO-OT. This lack of harmonization not only can lead to results being misinterpreted, it is also problematic for this submission because the treatment effect estimated from the primary analysis is found to over-state the estimated ITT treatment effect using our preferred approach.

The primary efficacy endpoints of percent change in fasting body weight from baseline and 5% responders is consistent with what is described in the Draft FDA Guidance. The 10% responder

endpoint (Trials 1839 and 1922) is not described in the Guidance but is included due to different regulatory requirements for the European Medicines Agency.

In Trial 3970 AHI is captured during an overnight visit using polysomnography. An AHI event is characterized by either a transient reduction in, or cessation of breathing. The criteria for an event are included in the Appendix. Importantly, the ability to establish benefit by comparing the average change in AHI rate between treatment groups is limited because, as noted by the sponsor (protocol, page 82) “clinical relevant change in AHI has not been established.”

Table 2. Primary efficacy endpoints by trial

Trial ID	1st primary	2nd primary	3rd primary	4th primary
1839, 1922 (at week 56)	Change in fasting body weight from baseline (%)	Proportion of subjects losing at least 5% of fasting baseline body weight (5% responders)	Proportion of subjects losing at least 10% of fasting baseline body weight (10% responders)	Onset of type 2 diabetes in subjects with pre-diabetes (at week 160)
1923 (at week 56)	Change in fasting body weight from baseline (%)	Proportion of subjects that maintained the $\geq 5\%$ reduction in initial fasting body weight achieved during the low calorie diet run-in period	Proportion of subjects losing at least 5% of fasting baseline body weight (5% responders)	-
1807 (at week 20)	Change in fasting body weight from baseline (kg)	Proportion of subjects losing at least 5% of fasting baseline body weight (5% responders)	-	-
3970 (at week 32)	Change in AHI rate (events per hour)	-	-	-

Source: FDA statistical reviewer

3.2 Patient Disposition and Missing Data

Patient Disposition: Patient disposition is summarized for the individual trials in Table 12 in the Appendix. A large proportion of subjects, 29%, withdrew from the Phase 3 trials prior to study specific landmark visit. This observation is not unexpected for weight management programs. In the placebo group the proportion of discontinuations was greater overall than in the liraglutide arms. Across the Phase 3 trials the key reasons for study discontinuation were as follows:

- *Adverse Events:* Adverse events accounted for 9.5% of early study discontinuations in the liraglutide arms compared to 4.1% in the placebo arms. In the liraglutide arm discontinuation tended to occur shortly after randomization.
- *Withdrawal Criteria:* In Trials 1839, 1922 and 1923 study discontinuations due to withdrawal criteria are non-specific and comprise several components including consent withdrawal, pregnancy, and target dose not tolerated. The majority of study discontinuations criteria were consent withdrawal. Subjects in the placebo group were more likely have a withdrawal related to withdrawal criteria than liraglutide.
- *Ineffective Therapy:* A small number of overall discontinuations were attributed to Ineffective Therapy (liraglutide 3.0 mg, 25 subjects; placebo, 42 subjects). From a sampling of subjects in Trial 1839 that discontinued for reasons other than this, several

commented on the ineffectiveness of the therapy (Table 13 in the Appendix). The extent to which this occurred in Trial 1839 and the other trials is not known.

In Trial 1807, 472 or 84% of the 564 randomized subjects completed the 20 week main treatment period, with 74 of them not enrolling into the 84 week extension period. The decision not to continue follow-up appears to be associated with degree of weight loss at week 20, with the subjects that enrolled in the extension having more favorable average weight reductions than those that did not (Table 3). This trend was consistent across study arms except for the 1.2 mg liraglutide dose.

Table 3. Mean change from baseline (kg) at week 20 by missing status and enrollment into the 84 week extension period (Trial 1807).

Consented for 84 week extension	Yes		No		No	
Weight at week 20	Available		Available		Missing	
Treatment Group	N	Mean Change	N	Mean Change	N	Mean Change*
Liraglutide 1.2 mg	68	-5.5	17	-5.7	9	-1.0
Liraglutide 1.8 mg	59	-7.1	15	-5.2	16	-2.2
Liraglutide 2.4 mg	65	-7.7	8	-4.6	19	-3.7
Liraglutide 3.0 mg	72	-8.4	10	-5.9	10	-3.4
Orlistat	67	-5.7	12	-0.3	16	-1.9
Placebo	67	-3.6	12	-2.6	19	-1.2

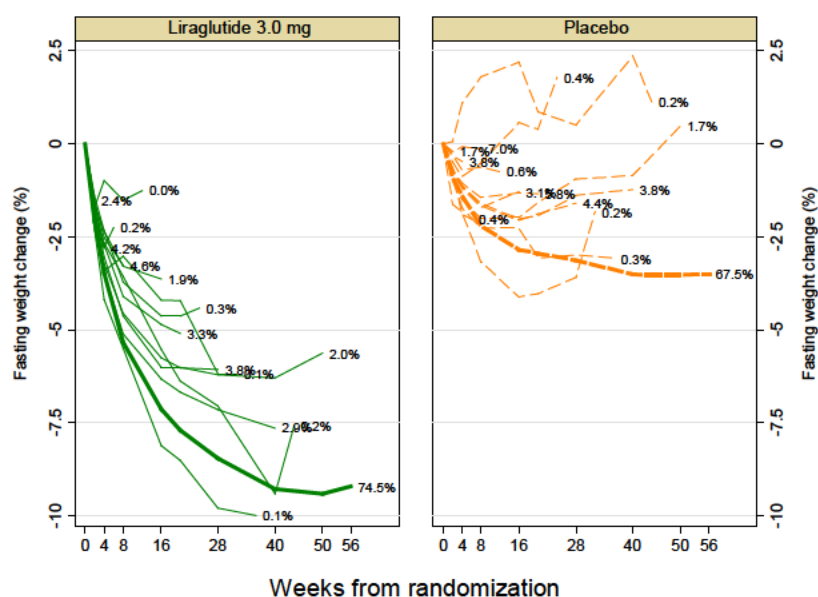
Source: FDA statistical reviewer

* Based on last available observation

A relationship was also observed between the timing of the last on-treatment assessment and the change in the primary endpoint for Trial 1839 (Figure 1) and Trial 1922 (Figure 5 in the Appendix). In particular:

- Subjects that had a 56 week on-treatment assessment (thick lines) consistently had a more favorable mean response profile over the study duration than the subjects that did not have a week 56 assessment. This observation was consistent across treatment groups.
- There was a positive relationship between the timing of the last on-treatment assessment and weight loss, with the average reduction being more favorable for subjects that had their assessment later in the trial compared to earlier.
- The distribution of the timing of the last available on-treatment was not the same across treatment arms.
- The plots do not describe what the average response at week 56 would have been for those that did not have an on-treatment assessment at week 56. For subjects that prematurely discontinued and returned for a week 56 assessment, the LAO-OT was found not to adequately characterize the week 56 response.

Figure 1. Mean profile of fasting bodyweight change (%) by last available on-treatment assessment (FAS, Trial 1839)



Source: FDA statistical reviewer

Missing Data in Trials 1839, 1922, and 1923: A sizable proportion of subjects did not have a 56 week weight assessment, with missing data occurring more frequently in the placebo group than in the liraglutide 3.0 mg group (Table 4). Across trials the proportion of missing data ranged from 17% to 20% for liraglutide 3.0 mg and from 19% to 26% for placebo. Importantly, these frequencies do not reflect the extent of missingness or treatment adherence as it relates to the primary analysis which was based on LAO-OT; the proportion of randomized subjects that did not have an on-treatment assessment at the week 56 visit ranged from 25% to 27% for liraglutide 3.0 mg and was more favorable than the 31% to 45% for placebo.

Included in the counts of subjects with a week 56 assessment are subjects that prematurely discontinued the study but returned for an assessment 56 weeks after randomization (“retrieved dropout”). The majority of subjects that prematurely discontinued did not return for the 56 week assessment, with approximately 30% of subjects doing so. In the sponsor’s report on missing data they appropriately question whether subjects that did return are representative of those that did not return. It is also notable that study site also appears to impact the likelihood of returning for a follow-up assessment; sites that had a greater frequency of study discontinuations were less likely to have a follow-up assessment (Figure 2). A noteworthy example is the site that had none of the 23 subjects that discontinued returned for the 56 week assessment. How this additionally impacts the representativeness of subjects that did not return for a follow-up assessment is unclear, but it raises concern that site investigators did not uniformly adhere to the study protocol.

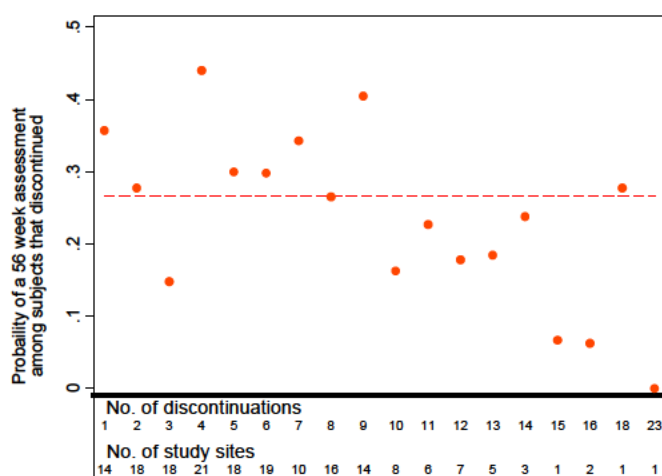
Table 4. Summary of missing data at week 56 (Trials 1839, 1922 and 1923)

	1839		1922			1923	
	Lira 3.0 mg N=2487	Placebo N=1244	Lira 3.0 mg N=423	Lira 1.8 mg N=211	Placebo N=212	Lira 3.0 mg N=212	Placebo N=210
Missing	492 (20%)	318 (26%)	67 (16%)	39 (18%)	56 (26%)	35 (17%)	39 (19%)
Available	1995 (80%)	926 (74%)	356 (84%)	172 (82%)	156 (74%)	177 (83%)	171 (81%)
On-treatment	1811 (73%)	818 (66%)	317 (75%)	158 (75%)	116 (55%)	156 (74%)	144 (69%)
Retrieve dropout	180 (7%)	103 (8%)	36 (9%)	11 (5%)	23 (11%)	21 (10%)	25 (12%)
Other [‡]	4 (0%)	5 (0%)	3 (1%)	3 (1%)	17 (8%)	0 (0%)	2 (1%)

Source: FDA statistical reviewer

[‡] A subject that had a fasting weight measurement within the visit window for the primary landmark visit (56 weeks \pm 3 days) but was neither retrieve dropout or on-treatment.

Figure 2. Relationship between having a retrieve dropout assessment and the number of discontinuations in a study site (Trial 1839)



Source: FDA statistical reviewer

Comparison of LAO-OT with primary endpoint: This section presents findings from an empirical comparison of responses at LAO-OT and week 56 for subjects that discontinued but returned for a week 56 assessment. Notable differences between liraglutide and placebo were observed (Table 5), which include:

- For liraglutide the LAO-OT over-estimates the weight reduction at week 56, with the CI excluding the value of no difference. The proportion of subjects that maintained the weight reduction at LAO-OT was low for the 3.0 mg dose, with only 29%, 30%, and 8% doing so in Trials 1839, 1922, and 1923, respectively.
- For placebo the LAO-OT consistently under-estimated the weight reduction at week 56 although the CIs all included the value of no difference.
- The responses at week 56 had greater variability than the responses at the LAO-OT. This finding was consistent across trials and treatment groups.

These findings provide empirical confirmation that the primary analysis cannot be used to describe the ITT effect. This also extends to the analysis of categorical (responder) endpoints, for reason described next.

Table 5. Comparison of fasting weight change (%) at LAO-OT and week 56 for subjects that withdrew and returned for a week 56 follow-up assessment

Treatment Group	N	LAO-OT Mean (SE)	Week 56 (Actual) Mean (SE)	Mean Difference; LAO-OT – Week 56 (95% CI)
Trial 1839				
Liraglutide 3.0 mg	171	-4.9% (0.4)	-3.0% (0.6)	-1.8% (-2.7, -1.0)
Placebo	100	-0.4% (0.4)	-1.3% (0.7)	0.9% (-0.4, 2.1)
Trial 1922				
Liraglutide 3.0 mg	33	-4.4% (0.7)	-2.5% (0.8)	-1.8% (-3.2, -0.5)
Liraglutide 1.8 mg	8	-4.3% (1.3)	-2.4% (1.8)	-1.9% (-5.1, 1.3)
Placebo	23	-1.4% (0.4)	-1.7% (0.7)	0.3% (-1.5, 2.0)
Trial 1923				
Liraglutide 3.0 mg	12	-6.4% (1.0)	-1.1% (1.9)	-5.3% (-7.8, -2.8)
Placebo	18	-0.5% (1.0)	-1.1% (2.0)	0.5% (-2.8, 3.8)

Source: FDA statistical reviewer

Differences were observed in the frequency of responders based on LAO-OT and week 56. In Trial 1839 the proportion of 5% responders for placebo using LAO-OT under-estimated the response rate at week 56 (9% vs. 22%); for liraglutide the proportion of responses were fairly similar (LAO-OT: 34%; week 56: 32%). In Trial 1923, the proportion subjects that were able to maintain their baseline weight (i.e., the weight after a 5% reduction during the LCD run-in) was over-estimated at week 56 using LAO-OT for liraglutide (LAO-OT: 11/12; week 56: 7/12) and under-estimated using LAO-OT for placebo (LAO-OT: 7/18; week 56: 11/18).

3.3 Statistical Methods

Analysis Populations: Two of the sponsor’s analysis populations were the full analysis set (FAS) and the completers. The FAS was the primary analysis population, and included all randomized subjects exposed to at least one dose of the trial product and with at least post-baseline assessment of body weight in Trials 1807 and 1923, or of any efficacy endpoint in Trials 1839 and 1922. The FAS in Trial 3970 was defined as all randomized subjects. This population is consistent with the modified ITT population defined in the Draft FDA Guidance (Box 2). The completer population included subjects in the FAS with a valid end of trial efficacy assessment.

The FDA analyses are performed on the ITT population, defined as randomized subjects with a baseline assessment.

All analyses use the randomized treatment.

Statistical methods for the primary analysis of the primary efficacy endpoints: Consistent with the Draft FDA Guidance the primary analysis was performed on the FAS using LAO-OT. In Trial 1922 the analysis was performed using last available pre-rescue observation on treatment. Continuous primary endpoints were analyzed using an analysis of covariance (ANCOVA) model that included treatment, country, sex, baseline response, and randomization stratum as independent variables. Categorical endpoints were analyzed using a logistic regression model using the same independent variables.

Note that in Trial 1922 the decision to limit the analysis to pre-rescue observation has the potential to inflate the treatment effect since subjects randomized to placebo were more likely to require rescue medication overall and earlier on average in the trial.

Sample size: The Phase 3 trials were individually powered to test the individual study endpoints with at least 85% power. The trials, in particular Trial 1839, were over-sized for the efficacy endpoints to comply with safety considerations outlined in the Draft FDA Guidance. The Guidance recommends approximately 3,000 subjects are randomized to active doses and no fewer than 1,500 subjects are randomized to placebo.

Approach to multiplicity: The Phase 3 trials (1839, 1922, 1923, 3970) individually preserved the study-wise type-I error at 5% by hierarchically testing the study endpoints according to their order in Table 2. Under this approach the statistical testing for an endpoint is performed only if the statistical test for the preceding endpoint in the hierarchy is statistically significant at the two-sided 5% level. For Trial 1922 that investigated two liraglutide doses, the hierarchy ordered the hypotheses for the 3.0 mg dose first followed by hypotheses for the 1.8 mg dose.

Approximately 15 to 20 secondary endpoints were prespecified for investigation in each of the Trials. None of the secondary endpoints, including those related to body composition in Trial 3970, were incorporated into the hierarchical testing sequence to preserve the study-wise type-I error.

For Trial 1807 the pairwise comparisons at week 20 between the separate liraglutide doses to placebo and orlistat were done using Dunnett's method for simultaneous confidence intervals. The nominal study-wise error was not preserved at the 5% level as a separate 5% alpha was used for the placebo comparison and the orlistat comparison.

Sensitivity analyses for the primary efficacy endpoints: In my opinion, the sponsor's sensitivity analyses used to assess the potential impact of missing data are inadequate. None of their analyses attempted to estimate the ITT effect at week 56 under a reasonable set of assumptions. Our recommended/preferred approach represent the missing week 56 response for subjects that prematurely discontinued using information from the subjects that also prematurely discontinued but returned for their week 56 assessment. This approach can be implemented only for Trials 1839, 1922 and 1923 because they retrieved dropouts. Additionally, I do not concur with the sponsor's definition/notion of missing data. Our notion is that all study subjects (if alive) have a weight at week 56, with their missing status being defined by whether or not the endpoint was assessed. Thus, the retrieve dropouts have a valid endpoint even though they were no longer receiving study therapy. In the sponsor's investigation of missing data the majority of their analyses did not use a subject's actual off-treatment week 56 measurements. This approach has significant implications on the interpretation of treatment effect at week 56, as detailed for the sponsor's MMRM and imputation analysis below.

Continuous endpoints (Sponsor's): Below is a description of the sponsor's sensitivity analyses that are presented in this document. With the exception of the MMRM analyses the endpoint was analyzed using an ANCOVA model using the covariates in the primary analysis.

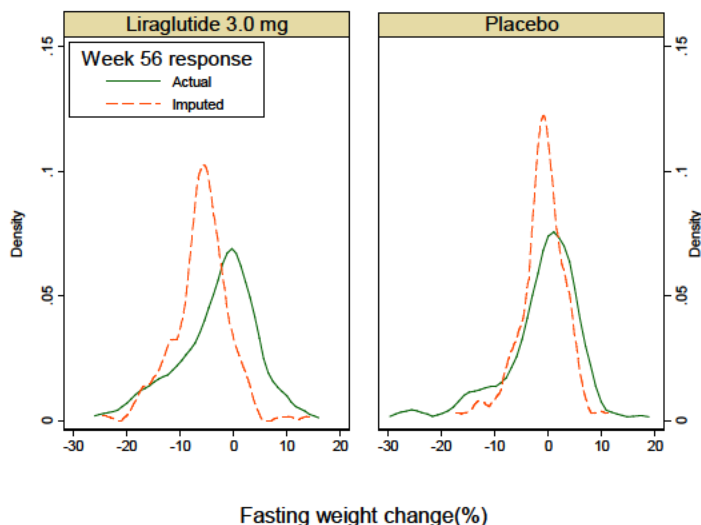
1. *Completers* –Subset analysis that includes subjects that did not have their endpoint imputed in the primary analysis.
2. *Last available observation (LAO)* – Used fasting or nonfasting weight measurements, off-drug measurements, post-rescue and the follow-up weight measurements after 56 weeks after randomization for early withdrawal (retrieve dropout). The analysis for Trial 1923 excluded post-rescue measurements.
3. *Baseline observation carried forward (BOCF)* – Baseline observations were carried forward for subjects without a valid post-baseline assessment. This analysis was applied to all randomized subjects. This analysis was not performed in Trial 1923.
4. *MMRM* –a longitudinal analysis of on-treatment fasting weights that set off-treatment measurements to missing. A contrast and 95% CI was constructed for the difference in percent weight change for liraglutide compared to placebo at week 56.
5. *Multiple imputation (MI)* – Off-treatment responses in both treatment groups were imputed assuming the distribution of their pre- and post- withdrawal values is the same as the distribution of placebo completers. Off-treatment follow-up measurements were not included in either the imputation or the analysis.

Comments on the limitation of the sponsor’s MMRM and MI analysis:

MMRM—The MMRM model assumes missing data are missing at random. Under this assumption the statistical behavior of the missing data (given the observed responses and model covariates) is assumed to be same as the observed data. Because the model uses only on-treatment observations, the model estimates the treatment effect at week 56 assuming all subjects in the FAS could adhere to randomized therapy, contrary to the fact that a sizable number could not. This analysis therefore attempts to estimate a treatment effect under conditions that were not observed in the clinical trials, nor could occur in clinical practice. Therefore, it is my opinion that the findings from this sensitivity analysis lack clinical relevance due to the underlying implausibility of achieving perfect treatment adherence.

Multiple imputation—The analysis anchors the imputed week 56 responses based on the placebo completers. Whether this is appropriate is debatable and was not justified by the sponsor. An assumption of their imputation model is, for a liraglutide treated subject, the on-treatment experiences are attributable to placebo and not the treatment received. Due to the sponsor’s approach to missing data the implication of this assumption can be empirically evaluated. This was done for Trial 1839 by comparing the average imputed value with their actual value for the retrieve dropouts (Figure 3). It is evident that for liraglutide treated subjects the imputation model had them having greater average loss at week 56 than they actually did. The average decrease at week 56 from baseline was 6.1% based on the imputation, which was double the 3.0% average decrease that was actually observed and surprisingly greater than the 4.9% average decrease at the LAO-OT. For placebo the differences between imputed and observed values were not dramatic. As a consequence of these findings, it is likely that this analysis will over-state the ITT effect at week 56.

Figure 3. Kernel density plot (smoothed histogram) comparing the actual week 56 fasting weight change (%) with the average imputed value from the sponsor's MI analysis for subjects that withdrew and returned for a week 56 follow-up assessment (Trial 1839)



Source: FDA statistical reviewer

Categorical endpoints: Below is a description of the sponsor's sensitivity analyses that are presented in this document. Instead of comparing event probabilities using the odds ratio metric from a logistic regression model as done by the sponsor, this review will present the risk difference due to the ease of interpretation. Unadjusted estimates will be provided along with asymptotic 95% confidence interval (CI).

1. *Completers* – See description above.
2. *Off-treatment as failures* – Subjects in the FAS without a valid week 56 assessment were classified as non-responders. This analysis is consistent with a sensitivity analysis described in the Draft FDA Guidance.

Sensitivity analyses for the primary efficacy endpoints done by FDA: Two sensitivity analyses were performed by FDA to attempt to estimate the ITT effect. This was not done in Trials 1807 and 3970 since subjects that prematurely discontinued were not asked to return for an assessment at the landmark visit. How subjects were handled was not uniform across trials due to the varying number of subjects that returned for a follow-up assessment after discontinuation. Additional details of the approaches are provided in the Appendix.

Multiple imputation using retrieve dropout (MI-RD) – Our preferred approach imputes missing week 56 responses based on subjects that discontinued and had a week 56 fasting measurement. The imputation was done within groups defined by randomized treatment and the timing (month) of their last on-treatment measurement. Values were imputed using measurements from baseline and LAO-OT, when possible. This approach was not done for Trial 1923 and the liraglutide 1.8

mg arm in Trial 1922 due to the small number of retrieve dropouts; our preferred approach for Trial 1922 and comparison involving liraglutide 1.8 mg is described below.

For the continuous endpoints a total of 100 imputed datasets were created, and results were combined using Rubin's rule (Rubin, D., *Multiple Imputation for Nonresponse in Surveys*, New York: Wiley & Sons (1987)). For the categorical endpoints response status was determined from the imputed continuous response. A total of 1000 imputed data sets were created. The imputed data were analyzed using a Beta-Binomial model with a uniform prior. For each imputed dataset a sample for each group was drawn from their respective posterior distribution, which thus incorporated imputation variability. Difference in probabilities was summarized using 50th, 2.5th and 97.5th percentiles of the distribution.

Retrieve dropout weighted analysis (RD-Weighted) – In this analysis subjects were assigned differential weights, which up-weighted the contribution of subjects that prematurely discontinued and returned for a week 56 measurement while those missing a week 56 measurement were assigned zero weight (and did not contribute to the analysis). A subject with an on-treatment or other week 56 measurement was assigned a weight of one. The degree to which a subject was up-weighted depended on their treatment group and the timing of their LAO-OT.

For the continuous endpoints the data were analyzed using a weighted ANCOVA model. For the categorical endpoints the weighted sample was analyzed using a Beta-Binomial model with a uniform prior. A total of 100,000 samples were taken for each treatment group, and the difference in probabilities was summarized using 50th, 2.5th and 97.5th percentiles of the distribution.

3.4 Results

3.4.1 Trial 1807

Results from the analysis of primary endpoints at week 20 are shown below (Table 6); results for week 52 analysis are displayed in Table 14 in the Appendix. For both endpoints at week 20 only the 2.4 mg and 3.0 mg liraglutide doses had changes that were statistically significantly different than both placebo and orlistat, with the change for the 3.0 mg dose being more favorable. For the week 52 comparison the results 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. It is unclear what impact these subjects would have had if they continued in the study since they tended to have less favorable responses (Table 3).

