CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206321Orig1s000

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF NEUROLOGY PRODUCTS

CONSULT M E M O R A N D U M

DATE: June 5, 2014

TO: Pat Madera, HFD 510, Division of Metabolism and Endocrinology Products (DMEP)

THROUGH: Billy Dunn, MD, Acting Director, Division of Neurology Products (DNP)

FROM: Ronald Farkas, MD, PhD, Clinical Team Leader, DNP

RE: NDA 206321, Lariglutide injection for obesity: sleep apnea study

1. Background

Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist currently approved for the treatment of type 2 diabetes mellitus (Victoza, NDA 022341). Novo Nordisk submitted an NDA in December 2013 for liraglutide for weight management (NDA 206321). The Division of Metabolism and Endocrinology Products (DMEP) notes that one of the trials supporting this application was a 32-week trial in patients with moderate to severe obstructive sleep apnea (OSA).

The sponsor proposes the following text for the *INDICATIONS AND USAGE section of labeling:*

> 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) (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** [emphasis added]

The sponsor is not proposing a more specific sleep apnea indication than above, (b) (4)

(b) (4)

DMEP consulted the Division of Neurology Products (DNP) to evaluate the trial, including the patient population, study design, and endpoints, (b) (4)

2. Liraglutide OSA Study

Title: NN8022-3970, *Effect of liraglutide in obese subjects with moderate or severe obstructive sleep apnea – a 32 week randomised, double-blind, placebo-controlled, parallel group, multi-centre and multinational trial*).

The study was conducted at 40 sites in the United States and Canada.

Key Inclusion Criteria:

- BMI ≥30 kg/m2
- Diagnosis of moderate or severe OSA (AHI ≥ 15)
- Unwilling or unable to use 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) ≥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)
- 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.

Secondary endpoints pertinent to OSA included the following:

- Subjects achieving OSA remission defined as AHI <5 events/hour (yes/no) after 32 weeks of treatment
- Subjects achieving 50% reduction in AHI from baseline after 32 weeks of treatment
- Subjects with improved AHI severity category (none ≤4.9, mild 5.0−14.9, moderate 15.0−29.9, severe ≥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) ≥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

Efficacy Findings

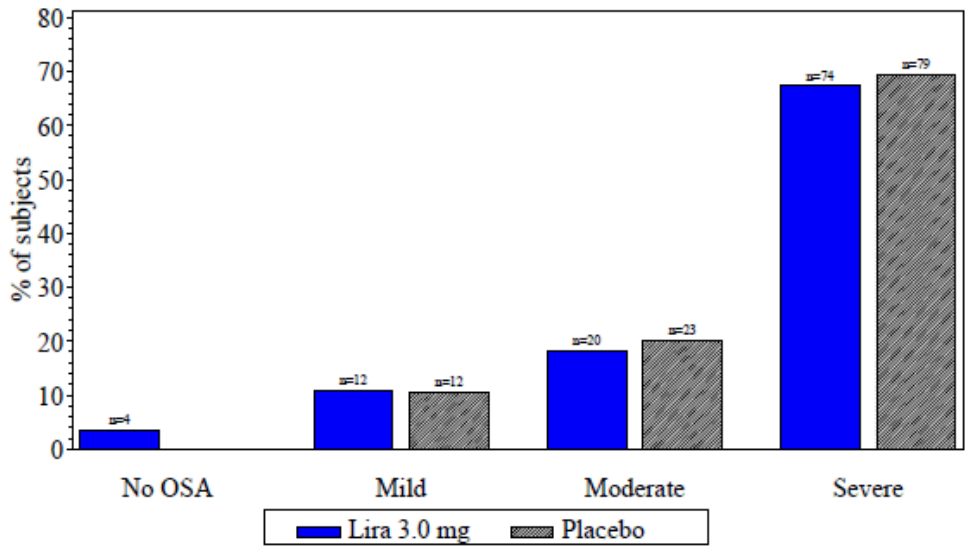
A total of 359 patients were randomized, with 72% male, and 80% between the ages of 40 and 65 years. The majority, 67%, had severe sleep apnea, and the mean baseline AHI was 49 events/hour, which the sponsor notes as "highly severe."

Withdrawals from the study were higher in the liraglutide vs. placebo group, 26% vs. 21%, respectively, and were related to adverse effects.

From a baseline AHI of 49 in each group, at week 32 the drug arm decreased by 12 events/hour and the placebo group by 6 events/hour (sponsor-reported p-value of 0.015; LOCF imputation). Results for females were numerically similar to males, but not statistically significant (p = 0.24). Sensitivity analyses were either positive (e.g. "completers" p-value 0.03) or close to positive (e.g. multiple imputation p = 0.054)

Secondary endpoints showed the following:

- OSA remission (AHI <5 event/hours) 5.4% drug vs. 1.2% placebo (reported p = 0.07)
- 50% reduction in AHI: 32% drug vs. 22% placebo (reported p = 0.05)
- Subjects with improved OSA severity category: the sponsor represents a number of analyses, including the below figure showing final (not change) in OSA severity in patients with severe baseline OSA.



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.

/nn8022/nn8022-3970/freeze_20131004_ctr
04OCT2013:14:37:53 - f_chart_osa_cat_bar.sas/e_osacat_shift_severe_w32_fas.cgm

Cross-reference: EOT Figure 14.2.28

Figure 11–4 OSA category at week 32 for subjects with severe sleep apnoea at baseline - full analysis set

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

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

Fasting body weight decreased 5.7% with liraglutide and 1.6% with placebo (reported p <0.0001).

Findings on the Epworth Sleepiness Scale and most domains of the two other PROs were not statistically significant.

The sponsor's efficacy conclusions regarding OSA endpoints are as follows:

Primary endpoint:

- From a mean baseline AHI of approximately 49 events/hour in both treatment groups, the mean changes in AHI were −12.2 events/hour with liraglutide 3.0 mg and −6.1 events/hour with placebo after 32 weeks of treatment. The ETD was statistically significant in favor of liraglutide 3.0 mg (−6.10 events/hour, p=0.0150).

Secondary endpoints:

- No statistically significant differences between groups were observed after 32 weeks of treatment for the secondary endpoints related to OSA.
- Numerical improvement in favor of liraglutide 3.0 mg was observed for 14 out of 15 sleep related endpoints

3. Discussion and Conclusions

Elevated BMI is a strong risk factor for OSA, and weight loss is associated with improvement in OSA, with the degree of improvement correlated to the degree of weight loss. OSA severity can be classified by AHI, but, as the sponsor notes in the study report, the correlation between any specific improvement in AHI and clinically relevant benefit remains poorly established. For example, while OSA may resolve after weight loss in patients with mild OSA, clinical benefits in terms of improved psychomotor performance and decreased risk of cardiac and metabolic adverse events can be difficult to measure, while in patients with more severe OSA, weight loss usually does not result in resolution of OSA or substantially decrease the need for other OSA treatments like continuous positive airway pressure (CPAP).

This study of liraglutide in obese patients with OSA was generally well-designed and conducted, with appropriate efficacy endpoints for characterizing a number of different aspects of OSA severity. However, the study also had important limitations in both design and findings that impacts interpretability:

- The study enrolled a relatively narrow population with moderate or severe OSA who were unable or unwilling to use CPAP. The specific size of change in endpoints like AHI, the primary endpoint, is affected by baseline values, and thus appears to be of limited usefulness for communicating effects of the drug in patients with less severe OSA. While some patients with OSA are intolerant to CPAP, clinical meaningfulness of change would seemingly be strongly affected by CPAP use; a patient with severe sleep apnea who *used* CPAP might gain little or no clinical benefit for OSA from liraglutide.
- Secondary endpoints measuring daytime sleepiness (e.g. Epworth), nighttime sleep (e.g. wake after sleep onset), and potential biomarkers of cardiovascular risk (e.g. blood oxygen saturation) were essentially all negative. This increases concern that the AHI finding is of unclear clinical meaningfulness.
- The study was only 32 weeks duration, yet clinical meaningfulness involves duration of effect for essentially life-long conditions like OSA. Even if reassurance is taken from other studies suggesting that weight loss has sustained benefit over several years in OSA (e.g. Kuna et al., Sleep 2013), it is not clear that the change in AHI at week 32 predicts a durable effect in the intended patient population for this drug.

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/s/

RONALD H FARKAS
10/20/2014

WILLIAM H Dunn
10/21/2014

CLINICAL REVIEW

Application Type	NDA
Application Number	206321
Priority or Standard	Standard
Submit Date	20 December 2013
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Division / Office	DMEP / ODE2
Reviewer Name	Julie Golden, M.D.
Review Completion Date	18 October 2014
Established Name	Liraglutide
Proposed Trade Name	Saxenda
Therapeutic Class	GLP-1 analog
Applicant	Novo Nordisk, Inc.
Formulation	Injection
Dosing Regimen	Daily
Indication	Chronic weight management
Intended Population	BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of at least one weight-related co-morbidity

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of this application.

As I describe further in section 1.2, I believe that some patients will derive substantial weight loss and associated health benefits from liraglutide 3 mg. While there are significant risks associated with this drug, I believe these risks are adequately addressed in labeling and with risk management strategies, and will continue to be characterized with post-marketing study.

My recommendation is influenced by the endorsement of the 11 Sep 2014 Endocrinologic and Metabolic Drugs Advisory Committee that voted 14 to 1 in favor of approval, as well as by the lack of treatment options for the obese patient population.

1.2 Risk Benefit Assessment

According to the 2013 American Heart Association / American College of Cardiology guidelines on the management of overweight and obesity, obesity raises the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some cancers, and is also associated with increased risk of all-cause and CVD mortality.[1] Obesity affects millions of American adults, is notoriously difficult to treat, and is therefore a significant public health issue.

The effort to treat obesity with drugs has been plagued with safety concerns and has led some drugs to never be approved in the United States (rimonabant) or to be removed from the U.S. market after approval (fenfluramine, dexfenfluramine, phenylpropanolamine, and sibutramine) due to serious toxicities. However, in recent years, new drugs have been approved, and as of this writing there are four agents approved for the chronic treatment of obesity: orlistat, lorcaserin, phentermine/topiramate, and naltrexone/bupropion. Although the landscape has changed with the availability of new drugs, obesity is a heterogeneous and relapsing condition, supporting the need for additional treatment options.

1 Jensen MD, et al. Executive summary: Guidelines (2013) for the management of overweight and obesity in adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Obesity 2014. 22(S2): S5-39.

Liraglutide is a glucagon like peptide-1 (GLP-1) receptor agonist that was approved for the treatment of type 2 diabetes in 2010. It impacts glucose control by increasing insulin secretion in the presence of elevated glucose concentrations. It also decreases glucagon secretion in a glucose-dependent manner and delays gastric emptying. Liraglutide is thought to act on appetite centers in the brain to decrease energy intake. The sponsor undertook a comprehensive evaluation of liraglutide for weight management after observing favorable weight changes with liraglutide for type 2 diabetes, and identified a higher dose that would be effective (3 mg, as compared to 1.2 mg and 1.8 mg doses approved for type 2 diabetes).

The effect of liraglutide 3 mg on weight is clear. According to Dr. Bradley McEvoy's biostatistics review, which utilized an intent-to-treat (preferred) analysis at week 56, mean percent placebo-subtracted weight change was -4.6% in the largest trial, -3.4% in a trial in patients with type 2 diabetes, and an additional -5.3% in a trial of patients who had lost at least 5% during a low calorie diet run-in period. Using the statistical reviewer's preferred analysis, 62% of patients on liraglutide 3 mg as compared to 34% of patients on placebo lost 5% of their body weight; in the trial in patients with type 2 diabetes, the proportions were 50% and 20%. When considering liraglutide- and placebo-treated patients who lost 10% of their body weights, the proportions were 34% and 15%, respectively, for the large trial, and 23% and 7%, respectively, for the trial in patients with type 2 diabetes. In addition to being statistically significant differences, these are clinically meaningful treatment differences. A weight loss of 5 to 10% is associated with improved cardiometabolic health, and therefore is the established endpoint for efficacy of weight loss drugs.[2]

Liraglutide also improves some of the biomarkers for cardiometabolic risk that are associated with weight. As expected (due to its effects on blood glucose), liraglutide lowered glucose and HbA1c in patients with and without type 2 diabetes. Although the benefits of improving glycemic parameters in patients without type 2 diabetes is not entirely clear, the Diabetes Prevention Program demonstrated that intensive lifestyle intervention delayed or prevented type 2 diabetes in patients at high risk over an average follow-up of 2.8 years,[3] and one could assume that improvements in glycemic parameters in those at risk for type 2 diabetes would be salutary. Liraglutide was also associated with reductions in systolic blood pressure of approximately 2.6 to 2.8 mmHg and diastolic blood pressure of 0.3 to 0.9 mmHg, in addition to placebo-subtracted low density lipoprotein (LDL) cholesterol decreases of 2.2 to 3.3%, high density lipoprotein (HDL) cholesterol increases of 0.6 to 2.8% and triglyceride (TG) decreases of 8.6 to 13.7%. These changes are small, but were directionally favorable and seen in the presence of decreases in the use or dose of concomitant medications.

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

3 Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New Engl J Med 2002; 346:393-403.

Other endpoints evaluated by the sponsor included the change in apnea-hypopnea index in obese patients with obstructive sleep apnea, and changes in patient reported outcomes (PROs). (b) (4) it is reassuring that changes were in a generally favorable direction, as one would expect for weight loss. Nevertheless, the clinically relevant improvement in apnea-hypopnea index has not been established, (b) (4) , fairly consistent improvements were observed in scores for physical functioning in two of the questionnaires. This supports the conclusion that the magnitude of weight loss observed with liraglutide likely improves how a patient feels or functions.

Despite these demonstrated benefits, there are very significant risks associated with liraglutide.

The risk of medullary thyroid cancer (MTC) is a serious concern with the use of this drug. It is unknown if the risk will increase with a higher dose, but it is theoretically possible. Although MTC was not observed with liraglutide 3 mg in the weight management program, the duration of exposure was likely not long enough to detect a treatment effect on thyroid C-cells. Cases seen in the post-marketing setting associated with Victoza were presented to an advisory committee meeting; as discussed at the meeting, there was not enough clinical information to determine causality. Liraglutide may increase calcitonin, which is produced by the C-cells and is a biomarker for MTC; however, it is not clear whether monitoring for MTC with calcitonin will have clinical utility or will instead lead to unnecessary thyroidectomies. Currently, monitoring with calcitonin is not recommended in the Victoza label. MTC is labeled in a boxed warning and in Warnings and Precautions. It is included in a REMS to communicate the risk to prescribers.

Other neoplasms were seen with liraglutide treatment. An excess in papillary thyroid cancer was also seen in the clinical trials; the majority of these cases were detected incidentally. Breast cancer was reported to a greater extent in liraglutide-treated patients. Although this finding has not been described previously with liraglutide (and a blinded assessment of adjudication of breast cancer to date in the post-marketing cardiovascular outcomes LEADER trial does not suggest an increased event rate in either of the treatment arms), there is a theoretical possibility that if liraglutide acts as a breast cancer promoter, the higher dose of liraglutide utilized in the weight management program could contribute to an increased risk for breast cancer. However, the possibility that the observed excess in the weight management trials is a chance finding, or ascertainment bias due to weight loss or other factors, cannot be discounted. At this time we are left with a safety signal of unclear clinical significance, but one that should be carefully followed in post-marketing studies. Similarly, an imbalance in colorectal

neoplasms (benign and malignant) was observed of unclear clinical significance. It is unknown if an increase in colorectal screening was undertaken in the liraglutide arm as a result of gastrointestinal adverse events, or if there is a drug effect leading to proliferative cellular changes. All of these neoplasms (papillary thyroid cancer, breast cancer, colorectal neoplasms) will be labeled, and additional adjudicated neoplasm data will be obtained from ongoing trials, including LEADER. Pancreatic cancer is an event of interest, although no cases of exocrine pancreatic cancer were seen in the weight management trials. The one case of neuroendocrine pancreatic cancer associated with liraglutide treatment was reported in a patient diagnosed with MEN1 (a genetic condition).