Table 6. Analysis results for primary endpoints at week 20 in Trial 1807

Endpoint	Treatment Group	N	Adj. mean change from baseline / 5% response n (%)	Difference in means* / Risk difference Lira-Placebo (95% CI)	Difference in means* / Risk difference Orlistat-Placebo (95% CI)
Fasting weight change (kg)	Lira 3.0 mg	92	-7.2 kg	-4.4 kg (-5.9, -2.9)	-3.0 kg (-4.5, -1.4)
	Lira 2.4 mg	92	-6.3 kg	-3.5 kg (-5.0, -2.0)	-2.1 kg (-3.7, -0.6)
	Lira 1.8 mg	90	-5.5 kg	-2.8 kg (-4.3, -1.3)	-1.4 kg (-3.0, 0.2)
	Lira 1.2 mg	94	-4.8 kg	-2.1 kg (-3.6, -0.6)	-0.7 kg (-2.2, 0.9)
	Orlistat	95	-4.1 kg		
	Placebo	98	-2.8 kg		
5% responders	Lira 3.0 mg	92	70 (76%)	46.5% (33.9, 59.1)	31.9% (18.6, 45.1)
	Lira 2.4 mg	92	56 (61%)	31.3% (17.8, 44.7)	16.7% (2.5, 30.8)
	Lira 1.8 mg	90	18 (53%)	23.7% (10.0, 37.4)	9.1% (-5.2, 23.5)
	Lira 1.2 mg	94	49 (52%)	22.5% (9.0, 36.1)	7.9% (-6.3, 22.1)
	Orlistat	95	42 (44%)		
	Placebo	98	29 (30%)		

Source: FDA statistical reviewer

* Results for fasting weight are adjusted and for the 5% responder endpoint is unadjusted.

3.4.2 Trials 1839, 1922, and 1923

In each of the Phase 3 weight management trials all of the efficacy endpoints evaluated under the hierarchical testing sequence were statistically significant. To allow for a more fluid discussion of study findings the results will not be presented according to the pre-specified testing sequence. Furthermore, we caution contrasting results across trials since the trials differed in important ways with respect to study design and study population.

Change in body weight: Results from the pre-specified primary analysis of the primary efficacy endpoint is shown in Table 7. In each of the Trials liraglutide 3.0 mg treated subjects had a statistically significant greater reduction in body weight change from baseline compared to placebo. For Trials 1839 and 1922 the confidence interval did not rule out the difference in average reduction for liraglutide compared to placebo of 5%.

In Trial 1922 the liraglutide 1.8 mg treated subjects had a statistically significant greater weight reduction compared to placebo, although the difference was not as large as the reduction observed for the 3.0 mg dose.

In our preferred analysis (MI-RD for Trials 1839 and 1922, and RD-Weighted for Trial 1923) the estimate of the ITT effect remained statistically significantly better than placebo (Table 8) but the magnitude of the estimated treatment effect was attenuated relative to the primary prespecified analysis. For Trial 1839 the estimated effect was 11% smaller and 15% smaller for Trials 1922 and 1923. These findings were reasonably aligned with the second FDA sensitivity analysis that attempted to estimate the ITT effect albeit with smaller. Results from the sponsor's sensitivity analyses were found to be aligned with the findings from the primary pre-specified analysis.

Table 7. 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

Table 8. 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)	-4.8% (-5.3, -4.3)	-3.4% (-4.5, -2.3)	-	-
RD-Weighted (ITT)	-4.6% (-5.4, -3.9)	-3.8% (-4.7, -2.9)	-2.5% (-3.5, -1.5)	-5.3% (-6.8, -3.8)

Source: FDA statistical reviewer

Responder endpoints: Results from the pre-specified primary analysis of the responder endpoints is shown in Table 7. In each trial for each of the two responder endpoints, the liraglutide 3.0 mg treated subjects had a statistically significant excess number of subjects respond compared to placebo. For Trials 1839 and 1922 the estimated proportion of liraglutide 3.0 mg treated subjects having a 5% response were notably greater than 35% and more than double the proportion in placebo.

In Trial 1922 the liraglutide 1.8 mg treated subjects also had a statistically significant excess number of subjects responders compared to placebo. The estimated proportion of liraglutide 1.8 mg treated subjects having a 5% response was similar to 35% (36%) and more than double the proportion in placebo.

In our preferred analysis the estimate of the ITT effect remained statistically significantly better than placebo (Table 10) but, similar to the findings from the continuous endpoint, the magnitude of the estimated treatment effect was attenuated relative to the primary prespecified analysis.

For Trials 1839 and 1922 this attenuation can be attributed the statistical model predicting a greater number placebo treated subjects having a 5% response compared to LAO-OT (Trial 1839: 34% vs. 27%; Trial 1922: 20% vs. 14%). For these two trials the estimated proportion of liraglutide 3.0 mg treated subjects having a 5% response remained above 35% and approximately double the proportion in placebo.

Table 9. 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

Table 10. Sensitivity analysis results for responder endpoints in Trials 1839, 1922, and 1923

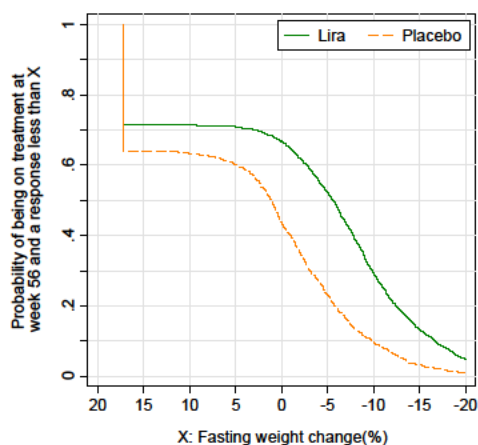
	1839			1922			1923		
Endpoint/ Sensitivity Analysis	Lira 3.0mg n (%)	Placebo n (%)	Difference: Lira - Placebo (95% CI)	Lira 3.0mg n (%)	Placebo n (%)	Difference: Lira - Placebo (95% CI)	Lira 3.0mg n (%)	Placebo n (%)	Difference: Lira - Placebo (95% CI)
5% responder									
Completers	1317 (73%)	292 (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)	94 (44%)	47 (23%)	22% (12, 31)
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

Cumulative distribution plots were constructed to allow investigating of different thresholds beyond those considered above. (Plots for Trials 1922 and 1923 are displayed in the Appendix.) Importantly, randomized subjects that were no longer on-treatment by week 56 and/or did not have an endpoint assessment were assigned the worst possible weight change. This resulted in the initial step in the curves, but removed the potential of having time-confounded curves. The expectation in such a plot is that if liraglutide was not efficacious the liraglutide curve would be similar or worse (due to potential adverse effects) than placebo over the changes from baseline that are considered meaning (e.g., > 5%). This was not what was observed, with the proportion of responders being greater in the liraglutide group.

This plot also enables one to answer the following question regarding a treatment decision: 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 a certain degree. Such a question could not be answered from a plot using LAO-OT.

Figure 4. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1839)



Source: FDA statistical reviewer

3.4.3 Trial 3970

Results from the analysis of the primary efficacy endpoint (AHI) and the secondary body weight endpoints are shown in Table 11. For on-treatment changes in AHI up until week 32, liraglutide treated subjects had a statistically significant greater reduction from baseline relative to placebo; the excess reduction was -6.1 events/per hour with 95% CI (-11.0, -1.2). Based on previous discussions it is unclear whether this reduction is clinically relevant.

For the weight endpoints, compared to placebo by week 32, the liraglutide treated subjects experienced an additional decrease in body weight of 4.2%, and an estimated additional 27.7 and 21.7 subjects per 100 treated that would have had weight reductions of at least 5% and 10%, respectively.

Table 11. Analysis results for change in AHI (events/hour) and secondary weight endpoints in Trial 3970

Endpoint	Treatment Group	N	Adj. mean change from baseline/ response n (%)	Diff. in means* Lira-Placebo (95% CI)
AHI	Liraglutide 3.0 mg	168	-12.2	-6.1 (-11.0, -1.2)
	Placebo	166	-6.1	
% change	Liraglutide 3.0 mg	175	-5.7%	-4.2% (-5.2, -3.1)
	Placebo	178	-1.6%	
5% responders	Liraglutide 3.0 mg	175	81 (46%)	27.7% (18.4, 37.1)
	Placebo	178	33 (19%)	
10% responders	Liraglutide 3.0 mg	175	41 (23%)	21.7% (15.2, 28.3)
	Placebo	178	3 (2%)	

Source: FDA statistical reviewer

* Results for AHI and fasting weight change (%) are adjusted and the responder endpoints are unadjusted.

4 Summary results

Based on our preferred analysis subjects treated with liraglutide were found to have statistically significant changes in body weight. Compared to placebo, the excess reduction in fasting weight from baseline to week 56 for liraglutide 3.0 mg was 4.8% (95% CI =4.3, 5.3) in Trial 1839 and 3.4% (95% CI =2.3, 4.5) in Trial 1922. When liraglutide was used after an initial 5% weight reduction from a LCD, liraglutide 3.0 mg treated subjects lost an additional 5.3% (95% CI =3.8, 6.8) compared to placebo. Although the magnitude of the estimated treatment effects from our preferred approach were attenuated relative to the pre-specified primary analysis, the changes that were observed for liraglutide 3.0 mg relative to placebo were in-line with the efficacy benchmarks outlined in the 2007 Draft FDA Guidance.

5 APPENDIX

5.1 Supportive Material

Definition of obstructive apnea and hypopnea events per study protocol (Section 3.2)

Apnea Rules

Score an apnea when all of the following criteria are met:

- There is a drop in the peak thermal sensor excursion by $\geq 90\%$ of baseline
- The duration of the event lasts at least 10 seconds
- At least 90% of the event's duration meets the amplitude reduction criteria of apnoea

Hypopnea Rules

Score a hypopnea if all of the following criteria are met:

- The nasal pressure signal excursions (or those of the alternative hypopnea sensor) drop by $\geq 30\%$ of baseline
- The duration of this drop occurs for a period lasting at least 10 seconds
- There is a $\geq 4\%$ desaturation from pre-event baseline
- At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea

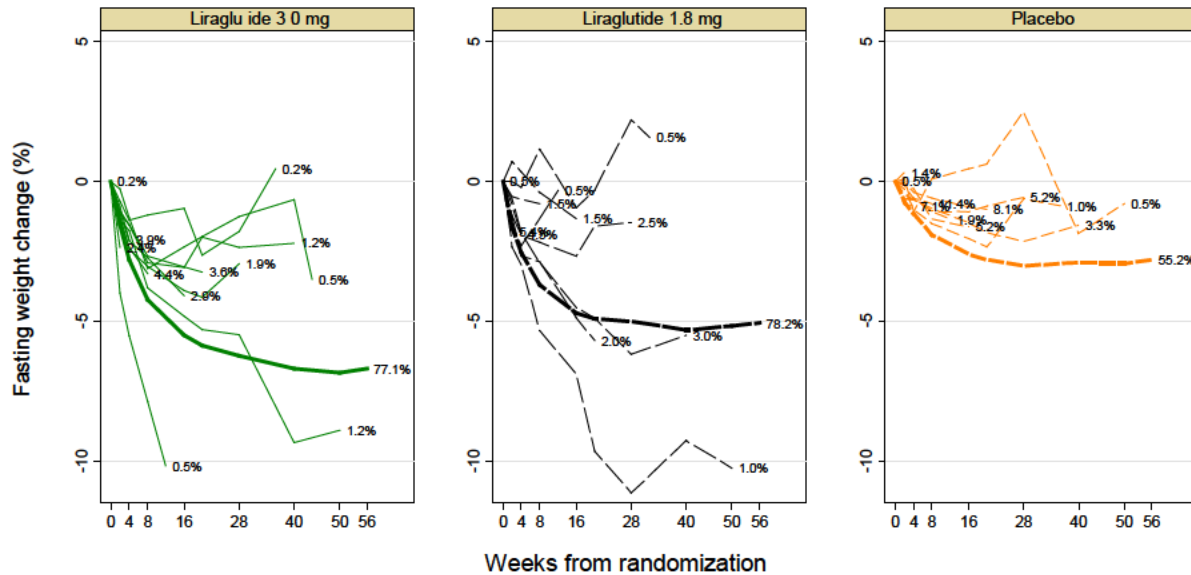
Details of the FDA sensitivity analyses

MI-RD –The imputation was done within groups defined by randomized treatment and the timing (month) of their last on-treatment measurement. In Trial 1839 the visits were grouped by month as follows: 0 to 1, 2 to 3, 4 to 6, 7 to 9, after 10. In Trial 1922 the visits were grouped based on whether the last on-treatment measurement was on or before month 5. For subjects in the FAS the imputation model, fit within each group, included baseline and last on-treatment measurement. Imputation for randomized subjects excluded from the FAS was done as follows. These subjects were first grouped with the subjects that had their last on-treatment measurement during the first time period (Trial 1839: 0 to month 1; Trial 1922: 0 to month 5). In the first step the missing week 56 response was imputed using only their baseline measurement. Next, the distribution of imputed values was centered per subject around their baseline measurement (i.e., MI version of BOCF).

RD-Weighted – Subjects with a week 56 assessment that were not a retrieve dropout were assigned an analysis weight of one. Subjects without a week 56 assessment were assigned an analysis weight of 0. The retrieve dropouts were assigned weights that depended on the time of their last on-treatment observation and randomized treatment. Specifically, the analysis weight assigned to a subject that was a retrieve dropout in group i was $(A_i + B_i)/A_i$ where A_i is the number of retrieve dropouts in the group and B_i is the number of subjects in the group with the missing endpoint. For Trial 1839 and 1922 the timing used to define the groups was based on the MI-RD analysis (see above). In Trial 1923 the visits were grouped based on whether the last on-treatment measurement was on or before month 4

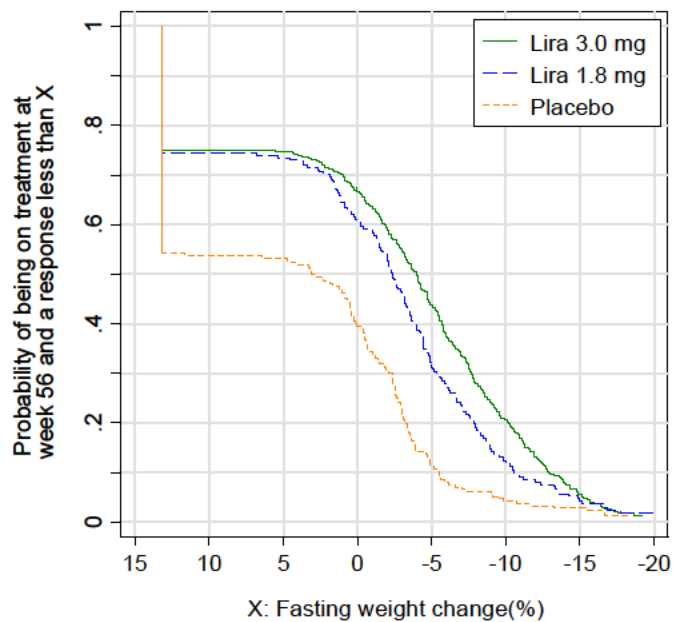
5.2 Additional Tables and Figures

Figure 5. Mean profile of fasting bodyweight change (%) by last available on-treatment follow-up visit (FAS, Trial 1922)



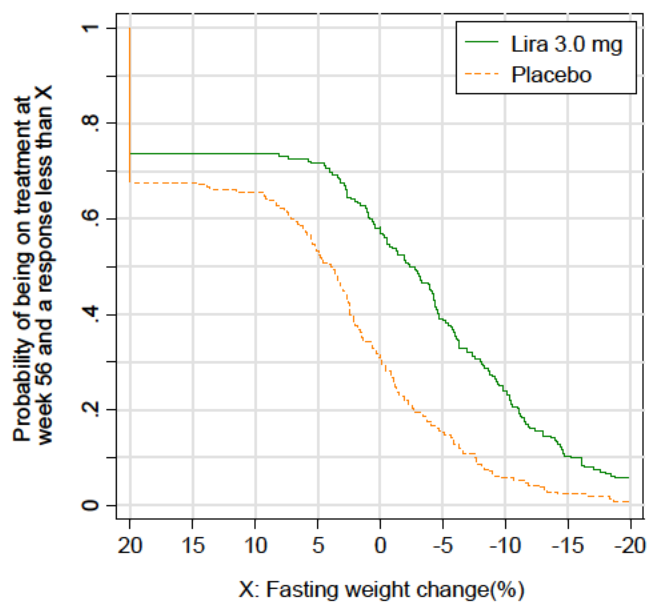
Source: FDA statistical reviewer

Figure 6. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1922)



Source: FDA statistical reviewer

Figure 7. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1923)



Source: FDA statistical reviewer

Table 12. Patient Disposition by trial

	1807			1839		1922			1923		3970	
	Lira 3.0 N	Orlistat N	Placebo N	Lira 3.0 N	Placebo N	Lira 3.0 N	Lira 1.8 N	Placebo N	Lira 3.0 N	Placebo N	Lira 3.0 N	Placebo N
Randomized	93	95	98	2487	1244	423	211	212	212	210	180	179
Exposed	93	95	98	2481	1242	422	210	212	212	210	176	179
Completed treatment period*	82	79	79	1789	801	324	164	140	159	146	134	142
Withdrawn*	11	16	19	698	443	99	47	72	53	64	46	37
Adverse event	5	3	3	238	45	39	18	7	18	18	20	6
Ineffective therapy	0	1	2	23	36	0	0	3	0	2	2	1
Non-compliance with protocol	2	2	3	65	38	12	8	13	8	5	8	5
Other	4	10	11	79	63	16	7	12	10	15	14	25
Withdrawal criteria	0	0	0	293	261	32	14	37	17	24	2	0
Consented to 84 Week Extension Interim Period (Weeks 20 – 52)	72	67	67	-	-	-	-	-	-	-	-	-
Completed	65	55	62	-	-	-	-	-	-	-	-	-
Withdrawn	7	12	5	-	-	-	-	-	-	-	-	-
Adverse event	2	0	0	-	-	-	-	-	-	-	-	-
Ineffective therapy	0	0	2	-	-	-	-	-	-	-	-	-
Non-compliance with protocol	0	1	0	-	-	-	-	-	-	-	-	-
Other	5	11	3	-	-	-	-	-	-	-	-	-
Withdrew but attended 1yr visit	-	-	-	202	111	36	12	23	22	25	-	-
Entered re-randomization	-	-	-	701	304	-	-	-	-	-	-	-
Completed re-randomization	-	-	-	685	289	-	-	-	-	-	-	-
Full analysis set	92	95	98	2437	1225	412	204	211	207	206	180	179

Source: FDA statistical reviewer

% of randomized subjects; *During 20 week main treatment period for Trial 1807

Table 13. Select instances of withdrawal criteria related to inadequate weight loss (Trial 1839)

Subject ID	Reason noted in dataset
440012	Subject is tired of daily injections without weight loss over the year of participation
446016	WITHDREW BECAUSE SUBJECT WAS NOT LOSING WEIGHT
440026	Subject did not care to commit time and effort to study since she was not losing significant weight and did not want to continue daily injections.
445001	Weight loss stopped..Patient does not want to continue giving injections for no weight loss
446001	WITHDREW CONSENT BECAUSE SUBJECT WAS NOT LOSING WEIGHT
446010	WITHDREW CONSENT BECAUSE SUBJECT WAS NOT LOSING ANY WEIGHT
446011	WITHDREW CONSENT BECAUSE SUBJECT WAS NOT LOSING ANY WEIGHT

Source: FDA statistical reviewer

Table 14. Analysis results for primary endpoints at week 52 in Trial 1807

Endpoint	Treatment Group	N	Adj. mean change from baseline / 5% response n (%)	Difference in means / Risk difference Lira-Placebo (95% CI)	Difference in means / Risk difference Orlistat-Placebo (95% CI)
Fasting weight change (kg)	Lira 3.0 mg	92	-7.8 kg	-5.8 kg (-7.9, -3.7)	-3.8 kg (-6.0, -1.6)
	Lira 2.4 mg	92	-6.1 kg	-4.1 kg (-6.2, -2.0)	-2.2 kg (-4.4, -0.0)
	Lira 1.8 mg	90	-5.4 kg	-3.4 kg (-5.5, -1.2)	-1.5 kg (-3.7, 0.7)
	Lira 1.2 mg	94	-3.8 kg	-1.8 kg (-3.9, 0.4)	0.2 kg (-2.0, 2.4)
	Orlistat	95	-3.9 kg		
	Placebo	98	-2.0 kg		
5% responders	Lira 3.0 mg	92	68 (74%)	45.3% (32.7, 58.0)	28.6% (15.2, 42.1)
	Lira 2.4 mg	92	49 (53%)	24.7% (11.1, 38.3)	8.0% (-6.3, 22.3)
	Lira 1.8 mg	90	47 (52%)	23.7% (10.0, 37.3)	7.0% (-7.4, 21.3)
	Lira 1.2 mg	94	42 (45%)	16.1% (2.7, 29.6)	-0.6% (-14.8, 13.6)
	Orlistat	95	43 (45%)		
	Placebo	98	28 (29%)		

Source: FDA statistical reviewer



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW BRIEFING MATERIAL

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON LIRAGLUTIDE

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory Committee,
September 11, 2014

Rongmei Zhang, PhD
Mat Soukup, PhD
Mark Levenson, Ph.D.

Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Document Date: July 31, 2014

TRIAL DATABASE

The assessment of cardiovascular (CV) risk for liraglutide utilized two databases: a database incorporating 5 trials conducted in the weight management (WM) program and a database incorporating 20 trials conducted in the Type 2 diabetes mellitus (T2DM) program. For the current sought indication of weight management, the primary database for evaluating CV risk was based upon the WM database with supportive CV information from the T2DM database. The maximum daily doses of liraglutide investigated in the WM program and the T2DM program were 3.0mg and 1.8mg, respectively. A high-level summary of the information included in each database is provided in Table 1.

Table 1: Weight Management (WM) and Type 2 Diabetes Mellitus (T2DM) Databases to Evaluate CV Risk

	WM Database		T2DM Database	
	Liraglutide	Comparator	Liraglutide	Comparator
Number of Subjects	3872	2036	5498	2735
Person Years Exposure	3982	1957	4323	2078

All five trials conducted in the WM program were randomized, double-blinded, placebo-controlled, and parallel-group designs. CV safety information from these 5 trials was based upon a database lock date of July 2, 2013. A summary of the 5 clinical trials in weight management are provided in Table 2. Note that all trials in the WM program excluded subjects with T2DM at baseline other than Trial 1922.

Table 2: Design Summary of the Five WM Trials

Trial ID	Phase	Treatment Arms (N)	Duration of Trial
1807	2	Lira 1.2mg (95), Lira 1.8mg (90), Lira 2.4mg (93), Lira 3.0mg (93), Placebo (98), Orlistat 120mg (95)	20 + 84 weeks ^a
1839	3	Lira 3.0mg (2481), Placebo (1242)	56 + 12 weeks ^b
1922 [†]	3	Lira 1.8mg (210), Lira 3.0mg (422), Placebo (212)	56 weeks
1923	3	Lira 3.0mg (212), Placebo (210)	56 weeks
3970	3	Lira 3.0mg (176), Placebo (179)	32 weeks

[†] Trial 1922 was the only trial that enrolled subjects with T2DM

^a Trial 1807: main trial 20 weeks plus an extension period of 84 weeks.

^b Trial 1839: main trial 56 weeks plus a 12-week re-randomized treatment period was applicable for subjects without pre-diabetes

The T2DM supportive meta-analysis included all intermediate and long term trials (phase 2 and 3) in the T2DM program conducted by NovoNordisk (NN) which included one or more treatment arms with liraglutide. This included a total of 20 trials with treatment durations ranging from 5 to 104 weeks.

STATISTICAL METHODS

The statistical evaluation of CV safety for the WM program did not pre-specify a CV risk margin to rule out. Results reported are based upon the nominal two-sided $\alpha=0.05$ level.

PRIMARY ENDPOINT

The primary endpoint is a composite of major adverse cardiovascular events (MACE) comprising CV death, non-fatal myocardial infarction, and non-fatal stroke. All events were either prospectively or post hoc adjudicated by an independent event adjudication committee (EAC).

ANALYSIS METHODS

All analyses in the WM and T2DM databases were based on the safety analysis set, defined as all randomized subjects receiving at least one dose of trial treatment. Two censoring schemes were utilized in this analysis set for assessment of CV risk in the WM database:

- The primary analysis was based on an “on treatment” censoring scheme which incorporates information only while a subject is exposed to randomized treatment plus a 30 day window.
- A sensitivity analysis was based on an “on study” censoring scheme which incorporates information throughout the duration of the trial, regardless of a subject’s treatment exposure status.

The primary and sensitivity analyses were based on Cox proportional hazards models, each of which was stratified by trial with a fixed effect for treatment (pooled liraglutide doses or pooled comparators).

The supportive analysis in the T2DM database was based on a Cox proportional hazards model, stratified by trial with fixed effect for treatment, using an “on-treatment” censoring scheme.

RESULTS

WEIGHT MANAGEMENT PROGRAM

Table 3 provides a summary of MACE overall and broken down by trial and treatment group. Based upon the primary censoring scheme (“on treatment”), a total of 17 MACE were observed across the WM program: 8 in 3872 liraglutide subjects (0.2%) and 9 in 2036 comparator subjects (0.4%).

Table 3: Summary of MACE Overall and by Trial in the WM primary analysis

Trial	Liraglutide Arms					Comparator Arms		
	1.2mg	1.8mg	2.4mg	3.0mg	All	Orlistat	Placebo	All
	n/N(%)	n/N(%)	n/N(%)	n/N(%)	n/N(%)	n/N(%)	n/N(%)	n/N(%)
1807	0/95(0.0)	0/90(0.0)	0/93(0.0)	0/93(0.0)	0/371(0.0)	0/95(0.0)	0/98(0.0)	0/193(0.0)
1839	-	-	-	3/2481(0.1)	3/2481(0.1)	-	3/1242(0.2)	3/1242(0.2)
1922	-	3/210(1.4)	-	2/422(0.5)	5/632(0.8)	-	3/212(1.4)	3/212(1.4)
1923	-	-	-	0/212(0.0)	0/212(0.0)	-	1/210(0.5)	1/210(0.5)
3970	-	-	-	0/176(0.0)	0/176(0.0)	-	2/179(1.1)	2/179(1.1)
Overall	0/95(0.0)	3/300(1.0)	0/93(0.0)	3/3384(0.1)	8/3872(0.2)	0/95(0.0)	9/1941(0.5)	9/2036(0.4)

The primary analysis based on the Cox proportional hazards model using an “on treatment” censoring scheme estimated the HR to be 0.4 with 95% CI (0.15, 1.05) as shown in Table 4 below. The sensitivity analysis using an “on study” censoring scheme was consistent with the primary analysis.

Table 4: Meta-analysis Results of MACE in WM

	Liraglutide (N = 3872)	Comparator (N = 2036)	HR (95% CI)
<i>Censoring: On treatment</i>			
MACE (%)	8 (0.2%)	9 (0.4%)	0.40 (0.15, 1.05)
<i>Censoring: On Study</i>			
MACE (%)	10 (0.3%)	9 (0.4%)	0.49 (0.20, 1.23)

TYPE 2 DIABETES MELLITUS PROGRAM

A total of 49 MACE were observed in the T2DM program; 26 MACE in 5498 subjects randomized to liraglutide (0.5%) and 23 MACE in 2735 subjects randomized to the comparator (0.8%). Using an “on treatment” censoring scheme, the estimate of the HR was 0.64 with 95% CI of (0.35, 1.15).

Liraglutide Pharmacokinetics: Comparison between obesity (3.0 mg dose) and type 2 diabetes (1.8 mg dose) population

Office of Clinical Pharmacology

Prepared by: Jayabharathi Vaidyanathan, Ph.D, Immo Zadezensky, Ph.D and Nitin Mehrotra, Ph.D

Executive Summary: The purpose of this document is to provide information regarding the pharmacokinetics (PK) of liraglutide and to provide comparison of liraglutide exposure following administration of 1.8 mg dose in type 2 diabetes (T2DM) program to that following 3.0 mg dose in the obesity program. Body weight was determined to be the significant covariate that affects the clearance of liraglutide and this was consistent between the two programs. Subjects with lower body weight are expected to have a higher liraglutide exposure (AUC) as compared to those with higher body weight. There was substantial overlap in body weight between the T2DM and the obesity programs. Similarly, there was overlap in AUCs observed in the two programs, however the proportion of subjects having higher AUC with 3.0 mg dose appeared to be greater compared to T2DM patients receiving 1.8 mg dose. About 16% of obese subjects receiving the 3.0 mg dose had higher exposure (AUC) than the maximum exposures seen in the T2DM following administration of 1.8 mg dose. Exposure-response analysis conducted to understand the impact of increase in exposure on safety did not reveal any clinically meaningful relationship. Furthermore, analysis of efficacy and safety by body weight categories did not reveal any clinically meaningful trends.

Background: Liraglutide is a glucagon-like-peptide (GLP-1) approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2DM). The maximum recommended dose for T2DM is 1.8 mg. In this application, the sponsor is seeking approval for liraglutide for the following proposed indication:

Liraglutide 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/m² or greater (obese) (1) or
- 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea

The recommended dose is to initiate at 0.6 mg per day for one week. In weekly intervals the dose is to be increased until the maintenance dose of 3.0 mg is reached. Refer to clinical review for details on the dose-finding trial.

Liraglutide Pharmacokinetics (PK):

Liraglutide PK and pharmacodynamics (PD) has been characterized following subcutaneous administration of 1.8 mg under the Victoza program in T2DM subjects and following 3.0 mg dose in obese subjects. The proposed drug product formulation of liraglutide (3.0 mg) used in the obesity development program is similar to the currently marketed formulation (1.8 mg). A population PK analysis was submitted under NDA 22-341 (Victoza) and for the current NDA for obesity (NDA206321). The sponsor is referring to the data provided under the T2DM program to bridge clinical pharmacology and safety information (e.g., QT).

Baseline body weight was the most significant covariate affecting the clearance (CL/F) of liraglutide as determined by the population PK analysis conducted by the sponsor for both programs. The data indicates an increase in liraglutide clearance with increasing body weight. Hence, subjects with lower body weight are expected to have a higher liraglutide exposure (AUC) as compared to those with higher body weight. The PK parameter estimates (e.g., clearance, volume of distribution) obtained from the population PK analysis using data from the obesity program was consistent with those observed with the population PK analysis conducted in T2DM patients.

In the population PK analyses conducted using data from the obesity program, the effect of various covariates on the clearance (CL/F) of liraglutide was analyzed using data from trials 1839 and 1922. The covariates analyzed in addition to baseline body weight were: age, gender, race, ethnicity, dose and glycemic status at baseline (normoglycemia, pre-diabetes, T2DM). Among these, gender was the other significant covariate with males having 24% lower liraglutide exposure than females (after accounting for body weight differences). About 72% of subjects included in the population PK analyses of obesity trials were females. When exposure following administration of 3.0 mg liraglutide was compared in obese subjects in Trial 1922 with different baseline glycemic status, there appears to be about 16% lower exposure in diabetic obese subjects as compared to obese subjects with normal glycemic or prediabetic status. None of the other covariates examined were found to have a significant effect on liraglutide PK. No dose adjustments are recommended based on gender or diabetic status.

Comparison of exposure (AUC and C_{max}) of liraglutide: 1.8 mg dose [T2DM (NDA 22-341)] versus 3.0 mg dose [obesity (NDA206321)]:

It should be noted that the doses are different in the two programs, with the dose in the obesity program being higher (3.0 mg) as compared to the T2DM program (1.8 mg).

AUC comparison: In order to relate the observed exposure of liraglutide in the obesity to that of T2DM population, it is important to understand the body weight distribution in the two programs as body weight was the important covariate affecting the clearance of liraglutide. The body weight range of the subjects in population PK analysis conducted for the T2DM and obesity program was 44 – 163 kg and 60 kg – 234 kg, respectively. Figure 1 shows the body weight distribution in the two programs. As shown, although there was substantial overlap in the subject's body weight in the two development programs, as expected, the proportion of subjects with higher body weight was greater in the obesity program as compared to that in T2DM program.

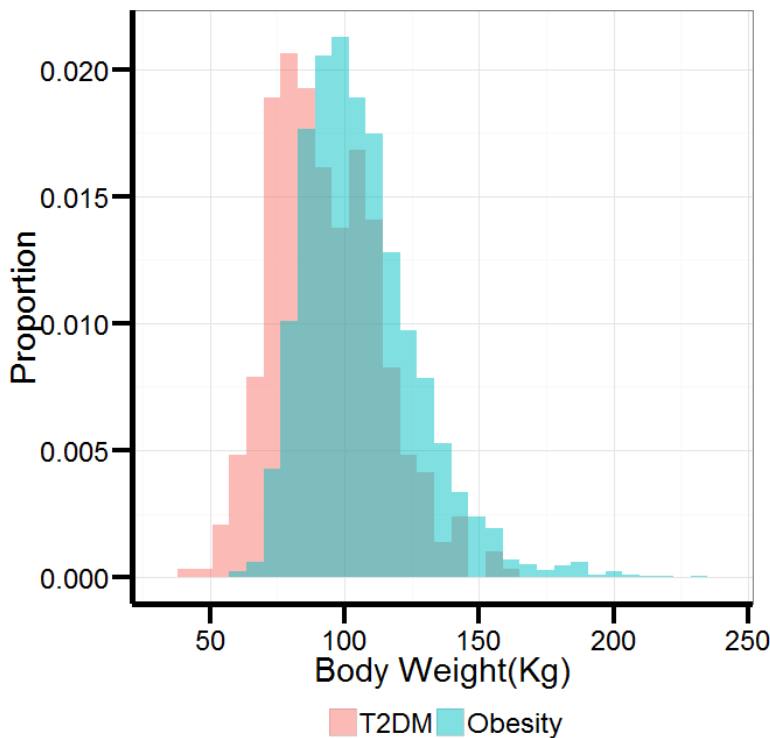


Figure 1: Body weight distribution in the T2DM and obesity programs

Figure 2 shows the correlation of body weight to the AUC for patients receiving 3.0 mg dose in the obesity trials and Figure 3 shows the distribution of AUC in the T2DM and obesity programs. There is considerable variability in the observed exposure of liraglutide (Figure 2 and 3). Although overlap in AUCs was observed in the two programs, the proportion of subjects in the obesity program having higher AUC at 3.0 mg dose appeared to be greater compared to T2DM patients receiving 1.8 mg dose (Figure 3). About 16% of subjects in the obesity trials receiving the 3.0 mg dose had higher exposure than the maximum exposure observed in the T2DM trial ($> \sim 4$ mg.h/L) with 1.8 mg dose (Figure 2 and 3). This observation is consistent with the Figure 1, which shows a significant overlap of body weights between the two populations. Thus, subjects with similar body weight will likely have a higher exposure if the dose is increased from 1.8 to 3.0 mg.

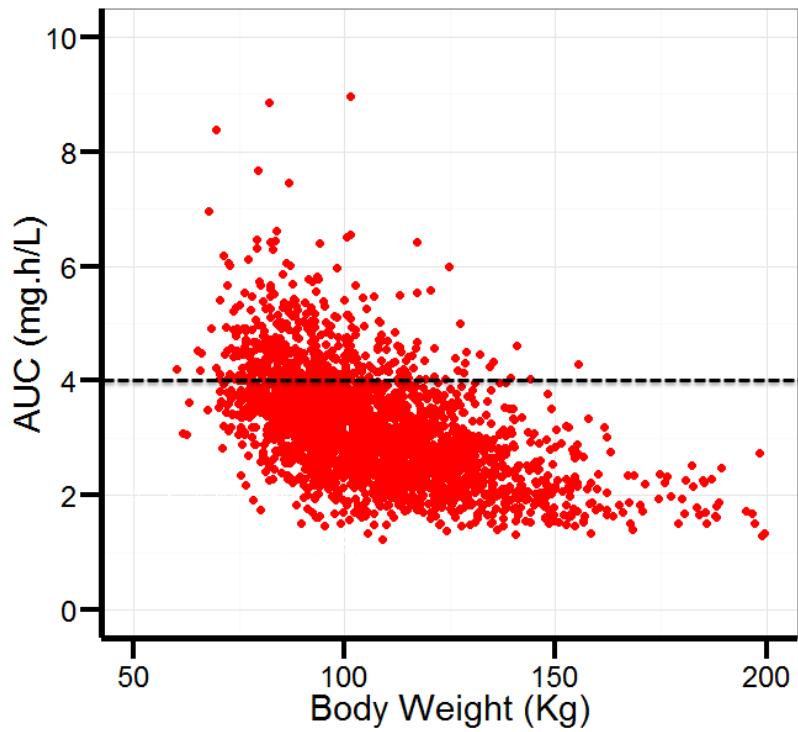


Figure 2: Correlation of liraglutide exposure to body weight in Obesity trials. Data for subjects receiving 3.0 mg dose is shown.

The horizontal line shows the maximum exposure level observed in the T2DM population receiving 1.8 mg dose.

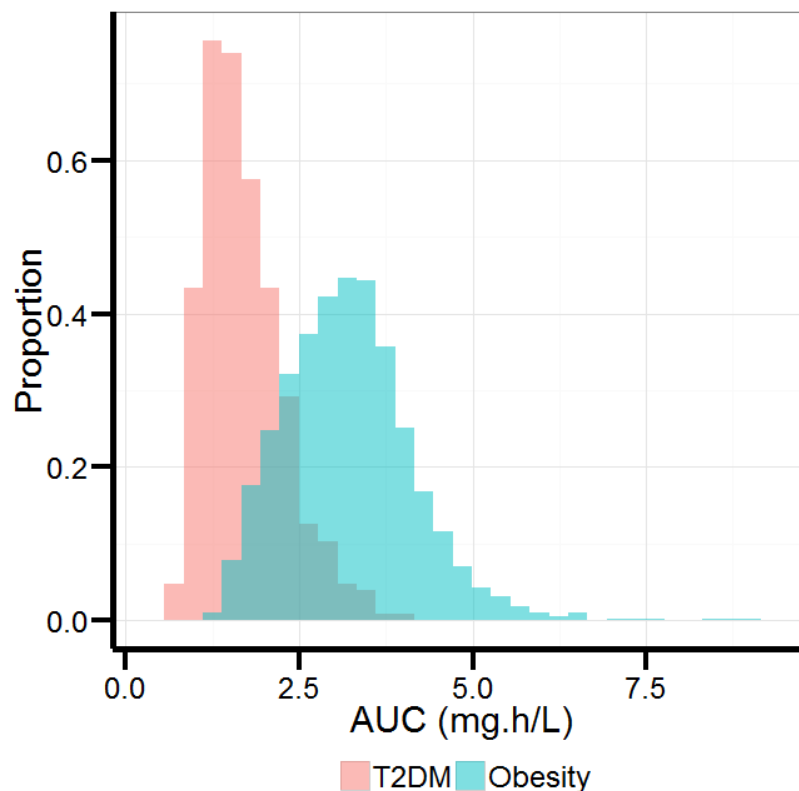


Figure 3: Distribution of liraglutide exposure obtained from population PK analysis following administration of 1.8 mg dose in T2DM program (Pink) and 3.0 mg dose in obesity program (Blue)

Note: The output from the T2DM and obesity population PK analyses was used for this purpose. All the patients in the T2DM population PK analysis were used. For patients on 1.8 mg dose, AUC was calculated using the formula, $AUC = (1.8/CL)$. There were 235 patients at 1.2 mg in the T2DM population. For these patients, the clearance (L/h) obtained from the population PK analysis was used to calculate the AUC following 1.8 mg dose ($AUC = Dose/CL$). In case of obesity trials, the AUC was calculated using individual clearance values for the patients receiving the 3.0 mg dose.

C_{max} comparison: The sponsor compared the observed liraglutide maximum concentrations (C_{max}) from various trials – cardiac electrophysiology (QTc) trial (NN211-1644, conducted under T2DM NDA program), C_{max} sub study in 1839, 1807 and trial 3630 (Figure 4). There appears to be substantial overlap in the observed individual liraglutide concentrations in these studies conducted following administration of either 1.8 mg or 3.0 mg dose.

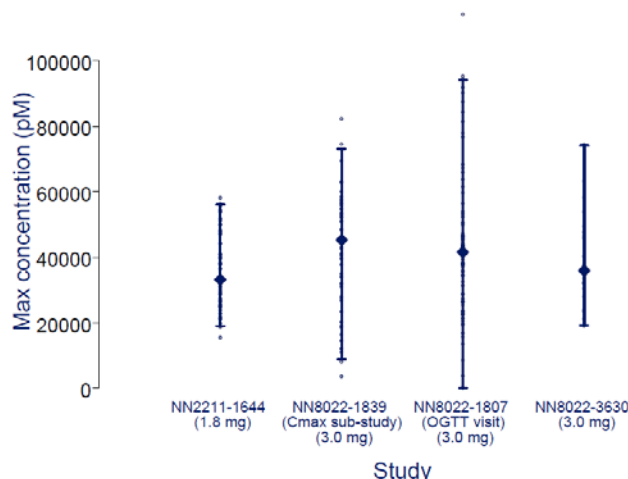


Figure 4: C_{\max} values obtained from various trials. Data are individual C_{\max} values with medians and 2.5-97.5% percentiles

Source: Sponsor report: Summary of Clinical pharmacology, page 45

Exposure-Response analysis

Since some obese subjects with lower body weight have an increased exposure with liraglutide 3.0 mg (Figure 2), the Agency requested the sponsor to conduct an exposure-response analyses for adverse events such as nausea (all grade and moderate-severe), vomiting (all grade and moderate-severe) and hypoglycemia. The Agency also requested sponsor to conduct efficacy and safety analysis based on baseline body weight. In addition, since patients lose body weight over time while on treatment with liraglutide, and clearance is related to body weight, there is a possibility that the drug exposure can increase over time based on the magnitude of weight loss. This increase in drug exposure with weight loss can potentially lead to higher adverse events in patients experiencing higher weight loss. Therefore, Agency recommended the sponsor to conduct an analysis of adverse events based on magnitude of weight loss and also evaluate if there is any time dependency of occurrence.

Sponsor's analysis of exposure-response analysis data from the obesity trials did not reveal any significant relationship with observed adverse events such as nausea, vomiting, and hypoglycemia. The adverse events profile was also not different for different baseline body weight quartiles. Moreover, there appeared to be no trend in the efficacy by baseline body weight.

Evaluations of adverse event based on the weight loss categories also did not reveal any differences between the different groups. Further, adverse events over time in patients treated with liraglutide did not show an increase with treatment duration. Most of the events occurred within 0-3 months and did not increase in frequency over the duration of the trial.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Clinical Trials

Date: August 14, 2014

Reviewer: Christian Hampp, PhD
Division of Epidemiology I

Team Leader: Diane K. Wysowski, PhD, MPH
Division of Epidemiology I

Deputy Division Director: David Shih, MD, MS
(Acting) Division of Epidemiology I

Drug Name: liraglutide (Saxenda, Victoza)

Subject: Analysis of cancers observed in clinical trials of liraglutide
- revised

Application Type/Number: NDA 206321 (Saxenda), NDA 22341 (Victoza)

Applicant/sponsor: Novo Nordisk, Inc.

OSE RCM #: 2014-1200

TSI #: 894 (thyroid tumors with GLP-1 analogs)

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EXECUTIVE SUMMARY

This Division of Epidemiology-I review of cancer incidence rates in the liraglutide clinical development program includes internal across-trial calculations of incidence rate ratios and external comparisons of observed and expected cancer incidence rates to help the Division of Metabolism and Endocrinology Products (DMEP) assess the safety of liraglutide for the proposed use as a weight-loss agent.

On July 9, 2014, the sponsor provided age-, sex-, trial-, and exposure-specific follow-up time and counts of malignant neoplasms observed during phases 2 and 3 of the liraglutide weight management and diabetes programs. Follow-up was calculated according to the intent-to-treat principle with a preference given to liraglutide, that is, any person-time after first liraglutide exposure was categorized as exposed to liraglutide, even in the case of re-randomization to a comparator arm in a second study phase. The sponsor provided data up to the 120-day safety update cut-off date, November 11, 2013, and grouped the data according to three clinical trial pools: weight management, diabetes, and their combination. The sponsor split the weight management pool into two to reflect that only four of the five trials in that pool included adjudication for cancer outcomes. Cancer outcomes were not adjudicated in the trials included in the diabetes pools.

For internal comparisons, I calculated rate ratios (RR_{MH}) and rate differences (RD_{MH}) for thyroid, female breast, and colorectal cancer according to the Mantel-Haenszel method, separately for each trial pool. I further calculated RR_{MH} and RD_{MH} for all reported cancer types using only adjudicated malignant events in the weight management pool and non-adjudicated malignant and unspecified events in all liraglutide trial pools.

For external comparisons, I compared sex- and exposure-specific cancer incidence rates observed in clinical trials to expected rates based on population level data extracted from the National Cancer Institute's Surveillance, Epidemiology, and End Results database. I calculated sex- and exposure-specific standardized incidence ratios, which summarize observed vs. expected event counts using age- and sex-standardization.

Clinical trial data with event adjudication in the weight management pool suggest the possibility of increased rates of thyroid cancer (RR_{MH} , 1.90; 95% CI, 0.27-13.35) and female breast cancer not including *in situ* (RR_{MH} , 2.98; 95% CI, 0.69-12.81) among patients exposed to liraglutide compared with patients in comparison arms. However, these associations did not reach statistical significance. Furthermore, rate ratios for all cancers grouped together were not increased and several cancer types occurred less frequently with liraglutide. This pattern would not be unexpected in a multiple testing situation in the absence of a treatment effect and these data can neither confirm nor exclude a causal role of liraglutide in the etiology of thyroid and female breast cancer.

In the clinical trial program of liraglutide, thyroid cancers occurred somewhat more frequently than what would be expected in an age- and sex-standardized U.S. population. This was not the case for other cancers to the same extent. Limitations suggest that comparisons between clinical trial data and an external reference population be interpreted with caution.

Section 6 of this review contains recommendations to DMEP.

1 INTRODUCTION

This Division of Epidemiology-I (DEPI-I) review of cancer incidence rates in the liraglutide clinical development program includes internal across-trial calculations of incidence rate ratios and external comparisons of observed and expected cancer incidence rates to help the Division of Metabolism and Endocrinology Products (DMEP) assess the safety of liraglutide for the proposed use as a weight-loss agent.

1.1 BACKGROUND

During the review of clinical trial data for liraglutide in its proposed indication as a weight-loss agent, staff of DMEP noted numeric imbalances in breast cancer and colorectal (benign) and thyroid neoplasms (malignant and benign) compared to placebo. In addition, pooled data from the liraglutide diabetes program demonstrated imbalances in thyroid and breast cancers. DMEP consulted DEPI-I for background incidence rates of these neoplasms, DEPI-I's opinion regarding the likelihood of liraglutide contributing to the observed imbalances, and recommendations including, but not limited to, risk management, labeling, monitoring, and post-marketing studies.

1.2 REGULATORY HISTORY

Liraglutide (Victoza, Novo Nordisk, Inc., NDA 22341) was approved on January 25, 2010, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Currently, the FDA is reviewing a New Drug Application for Saxenda (NDA 206321), a higher dose version of liraglutide proposed for use as a weight-loss agent.

In the Integrated Summary of Safety from November 27, 2013, the sponsor calculated rates of selected types of Event Adjudication Committee (EAC) confirmed neoplasms (breast (malignant and *in situ*), colorectal (benign), pancreatic, and thyroid cancer). The sponsor detected imbalances not favoring liraglutide for breast cancer and benign colorectal neoplasms and a slight imbalance for thyroid cancer. The sponsor did not stratify analyses to incorporate variable treatment allocation ratios between clinical trials. Thus, the comparison of pooled data across clinical trials may not have preserved the benefits of randomization.

1.3 PRODUCT LABELING

The labeling for Victoza contains the following boxed warning:

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid

ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)].

2 REVIEW METHODS AND MATERIALS

This review includes internal and external comparisons of malignancies observed in various trial pools in the clinical development program of liraglutide.