Acute pancreatitis was seen to a greater extent in liraglutide-treated patients and may be drug-related. Whether this adverse event is a direct effect of the drug or an effect mediated by an increase in gallstones (cholelithiasis and cholecystitis were also reported to a greater extent with liraglutide) cannot be determined with certainty, since cases of gallstone-associated and non-gallstone-associated pancreatitis were reported with liraglutide. In the post-marketing setting, hemorrhagic and necrotizing pancreatitis has been reported with Victoza and other incretin mimetics. Risks of pancreatitis and acute gallstone disease will be labeled in Warnings and Precautions (pancreatitis is also included in the REMS), and the mechanism of gallstones will be investigated further in a post-marketing commitment (PMC) study. Because gallstone-related adverse events were reported to a greater extent in liraglutide- than placebo-treated patients even after accounting for degrees of weight loss, there is a possibility that liraglutide has direct effects on gallbladder function and/or gallstone formation.

With respect to cardiovascular risk, the sponsor has conducted an assessment of (prospectively and retrospectively) adjudicated major adverse cardiovascular events (MACE) in their development programs – weight management and type 2 diabetes. Although upper bound of the 95% confidence intervals for the primary and numerous sensitivity analyses were well below cut-offs for approval of type 2 diabetes drugs,[4] these analyses were based on a small number of events. The LEADER trial, when complete, will characterize the CV risk of liraglutide, albeit for a lower (1.8 mg) dose. Liraglutide is associated with an increase in heart rate, although the increase did not appear convincingly dose-dependent. Notably, two other recently approved drugs for obesity also have a heart rate signal, phentermine/topiramate and naltrexone/bupropion. (The latter was recently evaluated in an interim analysis of a CV outcomes trial and was not considered to be associated with excess CV risk.) The advisory committee was asked to opine whether they thought a separate CV outcomes trial needed to be conducted for liraglutide 3 mg in the obese patient population, and there appeared to be agreement that a separate trial did not need to be done.

4 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

Committee members felt, however, that there may be additional CV risks that might not be best captured by MACE, including arrhythmias and pulmonary embolism. Other CV adverse events associated with liraglutide in the clinical trials included cardiac conduction disorders (first degree atrioventricular block, and right and left bundle branch blocks). This imbalance will be labeled.

There are a number of significant additional adverse events associated with liraglutide, including renal impairment, severe hypersensitivity, and severe hypoglycemia in patients on insulin secretagogues, that are fairly well-characterized with the class and will be labeled in Warnings and Precautions. In addition, because an imbalance in suicidality, including suicidal ideation and behavior, was reported in the clinical trials, this risk will be included in Warnings and Precautions. Psychiatric adverse events should continue to be followed in the post-marketing setting and in ongoing trials.

Because weight is a "symptomatic" condition, that is, patients are able to monitor the treatment effects, it is likely that patients will discontinue treatment if they are not achieving benefit. In my opinion, this will serve to enhance the benefit to risk ratio by exposing those patients who are most likely to receive long-term benefit. (Notably, 73% and 41% of liraglutide-treated patients who completed 56 weeks in the large trial, compared to 36% and 15% of placebo-treated completers, lost at least 5% and 10% of baseline body weight, respectively.) Ultimately, the label will serve to inform prescribers and patients on the risks and benefits of liraglutide. Patient selection (i.e., selecting patients at high risk from their obesity as treatment candidates) will be critical to ensure favorable benefit-risk.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

All GLP-1 receptor agonists, including liraglutide for diabetes (Victoza) have been approved with a REMS. Victoza's REMS has a communication plan that communicates the risk of thyroid C-cell tumors and pancreatitis. The REMS proposed for liraglutide will include the same risk messages and include a warning about the risk for duplicative therapies. See Dr. Amarylis Vega's REMS review for more details. I agree with the proposed changes by DRISK for risk communication and REMS assessments.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarketing Requirements

1. A juvenile rat toxicity study with liraglutide treatment from pre-puberty through reproductive maturity

2. A clinical pharmacology trial (NN8022-3967) to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 12 to 17 years (inclusive)

3. A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive)

4. A clinical pharmacology trial to assess pharmacokinetic and pharmacodynamic parameters of Saxenda in obese pediatric patients ages 7 to 11 years (inclusive)

5. A 56-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Saxenda for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). The trial may not be initiated until results from the Saxenda adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

6. A medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Saxenda (liraglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Saxenda (liraglutide).

7. To assess the risk of breast cancer associated with liraglutide, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the cardiovascular outcomes trial (LEADER), including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy

8. To assess the risk of breast cancer associated with liraglutide, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in Trial 1839, including (but not limited to) prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, age at menopause, history of radiation to the chest, age at menarche, and current/prior use of hormonal therapy.

Postmarketing Commitment

9. A study evaluating gallbladder ejection fractions in liraglutide treated subjects to further characterize the effect of liraglutide on gallbladder motility.

2 Introduction and Regulatory Background

2.1 Product Information

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 recreation 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,[5,6] 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.[7]

Liraglutide has also been shown to increase heart rate in humans and cause c-cell tumors in rodents.[5] The relationship of liraglutide to pancreatitis or pancreatic or thyroid tumors (including non-c-cell tumors) in humans has been speculated, but remains controversial.[8,9,10,11,12] This review focuses on liraglutide clinical trial data for weight loss efficacy as well as for human safety.

5 Victoza (liraglutide) prescribing information.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf
6 Byetta (exenatide) prescribing information.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf
7 Sisley S, et al. Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. J Clin Invest. 2014; 124(6): 2456-63.
8 Egan AG, et al. Pancreatic safety of incretin-based drugs – FDA and EMA assessment. N Engl J Med 2014; 370:794-7.
9 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.
10 Gier B, et al. Glucagon like peptide-1 receptor expression in the human thyroid gland. J Clin Endocrinol Metab. 2012; 97: 121-31.
11 Pyke C and Knudsen LB. The glucagon-like peptide-1 receptor – or not? Endocrinology. 2013; 154(1): 4-8.
12 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.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. FDA-approved Medications for Chronic Weight Management

Drug NDA Number	Year Approved	Mechanism of Action	Indication
Xenical (orlistat) NDA 20766	1999	Lipase inhibitor	XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).
Belviq (lorcaserin HCl) NDA 22529	2012	Serotonin 2C receptor agonist	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of • 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus)
Qsymia (phentermine/topiramate XR) NDA 22580	2012	Sympathomimetic amine anorectic and antiepileptic drug	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of • 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia
Contrave (naltrexone HCl and bupropion HCl) NDA 200063	2014	Opioid antagonist and aminoketone antidepressant	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

			• 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)

Source: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

2.3 Availability of Proposed Active Ingredient in the United States

Liraglutide is approved as Victoza for the treatment of type 2 diabetes at doses up to 1.8 mg. A limitation of use is included in labeling that Victoza is not recommended as first-line therapy due to the risk of thyroid C-cell tumors.

2.4 Important Safety Issues With Consideration to Related Drugs

- Thyroid C-cell tumors (medullary thyroid cancer): discussed in sections 4.3 and 7.3.5
- Pancreatitis and pancreatic cancer: discussed in section 7.3.5
- Serious hypoglycemia: discussed in section 7.3.5
- Renal impairment: discussed in section 7.3.5
- Hypersensitivity: discussed in section 7.4.6
- Cardiovascular risk: discussed in section 7.3.5

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- At the completion of the type 2 diabetes program, the sponsor proposed the weight management program in a pre-IND/end-of-phase 2 meeting (3 Apr 2008). At that meeting, preliminary clinical data from trial 1807 were presented and liraglutide (b) (4) mg was proposed.
- 28 May 2010, FDA provided advice on the proposal for the clinical development of liraglutide 3 mg for obesity. In general, FDA agreed with the extent of exposure and safety monitoring proposed.
- 4 Nov 2011, FDA confirmed with the sponsor that the thorough QT study conducted in support of the approval of liraglutide for diabetes (NDA 22341) was sufficient for the weight management program, despite the fact that the highest dose studied was 1.8 mg.

- 12 Jun 2012, FDA stated that it was unlikely that additional drug-drug interaction studies would be required.

- 14 Sep 2012, the Controlled Substance Staff stated in a letter to the sponsor that they did not recommend any further studies to assess the abuse potential of liraglutide.

- The sponsor proposed to the Agency conducting a meta-analysis of MACE in the clinical trials to assess cardiovascular risk prior to approval. FDA recommended that the sponsor provide a justification for including comparators associated with cardiovascular risk in an initial correspondence (14 Sep 2012), and then additionally recommended in a follow-up correspondence that all adverse events within relevant SMQs from trials that did not implement prospective adjudication should adjudicate MACE post-hoc (5 Oct 2012).

- In a correspondence from the biostatistics team dated 6 May 2013, reservations regarding combining efficacy results from the various phase 3 trials into the ISE were conveyed. In addition, they informed the sponsor that analyses other than LOCF for assessing the primary endpoint were preferred in order to properly account for missing data.

- 29 May 2013, DMEPA and CDRH provided written guidance to the sponsor regarding the pen-injector device.

- The pre-NDA meeting was held with the sponsor 10 Sep 2013. The data presentation in the weight management and supplementary (type 2 diabetes) pools were discussed.

2.6 Other Relevant Background Information

As described in the FDA draft guidance for developing weight management drugs,[2] 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.[13]

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.

13 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.

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)].[14] The results from this trial led to sibutramine being removed from the U.S. market.

The Look AHEAD (Action for Health in Diabetes) trial[15] 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 7.3.5.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

I had a number of difficulties with this NDA that decreases my confidence in the safety assessment.

- Conducting my own explorations of the data was challenging, and I had to rely on the sponsor's safety analyses in many cases
    - Reproducing the sponsor's laboratory or adverse event tables was difficult (required manipulation of the dataset that was not intuitive or obvious)
    - Data were difficult to find
    - Data definitions for variables were in many cases unclear

- Laboratory and vital sign data were a particular challenge:
    - Not assessed for outliers except for calcitonin, amylase, and lipase; calcitonin analyses did not include mean/median change from baseline

14 James WPT, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010; 363:905-17.
15 The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369: 145-54.

  - The company relied on investigator interpretation, which was inconsistent; e.g., some results that appeared inconsequential were reported as SAEs, other very abnormal lab / HR results not reported as AEs at all:
    - ALT value > 1500 U/L not reported as an AE

- There was limited patient-level information if an AE was not considered an SAE or MESI

- Data convention of only one value per visit flagged for inclusion in database excluded some laboratory and questionnaire data excluded from categorical analyses (such as abnormally high ALT and PHQ-9 total score)

- Data management issues:
  - A HR value reported as 208 bpm was not caught in data QA (data entry error)
  - The coding of ALT excluded clinically "impossible" values, defined in one example as an ALT over 1500 U/L (which is most definitely *not* clinically impossible)

- 120-day safety update (which updated an interim safety analysis using a new data cut of the ongoing trial 1839-ext): "data cleaning" resulted in a number of "corrected" SAEs from what was reported in the integrated summary of safety (ISS) from the original NDA; i.e., deleted or downgraded from serious to non-serious. The significance of these changes during the course of an ongoing trial is unclear, although it is noted that 15 of the events were in patients treated with liraglutide, whereas only two events were in patients treated with placebo.

The sponsor answered all of my queries in a timely fashion, and did follow up with investigators many years after a study had been completed to obtain information about a particular adverse event or abnormal laboratory or vital sign data point.

3.2 Compliance with Good Clinical Practices

For each trial, the sponsor stated that the protocol, the protocol amendments, the consent form and the subject information sheet were reviewed and/or approved by the Health Authorities and independent ethics committees (IECs) or IRBs in each country involved, according to local regulations, prior to trial initiation.

The trials were performed in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial, as stated in the protocol. The patients were informed of the risks and benefits of the trials.

Trials 1839, 1922, and 3970 were additionally conducted in accordance with the International Conference on Harmonisation Good Clinical Practice, and the FDA 21 Code of Federal Regulations, parts 312, 50, and 56 were followed.

Trial 1923 was additionally conducted in accordance with FDA 21 CFR 312.120.

Six clinical sites (five domestic and one foreign) and Novo Nordisk were inspected by the Office of Scientific Investigations, and are summarized in the table below. Two of the sites (Drs. Frederick and Soufer) were issued a Form FDA-483. Preliminary classifications for these inspections are Voluntary Action Indicated (VAI). Dr. Cynthia Kleppinger from the Division of Good Clinical Practice Compliance notes in her review that the regulatory violations observed at these sites were unlikely to significantly impact primary safety and efficacy analyses, and data reliability is considered acceptable. Drs. Bays, Wittmer, Orr and Veenendaal and the sponsor were not issued a Form FDA-483; the classifications are all NAI (No Action Indicated). Data from these sites and the sponsor are considered reliable based on the available information. Please see Dr. Kleppinger's review for more information.

Table 2. Clinical Inspections

Name of CI/Site #	Protocol # and # of Subjects Randomized	Inspection Date	Preliminary Classification
Harold Bays Site #11519/939	NN8022-1922 10 subjects	5/22-29/2014	NAI
Bret Wittmer Site #11161/126	NN8022-1923 16 subjects	6/23/27/2014	NAI
Mark Fredrick Site #2816/428	NN8022-1839 25 subjects	6/06-26/2014	VAI 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. • Subjects 428010 and 428014 were randomized incorrectly • Subject 428018 met the exclusionary criterion of major depression within the last 2 years • Subject 428016 was on exclusionary medication (topiramate) • Subject 428019 was randomized without a pregnancy test • All concomitant medications for at least three subjects were not captured into the electronic database • Past medical history was entered incorrectly into the electronic database for Subjects 428024 and 428015 (both had history of depression). Dr. Fredrick responded to the observations in a letter dated July 9, 2014.

			Corrective actions have been taken and the response is acceptable.
Robert Orr Site #44642/965 Site#14544/118	NN8022-1922 6 subjects NN8022-1923 20 subjects	6/19-25/2014	NAI
Joseph Soufer Site #11157/481	NN8022-1839 28 subjects	6/9-24/2014	VAI 1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. • Females of childbearing potential were to have a serum pregnancy test (hCG) performed in connection with Screening Visit 1 and the End of Treatment visit (Visit 17, 21a or 43b). A serum pregnancy test was not performed at Visit 17 for 7/10 subjects who met this requirement and 2/10 subjects at Visit 21A. There were no known reported pregnancies in these subjects. • A repeat oral glucose tolerance test was not performed on one subject (481005) who had a fasting plasma glucose that exceeded 200 mg/dL 2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation • The source document and case report form did not match for one adverse event (upper left quadrant pain vs. intermittent upper right quadrant pain) reported for one subject (481029) Dr. Soufer responded to the observations in a letter dated July 1, 2014. Corrective actions have been made and the response is acceptable.
Aletha Veenendaal Site #11241/251	NN8022-1839 47 subjects	5/19-27/2014	NAI
Novo Nordisk	NN8022-1922 NN8022-1923 NN8022-1839	6/03-19/2014	NAI

Source: C. Kleppinger, OSI, signed 2 Sep 2014

3.3 Financial Disclosures

The applicant has adequately disclosed financial interests/arrangements with clinical investigators (see the Appendix, section 9.5). Disclosed interests/arrangements or lack of disclosure despite due diligence do not raise questions about the integrity of the data. These were large, randomized controlled trials with objective endpoints and many investigators. It is unlikely the relatively small number of investigators with disclosed interests would impact the overall results. The total number of randomized patients at sites with investigators with disclosed interests was 215, out of 5827 total patients randomized in phases 2 and 3.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no CMC efficacy or safety issues.

4.2 Clinical Microbiology

There are no drug product or drug substance microbiology safety issues.

Liraglutide is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

Nonclinical studies evaluating the safety and toxicity of liraglutide were conducted under NDA 22341 and cross-referenced to NDA 206321. Please refer to reviews of NDA 22341 for full discussion of nonclinical safety; in particular the risk of thyroid C-cell tumors observed in rodents that is the basis of a boxed warning and REMS.

Safety margins for toxicities under NDA 22341 were calculated utilizing steady state systemic exposure in healthy adults at the 1.8 mg/day dose of liraglutide, which is similar to the exposure in obese adults at the 3 mg/day dose based on plasma liraglutide AUC.