2.1 DATA REQUEST

On June 20, 2014, FDA requested from the sponsor age-, sex-, and trial-specific follow-up time and counts of malignant neoplasms observed during phases 2 and 3 of the liraglutide weight management and diabetes programs. The sponsor submitted a proposal on how to address the request on June 23, 2014, which FDA accepted on the same day. The sponsor provided the requested information on July 8, 2014, and a revised version on July 9, 2014. Following another information request on August 12, 2014, the sponsor explained on August 13, 2014, that the July 9, 2014, response inadvertently omitted one event each of colorectal carcinoma, bone metastasis, and lung metastasis. These events occurred in comparator patients in one of the diabetes trials and were included in the current, revised, analyses.

2.2 CLINICAL TRIAL POOLS

Clinical trials in the liraglutide development program (diabetes and weight management programs) included phase 2 and 3 trials with all doses of liraglutide (0.6, 1.2, 1.8, 2.4, and 3.0 mg) and placebo, orlistat, or antidiabetic drugs as comparators. Only comparator arms with drugs approved by the FDA were included in this analysis, which led to the exclusion of insulin degludec and semaglutide comparator arms. Appendix Table 1 contains an overview of trials in the weight management program.

When computing follow-up times, the sponsor applied the intent-to-treat principle with a preference for liraglutide, that is, all person-time occurring after first exposure was categorized as exposed to liraglutide. In trials that featured re-randomization after a certain period (e.g., after 56 weeks in trial 1839) all person-time for patients originally randomized to liraglutide was attributed to liraglutide, regardless of re-randomization to liraglutide or comparator. Follow-up included time when patients were part of the protocol-defined trial (including extensions and observational follow-up), calculated as time from first drug date until last date/date of last visit/date of last contact, whichever came last. The sponsor provided data up to the 120-day safety update cut-off date, November 11, 2013.

FDA requested grouping of the data according to three clinical trial pools: weight management, diabetes, and their combination. The sponsor proposed to split the weight management pool into two (Pools 1a and 1b in Table 1), to reflect that only some of the trials included adjudication for cancer outcomes, as described in Section 2.3. The analyses presented in this document were conducted in the following trial pools:

Table 1. Clinical Trial Pools

Pool	Description	Number of trials
1a	All weight management trials	5
1b	Weight management trials with adjudication of cancer events	4
2	All diabetes trials	25
3	Combination of 1a and 2	30

Appendix Table 2 lists individual trials included in each pool and trial- and exposure-specific cumulative follow-up times.

2.3 STUDY OUTCOMES

Outcomes of interest in this analysis were newly diagnosed malignant neoplasms, specifically, invasive thyroid, colorectal, and female breast cancers, and also *in situ* female breast neoplasms.

An independent external EAC adjudicated neoplasms in four out of five trials in the weight management program (Pool 1b, Trials 1839, 1922, 1923, and 3970, see Appendix Table 2). None of the trials that constituted the liraglutide diabetes program included adjudication of neoplasms. To capture malignancy events in all trial pools, the sponsor conducted pre-defined Medical Dictionary for Regulatory Activities (MedDRA) searches using Preferred Terms within the Standardized MedDRA Query (SMQ) “Malignant or unspecified tumors” (MedDRA version 15.1). The sponsor grouped the individual Preferred Terms included in the SMQ ‘Malignant or unspecified tumors’ into categories similar to those used by the EAC in the weight management development program. These categories included: bladder, breast, colorectal, female reproductive, liver, lymphomas, male reproductive, oral, pancreatic, skin, and thyroid neoplasms. The sponsor further created a “miscellaneous” category for neoplasms that could not easily be classified into one of the above categories. For the presentation of breast neoplasms, the sponsor defined the SMQ “Breast neoplasms, malignant and unspecified,” which included a specific Preferred Term to identify *in situ* cases, as requested by the FDA.

According to the sponsor, the MedDRA-based tables included all reported events, but output based on event adjudication only included index events. In the situation where two or more events were linked by the EAC and one of the events was selected as the index event, only this event was counted.

2.4 STATISTICAL ANALYSES

2.4.1 Internal comparisons – randomized

Separately for each clinical trial pool listed in Table 1, I calculated rate ratios (RR_{MH}) and rate differences (RD_{MH}) for thyroid, female breast, and colorectal cancer according to the Mantel-Haenszel method.¹ This method represents a stratified analysis that computes

¹ Rothman, K.J., Greenland, S., & Lash, T.L. (2008). *Modern Epidemiology*, 3rd Edition, p273. Philadelphia, PA: Lippincott, Williams & Wilkins.

weighted averages across strata (trials), maintains the benefits of randomization, and accounts for different drug-comparator allocation ratios.

I further calculated RR_{MH} and RD_{MH} for all reported cancers using only adjudicated malignant events in the weight management pool (Pool 1b) and non-adjudicated, MedDRA coded malignant and unspecified events in all liraglutide trials (Pool 3).

Clinical trials with zero events of a cancer of interest were included in calculations of RD_{MH} but not in calculations of RR_{MH} . No continuity corrections were used in any of the calculations. The analyses were conducted using Episheet,² and all calculations of RR_{MH} and 95% confidence intervals were verified in SAS 9.3 using a SAS macro for the analysis of stratified clinical trials data.³

2.4.2 External comparisons – not randomized

I compared sex- and exposure-specific cancer incidence rates observed in clinical trials to expected rates based on population level data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.⁴ This database provided age- and sex-specific rates of invasive thyroid cancer, invasive female breast cancer not including *in situ*, *in situ* breast neoplasm, and invasive colorectal cancer for the years 2007 through 2011.

For each clinical trial pool listed in Table 1, I calculated sex- and exposure-specific standardized incidence ratios (SIRs) and 95% confidence intervals. SIRs summarize observed vs. expected event counts using age- and sex-standardization, that is, expected clinical trial event counts that would be observed in a sample of the U.S. population with the age- and sex-distribution and cumulative follow-up time of the clinical trials. Statistical significance was assumed when the 95% confidence intervals of the SIRs excluded the null value of 1.0. Calculations of SIRs and 95% confidence intervals were conducted using Open Epi.⁵

3 REVIEW RESULTS

3.1 INTERNAL COMPARISONS

3.1.1 Thyroid Cancer

Across all clinical trials (Table 2, Pool 3), 62 malignant and unspecified thyroid neoplasms (MedDRA) were counted among patients exposed to liraglutide and 10 among

² Rothman K. Episheet: Spreadsheet for the analysis of Epidemiologic Data. www.krothman.org/episheet.xls, accessed July 10, 2014.

³ Honda Y, Macaluso M, Brill I. A SAS Program for the Stratified Analysis of Follow-Up Data. *J Occup Health* 1998; 40: 154-157

⁴ National Cancer Institute. Surveillance, Epidemiology, and End Results, Fast Stats interactive tool. <http://seer.cancer.gov/faststats/selections.php?series=cancer>, accessed July 10, 2014.

⁵ Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 2.3.1. www.OpenEpi.com, updated June 23, 2011, accessed July 10, 2014.

patients in comparator arms, resulting in a statistically significant RR_{MH} of 2.00 (95% CI, 1.02-3.91). In the weight management pool with trials that included adjudication (Pool 1b) 15 and 4 malignant and unspecified events (MedDRA) were counted among patients on liraglutide or comparator, respectively, but only 4 and 1 events, respectively, were positively adjudicated as malignant events. Mantel-Haenszel-adjusted rate ratios were largely consistent across trial pools, but did not reach statistical significance, especially when only positively adjudicated malignant events were analyzed in Pool 1b (RR_{MH} , 1.90; 95% CI, 0.27-13.35). Of note, all 4 adjudicated events among patients exposed to liraglutide were categorized as papillary thyroid carcinoma and the event that occurred in the comparator arm (placebo) was categorized as medullary thyroid carcinoma. Effect estimates were somewhat higher for men compared with women, but only one male thyroid cancer case (exposed to liraglutide) was positively adjudicated.

Table 2. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Thyroid Neoplasms Observed in Clinical Trials with Liraglutide

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	Events, n	16	4	6	0	10	4
	Pt-years	5,325.6	2,484.3	1,465.0	663.2	3,860.6	1,821.1
	RR _{MH}	1.95		--		1.28	
	95% CI	0.67-5.71		--		0.41-3.98	
	RD _{MH}	15.51		41.74		6.19	
1b	Events, n	15	4	5	0	10	4
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	1.86		--		1.28	
	95% CI	0.63-5.45		--		0.41-3.98	
	RD _{MH}	15.28		39.28		6.81	
2	Events, n	46	6	24	3	22	3
	Pt-years	6,747.2	2,028.4	3,718.9	1,171.6	3,028.3	856.8
	RR _{MH}	2.03		2.63		1.70	
	95% CI	0.86-4.78		0.73-9.46		0.51-5.64	
	RD _{MH}	34.44		42.40		28.37	
3	Events, n	62	10	30	3	32	7
	Pt-years	12,072.8	4,512.7	5,183.9	1,834.8	6,888.9	2,677.9
	RR _{MH}	2.00		3.54		1.48	
	95% CI	1.02-3.91		1.02-12.33		0.65-3.36	
	RD _{MH}	24.01		42.16		13.29	
Adjudicated*							
1b	Events, n	4	1	1	0	3	1
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	1.90		--		1.51	
	95% CI	0.27-13.35		--		0.20-11.55	
	RD _{MH}	4.50		7.86		3.37	

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.1.2 Female Breast Cancer

This section describes two analyses for female breast cancer: breast cancer excluding *in situ* (3.1.2.1) and *in situ* neoplasms (3.1.2.2).

3.1.2.1 Female Breast Cancer (excluding *in situ*)

Mantel-Haenszel rate ratios for female breast neoplasms (excluding *in situ*, Table 3) across the different clinical trial pools ranged from 1.52 (95% CI, 0.17-13.36) in Pool 2 (malignant and unspecified) to 2.98 (95% CI, 0.69-12.81) when only positively adjudicated malignant events in Pool 1b were analyzed. None of the associations reached statistical significance.

Table 3. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Female Breast Neoplasms (excluding *in situ*) Observed in Clinical Trials with Liraglutide

Pool		Females	
		Lira.	Comp.
MedDRA*			
1a	Events, n	14	3
	Pt-years	3,860.6	1,821.1
	RR _{MH}	2.20	
	95% CI	0.64-7.57	
	RD _{MH}	20.03	
1b	Events, n	13	3
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.07	
	95% CI	0.60-7.15	
	RD _{MH}	19.64	
2	Events, n	9	1
	Pt-years	3,028.3	856.8
	RR _{MH}	1.52	
	95% CI	0.17-13.36	
	RD _{MH}	6.87	
3	Events, n	23	4
	Pt-years	6,888.9	2,677.9
	RR _{MH}	2.01	
	95% CI	0.69-5.89	
	RD _{MH}	15.82	
Adjudicated*			
1b	Events, n	12	2
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.98	
	95% CI	0.69-12.81	
	RD _{MH}	24.34	

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.1.2.2 Female Breast Neoplasm - *in situ*

Across the different clinical trial pools, Mantel-Haenszel-adjusted rate ratios for *in situ* female breast neoplasm (Table 4) ranged from 1.39 (95% CI, 0.15-13.40) when only positively adjudicated events in Pool 1b were analyzed to 2.09 (95% CI, 0.26-17.03) in Pools 1a, 1b, and 3 (MedDRA). No *in situ* breast neoplasms occurred in the diabetes trials (Pool 2) and none of the associations in other trial pools reached statistical significance.

Table 4. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for *in situ* Female Breast Neoplasms Observed in Clinical Trials with Liraglutide

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	Events, n	4	1
	Pt-years	3,860.6	1,821.1
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	6.08	
1b	Events, n	4	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	6.69	
2	Events, n	0	0
	Pt-years	3,028.3	856.8
	RR _{MH}	--	
	95% CI	--	
	RD _{MH}	0	
3	Events, n	4	1
	Pt-years	6,888.9	2,677.9
	RR _{MH}	2.09	
	95% CI	0.26-17.03	
	RD _{MH}	4.13	
Adjudicated			
1b	Events, n	3	1
	Pt-years	3,442.5	1,669.2
	RR _{MH}	1.39	
	95% CI	0.15-13.40	
	RD _{MH}	2.42	

3.1.3 Colorectal Cancer

Across all clinical trials (Table 5, Pool 3), 10 malignant and unspecified colorectal neoplasms (MedDRA) occurred among patients exposed to liraglutide and 3 among patients in comparator arms, resulting in a statistically non-significant RR_{MH} of 1.31 (95% CI, 0.36-4.83). In the weight management pool with trials that included adjudication (Pool 1b) 2 and 0 malignant and unspecified colorectal neoplasms (MedDRA) were counted in patients on liraglutide or comparator, respectively; however, 2 and 1 events, respectively, were positively adjudicated malignant cases. No increased risk was evident in the analysis of positively adjudicated events in Pool 1b (RR_{MH} , 0.82; 95% CI, 0.07-9.90), but the 95% confidence interval was wide.

Table 5. Combined and Sex-Specific Mantel-Haenszel-Adjusted Rate Ratios, 95% Confidence Intervals, and Mantel-Haenszel-Adjusted Rate Differences (per 10,000 person-years) for Colorectal Neoplasms Observed in Clinical Trials with Liraglutide

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	Events, n	2	0	1	0	1	0
	Pt-years	5,325.6	2,484.3	1,465.0	663.2	3,860.6	1821.1
	RR _{MH}	--		--		--	
	95% CI	--		--		--	
	RD _{MH}	3.36		4.92		2.60	
1b	Events, n	2	0	1	0	1	0
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1669.2
	RR _{MH}	--		--		--	
	95% CI	--		--		--	
	RD _{MH}	3.68		5.34		2.86	
2	Events, n	8	3	5	1	3	2
	Pt-years	6,747.2	2,028.4	3,718.9	1,171.6	3,028.3	856.8
	RR _{MH}	1.05		1.91		0.52	
	95% CI	0.27-4.01		0.21-17.36		0.09-2.96	
	RD _{MH}	0.74		8.20		-12.64	
3	Events, n	10	3	6	1	4	2
	Pt-years	12,072.8	4,512.7	5,183.9	1,834.8	6,888.9	2,677.9
	RR _{MH}	1.31		2.22		0.73	
	95% CI	0.36-4.83		0.25-19.83		0.14-3.71	
	RD _{MH}	2.18		7.01		-2.28	
Adjudicated*							
1b	Events, n	2	1	1	1	1	0
	Pt-years	4,766.2	2,286.9	1,323.7	617.7	3,442.5	1,669.2
	RR _{MH}	0.82		0.32		--	
	95% CI	0.07-9.90		0.01-7.62		--	
	RD _{MH}	-0.81		-11.40		2.86	

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

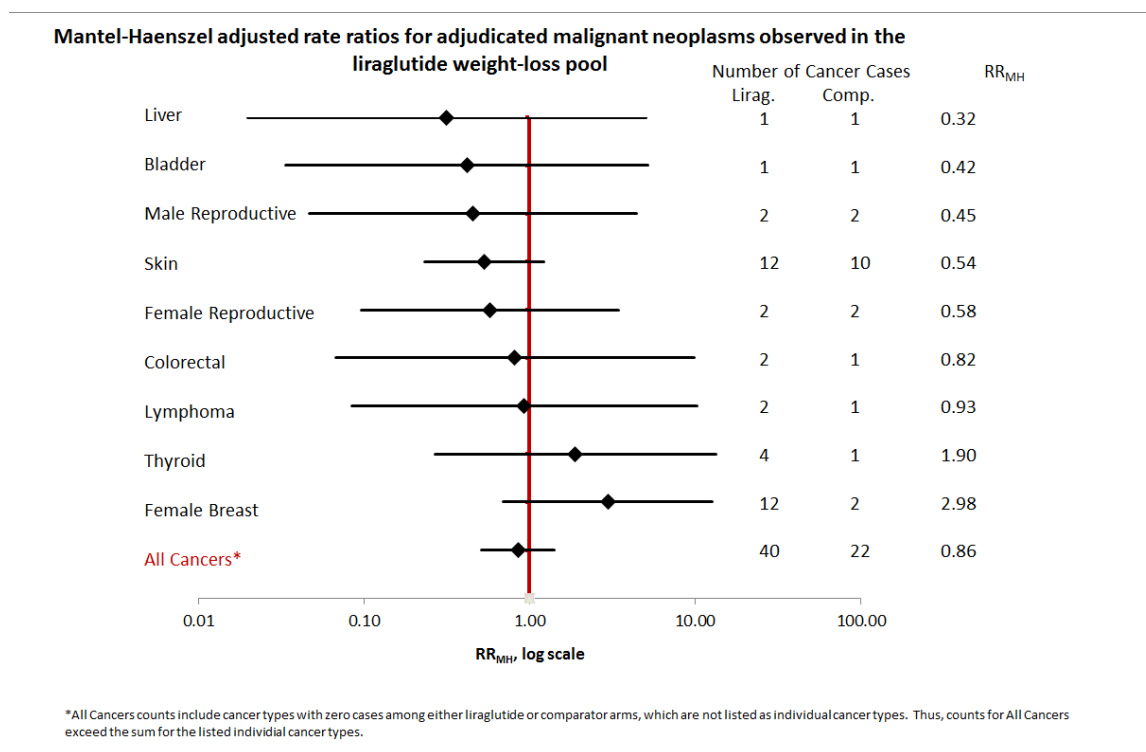
3.1.4 All Cancers

This section summarizes Mantel-Haenszel-adjusted rate ratios by cancer type for all cancers diagnosed in Pool 1b (adjudicated, Section 3.1.4.1) and malignant and unspecified neoplasms in Pool 3 (MedDRA, Section 3.1.4.2).

3.1.4.1 Trial Pool 1b - Adjudicated Malignant Cases

Among all cancer types analyzed in Pool 1b (Figure 1), only thyroid cancer and female breast cancer (excluding *in situ*) occurred more frequently among patients exposed to liraglutide compared with patients in comparator arms. Liraglutide was not associated with an increased risk for all adjudicated malignant cancers combined (RR_{MH} , 0.86; 95% CI, 0.52-1.42), but the 95% confidence interval includes the possibility of a modest increase or decrease in cancer risk. Event counts were small for most cancer types, resulting in wide confidence intervals.

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

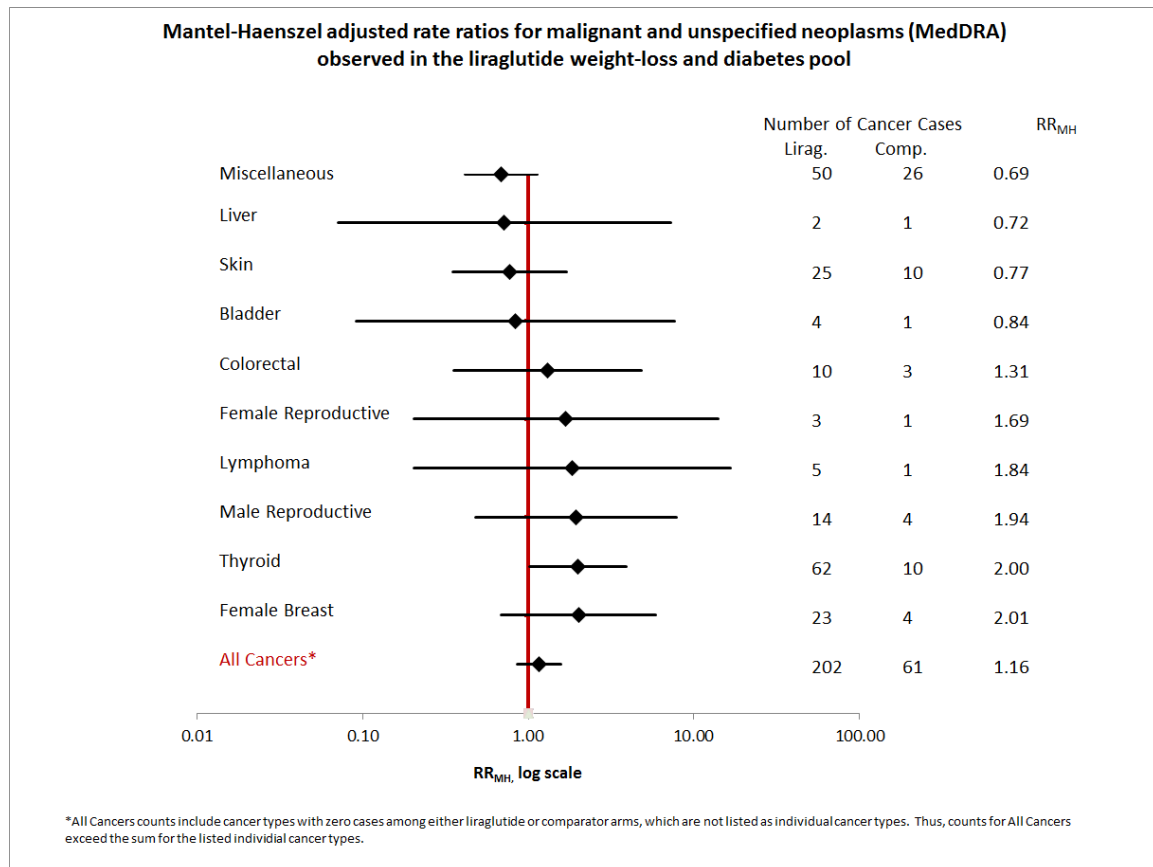


3.1.4.2 Trial Pool 3 – Cases based on MedDRA

Across the liraglutide trials in the weight management and diabetes pool (Pool 3, Figure 2), 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). These events were detected using MedDRA coding, without adjudication. Mantel-Haenszel-adjusted rate ratios were elevated for malignant and unspecified

neoplasms of the male and female reproductive systems, thyroid, female breast (excluding *in situ*), lymphoma, and colorectal neoplasms. Only the type-specific association for malignant and unspecified thyroid neoplasm reached statistical significance (RR_{MH} , 2.00; 95% CI, 1.02-3.91).

Figure 2. Mantel-Haenszel-Adjusted Rate Ratios for Malignant and Unspecified Neoplasms (MedDRA) Observed in the Liraglutide Weight Management and Diabetes Pool



3.2 EXTERNAL COMPARISONS

3.2.1 Thyroid Cancer

Across all study pools, regardless of sex, exposure status, or method of ascertainment (MedDRA or EAC adjudication), thyroid neoplasms were more common in the liraglutide clinical trials than what would be expected in the U.S. population with a comparable sex- and age distribution (Table 6). Standardized incidence ratios were highest for males exposed to liraglutide in the diabetes program (SIR, 51.00, 95% CI, 33.43-74.73) where 24 malignant and unspecified MedDRA cases occurred but only 0.47 malignant cases were expected. Smaller counts of EAC-adjudicated malignant thyroid neoplasms in the weight management pool 1b resulted in smaller, but sometimes still statistically significant, SIRs (e.g., liraglutide, both sexes: SIR, 3.43; 95% CI, 1.09-8.27).

Standardized incidence ratios were consistently higher among patients exposed to liraglutide compared to patients in comparator arms.

Table 6. Number of Thyroid Neoplasms Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	n(obs.)	16	4	6	0	10	4
	n(exp.)	1.31	0.61	0.16	0.07	1.15	0.54
	SIR	12.24	6.55	38.69	--	8.68	7.36
	95% CI	7.24-19.45	2.08-15.80	15.68-80.46	--	4.41-15.47	2.34-17.75
1b	n(obs.)	15	4	5	0	10	4
	n(exp.)	1.17	0.56	0.14	0.06	1.03	0.50
	SIR	12.85	7.14	35.43	--	9.75	8.04
	95% CI	7.47-20.73	2.27-17.21	12.98-78.54	--	4.95-17.38	2.55-19.39
2	n(obs.)	46	6	24	3	22	3
	n(exp.)	1.44	0.42	0.47	0.15	0.97	0.28
	SIR	31.91	14.17	51.00	20.29	22.65	10.89
	95% CI	23.63-42.19	5.74-29.47	33.43-74.73	5.16-55.20	14.56-33.74	2.77-29.64
3	n(obs.)	62	10	30	3	32	7
	n(exp.)	2.75	1.03	0.63	0.21	2.12	0.82
	SIR	22.55	9.67	47.94	13.96	15.07	8.54
	95% CI	17.44-28.72	4.91-17.24	32.94-67.58	3.55-37.99	10.48-21.02	3.74-16.90
Adjudicated*							
1b	n(obs.)	4	1	1	0	3	1
	n(exp.)	1.17	0.56	0.14	0.06	1.03	0.50
	SIR	3.43	1.78	7.09	--	2.92	2.01
	95% CI	1.09-8.27	0.09-8.80	0.35-34.95	--	0.74-7.96	0.10-9.91

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.2.2 Female Breast Cancer

3.2.2.1 Female Breast Cancer (excluding *in situ*)

Female breast neoplasms (excluding *in situ*) occurred somewhat more commonly than expected among women exposed to liraglutide and somewhat less commonly than expected among women in comparator arms. Adjudication of cancer events did not alter these associations. In the weight management pool (Pool 1b), 12 EAC-adjudicated malignant events occurred among women exposed to liraglutide, where 6.23 events would be expected (SIR, 1.92; 95% CI, 1.04-3.27). Two events occurred in the comparator arms, where 3.02 events would be expected (SIR, 0.66; 95% CI, 0.11-2.19). Standardized incidence ratios were somewhat higher in the weight management pools (Pools 1a and 1b), compared with the diabetes pool (Pool 2).