Dr. Anthony Parola notes in his review that no new safety concerns from nonclinical studies for the proposed indication have been identified.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

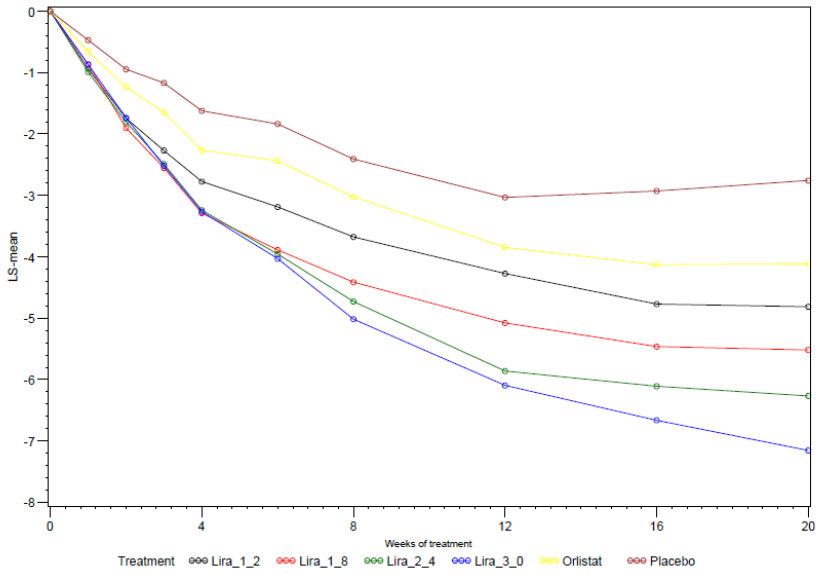
The following is described in section 12 of the proposed label:

Liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenylyl cyclase activation through the stimulatory G-protein, Gs. GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. In animal studies, peripheral administration of liraglutide resulted in the presence of liraglutide in specific brain regions regulating appetite, including the hypothalamus.

4.4.2 Pharmacodynamics

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 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 1 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.

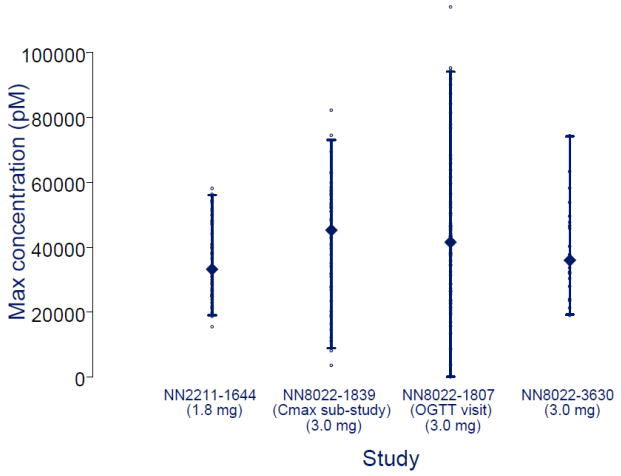
Figure 1. Plot of LS Mean Change in Body Weight versus Time, ITT, LOCF; Trial 1807



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 2); this finding supports the acceptability of the thorough QTc trial previously conducted for the weight management indication.

Figure 2. 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

4.4.3 Pharmacokinetics

Liraglutide is an analog of native GLP-1. Liraglutide was developed for once-daily administration due to its relatively slow absorption rate and a half-life of approximately 13 hours. The relatively long half-life (as compared to endogenous GLP-1) is thought to be due to a number of factors, including, 1) self-association, which results in slow absorption; 2) higher enzymatic stability towards degradation or inactivation by dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidase (NEP) enzymes, and 3) an *in vitro* plasma protein binding of greater than 98 percent.

Liraglutide is metabolized in a similar manner to native GLP-1 (i.e., by DPP-IV and NEP) although at a much slower rate. DPP-IV and NEPs are present ubiquitously in the body and therefore the elimination of liraglutide is not organ-specific.

Liraglutide exposure has been shown to increase proportionally with dose. Exposure increases with decreasing body weight and is higher for women than for men.

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. [a]Normoglycaemic plus pre-diabetes subjects,

Source: Population PK Modeling Report, Table 6

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4 lists the trials in the weight management and T2DM programs, and under which NDA they were submitted.

Table 4. Trials Included in the Liraglutide 3 mg NDA

Program	Trial	Location
Liraglutide in Weight Management	NN8022-1807	NDA 206321
	NN8022-1807-ext	NDA 206321
	NN8022-1839	NDA 206321
	NN8022-1922	NDA 206321
	NN8022-3970	NDA 206321
	NN8022-1923	NDA 206321
Liraglutide in Type 2 Diabetes (Victoza)	NN2211-1310	NDA 22-341 sequence 0000
	NN2211-1332	NDA 22-341 sequence 0000
	NN2211-1333	NDA 22-341 sequence 0000
	NN2211-1334	NDA 22-341 sequence 0000
	NN2211-1436	NDA 22-341 sequence 0000
	NN2211-1499	NDA 22-341 sequence 0000
	NN2211-1571	NDA 22-341 sequence 0000
	NN2211-1572	NDA 22-341 sequence 0000
	NN2211-1572-ext	NDA 22-341 sequence 0000
	NN2211-1572-ext2	NDA 22-341 sequence 0096
	NN2211-1573	NDA 22-341 sequence 0000
	NN2211-1573-ext	NDA 22-341 sequence 0000
	NN2211-1573-ext-2	NDA 22-341 sequence 0096
	NN2211-1573-ext-3	NDA 206321
	NN2211-1573-ext-4	NDA 206321
	NN2211-1574	NDA 22-341 sequence 0000
	NN2211-1697	NDA 22-341 sequence 0000
	NN2211-1700	NDA 206321
	NN2211-1700-ext	NDA 206321
	NN2211-1701	NDA 206321
	NN2211-1701-ext	NDA 206321
	NN2211-1796	NDA 206321
	NN2211-1797	NDA 22-341 sequence 0096
	NN2211-1797-ext	NDA 22-341 sequence 0096
	NN2211-1797-ext-2	NDA 206321
	NN2211-1799	NDA 206321
	NN2211-1842	NDA 22-341 sequence 0151
	NN2211-1842-ext	NDA 22-341 sequence 0151
	NN2211-1860	NDA 22-341 sequence 0148
	NN2211-1860-ext	NDA 22-341 sequence 0148
	NN2211-1860-ext-2	NDA 206321
	NN2211-2072	NDA 22-341 sequence 0000
	NN2211-3924	NDA 206321
	NN2211-3925	NDA 206321
Semaglutide in Type 2 Diabetes	NN9535-1821	NDA 206321
IDegLira in Type 2 Diabetes	NN9068-3697	NDA 206321
	NN9068-3697-ext	NDA 206321
	NN9068-3912	NDA 206321
Degludec in Type 2 Diabetes	NN1250-3948	NDA 206321

Source: Supplementary AE Report, Tables 1-1 and 1-2

The following table describes in more details the trials in the weight management program that were the focus of this review.

Table 5. Weight Management Trials

Trial ID	Type of Study	Trial Design; Type of Control	Test Drugs and Route of Administration	Number of Exposed Subjects (Males/Females)	Type of Subjects	Treatment Duration
NN8022-3630	PK and PD	Single-center, randomized, double-blind, incomplete cross-over trial Placebo control	Liraglutide: Once-daily s.c. dose of 1.8 mg or 3 mg (dose-escalated in weekly increments of 0.6 mg) Paracetamol: p.o. doses of 15 mg	49 (29/20) Liraglutide 1.8 mg / 3 mg: 49 Placebo: 33	Healthy, obese	35 days + 2 days
NN8022-1807	Efficacy and Safety	Multi-center, multi-national, randomized, double-blind (orlistat open-label) trial Placebo and active control	Liraglutide: Once-daily s.c. doses of 1.2, 1.8, 2.4, or 3 mg, dose escalated in weekly steps of 0.6 mg Orlistat: t.i.d. p.o. doses of 120 mg	564 (135/429) Liraglutide 1.2 mg: 95 Liraglutide 1.8 mg: 90 Liraglutide 2.4 mg: 93 Liraglutide 3 mg: 93 Orlistat: 95 Placebo: 98	Healthy, obese	20 weeks
NN8022-1807 Extensions	Efficacy and safety	Multi-center, multi-national, randomized, double-blind (orlistat open-label) extension trial Placebo and active control	Liraglutide: Once-daily s.c. doses of 1.2, 1.8, 2.4, or 3 mg Orlistat: t.i.d. p.o. doses of 120 mg	394 (298/100) Liraglutide 1.2 mg: 67 Liraglutide 1.8 mg: 58 Liraglutide 2.4 mg: 65 Liraglutide 3 mg: 71 Orlistat: 67 Placebo: 66	Healthy, obese	32 weeks + 52 weeks
NN8022-1839	Efficacy and safety	Multi-center, multi-national, randomized, double-blind, parallel-group trial Placebo control	Liraglutide: once-daily s.c. doses of 3 mg, dose-escalated in weekly increments of 0.6 mg	3723 (803/2928) Main period (56 weeks) Liraglutide 3 mg: 2481 Placebo:1242 Re-randomized period (12 weeks) Lira/lira: 351 Pbo/pbo:304 Lira/pbo: 350	Obese, overweight, with comorbidities	56 weeks + 12-week re-randomized period
NN8022-1922	Efficacy and safety	Multi-center, multi-national, randomized,	Liraglutide: once-daily s.c. doses of 1.8 or 3 mg, dose-escalated	844 (425/421) Liraglutide 1.8 mg: 210 Liraglutide 3 mg:	Obese or overweight with type 2 DM	56 weeks

		double-blind, parallel-group trial Placebo control Background medication: metformin, sulfonylurea and glitazone	in weekly increments of 0.6 mg Metformin and glitazone: individual, stable pre-trial dose and frequency Sulfonylurea: individual, stable pretrial frequency; dose reduced by 50%	422 Placebo: 212		
NN8022-3970	Efficacy and safety	Multi-center, multi-national, randomized, double-blind, parallel-group trial Placebo control	Liraglutide: once-daily s.c. doses of 3 mg, dose-escalated in weekly increments of 0.6 mg	355 (258/101) Liraglutide 3 mg: 176 Placebo: 179	Obese subjects with moderate or severe sleep apnea	32 weeks
NN8022-1923	Efficacy and safety	Multi-center, multi-national, randomized, double-blind, parallel-group trial Placebo control	Liraglutide: once-daily s.c. doses of 3 mg, dose-escalated in weekly increments of 0.6 mg	422 (79/343) Liraglutide 3 mg: 212 Placebo: 210	Healthy, obese	56 weeks

Source: Tabular Listing of All Clinical Studies

5.2 Review Strategy

The focus of this review was the 3 mg dose studied in the weight management program. The five phase 2 and 3 trials conducted in support of this indication were evaluated individually for efficacy and primarily pooled for safety (ISS). Trials conducted under other development programs were pooled by the sponsor into a supplementary pool for supportive safety. Those data were used to support the safety of the 3 mg dose for the weight management indication. I am the sole reviewer for this application, but relied on the expertise of a number of consultants and other disciplines to support my review. Those reviews are referred to throughout this document.

5.3 Discussion of Individual Studies/Clinical 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)

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.[2] 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 of body composition, cardiovascular risk factors, and glucose metabolism.

Trial 1839

This trial was a randomized, double-blind, placebo-controlled, parallel-group, multinational trial with obese (BMI 30 kg/m^2 or greater) patients or overweight (BMI 27 kg/m^2 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/m^2). 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 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.

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/m^2 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.

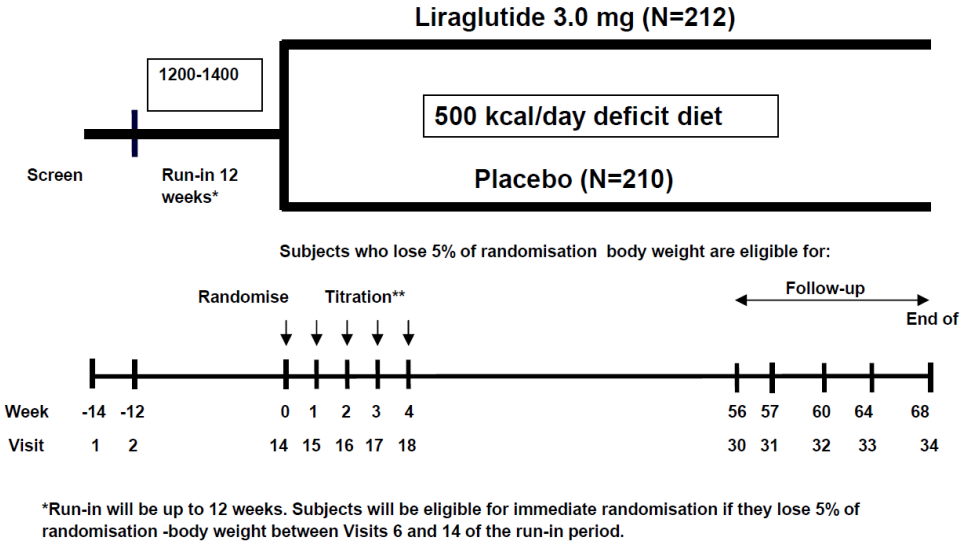
Trial 1923

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

Figure 3. Schematic of Study Design, Trial 1923



*Run-in will be up to 12 weeks. Subjects will be eligible for immediate randomisation if they lose 5% of randomisation -body weight between Visits 6 and 14 of the run-in period.

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%).

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/m^2
- 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) ≥ 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)
- 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 ≤ 4.9, mild 5.0−14.9, moderate 15.0−29.9, severe ≥ 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) ≥ 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.

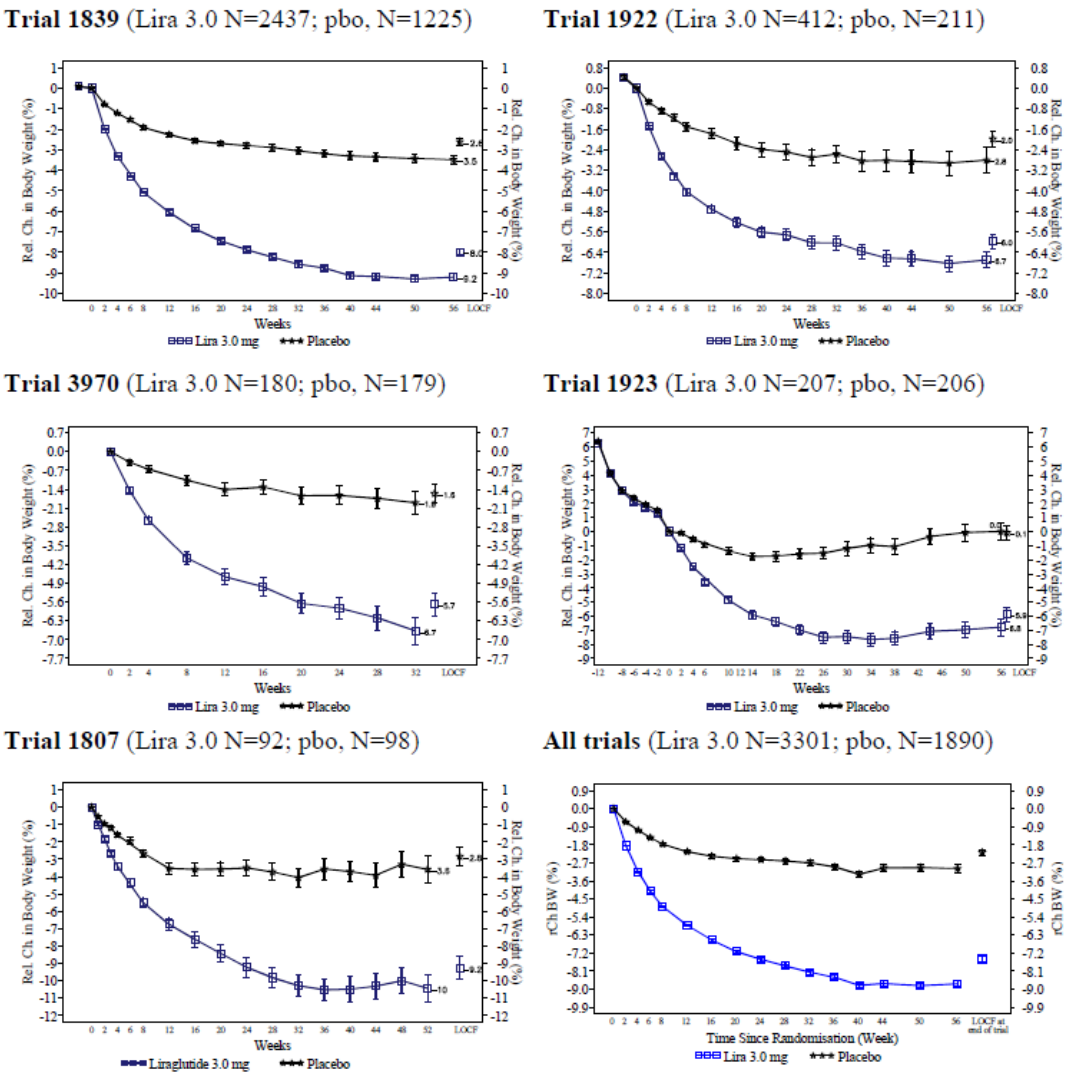
6 Review of Efficacy

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.