Table 7. Number of Female Breast Neoplasms (not including *in situ*) Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Females	
		Lira.	Comp.
MedDRA*			
1a	n(obs.)	14	3
	n(exp.)	6.98	3.27
	SIR	2.01	0.92
	95% CI	1.14-3.29	0.23-2.50
1b	n(obs.)	13	3
	n(exp.)	6.23	3.02
	SIR	2.09	0.99
	95% CI	1.16-3.48	0.25-2.70
2	n(obs.)	9	1
	n(exp.)	8.14	2.39
	SIR	1.11	0.42
	95% CI	0.54-2.03	0.02-2.07
3	n(obs.)	23	4
	n(exp.)	15.12	5.66
	SIR	1.52	0.71
	95% CI	0.99-2.25	0.22-1.71
Adjudicated*			
1b	n(obs.)	12	2
	n(exp.)	6.23	3.02
	SIR	1.92	0.66
	95% CI	1.04-3.27	0.11-2.19

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.2.2.2 Female Breast Neoplasm - *in situ*

In situ female breast neoplasms were not reported during the diabetes program (Pool 2), and were relatively uncommon overall. Regardless, SIRs matched the pattern observed for invasive female breast cancers (Section 3.2.2.1), with modestly higher event counts observed than expected in the weight management pools (Pools 1a and 1b) and somewhat higher SIRs in women exposed to liraglutide compared with women in comparator arms. None of the SIRs reached statistical significance.

Table 8. Number of *in situ* Female Breast Neoplasms Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Females	
		Lira.	Comp.
MedDRA			
1a	n(obs.)	4	1
	n(exp.)	1.99	0.94
	SIR	2.01	1.06
	95% CI	0.64-4.84	0.05-5.25
1b	n(obs.)	4	1
	n(exp.)	1.78	0.87
	SIR	2.25	1.16
	95% CI	0.72-5.43	0.06-5.70
2	n(obs.)	0	0
	n(exp.)	2.25	0.65
	SIR	--	--
	95% CI	--	--
3	n(obs.)	4	1
	n(exp.)	4.24	1.59
	SIR	0.94	0.63
	95% CI	0.30-2.27	0.03-3.10
Adjudicated			
1b	n(obs.)	3	1
	n(exp.)	1.78	0.87
	SIR	1.69	1.16
	95% CI	0.43-4.59	0.06-5.70

3.2.3 Colorectal Cancer

Observed counts of colorectal neoplasms were close to what would be expected in most study pools (Table 9). This was especially notable among EAC-adjudicated malignant events in the weight management pool (Pool 1b), where SIRs among both patients exposed to liraglutide and patients in comparator arms were very close to 1.0. Compared with adjudicated malignant cancers, event counts according to MedDRA (malignant and unspecified neoplasms) and resulting SIRs were slightly higher but none of the SIRs reached statistical significance.

Table 9. Number of Colorectal Neoplasms Observed in Clinical Trials with Liraglutide versus Expected Cases Based on U.S. SEER Population Data and Age- and Sex-Standardized Incidence Ratios and 95% Confidence Intervals

Pool		Both Sexes		Males		Females	
		Lira.	Comp.	Lira.	Comp.	Lira.	Comp.
MedDRA*							
1a	n(obs.)	2	0	1	0	1	0
	n(exp.)	2.48	1.10	0.91	0.40	1.50	0.70
	SIR	0.81	--	1.02	--	0.67	--
	95% CI	0.14-2.67	--	0.05-5.04		0.03-3.30	--
1b	n(obs.)	2	0	1	0	1	0
	n(exp.)	2.25	1.03	0.91	0.38	1.35	0.65
	SIR	0.89	--	1.10	--	0.74	--
	95% CI	0.15-2.93	--	0.06-5.44		0.04-3.66	--
2	n(obs.)	8	3	5	1	3	2
	n(exp.)	5.65	1.74	3.64	1.14	2.01	0.60
	SIR	1.42	1.72	1.38	0.88	1.49	3.31
	95% CI	0.66-2.69	0.44-4.69	0.50-3.05	0.04-4.34	0.38-4.06	0.56-10.94
3	n(obs.)	10	3	6	1	4	2
	n(exp.)	8.12	2.84	4.61	1.53	3.51	1.31
	SIR	1.23	1.06	1.30	0.65	1.14	1.53
	95% CI	0.63-2.19	0.27-2.88	0.53-2.70	0.03-3.22	0.36-2.75	0.26-5.06
Adjudicated*							
1b	n(obs.)	2	1	1	1	1	0
	n(exp.)	2.25	1.03	0.91	0.38	1.35	0.65
	SIR	0.89	0.97	1.10	2.65	0.74	--
	95% CI	0.15-2.93	0.05-4.79	0.06-5.44	0.13-13.08	0.04-3.66	--

*MedDRA cases contain malignant and unspecified neoplasms, while adjudicated cases contain only malignant neoplasms.

3.3 ADJUDICATION

Only Pool 1b contained both malignant and unspecified events detected using MedDRA and malignant events adjudicated by the EAC, which allows for a comparison of these methods. This pool included a total of 62 events confirmed by the EAC as malignant neoplasms and 4 as premalignant breast neoplasms. The sponsor found 12 EAC confirmed malignant neoplasms that were not identified by the SMQ search “Malignant and unspecified tumors.” In contrast, 54 events identified by the SMQ search were reviewed but not confirmed by the EAC as malignant neoplasms. The sponsor listed the following reasons for events not being confirmed as malignancies:

- 34 events were “downgraded” by the EAC; these events were typically reported with unspecific terms such as “neoplasm” or “tumor.”
- 10 events were confirmed either as a pre-malignant (n=7, not including the 4 premalignant breast neoplasms), benign (n=2) or unclassified neoplasm (n=1).
- 2 events were confirmed as a malignant neoplasm, but due to discrepancies between the investigator-reported onset date and that assigned by the EAC, they only appear on the SMQ-based list (as having onset during treatment), and not on the list of EAC-confirmed malignant neoplasms (as the EAC assigned event onset prior to treatment initiation).
- 6 events captured by the SMQ search were confirmed as malignant neoplasms through linking to another EAC-confirmed malignant neoplasm (index event), but only the index event appears on the list of EAC-confirmed malignant neoplasms.
- 1 event was never sent for adjudication and 1 could not be adjudicated due to incomplete source documentation.

Dr. Jonathan Jarow, Medical Officer in the Division of Oncology Drug Products-I, reviewed the sponsor’s external adjudication procedures and found them acceptable.⁶ In fact, they were similar to the methods utilized in the collection of data for the SEER database.

4 DISCUSSION

Analyses presented in this review include internal and external comparisons of neoplasms observed in various trial pools in the clinical development program of liraglutide.

Dr. Jonathan Jarow stated that the best safety population to utilize for describing the risk of cancer in the weight management program includes the adjudicated events from the four weight management trials (Pool 1b in this review).⁶ He further stated that using the larger data set, which also includes the diabetes trials (Pool 3 in this review), has the advantage of increased power, however, at the expense of reliability of event categorization. I agree with his statements. In addition, diabetes trials were of shorter duration (generally 26 weeks) than weight-loss trials (mostly 56 weeks or longer, Appendix Table 1), which makes the detection of a cancer-initiating or -promoting drug effect less likely. It is unfortunate that none of the events in the diabetes program were

⁶ Jonathan P Jarow. OHOP consult on liraglutide. June 24, 2014, available in DARRTS.

adjudicated. As a consequence, the pool with adjudication of malignancies (Pool 1b) included only 4 out of 30 clinical trials in the liraglutide development program, however, with approximately 39.2% of total person-time exposed to liraglutide and 50.8% of total person-time in comparator arms.

As presented in Section 3.1.4.1 and shown in Figure 1, using adjudicated malignant events in Pool 1b, only thyroid cancer and female breast cancer occurred more frequently among patients exposed to liraglutide compared with patients in comparator arms, albeit not statistically significantly. However, liraglutide was not associated with an increased risk of all cancers combined (RR_{MH} , 0.86; 95% CI, 0.52-1.42). In addition, point estimates for individual cancer types ranged from decreased rates for some to increased rates for other cancers. This is not unexpected in a multiple hypothesis testing situation, even in the absence of a treatment effect on the outcome of interest. Nevertheless, although these findings are somewhat reassuring, this analysis cannot exclude the possibility of a causal effect of liraglutide on thyroid cancer or female breast cancer.

With regard to colorectal neoplasm, staff of DMEP observed an imbalance in benign events. However, the scope of this review was limited to malignant or malignant and unspecified events, which were balanced between patients exposed to liraglutide and comparators.

External comparisons showed substantially more new diagnoses of malignant and unspecified thyroid neoplasm (MedDRA) than would be expected based on age- and sex-standardized U.S. population rates, which only include malignant cases. However, for thyroid neoplasm, adjudication rates were low. Of 15 and 4 cases (MedDRA) observed in Pool 1b among patients exposed to liraglutide and comparators, respectively, only 4 and 1 cases, respectively, were positively adjudicated as malignant events. The SIR of adjudicated thyroid cancer events, regardless of exposure status, was much smaller, but in the case of liraglutide-exposed patients still statistically significant. SIRs for female breast and colorectal cancer showed only modest deviations between observed and expected counts. Given the limitations inherent in external comparisons as listed below, modest deviations between observed and expected counts should be interpreted with caution.

Several considerations should be kept in mind when interpreting the data presented in this review. First, these analyses included all neoplasms diagnosed during follow-up, without consideration of induction times. For cases that were diagnosed shortly after study initiation, a cancer-inducing or even -promoting effect of study treatment may be questionable. I refer to Dr. Jarow's review, which includes additional detail and discussion of the timing of malignant events.⁶ Second, in the calculation of person-time, individual follow-up was not censored at the time of a cancer diagnosis. Ordinarily, the time after diagnosis should not be considered time at risk and, therefore, not be included in the denominators of incidence rate calculations. However, for simplicity and to use consistent denominators in the analyses of different cancer types, all available person-time was used. Because of the relative rarity of the endpoints of interest, including or not including person-time after diagnosis will have little effect on the total person-time and the calculation of incidence rates.

In addition to the aforementioned considerations, comparisons between treatment arms of clinical trials and an external standard (i.e. U.S. SEER data) are subject to inherent limitations. Several factors can bias these comparisons either towards higher or lower rates in clinical trials compared with the external standard and some factors could impact clinical trial rates in either direction.

The following factors could potentially lead to higher rates of neoplasms in the reviewed clinical trials compared with U.S. SEER data:

- Association of diabetes and obesity with increased risk of certain cancer types,⁷ including thyroid cancer,^{8,9} breast cancer,¹⁰ and colorectal cancer^{11,12}
- Surveillance bias due to regularly scheduled follow-up visits
- Detection bias related to labeling of liraglutide for thyroid cancer
- Detection bias due to drug effects (e.g. weight loss can facilitate detection of breast cancer; in fact, SIRs for breast cancer were higher in weight-loss than in diabetes pools)
- Inclusion of non-adjudicated events (MedDRA)
- Inclusion of both malignant and unspecified events in analyses based on MedDRA search terms, while U.S. SEER data only included malignant neoplasms
- Inclusion of MedDRA events that were not limited to index events (i.e. primary cancer)
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

The following factors could potentially lead to lower cancer rates in the reviewed clinical trials compared with U.S. SEER data:

- Voluntary participation can result in the selection of healthier patients with higher socioeconomic status and better access to healthcare and prevention
- Inclusion and exclusion criteria may result in a sample at lower risk for cancer
- Differences in cancer rates for international trial participants compared to U.S. population captured in SEER data

⁷ Renehan AG et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371: 569–78.

⁸ Kitahara CM et al. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of 5 prospective studies. *Cancer Epidemiol Biomarkers Prev.* 2011 March; 20(3): 464–472.

⁹ Meinhold CL et al. Nonradiation risk factors for thyroid cancer in the US Radiologic Technologists Study. *Am J Epidemiol* 2010; 171:242–252.

¹⁰ DeSantis C et al. Breast cancer statistics, 2013. *CA Cancer J Clin.* 2014 Jan-Feb; 64(1):52-62.

¹¹ Jiang Y et al. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol.* 2011; 26:863–876.

¹² Larsson SC et al. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst.* 2005; 97 (22): 1679-1687.

Although these factors can bias the results in opposing directions, their relative magnitude is difficult to predict and it would be imprudent to assume that they cancel each other out. As a consequence, SIRs resulting from comparisons with an external standard are subject to systematic error and should be interpreted with caution.

5 CONCLUSION

Internal comparisons based on clinical trial data suggest the possibility of increased rates of thyroid cancer and female breast cancer among patients exposed to liraglutide compared with patients in comparison arms. However, rate ratios for all cancers grouped together were not increased and several cancer types occurred less frequently with liraglutide. This pattern would not be unexpected in a multiple testing situation in the absence of a treatment effect and these data can neither confirm nor exclude a causal role of liraglutide in the etiology of thyroid and female breast cancer.

In the clinical trial program of liraglutide, thyroid cancers occurred somewhat more frequently than what would be expected in an age- and sex-standardized U.S. population. This was not the case for other cancers to the same extent. However, comparisons between clinical trial data and a reference population should be carefully interpreted.

6 RECOMMENDATIONS

A post-marketing observational study is currently ongoing to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to liraglutide (PMR 1583-6), of which DEPI-I has recently reviewed an interim report and posed questions to the sponsor.¹³ Conduct of a separate study focused on a weight-loss indication may be challenging due to limited ability to detect the indication in electronic healthcare data, despite different doses of the drug and different product names used for diabetes and proposed for weight loss. Should liraglutide be approved for weight loss, I do not recommend a separate observational study for cancer with the use of liraglutide as a weight-loss agent.

A cardiovascular outcomes trial is currently underway for liraglutide in the treatment of diabetes (PMR 1583-9). In it, the FDA required the sponsor to also assess long-term effects of Victoza, including neoplasms. If a separate cardiovascular outcomes trial is being considered for liraglutide as a weight-loss agent, it should include adjudication and analysis of malignant neoplasms.

I recommend that DMEP consider adding the observed clinical trial data imbalances in thyroid and female breast cancer in humans to the labeling of Victoza and Saxenda, together with a description of the uncertainty surrounding these estimates.

Christian Hampp, PhD

¹³ Christian Hampp. Year-3 interim report of observational safety study of liraglutide, PMR 1583-6. June 27, 2014, available in DARRTS.

Cc: Guettier JM /Colman E /Mahoney K /Pippins J /Smith J /Golden J /Pratt V
/Dharia P /Madara P /Hai M /DMEP
Wang C /Shih D /Wysowski D /Bright P /Calloway P /DEPI-I
Niak A /Brinker A /Jones C /Ryan D /Ready S /Chamberlain C /DPV
Jarow J /DODP-I
Charles J /Soukup M /Levenson M /OB
Iyasu S /Candida L /Thomas T /OSE

APPENDIX

Table 1. Clinical Trials in the Liraglutide Weight Management Program (Table 1-1, Saxenda 120-day Safety Report, April 15, 2014)*

Trial ID Phase	Duration of treatment	Population	Doses (mg) ^a	N ^b (SAS)	Trial design features including follow-up period/ Randomization
<i>Completed trials</i>					
<i>Clinical pharmacology</i>					
3630 Phase 1	5 weeks	BMI: 30–40 kg/m ² , T2DM excluded	Liraglutide 3.0 or 1.8 mg, Placebo	49 (total)	2-week follow-up/ Two-period balanced 6 sequence incomplete cross-over design with minimum 7 subjects in each treatment sequence
<i>Phase 2 and 3</i>					
1807 Phase 2	20 weeks + 84-week extension	BMI: 30–40 kg/m ² , T2DM excluded	Liraglutide 3.0, 2.4, 1.8, or 1.2 mg Orlistat 120 mg TID Placebo	564 (total), 98 to placebo, 95 to orlistat, 371 to liraglutide	Weeks 20–52 (single-blind): Subjects continued on their randomized treatment. Weeks 52–104 (open-label): Liraglutide/placebo-treated subjects switched to liraglutide 2.4 mg and then 3.0 mg as sites received Ethics Committee approval. Orlistat-treated subjects continued on orlistat. 2-week follow-up period after trial completion. Randomization: 1:1:1:1:1
1839 Phase 3 56-week (main part of trial)	56 weeks	BMI: ≥30 kg/m ² or ≥27 kg/m ² with dyslipidemia or hypertension T2DM excluded	Liraglutide 3.0 mg, Placebo	3723 (total), 1242 placebo, 2481 liraglutide	Subjects without pre-diabetes at screening: After completion of 56-week treatment period, liraglutide-treated subjects were re-randomized to either continue liraglutide or switched to placebo in the following 12 weeks Placebo-treated subjects continue on placebo. Randomization: 2:1
1922 Phase 3	56 weeks	BMI: ≥27 kg/m ² with T2DM	Liraglutide 3.0, 1.8 mg Placebo	844 (total), 212 placebo, 210 liraglutide 1.8 mg, 422 liraglutide 3.0 mg	12-week observational follow-up period after trial completion. Randomization: 2:1:1

*Trials included in analyses of malignant neoplasms are highlighted in yellow.

Table 1 continued

Trial ID Phase	Duration of treatment	Population	Doses (mg)^a	N^b (SAS)	Trial design features including follow-up period/ Randomization
3970 Phase 3	32 weeks	BMI: ≥ 30.0 kg/m ² with moderate or severe OSA. T2DM excluded	Liraglutide 3.0 mg Placebo	355 (total), 179 placebo, 176 liraglutide 3.0 mg	2-week follow-up period after trial completion. Randomization: 1:1
1923 Phase 3	56 weeks	BMI: ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia and/or hypertension T2DM excluded	Liraglutide 3.0 mg Placebo	422 (total) 210 placebo 212 liraglutide 3.0 mg	Maintenance of weight loss (min. 5%) achieved during a 4-12 week run-in using a low-calorie diet. 12-week observational follow-up period after trial completion. Randomization: 1:1
Ongoing trials					
3967 Phase 1 Ongoing	5-6 weeks	BMI: Corresponding to ≥ 30 kg/m ² for adults ^c Age: 12-17 years with Tanner stage 2-5 pubertal development	Liraglutide 3.0 mg Placebo	21 (total)	2-week follow-up Randomization: 2:1
1839-ext Phase 3 (104-week extension ongoing)	3 year: 56 weeks + 104- week	BMI: ≥ 30 kg/m ² or ≥ 27 kg/m ² with dyslipidemia or hypertension T2DM excluded	Liraglutide 3.0 mg Placebo	1584 (total) 497 placebo 1087 liraglutide 3.0 mg	Subjects with pre-diabetes at screening: Treated for up to 3 years (including the 104-week extension period), followed by a 12-week observational follow-up period.

BMI: body mass index; OSA: obstructive sleep apnea; T2DM: type 2 diabetes mellitus; TID: *ter in die*.

a. Once-daily dose with dose-escalation of liraglutide in weekly steps of 0.6 mg in all weight management trials (starting dose: 0.6 mg). **b.** Number of treated subjects. **c.** BMI corresponding to ≥ 30 kg/m² for adults by international cut-off points² and ≤ 45 kg/m² and $\geq 95^{\text{th}}$ percentile for age and sex

Table 2. Clinical Trials included in the Analyses of Malignant Neoplasms

Trial ID	Liraglutide		Comparator		Trial Pool			
	pts. (n)	p-yrs.	pts. (n)	p-yrs.	1a	1b	2	3
NN1250-3948	87	42.3	0*	0*			X	X
NN2211-1310	135	32.3	55	13.0			X	X
NN2211-1332	13	1.9	13	2.1			X	X
NN2211-1333	21	3.7	12	2.1			X	X
NN2211-1334	180	57.5	46	13			X	X
NN2211-1436	695	337.6	345	159.1			X	X
NN2211-1499	72	8.0	72	8.1			X	X
NN2211-1571	123	33.7	40	9.3			X	X
NN2211-1572	724	1022	363	446.5			X	X
NN2211-1573	497	782.2	248	330.3			X	X
NN2211-1574	355	157.2	175	73.4			X	X
NN2211-1697	230	112.3	346	172.3			X	X
NN2211-1700	268	249.4	132	123.6			X	X
NN2211-1701	176	172.6	88	76.3			X	X
NN2211-1796	697	201.6	231	74.1			X	X
NN2211-1797	421	448.4	232	103.5			X	X
NN2211-1799	16	4.2	33	8.6			X	X
NN2211-1842	987	971.4	0	0			X	X
NN2211-1860	573	550.6	219	182.4			X	X
NN2211-2072	176	41.4	34	8.5			X	X
NN2211-3924	240	233	120	117.8			X	X
NN2211-3925	127	88.3	130	89.8			X	X
NN8022-1807	433	559.4	193	197.4	X			X
NN8022-1839	2,481	3,714.3	1,242	1,730.1	X	X		X
NN8022-1922	632	721.3	212	229	X	X		X
NN8022-1923	212	233.4	210	223.4	X	X		X
NN8022-3970	176	97.2	179	104.4	X	X		X
NN9068-3697	1,237	1071	0*	0*			X	X
NA NN9068-3912	199	96.8	0*	0*			X	X
NN9535-1821	95	27.8	46	14.6			X	X
Total	12,278	12,072.8	5,016	4,512.7				

*comparator groups with insulin degludec or semaglutide not included

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Review

Date: August 13, 2014

Reviewers: Debra L. Ryan, PharmD, MBA, Safety Evaluator
Carolyn J. Tabak, MD, MPH, Medical Officer
Division of Pharmacovigilance I

Team Leaders: S. Christopher Jones, PharmD, MS, MPH
Safety Evaluator Team Leader
Allen Brinker, MD, MS
Medical Officer Team Leader
Division of Pharmacovigilance I

Acting Division Director: Robert L. Levin, MD
Division of Pharmacovigilance I

Product Name: Victoza™ (liraglutide)

Subject: Review of Select and Serious Events as Background
Information for the September 2014 Advisory Committee for
Saxenda™ (liraglutide)

Application Type/Number: NDA: 206-321

Applicant/Sponsor: Novo Nordisk, Inc.

OSE RCM #: 2014-634

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EXECUTIVE SUMMARY

Victoza™ (liraglutide) is indicated, at doses up to 1.8 mg, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). On December 20, 2013, the sponsor submitted an NDA (206-321), seeking approval of liraglutide, at a dose of 3 mg, for a new indication: as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults.

The Division of Metabolism and Endocrinology Products (DMEP) has requested an update of the postmarketing safety assessment for Victoza™ to further their understanding of the safety of liraglutide for this new indication and higher dose with specific interest in reports of gall-bladder related adverse events (AEs), breast cancer, hepatic injury, tachycardic /arrhythmogenic AEs, and psychiatric AEs.

The majority of the spontaneous reports and post marketing safety reviews for liraglutide have focused on pancreatitis, acute renal failure, anaphylaxis and hypersensitivity reactions, and medication errors due to patients using the wrong injection technique. The prescribing information has been updated to reflect these safety concerns. Analysis of spontaneous reports for gallbladder and cardiovascular adverse events is problematic, because these events are relatively prevalent in the age group represented in these reports i.e., individuals over 50 years old, with or without a diagnosis of diabetes mellitus. Analysis of spontaneous report for cancers of interest (breast, thyroid, and pancreatic) is also problematic, because these are relatively common cancers in adults unless a rare subtype, like medullary thyroid carcinoma, is specifically stated in the report. A known limitation of spontaneous reporting is the inability to perform adequate causality assessments for events which are relatively common in the general population. Because of this high background rate, among other limitations, FDA must rely on adequately powered, randomized controlled trials or well-designed observational studies to determine if common events in the recipient population can be attributed to liraglutide exposure.