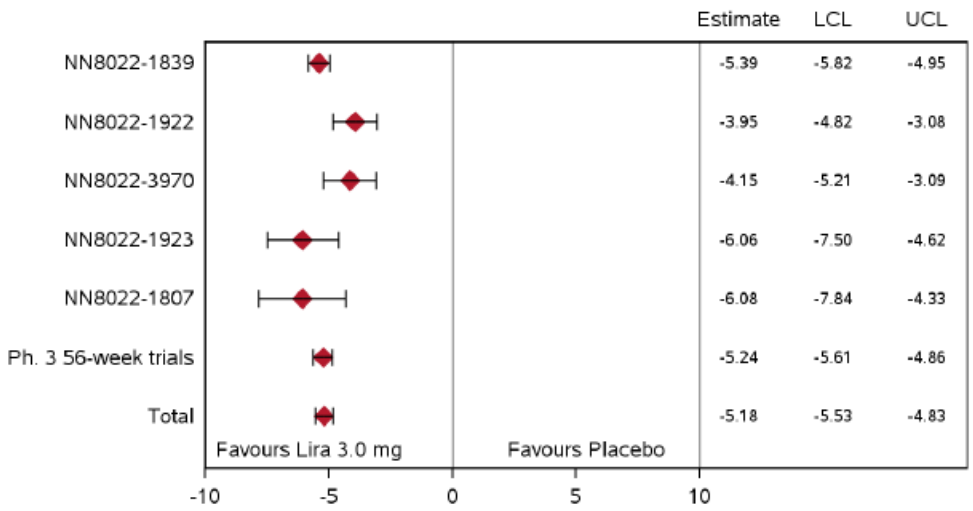
Figure 4 and Figure 5 describe the weight loss in the liraglutide 3 mg and placebo groups over time and the treatment differences for weight change from baseline, respectively. Results from the individual phase 3 56-week trials (1839, 1922, and 1923), the phase 3 32-week sleep apnea trial (3970), and 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 4. Percent Body Weight Change, Weight Management Trials



Source: Summary of Clinical Efficacy, Figure 3-1

Figure 5. 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 guidance[2] 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 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 6 and Table 7. These analyses impute missing data with LOCF.

Table 6. 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 7. 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.[2]

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.

6.1 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/m^2 or greater (obese), or*

- *27 kg/m^2 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.

6.1.1 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 clinical review utilized the sponsor's assessment of magnitude of treatment effects.

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

6.1.2 Demographics

Table 8 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/m^2. Patients had a wide range of BMIs (25.7 to 77.2 kg/m^2) 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.

For trials 1807, 1839, and 3970, demographics and baseline characteristics are summarized in Table 8, and were generally well-matched between treatment groups. Trials 1922 and 1923 demographics are additionally presented by group below.

Table 8. 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)
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 SMQs 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

Table 9. 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

In trial 1923, baseline characteristics were generally similar between treatment groups; small differences between groups in sex, race, and ethnicity are presented below.

Table 10. 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)

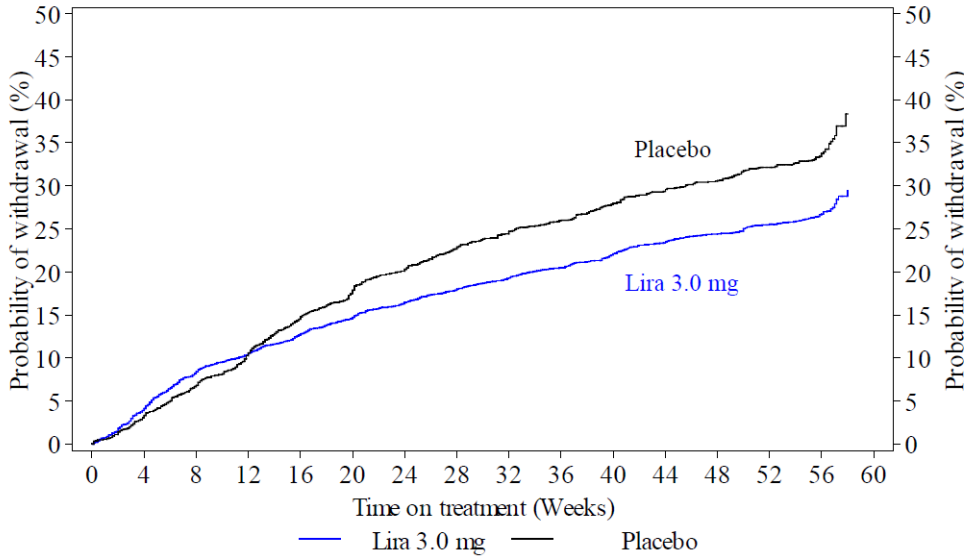
Source: NN8022-1923 Clinical Trial Report, Table 11-1

The majority of patients in trial 3970 had severe sleep apnea, and the mean baseline AHI was 49 events/hour, which the sponsor reports as “highly severe”.

6.1.3 Subject Disposition

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 6. Time to Discontinuation, Weight Management Pool



Source: ISS, Figure 1-2

Trial 1807

Disposition is summarized for the different phases of this trial in Table 11. 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 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 11. 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

Trial 1839

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 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 12. 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 ≥ 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 proportions 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.

Trial 1922

Patient disposition is summarized in the table below.

Table 13. 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)
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 ≥ 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 ≥ 50 ng/L (France)	0	0	0
Other	2 (0.6)	2 (1.2)	0

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

Trial 1923

Patient disposition is shown in the table below.

Table 14. 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.

Trial 3970

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.

6.1.4 Analysis of Primary Endpoints

Trials 1839, 1922, and 1923 each had three co-primary confirmatory weight-related endpoints that were tested in a hierarchical manner (see Table 15). Trial 1807 had two 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 15. 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 ≥ 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 ≥ 5% reduction of baseline body weight (5% responders)	Proportion of patients achieving ≥ 10% reduction of baseline body weight (10% responders)
1923 (at 56 wks)	Change in body weight from baseline (%, kg)	Proportion of patients that maintained ≥ 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 ≥ 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 ≥ 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; however, for the purposes of evaluating the long-term efficacy of the dose range, the 52-week analysis is primarily presented in section 6.

Source: Clinical overview, Table 4-1

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;[2,16,17] 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.

Results from trial 3970 are not presented in this section of the review, because the primary endpoint was change in apnea-hypopnea index (AHI), a sleep apnea endpoint. Weight and weight-related endpoints from this trial, such as cardiometabolic, will be

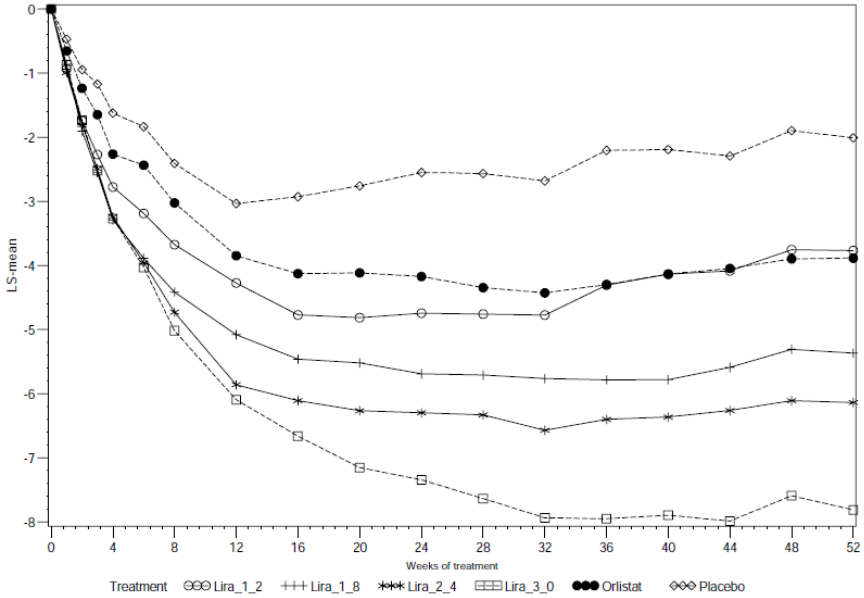
16 Xenical (orlistat) prescribing information.
17 Belviq (lorcaserin) prescribing information.

described under section 6.1.5 (secondary endpoints) and sleep apnea and other endpoints will be described under 6.1.6 (other endpoints).

Trial 1807

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 seen in Figure 7, Table 16, and Table 17, 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 16. 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 17. 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 18 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 18. 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

Trial 1839

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)

Proportion of patients losing more than 10% of baseline fasting body weight at week 56 (10% responders)

Percent Change in Body Weight

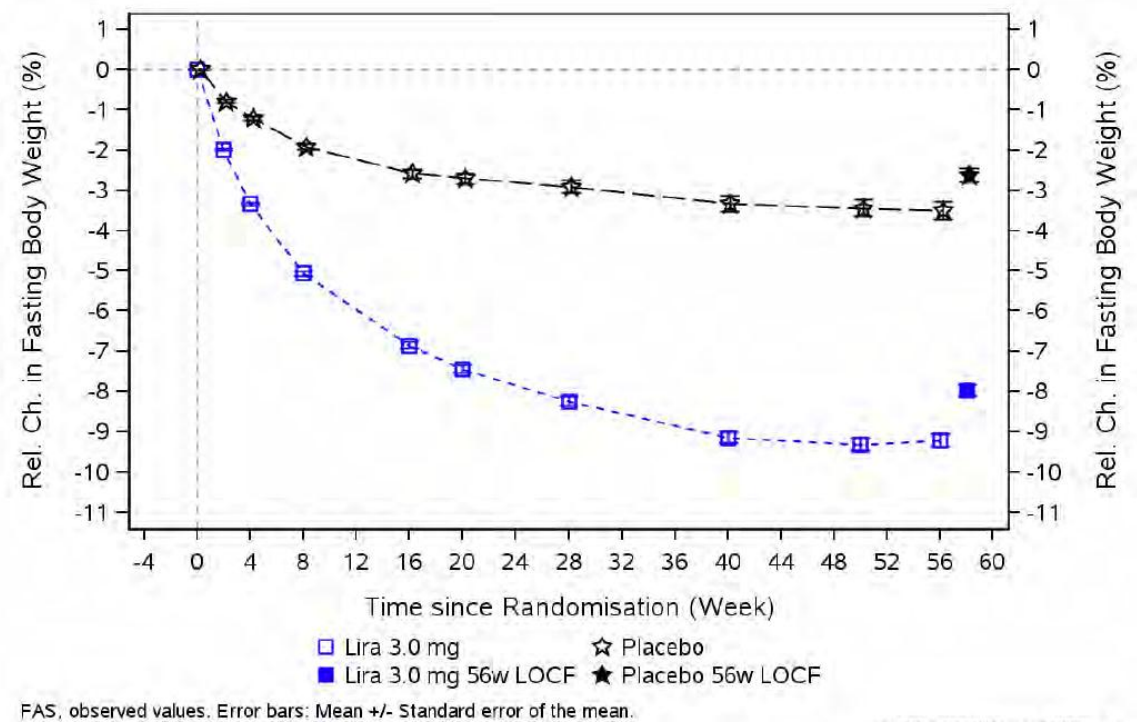
Patients treated with liraglutide 3 mg demonstrated statistically significantly greater mean weight loss at 56 weeks than patients treated with placebo, with a treatment difference at week 56 of 5.39%.

Table 19. 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



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:

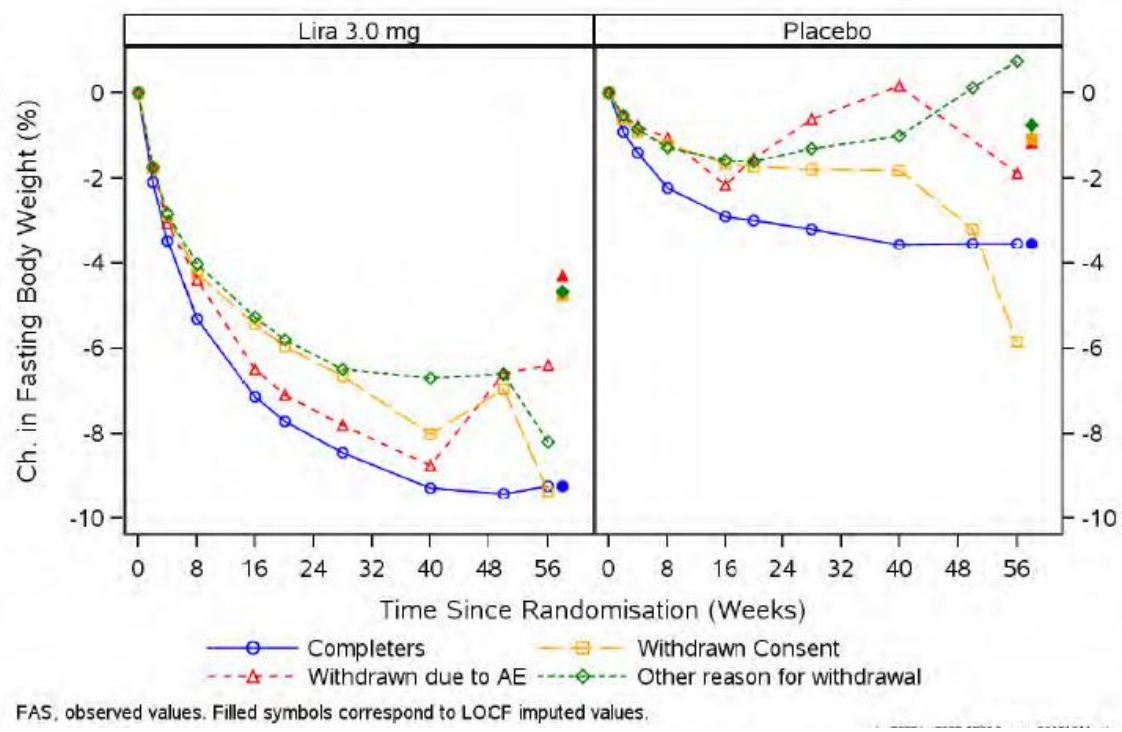
Table 20. Percent Change from Baseline after 56 Weeks of Treatment, Completers' Analysis, Trial 1839

Completers			
Treatment	**N**	**% Change from Baseline, Wk 56**	
Lira 3 mg	1781	-9.22	
Placebo	798	-3.53	
Between treatment difference		**Difference in LS means (95% CI)**	**p value**
Lira 3 mg vs. Placebo		-5.69 (-6.25, -5.13)	<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:

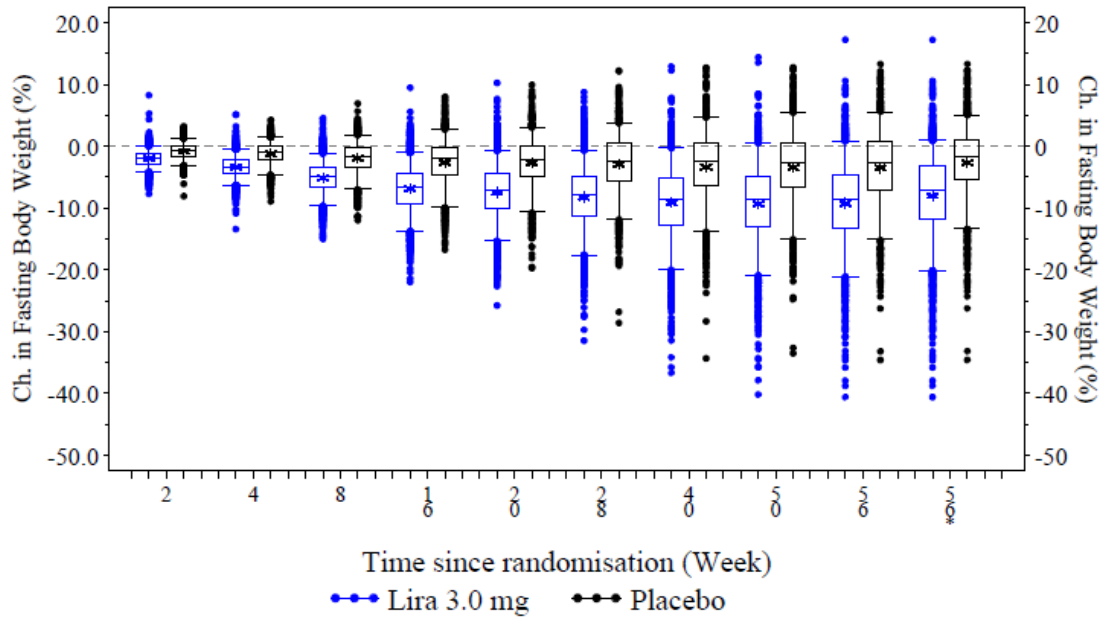
Figure 9. Percent Change from Baseline in Body Weight in the Main Treatment Period (0 to 56 Weeks) by Reason for Withdrawal, Trial 1839



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



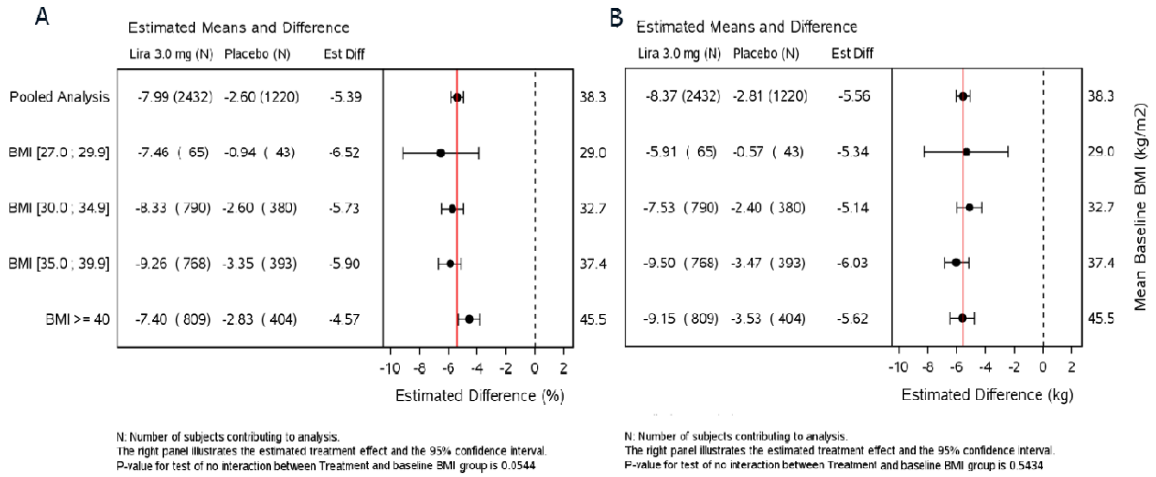
Source: NN8022-1839 Clinical Trial Report, Figure 14.2.32

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



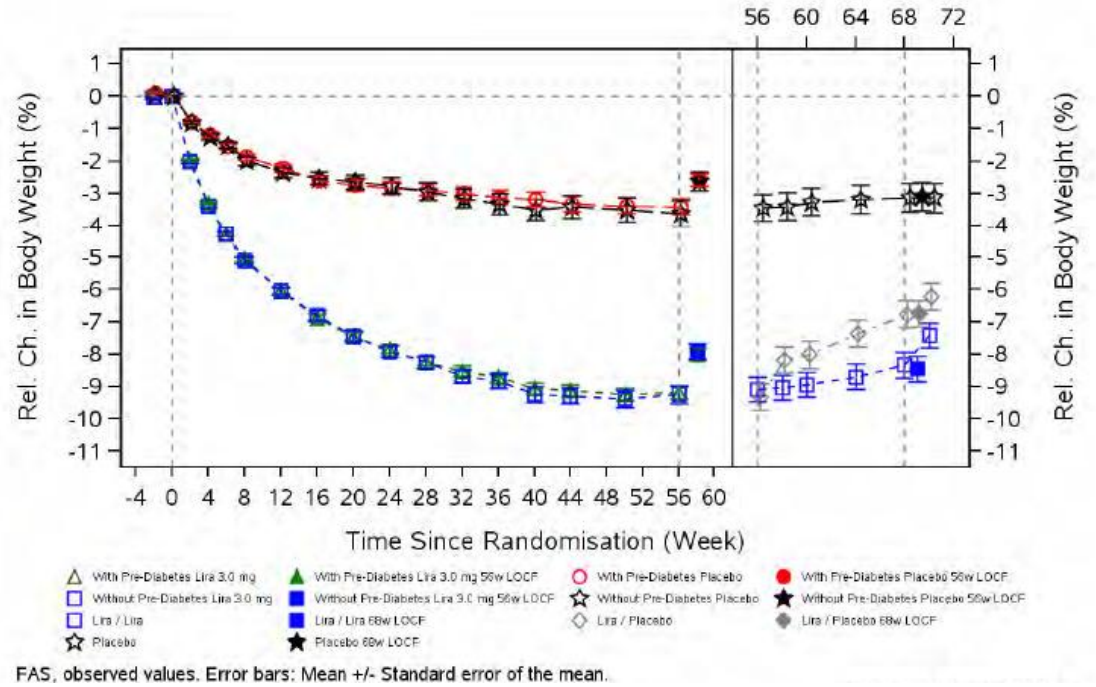
Source: NN8022-1839 Clinical Trial Report, Figure 11-5

Pre-Diabetes Status

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

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 21.

Table 21. 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)**	**p-value**
Lira 3 mg / Placebo		4.80 (4.12, 5.60)	<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 22. 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

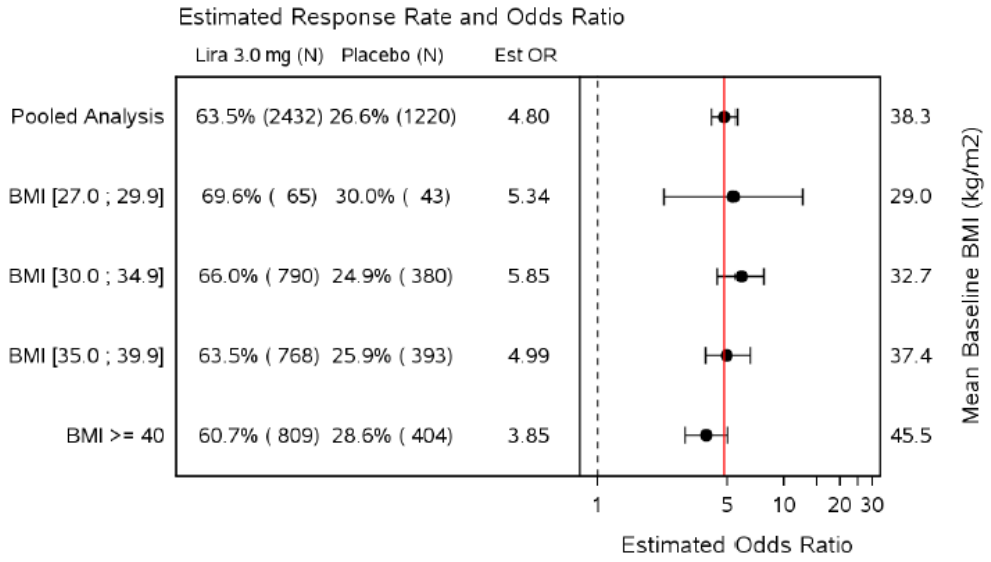
Source: NN8022-1839 Clinical Trial Report, Table 14.2.67

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 23. 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

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 24.

Table 24. 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 25. 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

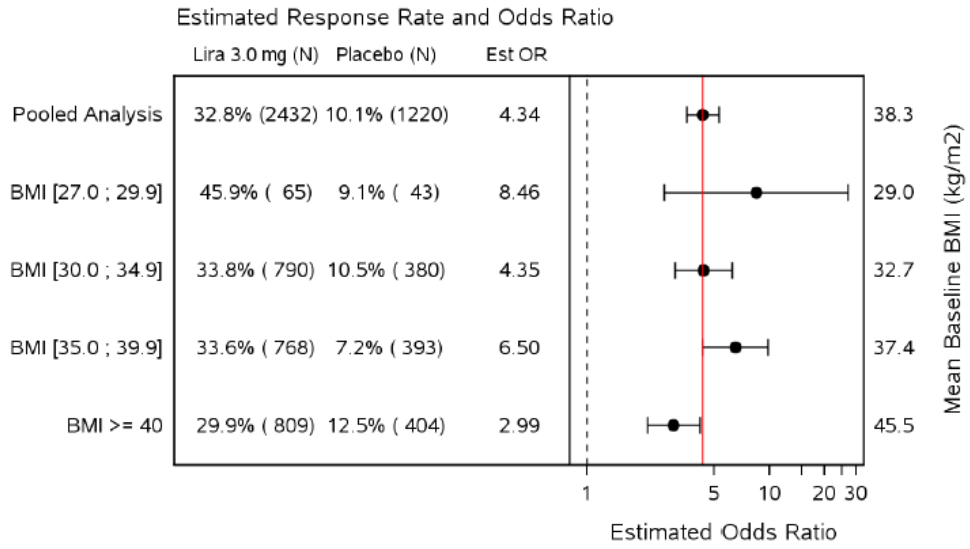
Source: NN8022-1839 Clinical Trial Report, Table 14.2.77

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 26. 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

Trial 1922

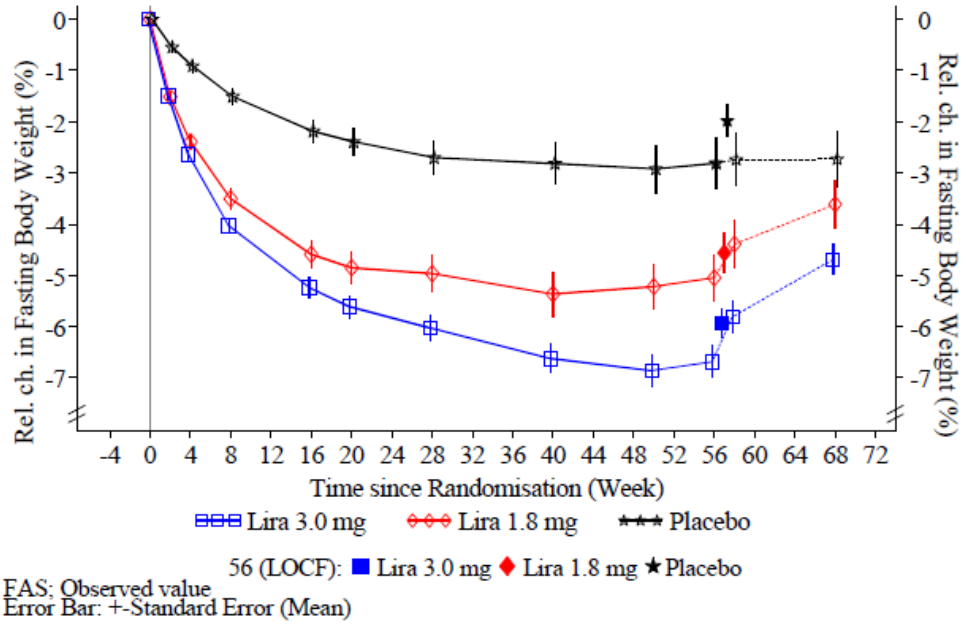
The primary endpoint consisted of three co-primary endpoint measures, evaluated by a hierarchical testing procedure.

- 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

Percent Change in Body Weight

As shown in Figure 15, fasting body weight decreased over time in a dose-dependent manner.

Figure 15. 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 27. 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 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 28. 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)**	**p-value**
Lira 3 mg vs. Placebo		-4.10 (-5.28, -2.93)	<0.0001
Lira 1.8 mg vs. Placebo		-2.67 (-4.00, -1.34)	<0.0001
Lira 3 mg vs. Lira 1.8 mg		-1.44 (-2.49, -0.38)	0.0078

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.

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/m^2) between the two liraglutide doses in this exploratory analysis.

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

Table 29. 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%
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

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 30. 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 31. 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)**	**p-value**
Lira 3 mg / Placebo		6.52 (3.86, 11.01)	<0.0001
Lira 1.8 mg/ Placebo		3.30 (1.86, 5.84)	<0.0001
Lira 3 mg / Lira 1.8 mg		1.98 (1.32, 2.97)	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)**	**p-value**
Lira 3 mg / Placebo		7.14 (4.47, 11.41)	<0.0001
Lira 1.8 mg/ Placebo		3.89 (2.31, 6.54)	<0.0001
Lira 3 mg / Lira 1.8 mg		1.84 (1.27, 2.64)	0.0011

Source: NN8022-1922 Clinical Trial Report, Table 14.2.23

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 32. 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)**	**p-value**
Lira 3 mg / Placebo		7.10 (3.48, 14.48)	<0.0001
Lira 1.8 mg / Placebo		3.84 (1.75, 8.41)	0.0008
Lira 3 mg / Lira 1.8 mg		1.85 (1.16, 2.95)	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 33. 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

Trial 1923

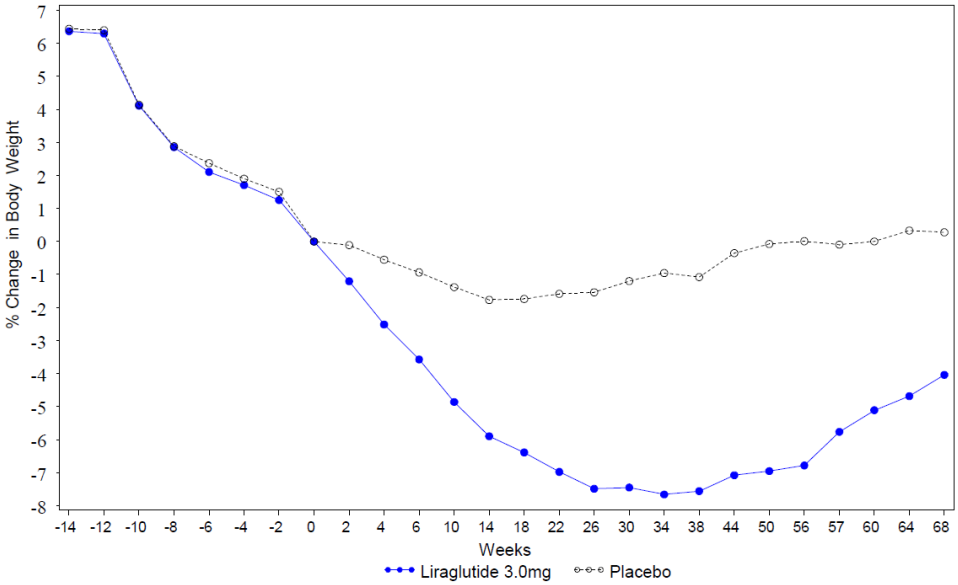
The primary endpoint consisted of three co-primary endpoint measures, evaluated by a hierarchical testing procedure.

- 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

Percent Change in Body Weight

Figure 16 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 16. 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 34).

Table 34. 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

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 35. 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

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 36. 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

6.1.5 Analysis of Secondary Endpoints

Secondary endpoints are presented for phase 3 trials (1839, 1922, 1923, and 3970). 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.

Trial 1839

Body Composition

Baseline waist circumference (~115 cm) and BMI (~38 kg/m^2) 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/m^2 compared with 1.01 kg/m^2 in patients treated with placebo (treatment difference -2.04 kg/m^2, 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.

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.