We note the continued accrual of a disproportionate number of liraglutide associated thyroid and pancreatic cancers relative to all other drugs in the FDA Adverse Event Reporting System (FAERS). However, the medical literature offers inconclusive data to determine the role that liraglutide may play in these malignancies. DPVI did not identify previously unknown safety signals for liraglutide in the FAERS database or the literature.

1 INTRODUCTION

1.1 BACKGROUND

This review provides an update to the safety profile for liraglutide (Victoza™) focusing on select and serious adverse events associated with the use of Victoza™ reported to the FDA Adverse Event Reporting System (FAERS) and reports from the published medical literature.

Victoza™ was approved on January 25, 2010 and is the second glucagon-like peptide-1 (GLP-1) agonist approved for marketing. Victoza™ is indicated, at doses up to 1.8 mg, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). On December 20, 2013 a new NDA (206-321) was submitted to the FDA seeking approval of liraglutide, at a dose of 3 mg, for a new indication: 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/m² or greater (obese) or 27 kg/m² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea.

The Division of Metabolism and Endocrinology Products (DMEP) has requested an update of the postmarketing safety assessment for Victoza™ to further their understanding of the safety of liraglutide for this new indication and higher dose with specific interest in reports of gall-bladder related adverse events (AEs), breast cancer, hepatic injury, tachycardic/arrhythmogenic AEs, psychiatric AEs, and potential safety signals for liraglutide.

The objective of this review is threefold; 1) To provide a postmarketing overview of the safety profile of Victoza™ since approval including potential safety signals; 2) To review the regulatory actions that have been taken in response to postmarketing reports; and 3) To evaluate serious postmarketing reports and the published medical literature regarding the events of special interest cited in the above paragraph.

1.2 OVERVIEW OF GLP-1 AGONISTS

There are four GLP-1 agonists approved for marketing in the US, each indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Byetta™ (exenatide), the first in class, was approved for marketing in the US on April 28, 2005. Thereafter, three additional GLP-1 agonists have been approved for marketing in the US. Victoza™ (liraglutide), approved on January 25, 2010; Bydureon™ (exenatide extended release), approved on January 27, 2012; and Tanzeum™ (albiglutide), approved on April 15, 2014.

The GLP-1 agonists stimulate insulin release, slow gastric emptying, and inhibit post-prandial glucagon release; effects mediated by the GLP-1 receptor which is widely distributed throughout a variety of tissues. All FDA approved GLP-1 agonists share a mechanism of action and generally have a similar adverse event FAERS profile with the exception of the potential risk of medullary thyroid carcinoma (MTC) which appears to be associated with only long-acting GLP-1 agonists. Byetta is not considered to be a long-acting agent.

Victoza™ carries a **Boxed Warning** to notify prescribers that the drug causes thyroid C-cell tumors at clinically relevant exposures in rodents; however the human relevance of this observation could not be determined by clinical or nonclinical studies. The complete **Boxed Warning** is provided below:

WARNING: RISK OF THYROID C-CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)*].

Bydureon™ and Tanzeum™ carry a similar **Boxed Warning** to notify prescribers that thyroid C-cell tumors have been observed in rodent studies with GLP-1 agonists at clinically relevant exposures.

1.3 PREVIOUS OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE) REVIEWS

DPVI has reviewed reports associated with the use of Victoza™ reported to the FAERS database from approval on January 25, 2010 through June 30, 2012 in two separate reviews^{1,2}. The following summarizes the safety issues identified in those reviews, other relevant OSE reviews, and the regulatory action taken:

Acute Renal Failure: An OSE safety review³ (RCM#2010-2606) was completed on April 6, 2011 that determined that there was a temporal association between the initiation of Victoza™ and dehydration leading to acute renal failure. The Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections of the labeling for Victoza™ were updated on May 18, 2011 to include additional information about dehydration, including reports of altered renal function requiring dialysis.

Anaphylaxis and Hypersensitivity Reactions: An OSE safety review⁴ (RCM#2011-4469) was completed on February 1, 2012 that determined that there was a temporal association between the initiation of Victoza™ and the onset of reported hypersensitivity reactions. The Contraindications and Warnings and Precautions sections of the labeling for Victoza™ were updated in April 2012 to include additional information about serious hypersensitivity reactions including anaphylaxis.

Pancreatitis (including Hemorrhagic Necrotizing Pancreatitis): On November 28, 2012 the sponsor submitted a supplement (S-018) to update the Warnings and Precautions and Adverse Reactions sections of the labeling to include additional information about pancreatitis. An OSE safety review⁵ (RCM#2013-270) was completed on March 14, 2013 evaluating seventy-six cases of acute pancreatitis reported for Victoza™, including three fatalities and four cases of hemorrhagic/necrotizing pancreatitis supporting the sponsor’s proposed labeling, with modifications. The supplement was approved on April 16, 2013.

Improper pen storage, wrong injection technique, and device malfunctions: A Post Marketing Medication Error Review⁶ (RCM#2013-270) evaluating the Instructions for Use (IFU) regarding proper pen storage, injection technique, and device malfunction was completed on February 15, 2013. On May 2, 2013 the sponsor submitted a supplement (S-020) revising the IFU by providing additional language and visual representation on dose selection and correct injection technique. The supplement (S-020) was approved on June 13, 2013.

Drug-Induced Liver Injury: An OSE safety review⁷ (RCM#2014-813) was completed on June 20, 2014 that identified six cases of liver injury possibly related to Victoza™ use. The FDA is currently considering whether these data warrant labeling changes for liraglutide.

2 SUMMARY ANALYSIS OF THE FAERS DATABASE

2.1 FAERS SEARCH STRATEGY

For this review we were interested in identifying postmarketing reports coded with Preferred Terms (PT) occurring with greater frequency, severity, or outcome than expected for liraglutide. In order to achieve this, we selected reports coded with a serious outcome that identified liraglutide as the primary suspect drug. Additionally, we limited our analysis of FAERS reports to those without the terms “Trial ID”, “Study ID”, “Attorney”, “litigation”, or “lawyer,” thereby eliminating reports originating from clinical trials or litigation. To focus our review on the serious cases requiring hospitalization, we further filtered out reports coded with the outcome “Other Serious” that did not report hospitalization. The FAERS database was searched with the strategy described in Table 1.

Table 1. FAERS Quick Query Search Strategy (n=4585)	
Date of search	June 10, 2014
Time period of search	January 25, 2010 (date of US approval) – May 31, 2014
Product Terms	Liraglutide
Outcome	Serious
FAERS Export to Excel Filters (n=3110)	
Primary Suspect Column	Filter to include reports that identify liraglutide as the Primary Suspect (n=4168)
Narrative Column Search	Exclude clinical trial and litigation reports by searching narrative for the terms “Trial ID” & “Study ID” (n=395) and for the terms “litigation”, “attorney”, “legal” (n=73)
Case Type and Outcome Column	Filter to exclude “Other Serious” Non-direct reports that do not report Hospitalization as an Outcome (n=590)

2.2 RESULTS

2.2.1 Results: Case Characteristics

Table 2. Descriptive Characteristics for Serious Adverse Events Associated with the Use of Liraglutide from January 25, 2010 through May 31, 2014 (N=3,110)	
Category	FAERS Cases
Age	Range: 14 – 92 years Average: 58 years Median: 59 years Not Reported: 945
Gender	Female: 1449 Male: 1267 Not Reported: 394
Age Bands	<17 years: 3 17-20 year-old: 7 21-30 year-old: 34 31-40 year-old: 114 41-50 year-old: 371 51-60 year-old: 675 61-70 year-old: 649 71-80 year-old: 258 81-92 year-old: 51 >90 years: 3
Outcome[†]: (case may have more than one coded outcome)	Death: 246 Hospitalization: 1,717 Life-Threatening: 230 Disability: 58 Congenital Anomaly: 5 Other: 1552
Year Report Received by FDA	2010: 511 2011: 888 2012: 709 2013: 664 2014: 338 (through May 31, 2014)
Country of Reporter	Domestic: 1,395 Foreign: 1,715
† Outcome as determined by the MedWatch reporter and categorized by 21 CFR 314.80	

Implementing the search strategy described in Section 2.1 DPVI identified 3,110 reports in the FAERS database for the time period January 25, 2010 through May 31, 2014. The 3,110 reports represent crude counts, and as such, duplicates have not been reconciled. In addition, reported outcomes are those submitted to the Agency; and the possibility of a causal role of liraglutide in these adverse events has not been fully analyzed for this evaluation.

Pediatric Use

Among the 3,110 reports were three patients under the age of 17 that received liraglutide for T2DM. The serious AE reported for each patient was Pancreatitis Acute (PT) n=1, Anaphylactic Reaction (PT) n=1, and Panniculitis (PT) n=1, respectively. All three patients were hospitalized and each recovered from the event.

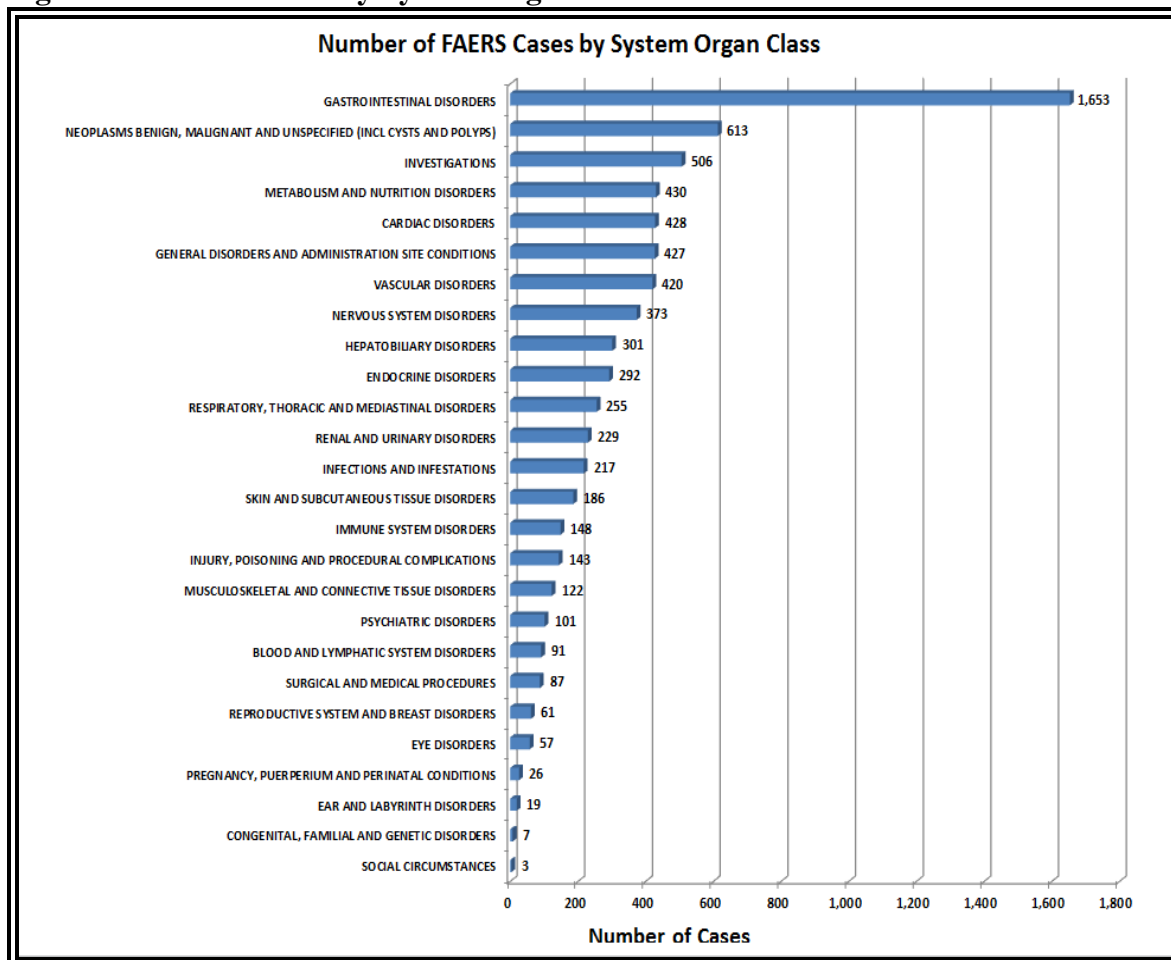
Deaths

The above search strategy identified 246 reported deaths associated with liraglutide use. Primary causes of death when reported were secondary to pancreatic carcinoma (n=88) or a cardiovascular event (n=57). For those cases reporting the age at death, the range was from 31 to 91 years-of-age. Nineteen reports were for individuals under the age of 50; myocardial infarction and morbid obesity were the most frequent reasons listed as a cause.

2.2.2 Results: FAERS Cases by SOC

The following figure represents the number of FAERS cases by System Organ Class (SOC). Note that the numbers do not sum to equal the number of cases identified by the search, because a case may be included in more than one SOC.

Figure 1: FAERS Cases by System Organ Class



The most frequently reported MedDRA PTs for serious adverse event reports associated with liraglutide are categorized under the following SOC: *Gastrointestinal disorders; Neoplasms Benign, Malignant and Unspecified; Cardiac Disorders; Investigations; Metabolism and nutrition disorders; and General Disorders and Administration Site Conditions*. In general, the majority of the cases in these SOC represent reports of pancreatitis, pancreatic cancer, cardiovascular events, thyroid neoplasms, acute renal failure, and those PTs that describe the symptoms, laboratory tests, and/or procedures associated with these diagnoses and/or with T2DM. In section 7.2 (Appendix B) of this document we further list the most frequently reported MedDRA preferred terms within select SOC.

2.2.3 Results: Top PTs for Events of Special Interest

In section 7.3 (Appendix C) of this document we list the most frequently reported MedDRA preferred terms for liraglutide. The following tables are the most frequently reported PTs within each MedDRA High-Level Group Term (HLGT) or SOC for the events of special interest.

Gallbladder Disorders (HLGT) n=104*

Event-Preferred Terms(PTs)	Total Cases
CHOLELITHIASIS	83
CHOLECYSTITIS ACUTE	26
CHOLECYSTITIS	20
GALLBLADDER DISORDER	12
CHOLECYSTITIS CHRONIC	7
CHOLECYSTITIS INFECTIVE	2
GALLBLADDER PAIN	2
GALLBLADDER POLYP	2
BILIARY DYSKINESIA	1
CHOLELITHIASIS OBSTRUCTIVE	1
GALLBLADDER NECROSIS	1
GALLBLADDER NON-FUNCTIONING	1
GALLBLADDER PERFORATION	1

*Numbers may not sum; a case may include more than one PT

Breast Neoplasms Malignant and Unspecified (Incl Nipple) (HLGT) n=22*

Event-Preferred Terms(PTs)	Total Cases
BREAST CANCER	16
BREAST CANCER RECURRENT	3
INTRADUCTAL PROLIFERATIVE BREAST LESION	2
INVASIVE DUCTAL BREAST CARCINOMA	2
INVASIVE LOBULAR BREAST CARCINOMA	1
LOBULAR BREAST CARCINOMA IN SITU	1

*Numbers may not sum; a case may include more than one PT

Gastrointestinal Neoplasms Malignant and Unspecified (HLGT) n=240*

Event-Preferred Terms(PTs)	Total Cases
PANCREATIC CARCINOMA	204
PANCREATIC CARCINOMA METASTATIC	40
ADENOCARCINOMA PANCREAS	22
PANCREATIC NEOPLASM	16
PANCREATIC CARCINOMA STAGE IV	10

*Numbers may not sum; a case may include more than one PT

Cardiac Arrhythmias (HLGT) n=96*

Event-Preferred Terms(PTs)	Total Cases
ATRIAL FIBRILLATION	29
TACHYCARDIA	17
SUDDEN DEATH	16
CARDIAC ARREST	11
ARRHYTHMIA	8
CARDIO-RESPIRATORY ARREST	7
SUPRAVENTRICULAR TACHYCARDIA	6
VENTRICULAR TACHYCARDIA	5
VENTRICULAR EXTRASYSTOLES	3
VENTRICULAR FIBRILLATION	3

*Numbers may not sum; a case may include more than one PT

Psychiatric Disorders (SOC) n=101 *

DEPRESSION	16
SUICIDAL IDEATION	10
CONFUSIONAL STATE	8
SOMNOLENCE	6
ANXIETY	5
SUICIDE ATTEMPT	5
DYSPHONIA	4
INSOMNIA	4
INTENTIONAL OVERDOSE	4
LETHARGY	4
APHASIA	3
COMPLETED SUICIDE	3

*Numbers may not sum; a case may include more than one PT

Endocrine Neoplasms Malignant and Unspecified (HLGT) n=100*

Event-Preferred Terms(PTs)	Total Cases
THYROID CANCER	42
THYROID NEOPLASM	23
PAPILLARY THYROID CANCER	14
MEDULLARY THYROID CANCER	9
INSULINOMA	2
NEUROENDOCRINE CARCINOMA METASTATIC	2
PANCREATIC NEUROENDOCRINE TUMOUR	2
PARATHYROID TUMOUR	2
CARCINOID TUMOUR	1
GASTRINOMA	1
MALIGNANT PITUITARY TUMOUR	1
NEUROENDOCRINE TUMOUR	1
PARATHYROID TUMOUR MALIGNANT	1
PROLACTIN-PRODUCING PITUITARY TUMOUR	1
THYROID CANCER METASTATIC	1
THYROID CANCER STAGE IV	1

*Numbers may not sum; a case may include more than one PT

3 DISCUSSION

The most frequently reported MedDRA PTs for serious adverse event reports associated with liraglutide are categorized under the following SOCs: Gastrointestinal disorders; Neoplasms Benign, Malignant and Unspecified; Cardiac Disorders; Investigations; Metabolism and nutrition disorders; and General Disorders and Administration Site Conditions. In general, the majority of the cases in these SOCs represent reports of pancreatitis, pancreatic cancer, cardiovascular events, thyroid neoplasms, acute renal failure, and those PTs that describe the symptoms, laboratory tests, and/or procedures associated with these diagnoses and/or with T2DM.

Previous DPVI reviews of the safety profile for liraglutide have identified the following postmarketing safety concerns and led to strengthening of the label regarding pancreatitis⁸, acute renal failure⁹, and hypersensitivity events.¹⁰ The resulting regulatory actions subsequent to these reviews have been summarized in Section 1.3.

Gallbladder Disorders

The most frequently reported preferred terms (PTs) for the 104 FAERS cases reporting gallbladder disorders are cholelithiasis and cholecystitis. However, three major risk factors for developing gallstones are present in the majority of the FAERS cases receiving liraglutide: 1) Age >40 years-old, 2) Obesity, and 3) History of Diabetes Mellitus. In addition, 59 of the FAERS cases reporting cholelithiasis and cholecystitis also report pancreatitis as an adverse event. Based on FAERS data alone, neither causality nor the contributory role of liraglutide in the presentation of cholelithiasis and cholecystitis can be clearly defined. DPVI recently authored a review of liraglutide-associated serious liver injury, and we determined that cases of hepatitis seemed to follow a cholestatic pattern of injury. In that same review, we were unable to determine the cause of liver injury. However, we speculate that if there are slight imbalances in hepatic safety findings from weight management trials, then these FAERS data may indicate a liraglutide-mediated effect on the biliary tract.

Drug-Induced Liver Injury

A literature report describing liraglutide-induced autoimmune hepatitis¹¹ prompted a recent review of postmarketing cases from the FAERS database, the published medical literature, and an assessment for disproportionality in reporting of liver adverse events using Empirica Signal to evaluate the risk of serious acute drug-induced liver injury (DILI) with liraglutide. This safety review,¹² completed on June 20, 2014 identified six cases of clinically serious liver injury associated with Victoza™. Using the WHO causality assessment scale, DPVI judged these cases to be possibly related to liraglutide therapy, meaning that the causal role of liraglutide could not be definitely established nor excluded in these cases. None of the six cases reported an outcome of death, liver transplant, or met criteria for Hy's law. The majority of the cases reported a cholestatic liver injury that resulted in hospitalization and drug discontinuation. The index literature case describing drug-induced autoimmune hepatitis was also reviewed by OSE hepatologist, Dr. Mark Avigan, who determined that a critical etiological question remains whether this was a case of idiopathic autoimmune hepatitis or autoimmune drug induced liver injury caused by liraglutide.

The true cause of liver injury in this patient remains in question, and despite our recent review that evaluated FAERS cases of suspected liraglutide induced liver injury, we could not definitively determine a cause.

Breast Cancer

The search strategy described in section 2.1 identified twenty-one reports of breast cancer in females between the ages of 51 to 72 years and one report for a 37 year-old female. Thirteen of the cases reported that they had been treated with liraglutide for less than a year when diagnosed with breast cancer, and five cases reported a recurrence of breast cancer, including one death. Breast cancer is the most common cancer in women, with an estimated 2014 annual incidence of 232,000 cases and approximately 2.9 million women in the United States living with the disease.¹³ Approximately 95% of new cases are diagnosed in women 40 years of age and older.¹⁴ FAERS spontaneous reports do not provide strong evidence of risk when an adverse event commonly occurs in the general population. Additionally, breast cancer is a disease that develops over an extended period of time, and FAERS is not a good tool to detect latent events attributed to a drug. Given these limitations, and based on FAERS data, we cannot infer a causal association between liraglutide exposure and the onset of breast cancer at this time. Controlled data are preferred and necessary to better evaluate this risk.

Major Cardiovascular Events (Including Cardiac Arrhythmias)

Although DPVI identified several reports coded with one or more MedDRA preferred terms associated with cardiovascular events, we are unable to attribute these events to liraglutide exposure. Cardiac dysrhythmias are prevalent among persons with type 2 diabetes. Spontaneous adverse events as reported to FAERS do not provide strong evidence of risk when the adverse event (i.e., cardiovascular events) frequently occurs in the general population. Spontaneous reporting systems are optimally used to detect rare and serious events. In addition, reports of cardiovascular safety concerns among diabetics are frequently confounded by the underlying disease being treated or other concurrent medical conditions. Controlled clinical studies assessing major adverse cardiac events (MACE) outcomes or studies that measure QTc changes are necessary to address this potential safety issue.

Psychiatric AEs

The FAERS search strategy described in section 2.1 identified 101 reports in the SOC Psychiatric Disorders, including three cases of Completed Suicide (PT). Two of the patients had previously attempted suicide; one patient had been recently diagnosed with pancreatic carcinoma, which was inferred as a potential reason for the suicide. Depression is the most frequently reported serious psychiatric event in these liraglutide cases, and it is a prevalent disease in the US (10% of the population). We are also unaware of a biological basis for liraglutide use to induce depression. Since diabetes and depression are well known comorbidities,¹⁵ we find it more plausible that diabetes could increase the risk for depression, independent of a specific drug therapy used to treat T2DM.

Thyroid Neoplasms

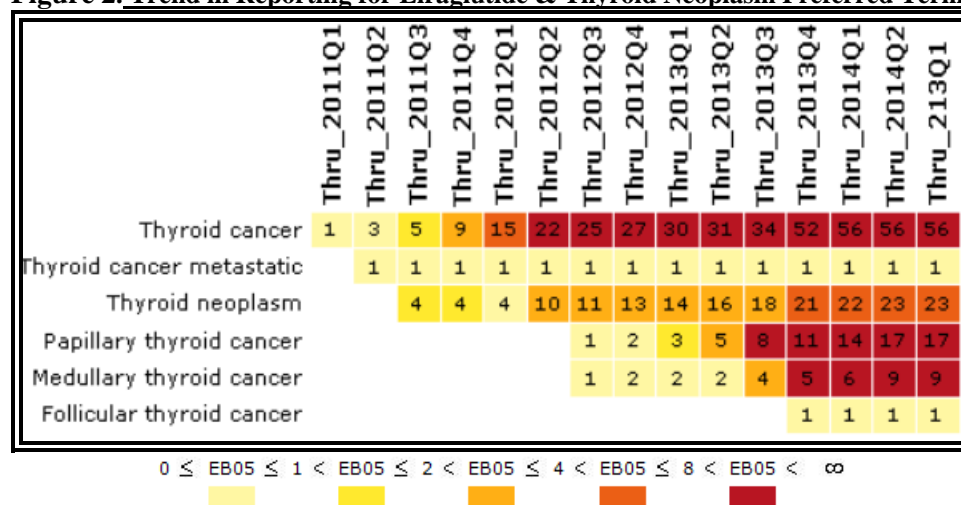
The FAERS search strategy described in section 2.1 identified 100 reports in the Endocrine Neoplasms Malignant and Unspecified (HLGT). DPVI reviewed the narratives of these 100 reports and found that the narratives reported 24 cases of unspecified thyroid cancer/neoplasm, 21 cases of papillary thyroid cancer, 8 cases of follicular thyroid cancer, and 9 cases of MTC. Sixteen cases were described as thyroid nodules. Pure papillary, mixed papillary-follicular, and follicular cancer represent over 90% of all thyroid carcinomas; they are characterized by the National Cancer Institute as common cancers, defined as occurring at a rate of greater than 35,000 new cases per year. A known limitation in analyzing spontaneous reporting is assessing causality for events which are relatively common in the general population.