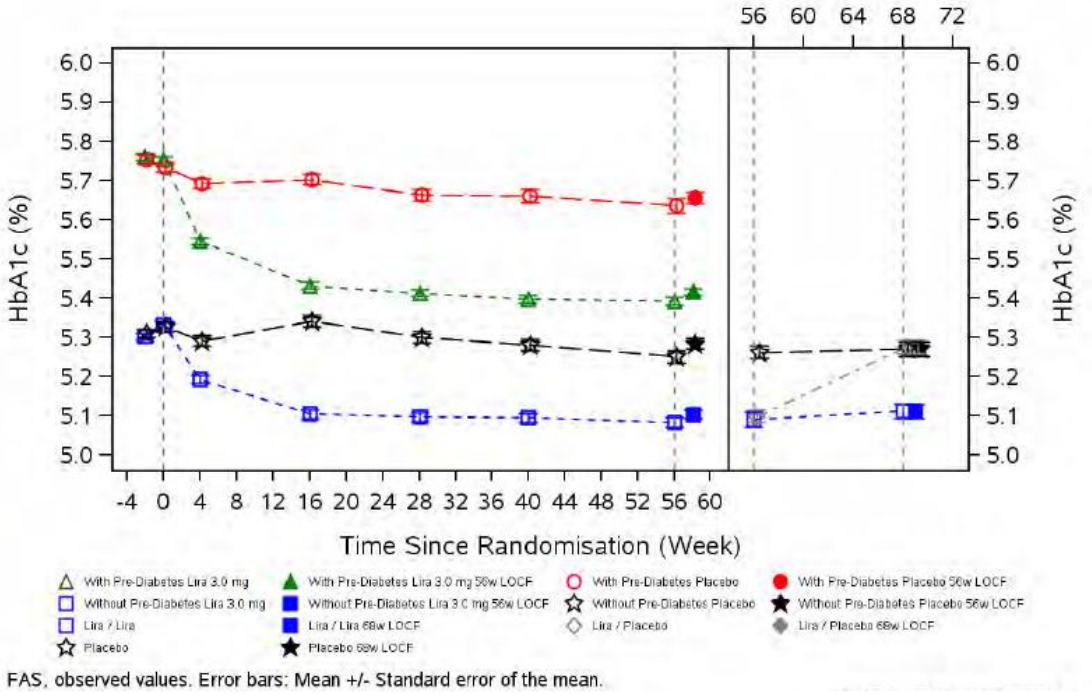
Table 37. Change in HbA1c (%) after 56 Weeks of Treatment, Trial 1839

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



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.

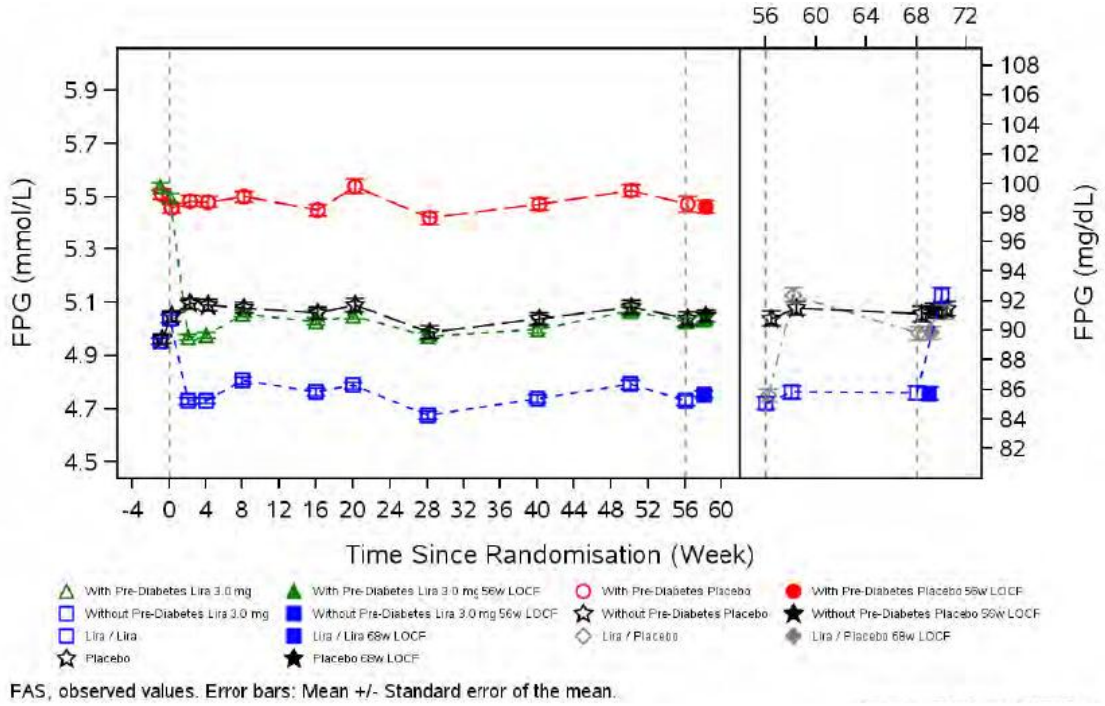
Table 38. Change in Fasting Plasma Glucose after 56 Weeks of Treatment, Trial 1839

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)**	**p-value**
Lira 3 mg vs. Placebo		-6.90 (-7.50, -6.31)	<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 18. 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 39. Summary of Fasting Glycemic Parameters, Trial 1839

	Lira 3 mg		Placebo		Lira 3 / Placebo
	Baseline	% Change	Baseline	% Change	Estimated ratio (95% CI)
Fasting insulin, µIU/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

Other Cardiometabolic Parameters

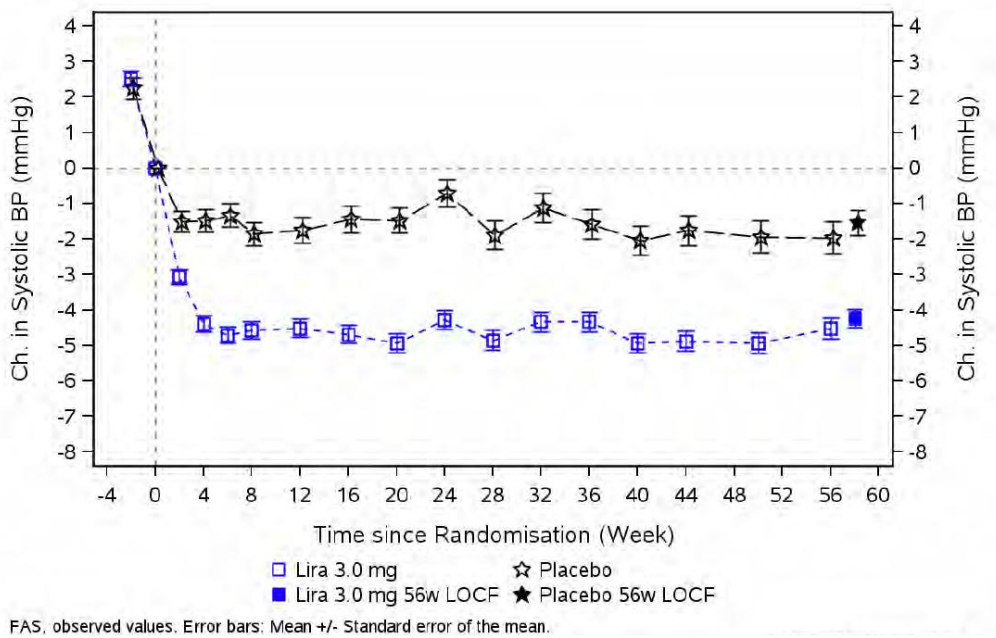
Blood Pressure

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

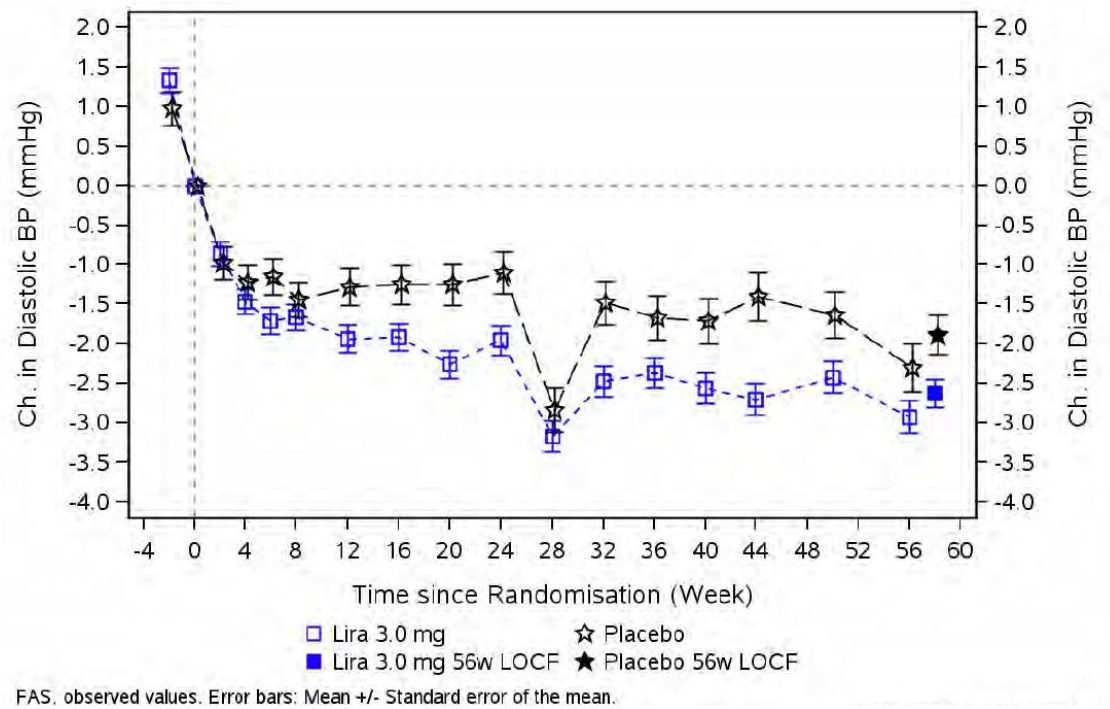
mmHg, placebo -1.90 mmHg). The reduction in SBP with liraglutide occurred within the initial 4 weeks of treatment.

Figure 19. Change in Systolic Blood Pressure, Trial 1839



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

Figure 20. Change in Diastolic Blood Pressure, Trial 1839



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 40.

Table 40. 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 lower[20] (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.

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
- 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).

20 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.

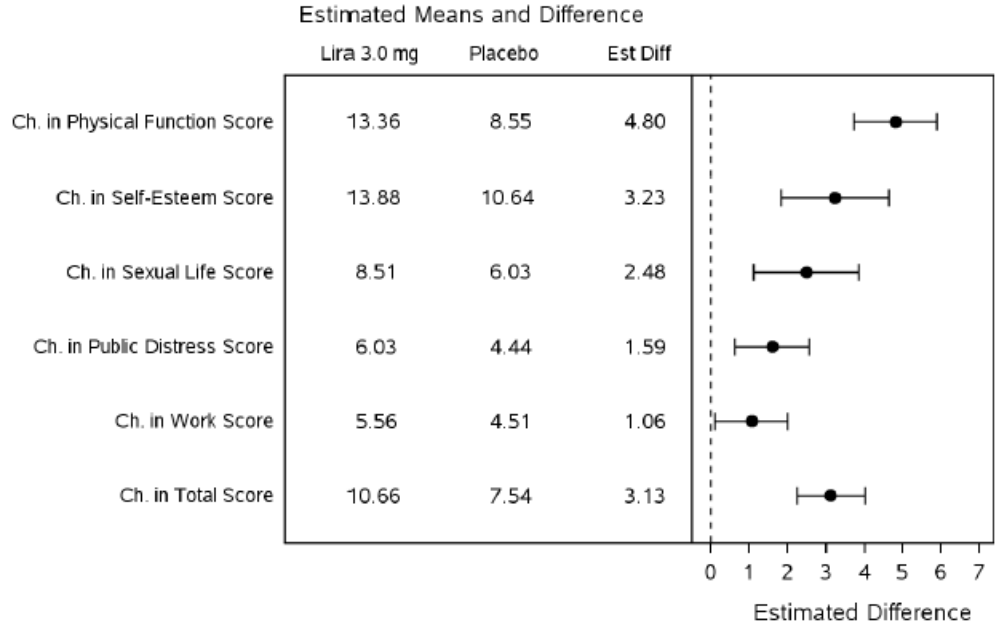
The TRIm-Weight questionnaire evaluates the overall impact and treatment satisfaction of individuals. It contains 22 items divided into five domains:

- 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.

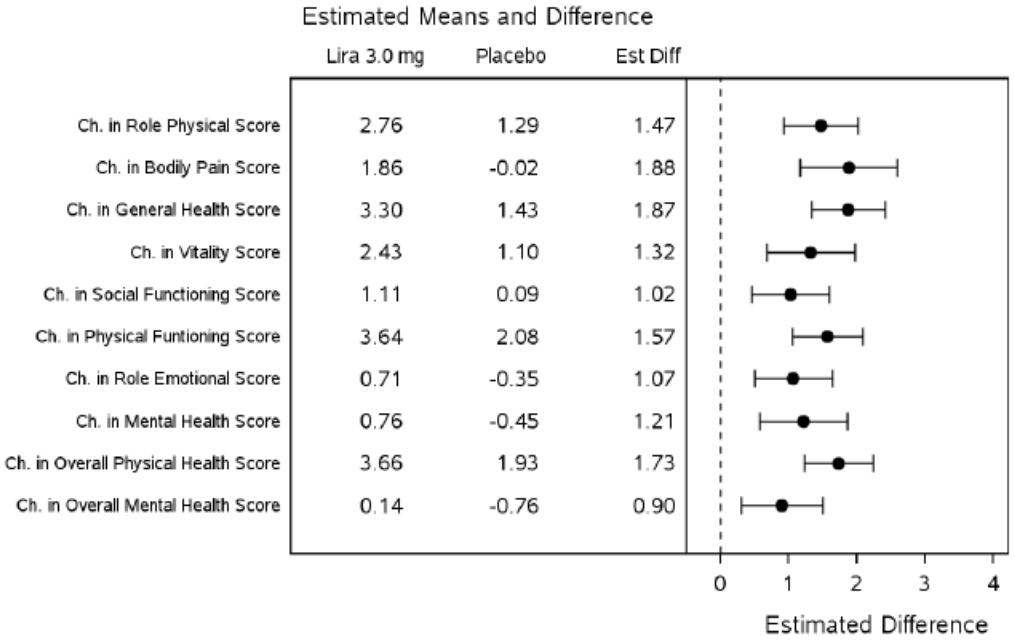
Improvements were seen in the IWQOL–Lite and SF-36 domains in liraglutide-treated patients compared to placebo, as shown in Figure 21 and Figure 22. In the TRIm-Weight PRO, improvements were reported in the total, weight management, and treatment burden scores, with a worsening seen in in the experience of side effects score.

Figure 21. IWQoL, Trial 1839



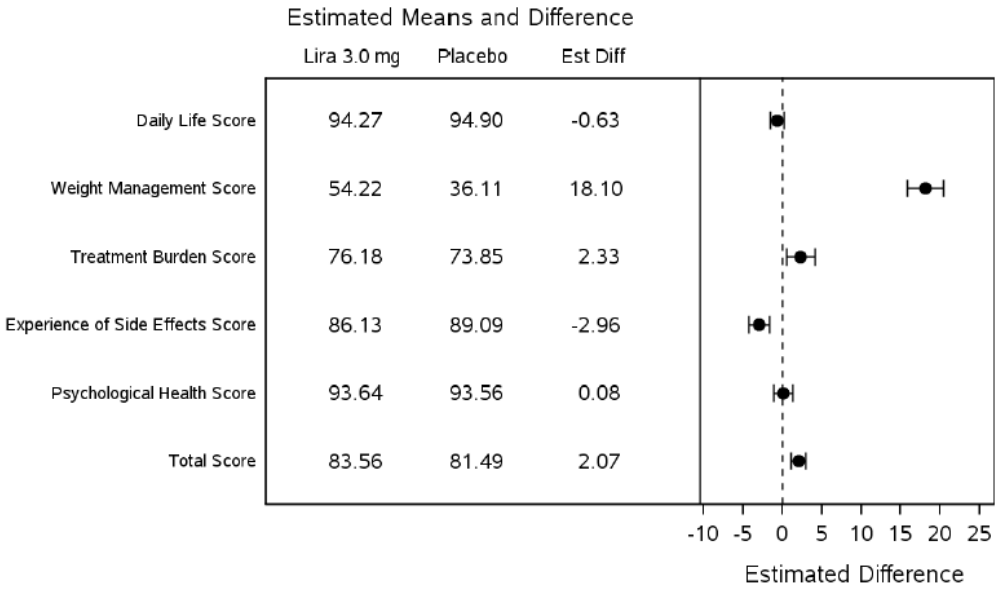
Source: NN8022-1839 Clinical Trial Report, Figure 11-40

Figure 22. SF-36, Trial 1839



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

Figure 23. 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 is 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.

Trial 1922

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.

Glycemic Parameters

HbA1c

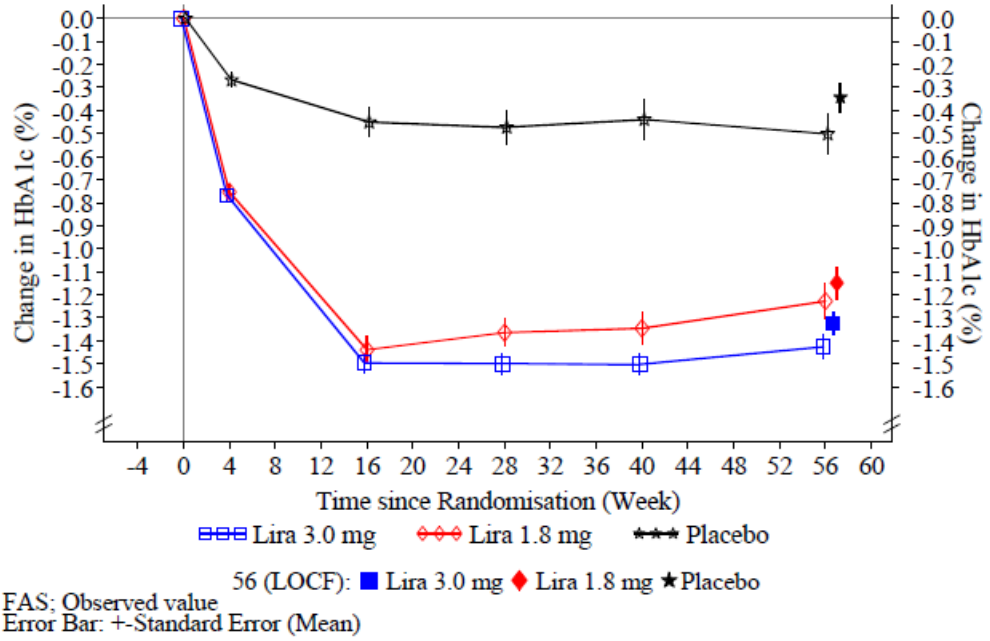
In this trial, both liraglutide 3 mg and 1.8 mg demonstrated statistically significant reduction in HbA1c at 56 weeks as compared to placebo (Table 41). During the first 16 weeks, mean HbA1c decreased in all three groups, with liraglutide groups showing more reduction than placebo. After week 16, mean HbA1c remained stable for liraglutide 3 mg and placebo, whereas a slight upward trend was observed for liraglutide 1.8 mg (Figure 24).

Table 41. 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 24. 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 42. Proportion of Patients Achieving HbA1c Below Specific Thresholds at Week 56, Trial 1922

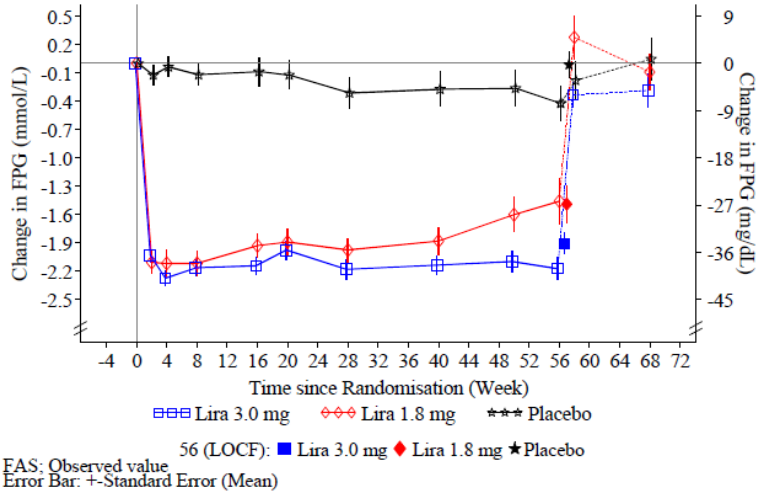
Treatment	**N**	**Proportion with HbA1c < 7%, Wk 56**	
Lira 3 mg	402	72.3%	
Lira 1.8 mg	195	69.6%	
Placebo	206	22.9%	
Between treatment comparison		**Treatment odds ratio (95% CI)**	**p-value**
Lira 3 mg / Placebo		8.79 (5.74, 13.44)	<0.0001
Lira 1.8 mg / Placebo		7.71 (4.76, 12.51)	<0.0001
Lira 3 mg / 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

Fasting Plasma Glucose

The time course for change in FPG from baseline by week is shown in Figure 25. 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 25. Change in Fasting Plasma Glucose by Treatment Week, Trial 1922



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

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 43. Diabetes Medication Changes, Trial 1922

	Lira 3.0 mg N (%)	Lira 1.8 mg N (%)	Placebo 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 44), 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 44. 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)

Cardiovascular

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

Table 45. 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 46. 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 47. 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

Patient Reported Outcomes

Patient Reported Outcome questionnaires were administered at baseline, week 28, and week 52 at a subset of sites. See the review of trial 1839 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 48. 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

Trial 1923

Weight-Related

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.

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%.

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/m^2 to 35.6 (5.9) kg/m^2, a -2.3 kg/m^2 (-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 kg/m^2, respectively, with an estimated treatment difference (SE) of -2.05 (0.24) kg/m^2 (95% CI -2.53, -1.57).

Cardiometabolic

Glycemia

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[21] 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-

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

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) pmol/L to 78.0 (50.7) 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) pmol/L in the liraglutide 3 mg treated group, and increased by 16.3 (55.5) 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 intravenous glucose tolerance test and hyperglycemic clamp (HOMA-β) and the euglycemic and hyperglycemic clamp (HOMA-IR).[22]

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).

Blood Pressure

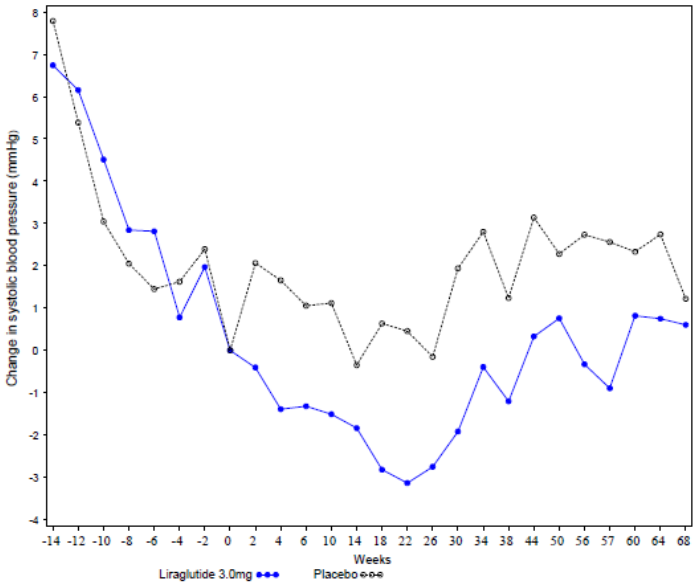
During the run-in, observed mean (SD) systolic BP decreased from 122.95 (12.69) mmHg to 117.23 (11.73) mmHg, a change of -5.7 mmHg (-4.7%), for patients who completed run-in. At randomization, observed mean (SD) SBP was 116.7 (12.6) mmHg and 117.7 (10.8) mmHg, for patients randomized to the liraglutide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

22 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.

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 26).

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).

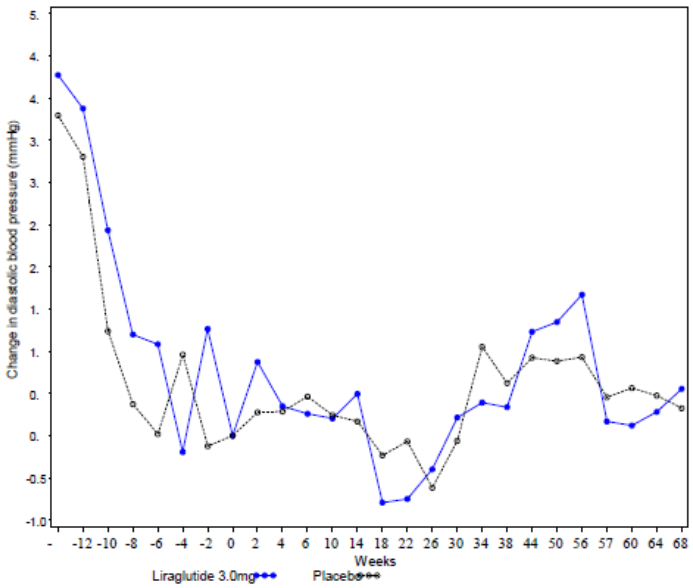
Figure 26. Change in Systolic Blood Pressure, Trial 1923



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 27). 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 27. Change in Diastolic Blood Pressure, Trial 1923



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

Lipids

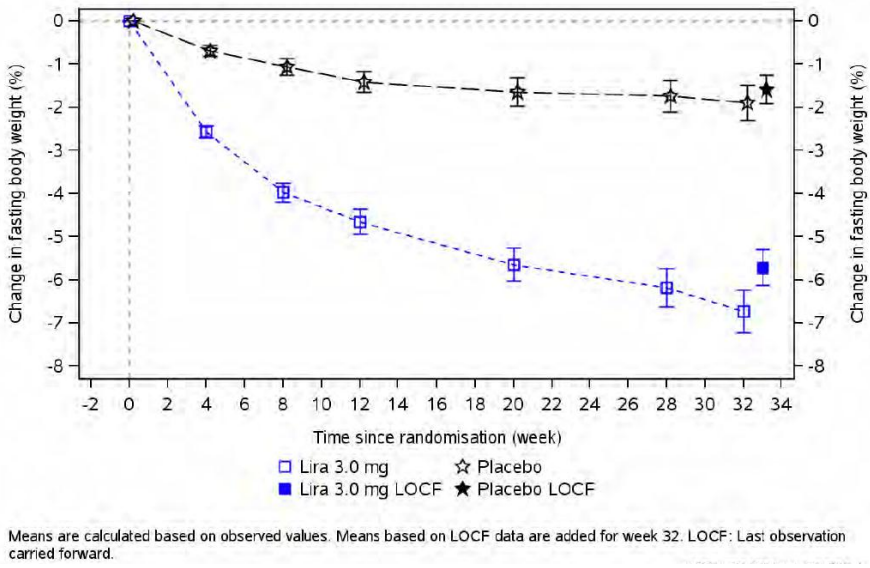
Changes in total cholesterol, LDL cholesterol, HDL cholesterol and VLDL cholesterol were modest with no statistically significant differences between groups.

Trial 3970

Weight Loss

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 28. Percent Change in Fasting Body Weight, Trial 3970



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.

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 7.3.5.

6.1.6 Other Endpoints

Trial 1807, 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.

Trial 3970, Sleep Apnea and Related Parameters

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).

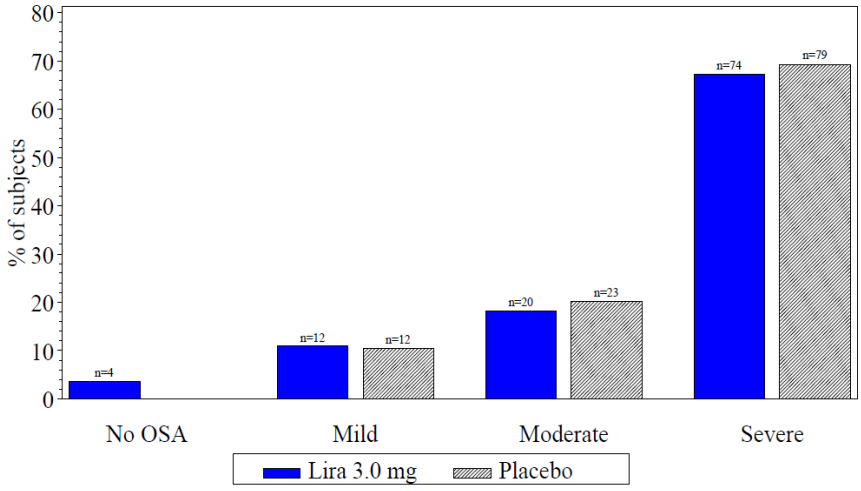
Results of this single trial were not robust to all sensitivity analyses (e.g., “completers” p-value 0.03; multiple imputation p = 0.054).

Other 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

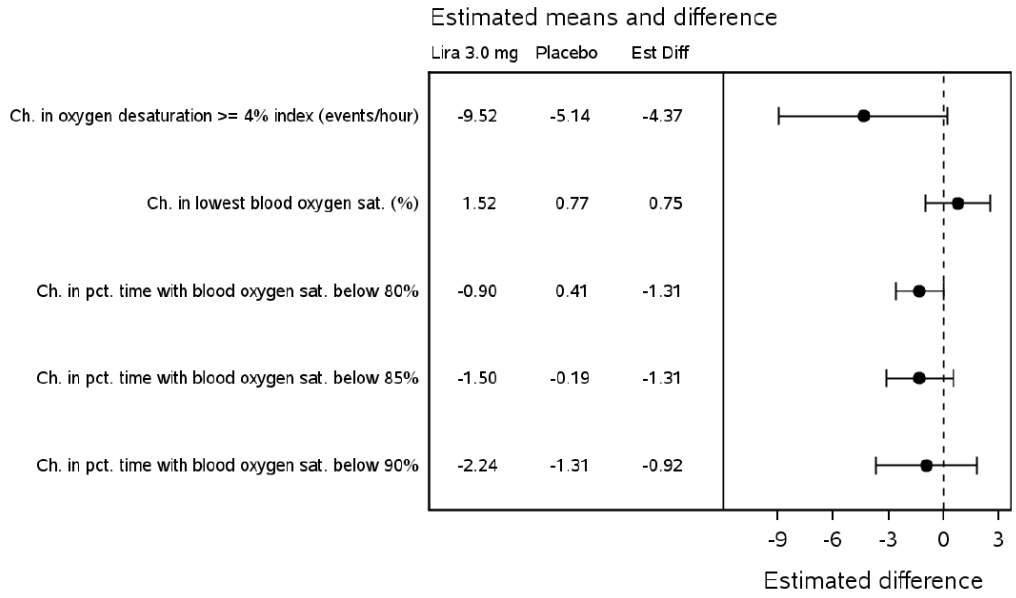


OSA: Obstructive sleep apnoea
No OSA (<= 4.9 events/hour), Mild (5.0-14.9 events/hour), Moderate (15.0-29.9 events/hour), Severe (>= 30.0 events/hour)
Chart includes subjects in full analysis set with post-baseline values.
Average values are based on observation carried forward (LOCF) values.

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.

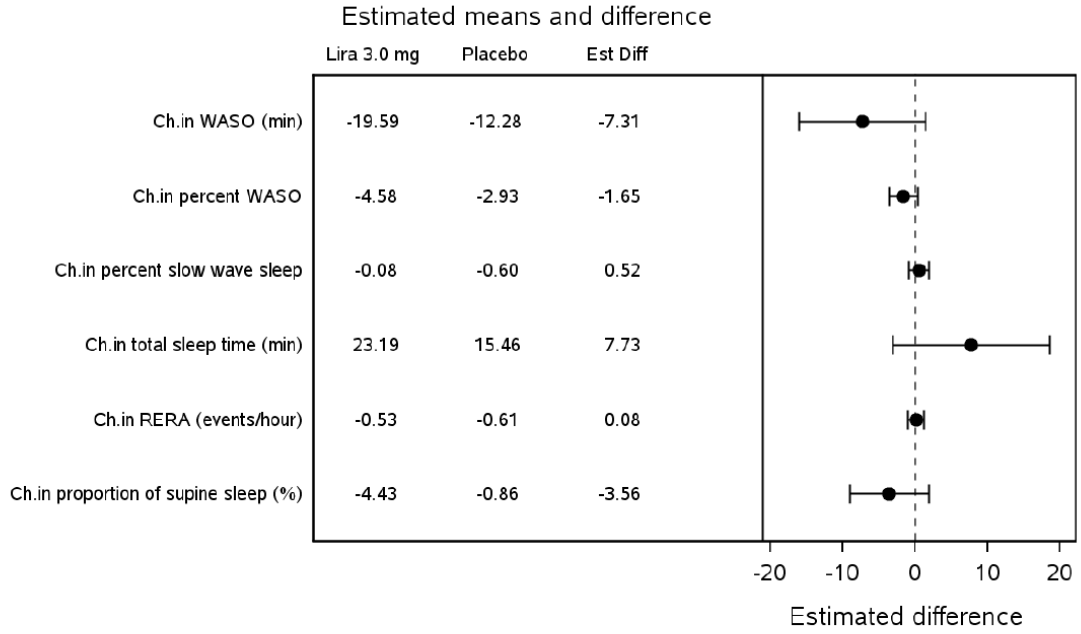
Figure 30. Change in Polysomnography Parameters Related to Blood Oxygen Saturation, Trial 3970



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).