However, MTC is a relatively rare cancer. Furthermore, liraglutide carcinogenicity studies in mice and rats demonstrated that liraglutide caused C-cell tumors in both species, in both genders, at clinically relevant exposures. Moreover, the occurrence of MTC in rodents was dose-related and treatment-duration-related. MTC is the human form of C-cell cancer. Current liraglutide labeling includes a **Boxed Warning** describing risk of thyroid C-cell tumors. At the time of approval, MTC had not been observed in humans exposed to liraglutide.

Our FAERS search yielded nine cases of MTC. DPVI forwarded these cases to the Division of Oncology Products 2 (DOP2) within FDA. We requested that they review these FAERS reports for clinical evidence confirming a diagnosis of MTC as well as to perform a causality assessment. Based on the clinical characteristics of the nine reports, DOP2 concluded that seven were consistent with the typical presentation of sporadic MTC and that six of these cases are possibly related to liraglutide.¹⁶ Based on the DOP2 review of MTC cases, we cannot exclude the possibility that liraglutide is a casual determinant. These cases remain under internal review by FDA.

DPVI also notes the FAERS reporting trend of thyroid neoplasm as demonstrated in Figure 2.¹⁷ We note increasing disproportionality of thyroid cancer, papillary thyroid cancer, and medullary thyroid cancer beginning in late 2011. We define disproportionate reporting as reporting for a drug-event combination in which the EB05 value is greater than two. Whether increasing disproportionality in reporting is attributable to a real increase in liraglutide-associated thyroid cancer, reporting bias related to litigation asserting that Victoza use may lead to thyroid cancer, detection bias in thyroid cancer screenings, or some other factor is unknown. We are limited in our ability to make causal inference from these reports for a potentially long latency event (e.g. cancer) using spontaneous data without a control group.

Figure 2. Trend in Reporting for Liraglutide & Thyroid Neoplasm Preferred Terms



Pancreatic Cancer

The FAERS search strategy described in section 2.1 identified 240 cases of pancreatic cancer associated with liraglutide use. A previous overview¹⁸ of FAERS reports for pancreatic cancer did not provide new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza. The patient ages in the reports were generally consistent with the ages that are typical for patients with pancreatic cancer; no apparent gender imbalance and no rare subtype of pancreatic malignancy were identified. Pancreatic cancer has been hypothesized, although not proven, as a potential incretin mimetic-related adverse event in the literature.^{19,20} To date, studies have been inconclusive in evaluating the risk of pancreatic cancer with incretin mimetic use.¹⁸⁻²² Both FDA and the European Medicines Agency (EMA) have explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal, which to date, do not support pancreatic cancer as an incretin mimetic-mediated event.²¹⁻²⁴

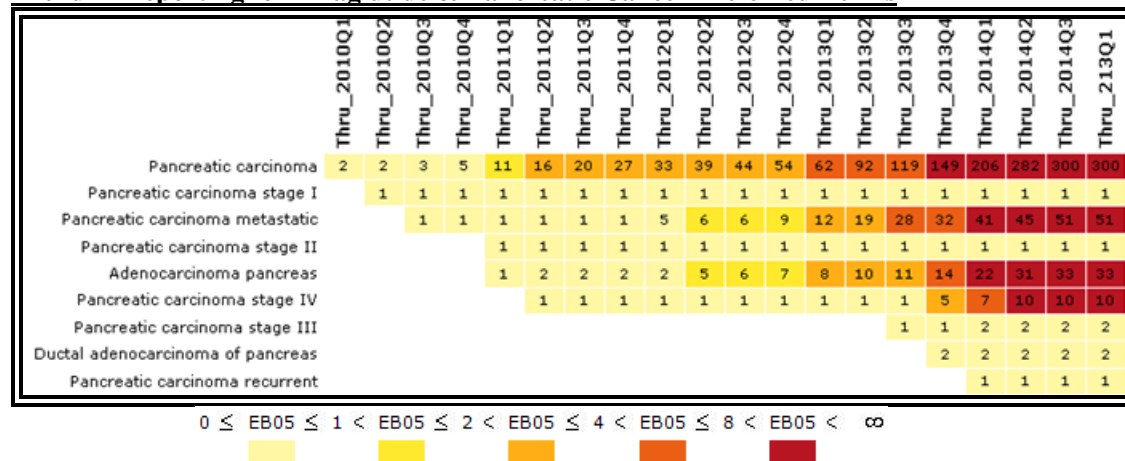
Pancreatic cancer is characterized by the National Cancer Institute as a common cancer, defined as occurring at a rate of greater than 35,000 new cases per year. Analysis of drug-related risk utilizing FAERS data does not provide strong evidence of risk when an event such as pancreatic cancer has a high prevalence (background rate) in the untreated population and has a long latency period. Because pancreatic cancer is relatively common, determining the risk compared to the background rate would require a well-designed, and adequately powered case-control or cohort study to better characterize this risk.²⁵ Therefore, using FAERS data alone is an inadequate approach to understanding the nature of the association. Currently, it is not possible using FAERS data to determine whether there is a causal association between exposure to liraglutide and pancreatic cancer.

DPVI also notes the FAERS reporting trend of pancreatic cancers as illustrated in Figure 3.²⁶ We note increasing disproportionality (EB05>2) of pancreatic cancers since approval of Victoza™. The volume of FAERS reports increased rapidly after the March 2013 FDA Drug Safety Communication²⁷ which discussed an association between pancreatitis and pre-cancerous findings of the pancreas with the use of incretin mimetics, though evidence of a reporting disproportionality existed prior to the March 2013 Drug Safety Communication.

Like the reporting trend for thyroid neoplasm, the drivers for this pancreatic cancer reporting trend have not been elucidated.

Figure 3.

Trend in Reporting for Liraglutide & Pancreatic Cancer Preferred Terms



4 LITERATURE REVIEW

In order to identify the most relevant articles for the literature review, three separate searches were conducted. The first search, conducted on May 14, 2014, used the terms “liraglutide AND (safety OR side effects OR adverse effects OR adverse events OR case reports)” and yielded 350 items. Titles were reviewed for relevance to safety issues, and of these, 24 were retrieved. These 24 articles were reviewed in depth; eleven contained relevant safety information.

Following the first search, two additional searches were conducted that targeted specific safety issues of interest. The second search contained terms directed at each potential adverse event that was requested in the consult (gallbladder disease, breast cancer, liver injury, arrhythmia, and psychiatric adverse events). The second search yielded eight articles, seven of which were retrieved, and were unique from those in the first search. One of these articles was written in Spanish, and translation was not readily available; another article was irrelevant. In total, six articles were reviewed in depth.

In previous reviews, other adverse events including thyroid neoplasms and pancreatic cancer were raised as potential concerns. Therefore, the third search added search terms that targeted these particular events. This search yielded 23 articles, of which three were duplicates identified in the second search (one of which was the Spanish article). Of the total yielded in the second and third search (27), three were not available from the library, one was written in Spanish, and through a careful reading of the abstracts, three were irrelevant.

The search strategy is shown in detail in Table 3. From the three searches combined, a total of 31 unique articles that contained relevant safety information were reviewed in depth.

Table 3. Literature Search Strategy	
Date of search	May 14, 2014, June 17, 2014, and July 15, 2014
Database	PubMed@FDA
Search Terms	<p>liraglutide AND (safety OR side effects OR adverse effects OR adverse events OR case reports)</p> <p>liraglutide AND (gallbladder or cholestasis or cholelithiasis or breast cancer or liver injury or arrhythmia or psychiatric adverse events)</p> <p>liraglutide AND (gallbladder OR cholestasis OR cholelithiasis OR breast cancer OR liver injury OR hepatic injury OR tachycardia OR arrhythmia OR psychiatric adverse events OR thyroid neoplasms OR pancreatic cancer)</p>
Years included in search	all through the date of each search
Limits	English

4.1 ADVERSE EVENTS OF INTEREST

4.1.1 Gallbladder related AE

None of the articles reviewed suggested that liraglutide, independent of its use in overweight or obese patients, is associated with gallbladder disease.

4.1.2 Breast Cancer

A meta-analysis, including 25 studies, indicated that liraglutide was not associated with an increased risk for cancer of any type.²⁸ The literature review did not identify a study specific to breast cancer risk alone.

4.1.3 Hepatic Injury

Liraglutide use, probably because of associated weight loss, resulted in reductions in ALT.²⁹ A case report recently published in June 2014 reported a case of autoimmune hepatitis in which history, laboratory test and liver biopsy results indicate a possible association with liraglutide use.³⁰ To date, no other reports of hepatic injury were identified in the literature search.

4.1.4 Tachycardic/arrhythmogenic AE

Mundil et al³¹ described a previous study that concluded that liraglutide did not cause a significant increase in QTc interval. A study using existing clinical data found liraglutide to have low rates (<1%) of MACE; these rates were similar to or lower than comparator drugs.³² A meta-analysis had similar findings and suggested that GLP-1 receptor agonists do not pose an increased risk of cardiovascular adverse events.³³

4.1.5 Psychiatric AE

One review article concluded, based on liraglutide clinical trials, that psychiatric disorders (insomnia, depressed mood, and nervousness) were reported with high-dose liraglutide (2.4 mg and 3.0 mg vs. placebo) and should be further investigated.³⁴ Because the dose of liraglutide indicated for obesity will be higher than that recommended for diabetes, special attention should be given to further reports of psychiatric adverse events associated with Saxenda.

4.1.6 Thyroid Neoplasms

GLP-1 agonists, such as liraglutide, have been shown to stimulate calcitonin secretion, C-cell proliferation, induction of C-cell hyperplasia, and development of C-cell adenomas and carcinomas in rodents.³⁵ At the time of approval, these events had not been observed in non-human primates or humans exposed to liraglutide. Serum calcitonin (CT) is a marker of C-cell proliferation, particularly in medullary thyroid carcinoma. Hegedus et al published a study in which CT concentrations were measured at 3-month intervals in subjects receiving liraglutide or control therapy for up to two years.³⁶ A review article also noted increased incidence of C-cell neoplasia in rodents exposed to liraglutide, however longitudinal data from clinical trials do not support any significant risk of activation or growth of C-cell cancer in humans.³⁷ Liraglutide was not associated with an increased risk of thyroid cancer in a meta-analysis of serious adverse events reported with GLP-1 agonists.³⁸ A commentary suggested that a careful history and physical exam pertaining to the thyroid be performed prior to initiating treatment with liraglutide or another GLP-1 receptor agonist.³⁹

4.1.7 Pancreatic Carcinoma

Two immunohistochemistry studies of GLP-1R expression in human pancreatic cancer demonstrated that GLP-1R activation has an antitumor effect, and suggests that liraglutide and other GLP-1R based therapies may be beneficial in patients with pancreatic cancer.^{40,41} A prospective study examined the risk of pancreatitis and pancreatic cancer with liraglutide and did not observe excess risk of either pancreatitis or pancreatic cancer compared to other antidiabetic drugs.⁴² A literature search concluded that pancreatitis is a potential complication of liraglutide therapy, and this might result in imaging studies and early detection of pancreatic cancer.⁴³ Writing in 2010, Anderson et al⁴⁴ reported four cases of pancreatitis among liraglutide-treated subjects (4 cases pancreatitis/1916 subjects exposed) and one case among comparator-treated subjects (1 case of pancreatitis/956 comparator subjects exposed) from three phase 3 trials known as the LEAD studies.⁴⁵⁻⁴⁷ We calculate a crude two-fold increase in the relative risk of pancreatitis among liraglutide users; however, this estimate is limited by a small number of events. Additionally, several case reports of pancreatitis that were possibly related to liraglutide have been reported.⁴⁸⁻⁵⁰ Finally, a meta-analysis, including 25 studies, indicated that liraglutide was not associated with an increased risk of acute pancreatitis or pancreatic cancer.⁵¹

4.2 ALL EVENTS LITERATURE REVIEW

A letter to the editor of The Journal of Clinical Pharmacology reported that a chronic (seven month) 10-fold liraglutide overdose resulted in only minor adverse effects.⁵² Another patient reportedly attempted suicide with liraglutide by injecting 80 times her daily dose (72 mg) and experienced gastrointestinal symptoms but not hypoglycemia.⁵³ This year, a case report of acute interstitial nephritis following liraglutide exposure was published.⁵⁴ The patient's kidney

function progressively improved after receiving steroids and transient dialysis, and liraglutide was discontinued. Another case report of presumably liraglutide-induced acute kidney injury was published in 2012.⁵⁵ Use of the Naranjo adverse drug reaction probability scale indicated a possible relationship between the patient's development of acute kidney injury and liraglutide. Several other review articles offered no new safety information.⁵⁶⁻⁶³

5 CONCLUSION

The majority of the spontaneous postmarketing reports that are the focus of this review have been previously assessed by OSE, and our reviews have identified several safety concerns: pancreatitis, acute renal failure, anaphylaxis and hypersensitivity reactions, and medication errors due to patients using the wrong injection technique. Accordingly, prescribing information has been updated to reflect these safety concerns.⁶⁴

The majority (75%) of these serious adverse event reports are for individuals over the age of 50. This demographic, in addition to the indication for which liraglutide is used, make any analysis of risk using spontaneous reporting for gallbladder, cardiovascular adverse events, or the cancers of interest (breast, thyroid, and pancreatic) problematic, because these events are relatively prevalent in individuals over 50 years old, with or without a diagnosis of diabetes mellitus. A known limitation analyzing spontaneous reporting is the inability to perform adequate causality assessments for events which are relatively common in the untreated population. Because of this high background rate, FDA must rely on adequately powered, randomized controlled trials, or well-designed observational studies, to better assess the cause and to determine if any of these events are attributable to liraglutide exposure. Additionally, there are a number of postmarketing investigations that are either complete or underway for Victoza™, including disease registries, animal models, and meta-analysis of controlled data that should aid in FDA's understanding of these safety risks.⁶⁵ Unfortunately, evidence that we have reviewed from FAERS and the literature in this current document do not substantially advance our knowledge of these safety risks. Better methods are needed to quantify and characterize these risks, preferably through large randomized trials or observational studies with controls.

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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.2 APPENDIX B. TOP PREFERRED TERMS FOR SELECT SOC'S

Gastrointestinal disorders (SOC) n=1,653

Event-Preferred Terms(PTs)	Total Cases
PANCREATITIS	395
NAUSEA	257
PANCREATITIS ACUTE	227
PANCREATIC CARCINOMA	204
VOMITING	200
DIARRHOEA	160
ABDOMINAL PAIN	142
ABDOMINAL PAIN UPPER	64
CONSTIPATION	44
PANCREATIC CARCINOMA METASTATIC	40

Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) n=613

Event-Preferred Terms(PTs)	Total Cases
PANCREATIC CARCINOMA	204
THYROID CANCER	42
PANCREATIC CARCINOMA METASTATIC	40
THYROID NEOPLASM	23
ADENOCARCINOMA PANCREAS	22
BREAST CANCER	16
PANCREATIC NEOPLASM	16
PAPILLARY THYROID CANCER	14
NEOPLASM MALIGNANT	11
PANCREATIC CARCINOMA STAGE IV	10
MEDULLARY THYROID CANCER	9

Cardiac disorders (SOC) n=428

Event-Preferred Terms(PTs)	Total Cases
CHEST PAIN	46
DIZZINESS	44
DYSPNOEA	42
ATRIAL FIBRILLATION	29
PALPITATIONS	29
MYOCARDIAL INFARCTION	26
CARDIAC FAILURE	23
SYNCOPE	23
CARDIAC FAILURE CONGESTIVE	20
TACHYCARDIA	17
SUDDEN DEATH	16
CHEST DISCOMFORT	15
ACUTE MYOCARDIAL INFARCTION	13
ANGINA PECTORIS	13
ANGINA UNSTABLE	13
CARDIAC ARREST	11

Vascular disorders (SOC) n=420

Event-Preferred Terms(PTs)	Total Cases
DIZZINESS	44
MYOCARDIAL INFARCTION	26
HYPOTENSION	25
CEREBROVASCULAR ACCIDENT	23
SYNCOPE	23
HYPERTENSION	17
ACUTE MYOCARDIAL INFARCTION	13
ANGINA PECTORIS	13
ANGINA UNSTABLE	13
TRANSIENT ISCHAEMIC ATTACK	13
GASTROINTESTINAL HAEMORRHAGE	10
PULMONARY EMBOLISM	10

7.3 APPENDIX C. TOP 100 PREFERRED TERMS REPORTED FOR LIRAGLUTIDE IN FAERS

Preferred Term (PT)	Total Cases	Percent Of Total
Pancreatitis	395	12.70096463
Nausea	257	8.263665595
Pancreatitis Acute	227	7.29903537
Pancreatic Carcinoma	204	6.559485531
Vomiting	200	6.430868167
Diarrhoea	160	5.144694534
Weight Decreased	156	5.01607717
Abdominal Pain	142	4.565916399
Dehydration	108	3.47266881
Cholelithiasis	83	2.668810289
Decreased Appetite	77	2.475884244
Blood Glucose Increased	76	2.443729904
Renal Failure Acute	72	2.31511254
Abdominal Pain Upper	64	2.057877814
Lipase Increased	60	1.92926045
Headache	57	1.832797428
Chest Pain	46	1.479099678
Diabetic Ketoacidosis	46	1.479099678
Constipation	44	1.414790997
Dizziness	44	1.414790997
Dyspnoea	42	1.350482315
Malaise	42	1.350482315
Thyroid Cancer	42	1.350482315
Renal Failure	41	1.318327974
Pancreatic Carcinoma Metastatic	40	1.286173633
Asthenia	38	1.221864952
Death	36	1.15755627
Loss Of Consciousness	35	1.125401929
Amylase Increased	34	1.093247588
Fatigue	34	1.093247588
Hypoglycaemia	34	1.093247588
Atrial Fibrillation	29	0.932475884
Palpitations	29	0.932475884
Abdominal Discomfort	28	0.900321543
Diabetes Mellitus Inadequate Control	28	0.900321543
Urinary Tract Infection	28	0.900321543
Hepatitis	27	0.868167203
Blood Glucose Decreased	26	0.836012862
Cholecystitis Acute	26	0.836012862
Myocardial Infarction	26	0.836012862
Off Label Use	26	0.836012862

Preferred Term (PT)	Total Cases	Percent Of Total
Hypotension	25	0.803858521
Pneumonia	24	0.77170418
Cardiac Failure	23	0.739549839
Cerebrovascular Accident	23	0.739549839
Gastroesophageal Reflux Disease	23	0.739549839
Syncope	23	0.739549839
Thyroid Neoplasm	23	0.739549839
Adenocarcinoma Pancreas	22	0.707395498
Condition Aggravated	22	0.707395498
Abdominal Distension	21	0.675241158
Heart Rate Increased	21	0.675241158
Cardiac Failure Congestive	20	0.643086817
Cholecystitis	20	0.643086817
Gastroenteritis	20	0.643086817
Hyperglycaemia	20	0.643086817
Pyrexia	20	0.643086817
Back Pain	19	0.610932476
Flatulence	19	0.610932476
Liver Function Test Abnormal	19	0.610932476
Fall	18	0.578778135
Hypersensitivity	18	0.578778135
Dyspepsia	17	0.546623794
Gastritis	17	0.546623794
Hypertension	17	0.546623794
Nephrolithiasis	17	0.546623794
Sepsis	17	0.546623794
Tachycardia	17	0.546623794
Breast Cancer	16	0.514469453
Depression	16	0.514469453
Pancreatic Neoplasm	16	0.514469453
Sudden Death	16	0.514469453
Chest Discomfort	15	0.482315113
Convulsion	15	0.482315113
Drug Interaction	15	0.482315113
Gastrointestinal Disorder	15	0.482315113
Hyperhidrosis	15	0.482315113
Pain	15	0.482315113
Tremor	15	0.482315113
Alanine Aminotransferase Increased	14	0.450160772
Blood Creatinine Increased	14	0.450160772
Exposure During Pregnancy	14	0.450160772
Hepatic Steatosis	14	0.450160772
Papillary Thyroid Cancer	14	0.450160772

Preferred Term (PT)	Total Cases	Percent Of Total
Acute Myocardial Infarction	13	0.418006431
Angina Pectoris	13	0.418006431
Angina Unstable	13	0.418006431
Blood Pressure Increased	13	0.418006431
Myalgia	13	0.418006431
Transient Ischaemic Attack	13	0.418006431
Urticaria	13	0.418006431
Anaemia	12	0.38585209
Coronary Revascularisation	12	0.38585209
Eructation	12	0.38585209
Gallbladder Disorder	12	0.38585209
Glycosylated Haemoglobin Increased	12	0.38585209
Jaundice	12	0.38585209
Liver Disorder	12	0.38585209
Vertigo	12	0.38585209

NDA 206,321 Saxenda (liraglutide) Advisory Committee Nonclinical Briefing Document

Reviewer: Anthony Parola, PhD
Pharmacologist, Division of Metabolism and Endocrinology Products

Introduction

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist from Novo Nordisk approved for marketing under the brand name Victoza in January 2010 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). NDA 206,321 from Novo Nordisk is seeking marketing approval for liraglutide as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in overweight adults with at least 1 weight-related comorbidity or obese adults under the brand name Saxenda. Saxenda and Victoza both consist of 3 mL of 6 mg/mL liraglutide solution for subcutaneous injection in a laminated rubber disc capped glass cartridge contained in a pen injector, and the only difference between the 2 products is the pen injector. The Victoza Flexpen is capable of delivering up to 1.8 mg liraglutide (0.3 mL) in a single injection, the maximum recommended human dose (MRHD) for the treatment of T2DM, while the Saxenda PDS290 pen injector is capable of delivering up to 3 mg/day liraglutide (0.5 mL dose volume) in a single injection, the only proposed maintenance dose and the MRHD for weight management.

Liraglutide is a lipidated human GLP-1 analog (Figure 1) with prolonged pharmacologic activity after subcutaneous injection due to delayed absorption, resistance to inactivation by endogenous peptidases (dipeptidyl peptidase IV and neutral endopeptidase) and high plasma protein binding in systemic circulation, which reduces renal excretion and also protects it from peptidases. Biologic effects of liraglutide are mediated by the GLP1R, a cell-surface receptor coupled to adenylyl cyclase through the stimulatory G-protein, Gs. *In vitro*, liraglutide is a selective GLP1R agonist pharmacologically active at cloned GLP1Rs from mice, rats, rabbits, pigs, monkeys, and humans. *In vivo*, liraglutide is active in animal models of T2DM and obesity. Liraglutide reduces body weight by reducing food consumption, a central effect mediated by GLP1Rs in areas of the brain that regulate food consumption.

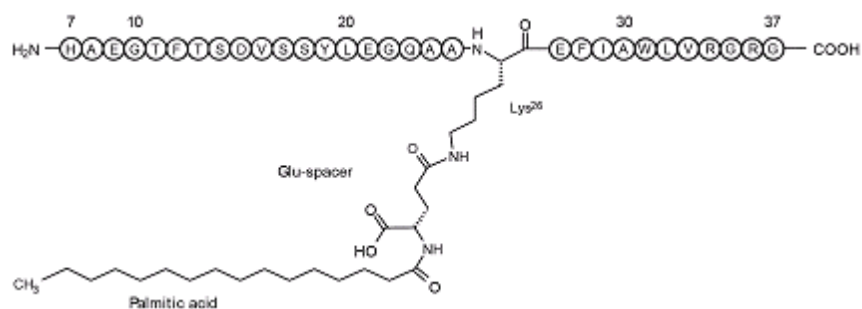


Figure 1 Structure of liraglutide

Pivotal nonclinical studies evaluating the safety of liraglutide previously reviewed under NDA 22-341 for Victoza (Parola 2009) were cross-referenced by NDA 206,321 for Saxenda. Liraglutide was well tolerated in repeat subcutaneous dose toxicity studies up to 26 weeks in rats and up to 52 weeks in monkeys. In rodent carcinogenicity studies, liraglutide caused benign and malignant thyroid C-cell tumors in rats at low multiples of human exposure and in mice at somewhat higher multiples of human exposure. Liraglutide associated tumors did not affect survival in 2-year carcinogenicity bioassays in mice or rats. There were no substantive

adverse effects of liraglutide on pancreas from mice, rats, cynomolgus monkeys, or insulin resistant diabetic rats.

Systemic clearance of subcutaneously injected liraglutide increases with body weight in humans. Despite the 1.7-fold higher MRHD for weight management (3.0 mg/day liraglutide) compared to the MRHD for the treatment of T2DM (1.8 mg/day liraglutide), estimated steady state plasma liraglutide exposure in humans using population pharmacokinetic data from obese adults treated with 3.0 mg/day liraglutide (AUC_{0-24h} 854 nM.hr) was only slightly higher than steady state systemic exposure in healthy adults administered 1.8 mg/day liraglutide (AUC_{0-24h} 809 nM.hr), based on AUC comparison. Therefore, human exposure multiples for findings in pivotal 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. Two major safety concerns with the use of liraglutide included in the approved label for Victoza and the proposed label for Saxenda concern the risk of thyroid C-cell tumors, based on rodent carcinogenicity studies, and the risk of pancreatitis, based on clinical studies and postmarketing safety reports.

Rodent Carcinogenicity

In 2-year life-time exposure studies in rats and mice treated by once-a-day bolus subcutaneous injection, liraglutide caused thyroid C-cell tumors in rats and mice and fibrosarcomas on the dorsal surface in male mice, the body surface used for drug administration. Liraglutide was not genotoxic in a standard battery of tests.

Mice

A 104-week lifetime-exposure carcinogenicity study of 0.03, 0.2, 1, or 3 mg/kg/day liraglutide injected subcutaneously once a day in CD-1 mice yielded systemic exposures 0.2-, 1.8-, 10-, and 38-times the estimated exposure in obese adult humans, respectively, at the maximum recommended human dose (MRHD) of 3.0 mg/day liraglutide based on plasma liraglutide AUC comparison. Mortality in mice was unaffected by liraglutide treatment. A dose-related increase in benign thyroid C-cell adenomas occurred at 1.0 and 3.0 mg/kg/day liraglutide in males and females (Table 1, below). A low incidence of treatment-related C-cell carcinomas occurred in females at 3.0 mg/kg/day liraglutide. 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). Thyroid focal C-cell hyperplasia, a preneoplastic C-cell lesion, occurred at ≥ 0.2 mg/kg/day in both sexes. Based on historical control group data from CD-1 mice, proliferative thyroid C-cell lesions, including focal hyperplasia, adenomas, and carcinomas, are rare (incidence < 1%). These data are consistent with dose-related progression of focal C-cell hyperplasia to adenomas in males and females with further progression to carcinomas in high dose females. The only distinction between focal C-cell hyperplasia and C-cell adenoma in rodents is the size of the lesion with foci of C-cells >5 average-sized contiguous follicles considered adenomas. Repeat subcutaneous dose studies of liraglutide in CD-1 mice show focal C-cell hyperplasia develops between 4 and 9 weeks of treatment and in the mouse carcinogenicity study, the earliest occurrence of C-cell tumors in decedents were malignant carcinoma in a female in week 64 and benign adenoma in a male in week 78 in the 3 mg/kg/day liraglutide group.

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

¹N = 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

²Human 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_{0-24h} 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)

Liraglutide-related fibrosarcomas in the dorsal skin and subcutis of male mice, the body surface used for drug administration, were increased above concurrent control and historical control group ranges at 3 mg/kg/day liraglutide (Table 2). Based on historical control group data, spontaneous fibrosarcomas in the skin and subcutis are common in mice (incidence > 1%), but fibrosarcomas at subcutaneous injection sites are rare (incidence <1%). Fibrosarcomas were attributed to the high local concentration of liraglutide near the injection site, and the concentration of liraglutide in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the 3 mg/kg/day liraglutide dosing formulation used in the mouse study (0.6 mg/mL).

Table 2. Incidence (% affected) of Fibrosarcomas on the Dorsal Skin and Subcutis or Injection Site in a 104-week Carcinogenicity Study of Liraglutide in CD-1 Mice

Sex		Males ¹					Females ¹				
		0	0.03	0.2	1	3	0	0.03	0.2	1	3
Liraglutide Dose (mg/kg/day)		-	0.001	0.007	0.02	0.10	-	0.001	0.007	0.02	0.10
Human Exposure Multiple ²		-	0.001	0.007	0.02	0.10	-	0.001	0.007	0.02	0.10
Injection Sites (dorsal surface)	Fibrosarcoma (malignant)	0	<u>1.5</u>	<u>1.5</u>	0	<u>5.1</u>	<u>1.3</u>	0	0	0	<u>2.5</u>
	Fibrosarcoma (malignant)	0	3.0	1.5	3.0	<u>8.9*</u>	1.3	1.5	1.5	0	2.5
Skin & Subcutis (dorsal surface)	Sarcoma, not otherwise specified (malignant)	1.3	0	0	0	1.3	1.3	0	1.5	0	<u>6.3</u>

¹N = 79 mice/sex examined in 0 and 3 mg/kg/day liraglutide groups, 67 mice/sex examined in 0.03, 0.2, and 1.0 mg/kg/day liraglutide groups

²Based on comparison of liraglutide concentration in dosing formulations used in mouse carcinogenicity study (0.006, 0.04, 0.12, and 0.6 mg/mL liraglutide for 0.03, 0.2, 1.0 and 3.0 mg/kg/day liraglutide, respectively) and the clinical formulation (6.0 mg/mL liraglutide).

*Statistically significantly different from control ($p < 0.05$)

Underlined value exceeds historical control incidence maximum for injection site fibrosarcomas (0% M, F), skins and subcutis fibrosarcoma (7.5% M, 5.0% F), and skin and subcutis sarcoma (2.0% M, 3.3% F)

Rats

A 104-week carcinogenicity study of 0.075, 0.25, or 0.75 mg/kg/day liraglutide injected subcutaneously once a day in Sprague Dawley rats yielded systemic exposures 0.5-, 2.7-, and 7.9-times the estimated exposure in obese adult humans, respectively, at the MRHD of 3.0 mg/day liraglutide based on plasma AUC comparison. A treatment-related increase in the incidence of thyroid C-cell adenomas occurred in males at 0.25 and 0.75 mg/kg/day liraglutide and in females at all liraglutide doses. A treatment-related increase in malignant C-cell carcinomas occurred in males at all liraglutide doses and in females at 0.25 and 0.75 mg/kg/day. A NOAEL for thyroid C-cell tumors was not established in this study. Thyroid C-cell adenomas are common tumors in 2 year studies in Sprague Dawley rats (historical control group incidence > 1%), but C-cell carcinomas are rare (historical control group incidence < 1%). The incidence of focal C-cell hyperplasia increased above concurrent control groups and above the historical control group range in males at all liraglutide doses and in females at 0.25 and 0.75 mg/kg/day. Although the incidence of thyroid C-cell focal hyperplasia and adenomas increase with age in rats, in repeat dose studies, liraglutide had no effect on the incidence of thyroid C-cell focal hyperplasia and it did not induce C-cell tumors in rats treated for up to 6 months.

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	<u>29</u>	<u>40</u>	<u>48*</u>	28	28	<u>55*</u>	<u>48</u>
	Adenoma (benign)	12	16	<u>42*</u>	<u>46*</u>	10	<u>27*</u>	<u>33*</u>	<u>56*</u>
	Carcinoma (malignant)	2	<u>8</u>	<u>6</u>	<u>14*</u>	0	0	<u>4.1</u>	<u>6</u>
	Total Tumors	14	22	42*	56*	10	27	37*	58*

¹N = 49 – 50 rats/sex/dose examined

²Human exposure multiple based on plasma AUC comparison at the maximum recommended human dose of 3.0 mg/day liraglutide yielding AUC_{0-24h} 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)

Human Relevance of Liraglutide-Induced Rodent Thyroid C-cell Tumors

In the development program for Victoza, Novo Nordisk performed mechanistic studies to address their hypothesis that thyroid C-cell tumors in rodents were not relevant to humans. The applicant proposed a mode-of-action for liraglutide induced C-cell tumors that included the following key steps: 1) activation of thyroid C-cell GLP1Rs by liraglutide, 2) stimulation of calcitonin secretion, 3) increased calcitonin synthesis, 4) C-cell hyperplasia due to persistent calcitonin secretion and increased calcitonin synthesis, and 5) progression of C-cell hyperplasia to adenomas with further progression to carcinomas. The applicant proposed that serum calcitonin was a C-cell “prehyperplasia” biomarker. During the review of Victoza NDA 22-341, the weight of evidence from mechanistic studies did not support the proposed mode of action in rats because:

1. Although published studies demonstrated GLP1Rs in rat thyroid by autoradiographic tissue binding, GLP1R agonist increased calcium-dependent calcitonin release from perfused rat thyroid cells, and inactivating the GLP1R in mice reduced thyroid calcitonin transcript levels, these studies along with the applicant's immunohistochemical and in situ hybridization studies did not conclusively demonstrate GLP1Rs localized to C-cells.
2. Calcitonin was not a biomarker for liraglutide-induced thyroid tumors in rats, and there was no consistent, sustained effect of liraglutide on plasma calcitonin levels.
3. Liraglutide did not consistently increase thyroid calcitonin mRNA.
4. Liraglutide increased the incidence of age-dependent focal C-cell hyperplasia, a preneoplastic lesion, but without accelerating its onset and without causing physiologic diffuse C-cell hyperplasia.
5. The incidence of liraglutide-induced thyroid C-cell tumors in rats increased with treatment duration, but required at least 7 months of treatment in both young and aged male rats. Therefore, liraglutide's C-cell tumorigenic effect was independent on the incidence of focal hyperplasia, which was higher in aged rats than in young rats.

The weight of evidence from mechanistic studies did not support the proposed mode of action in mice because:

1. Immunohistochemical localization and in situ hybridization studies of GLP1Rs in thyroid did not adequately demonstrate the receptor protein or transcript were localized to calcitonin immunoreactive C-cells. A published study showed that thyroid from 60% of mice (3/5) were positive for GLP1Rs detected by autoradiographic ligand binding, but GLP-1 binding activity wasn't localized to a specific cell-type.
2. Liraglutide caused focal C-cell hyperplasia, a preneoplastic lesion, without causing proliferation of normal C-cells (diffuse hyperplasia). These results indicated liraglutide transforms normal C-cells into preneoplastic C-cells in mice, a species lacking age-related increases in either plasma calcitonin or proliferative C-cell lesions.

CDER's Executive Carcinogenicity Assessment Committee (December 2008 meeting) and a large majority of members from a 2 April 2009 Endocrinologic and Metabolic Drug Advisory Committee convened to evaluate the safety and efficacy of liraglutide both concluded there was insufficient evidence to dismiss human relevance of liraglutide-induced C-cell tumors in mice and rats.

Approval of Victoza included two post-marketing requirements (PMRs) to further evaluate the risk of liraglutide-induced thyroid C-cell tumors: 1) PMR 1583-3, a 2-year study in mice to determine if 26 weeks of liraglutide treatment increases the lifetime risk of thyroid C-cell tumors and 2) PMR 1583-5, a 13-week study in mice to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid GLP1R and activation of the rearranged-during-transfection (RET) proto-oncogene, a receptor tyrosine kinase constitutively activated by mutation in the majority sporadic and familial medullary thyroid cancers.

The first PMR (PMR 1583-3) was fulfilled by a 104-week study in CD-1 mice subcutaneously administered 0 (vehicle), 0.2, 1.0, or 3.0 mg/kg/day liraglutide for 26 weeks followed by a 78 week recovery period (report 210145). In this study, at the end of the 26 week treatment period, liraglutide increased plasma calcitonin up to 14.1-fold in males at ≥ 0.2 mg/kg/day and up to 4.0-fold in females at ≥ 1.0 mg/kg/day and induced thyroid focal C-cell hyperplasia at ≥ 0.2 mg/kg/day in males (4.3% to 22.7% affected) and at 0.2 and 3.0 mg/kg/day in females (8.3% and 31.8%, respectively), but liraglutide did not induce C-cell tumors. By the end of the 78 week recovery period, plasma calcitonin remained elevated 1.4- to 1.8-fold in males previously treated with ≥ 0.2 mg/kg/day liraglutide, a low incidence of thyroid focal C-cell

hyperplasia exceeded the incidence in concurrent and historical control groups at 3.0 mg/kg/day liraglutide in males (3.8% affected at 3.0 mg/kg/day compared to 2.7% in concurrent controls and 0% in historical controls), and benign C-cell adenoma occurred in 1 female in the 3.0 mg/kg/day group (1.3% at 3 mg/kg/day liraglutide compared to 0% in concurrent and historical controls) (Table 4).

Table 4. Incidence (% affected) of Thyroid C-cell Proliferative Lesions in Mice During the 26-week Treatment Period or 78-week Recovery Period in Study 210145

	Sex Liraglutide Dose (mg/kg/day)	Male				Female			
		0	0.2	1	3	0	0.2	1	3
Human Exposure Multiple ¹		-	1.8	10	38	-	1.8	10	38
Death / Termination Period	Thyroid C-cell Pathology								
Treatment (weeks 1 - 27) ²	Focal Hyperplasia	0	4.3	8.3	22.7*	0	8.3	0	31.8*
Recovery (weeks 28 - 106) ³	Focal Hyperplasia	2.7	0	1.3	3.8	0	0	0	0
	Adenoma	0	0	0	0	0	0	0	1.3

¹Based on the AUC_{0-24h} ratio using toxicokinetic data from the same doses used in the mouse carcinogenicity study and estimated steady state plasma liraglutide AUC_{0-24h} 854 nM.hr in obese adult humans at the maximum recommended human dose of 3.0 mg/day liraglutide

²N = 22 - 25 mice/sex/dose examined

³N = 75 - 78 mice/sex/dose examined

*Statistically significantly different from control by pairwise comparison (p < 0.5)

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

Due to the low incidence of proliferative C-cell lesions in thyroid in male and female high dose recovery group mice and in concurrent control group male mice, a clear relationship to liraglutide treatment was not established for proliferative C-cell lesions in high dose recovery groups. Whether or not transient exposure to liraglutide increases the lifetime risk of proliferative C-cell lesions in mice could not be adequately addressed by this study because of the uncertainty that proliferative C-cell lesions in high dose recovery groups were related to liraglutide treatment.

The second PMR (PMR 1583-5) was fulfilled by a 13-week study of wild-type (WT) CD-1 mice subcutaneously injected once a day with 0 (vehicle), 0.03, 0.3, or 3 mg/kg/day liraglutide and genetically engineered GLP1R-deficient (GLP1RKO) mice subcutaneously injected once a day with 0 or 3 mg/kg/day liraglutide (report 209306). In this study, immunohistochemical analysis for calcitonin in thyroid tissue sections to identify C-cells showed liraglutide increased the incidence of minimal to slight diffuse C-cell hyperplasia at ≥ 0.3 mg/kg/day in both male and female WT mice, but 3 mg/kg/day liraglutide did not cause C-cell hyperplasia in GLP1RKO mice. Dose-dependent increased plasma calcitonin at the end of treatment occurring at ≥ 0.03 mg/kg/day liraglutide in WT mice (2.8- to 24.2-fold compared to controls in males and 2.5- to 12.1-fold in females) was consistent with drug-related C-cell hyperplasia. In GLP1RKO mice, liraglutide did not increase plasma calcitonin. Immunohistochemical analysis of thyroid tissue sections from WT mice in the control group without C-cell hyperplasia and 3 mg/kg/day liraglutide group with C-cell hyperplasia showed liraglutide induced phosphorylation of S235/S236 in ribosomal protein S6 in normal and hyperplastic C-cells, but without inducing phosphorylation of Y1062 in RET or S217/S221 in MEK1/2. Liraglutide induced thyroid C-cell hyperplasia in mice was GLP1R- dependent and liraglutide activated ribosomal protein S6 in C-cells, but without activating RET or MEK1/2 (Madsen 2012).

In addition to studies fulfilling Victoza nonclinical PMRs, the applicant submitted 3 mechanistic toxicity study reports in the Saxenda NDA: 2 studies in WT CD-1 mice and GLP1R knockout (GLP1RKO) mice evaluating the effects of a single subcutaneous dose of exenatide (report 205207) or liraglutide (report 209188) on plasma calcitonin and an *in situ* ligand binding study evaluating GLP1R localization in thyroid tissue sections from rats and humans (report CGo081003). GLP1R mediation of GLP1R agonist-induced increased plasma calcitonin was evaluated using wild-type (WT) and GLP1RKO mice. In single-dose studies of subcutaneously injected exenatide (1 or 5 mg/kg) or liraglutide (1 mg/kg), both exenatide and liraglutide increased plasma calcitonin levels in WT mice 6 hours after dosing, but not in GLP1RKO mice. GLP1R agonist-induced increased plasma calcitonin was GLP1R-dependent in mice. In an autoradiographic ligand binding study evaluating GLP1R binding activity in thyroid tissue sections from rats and humans, specific binding of the GLP1R antagonist [¹²⁵I]exendin(9-39) occurred in thyroid tissue from rats (8/8), but not humans (0/13). Calcitonin immunohistochemical staining showed thyroid tissue from 3 humans was devoid of C-cells and C-cell density was lower in thyroid tissue sections from humans compared to rats.

Since approval of Victoza (liraglutide) in 2010, one other long-acting GLP1R agonist approved for marketing in the US caused C-cell tumors in rodents. Exenatide long-acting release, an extended release formulation of exenatide administered once a week marketed as Bydureon (NDA 22-220), caused C-cell tumors in rats, but carcinogenicity was not assessed in mice. Albiglutide, a long acting GLP1R agonist administered subcutaneously once a week, was approved in 2014 (Tanzeum, BLA 125431), but carcinogenicity of albiglutide was not assessed due to the development of drug-clearing anti-drug antibodies in rodents. The GLP1R agonist lixisenatide (Lyxumia) was granted marketing authorization by the European Commission (EMA summary of approval), and it caused C-cell tumors in mice and rats. Several studies evaluating GLP1R expression in rodent and human thyroid were published after approval of Victoza (Boess 2013, Gier 2012, Pyke 2014, Waser 2011).

The weight of evidence from GLP1R localization studies is sufficient to conclude the receptor is localized on C-cells in thyroid from mice and rats and some proliferative C-cell lesions in humans. The weight of evidence is sufficient to conclude GLP1R agonist-induced proliferative changes in rodent thyroid C-cells are mediated by the GLP1R. However, there is insufficient evidence to support the sponsor's proposed mode of action in mice and rats for the reasons previously stated, except GLP1R expression has now been demonstrated on C-cells of mice and rats. Although evidence is accumulating the density of normal C-cells in thyroid is lower in primates compared to rodents and normal primate C-cells may not express GLP1Rs, at least to the same extent as rodents, GLP1Rs were demonstrated on C-cell lesions in humans. Furthermore, liraglutide was not a mitogen in rat C-cell lines CA77 and MTC 6-23 or in the human C-cell line TT (report 205295) suggesting the presence of other types of cells may be required for GLP1R agonist-induced C-cell tumors in rodents.

Despite additional nonclinical information, the proposed mode-of-action for liraglutide-induced thyroid C-cell tumors in rodents is not adequately supported by current nonclinical data. Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by nonclinical studies.

Pancreatitis

In clinical studies evaluating the use of liraglutide for the treatment of T2DM (Victoza) or weight management (Saxenda), the incidence of pancreatitis was higher in liraglutide-treated subjects compared to placebo and/or comparator treated subjects in both clinical development programs. Postmarketing reports for Victoza show acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, occurred in patients treated with Victoza. There were no findings in repeat dose toxicity studies or carcinogenicity studies of liraglutide consistent with pancreatitis.

Based on a higher incidence of pancreatitis in clinical studies of Victoza in patients with T2DM and a published study suggesting drugs that increase incretin activity may cause pancreatitis in a human islet amyloid polypeptide transgenic rat model of T2DM (Matveyenko 2009), approval of Victoza included a nonclinical post marketing requirement to determine the effects of liraglutide on the exocrine pancreas in a rodent model of insulin-resistant T2DM (PMR 1583-4).

PMR 1583-4 was fulfilled by a 3-month repeat subcutaneous dose toxicity study of 0 (vehicle), 0.4, or 1.0 mg/kg/day liraglutide administered once a day or 1.0 mg/kg/day administered twice a day (0.5 mg/kg/injection administered at least 8 hours apart) to male and female diabetic ZDF *fa/fa* rats evaluating the effects on the pancreas (study 208304). To minimize toxicity of high doses of liraglutide in diabetic rats, doses of liraglutide was titrated over 7 to 16 days to the final dose and the dose titration phase was immediately followed by a 12-week treatment period. Treatment-related mortality occurred in 3/8 diabetic males in a control group found dead from an unknown cause within 4 days after they were mistakenly administered a single dose of 0.5 mg/kg liraglutide on day 17. Liraglutide (0.4 or 1 mg/kg/day) was pharmacologically active in diabetic ZDF *fa/fa* rats decreasing food and water consumption, decreasing body weight gain, lowering non-fasting plasma glucose, and lowering HbA1c at ≥ 0.4 mg/kg/day in males and females. Increased pancreas β cell mass in diabetic females at 0.4 or 1.0 mg/kg/day liraglutide, but not in diabetic males, was attributed to improved β cell survival and consistent with increased glucose lowering efficacy in females. At several time points during the 12-week treatment period, 0.4 or 1.0 mg/kg/day liraglutide increased group mean plasma amylase in male and female diabetic rats, but without increasing plasma lipase or plasma triglycerides and without evidence of treatment-related macroscopic or microscopic pathology findings in the exocrine pancreas at the end of the study. In diabetic male rats, liraglutide had no effect on pancreas weight. In diabetic females, relative pancreas weight was significantly decreased at ≥ 0.4 mg/kg/day liraglutide, but decreased pancreas weight lacked correlative quantitative or qualitative changes in the exocrine or endocrine pancreas. Liraglutide did not affect exocrine cell mass (acinar or ductal cells) or exocrine cell proliferation in male or female diabetic rats. Liraglutide had no adverse effects on the exocrine pancreas of diabetic ZDF *fa/fa* rats (Vrang 2012).

In NDA 206,321 for Saxenda, the sponsor reported microscopic evaluation of pancreas from monkeys treated with 0 (vehicle), 0.25, or 5 mg/kg/day liraglutide for 87 weeks from a thyroid safety study titled "Effects on calcium homeostasis related parameters after up to 87 weeks daily subcutaneous administration in male and female cynomolgus monkeys – combined evaluation of in life phase including thyroid histopathological evaluation". Minimal focal inflammatory changes in the exocrine pancreas, characterized as perivascular inflammatory cell foci in 1 monkey, ductal inflammatory cell foci in a second monkey, and parenchymal inflammatory cell foci and focal lobular atrophy in a third, occurred in 3/5 males in the 5 mg/kg/day liraglutide group. In the absence of a consistent inflammatory effect in high dose group males or similar effects in liraglutide-treated females, the relation to treatment was considered equivocal. Findings in pancreas of monkeys in 5 mg/kg/day liraglutide high dose groups from 4 week (report 980184), 13 week (report 990191), and 52 week (report 200241) repeat dose toxicity studies and the 87 week thyroid toxicity study (report 203262) were evaluated against diagnostic criteria for human pancreatic intraepithelial neoplasia (PanIN) developed by the National Cancer Institute Pancreas Cancer Think Tank. There were no PanIN lesions present in monkeys treated with up to 5 mg/kg/day liraglutide for up to 87 weeks.

A recent published perspective from the FDA and the European Medicines Agency (EMA) concludes nonclinical data, clinical data, and postmarketing data for liraglutide and other incretin-based drugs are not sufficient to establish a causal relationship between the use of incretin-based drugs and pancreatitis or pancreatic cancer (Egan 2014). Based on results from repeat dose studies of liraglutide in mice, rats, and monkeys, including 104 week carcinogenicity

studies in mice and rats, an 87-week thyroid safety study in monkeys, and a 12-week study in a rat model of insulin resistant T2DM, there is no substantive evidence of liraglutide-induced injury to the pancreas in animals. An animal model of pancreatitis induced by incretin-based drugs has not been established.

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