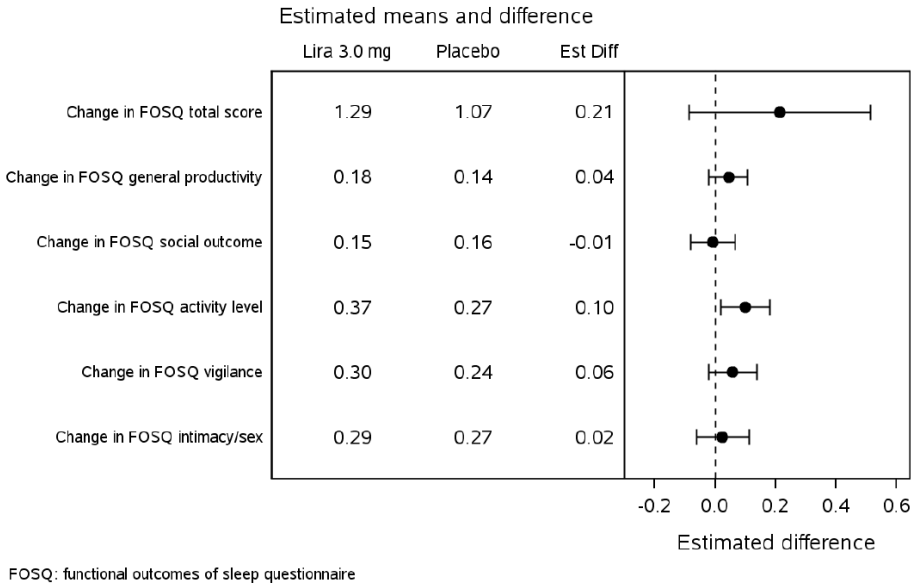
At baseline, mean total ESS scores were similar between the two treatment groups. After 32 weeks of treatment, the total ESS score decreased / improved by a similar degree in both treatment groups (−2.52 for liraglutide 3 mg and −2.33 for placebo at week 32).

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 domain/overall

score indicates more functional impairment and a high score indicates less functional impairment. The SF-36 is described in section 6.1.5, trial 1839.

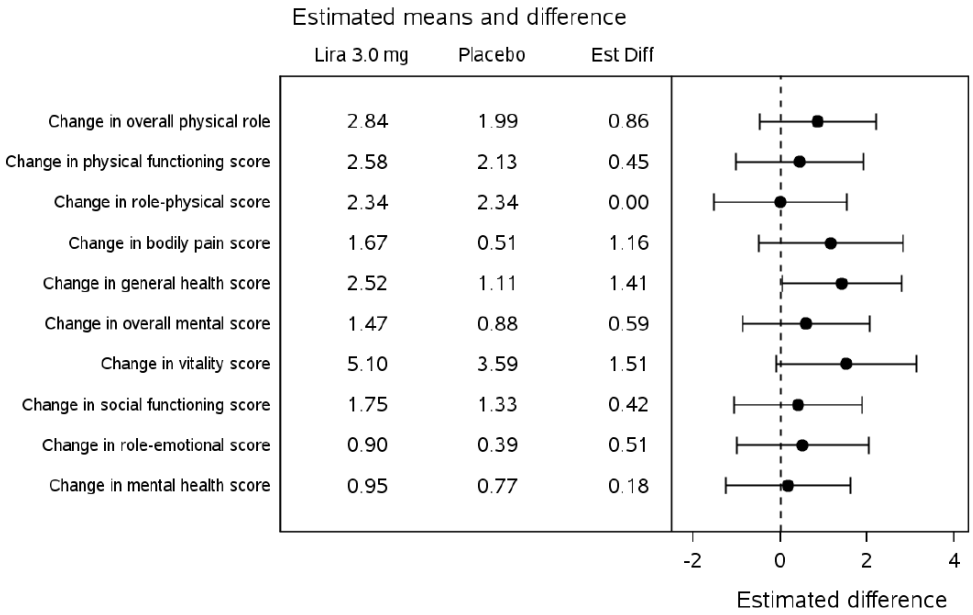
Most domains of the FOSQ and the SF-36 were not statistically significant.

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

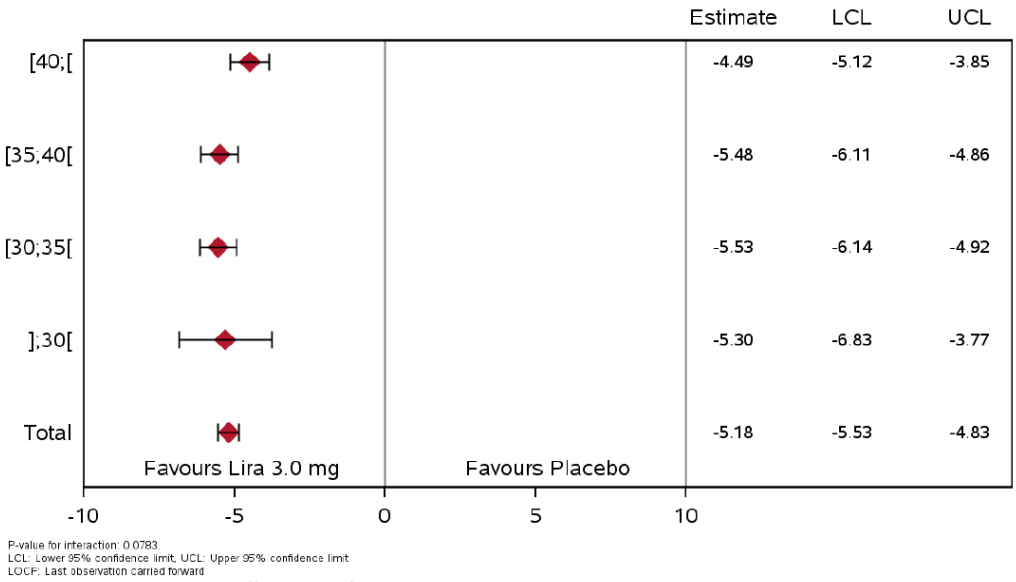
Reviewer comment: In addition to the uncertain clinical relevance of the treatment effect in AHI change (primary endpoint), the following limitations with the OSA-related results of this trial were noted by DNP:

- ***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***

6.1.7 Subpopulations

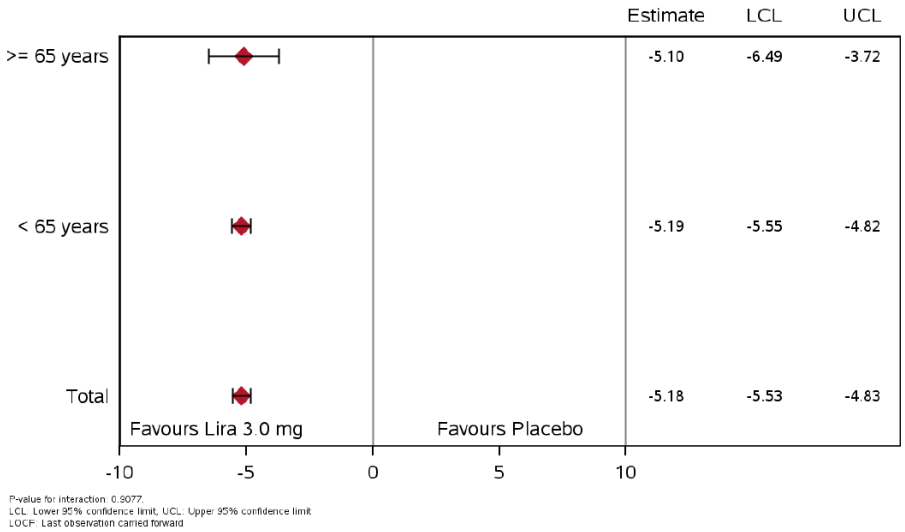
The following subpopulation forest plots were generated by the sponsor utilizing mean percent weight change to end of trial, LOCF. Notably, females appear to have a greater treatment effect than males, and patients without type 2 diabetes appear to have a greater treatment difference than those with T2DM.

BMI



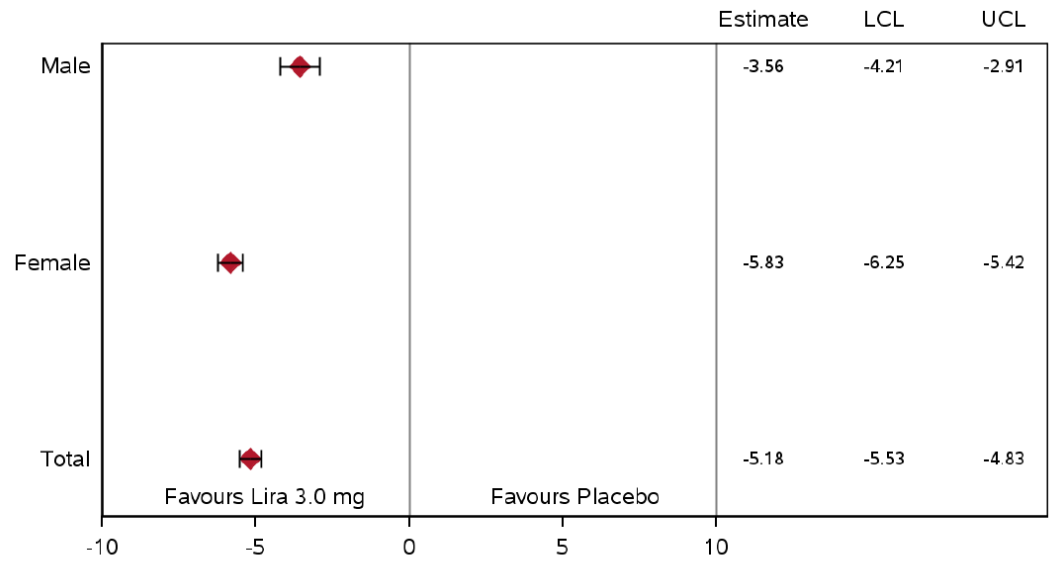
Source: ISE, Appendix 6.4, Figure 2

Age



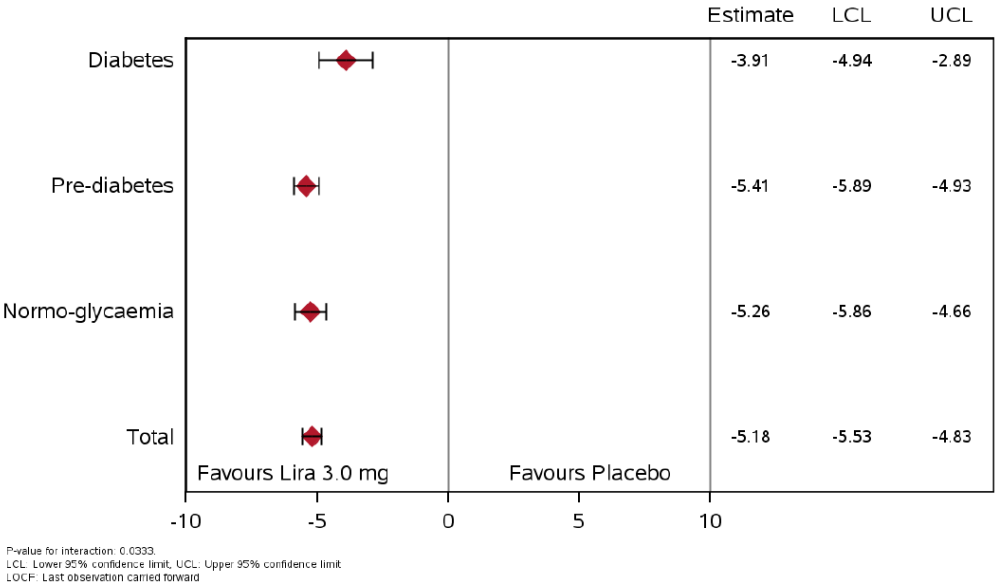
Source: ISE, Appendix 6.4, Figure 5

Sex



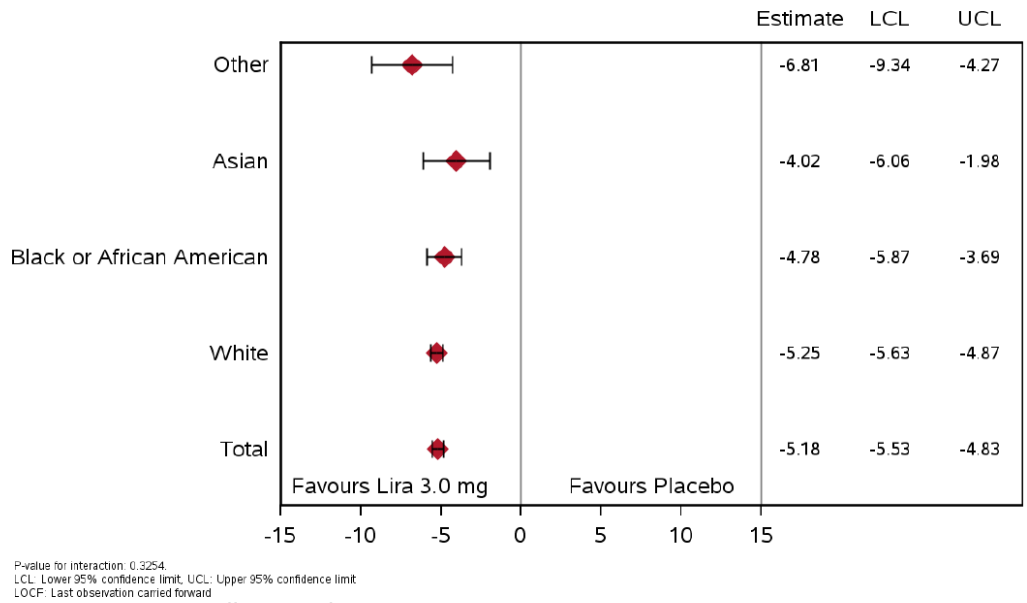
Source: ISE, Appendix 6.4, Figure 8

Glycemic Status



Source: ISE, Appendix 6.4, Figure 14

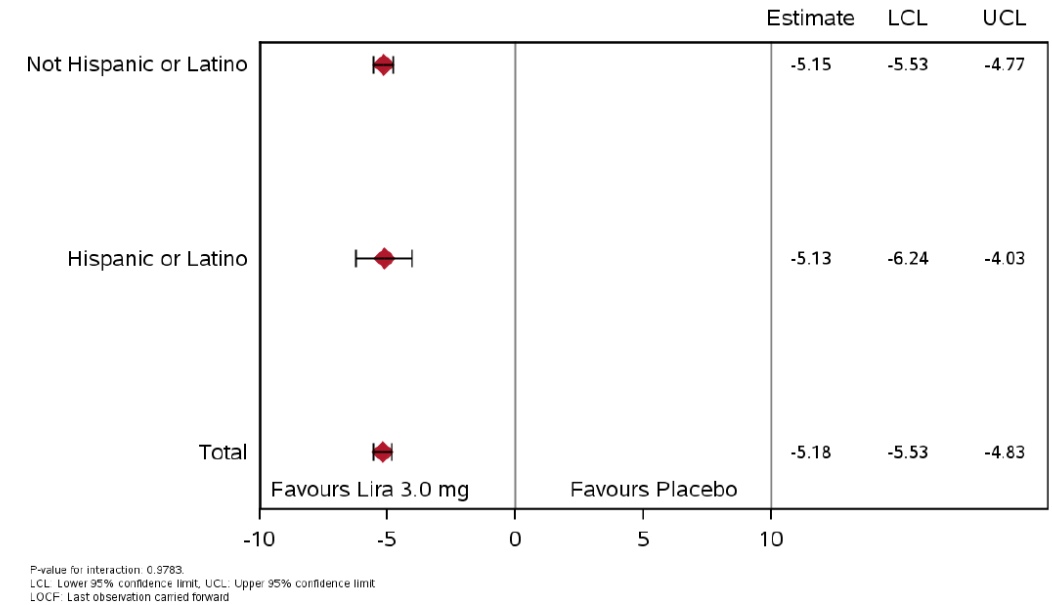
Race



P-value for interaction: 0.3254.
LCL: Lower 95% confidence limit, UCL: Upper 95% confidence limit
LOCF: Last observation carried forward

Source: ISE, Appendix 6.4, Figure 17

Ethnicity



P-value for interaction: 0.9783.
LCL: Lower 95% confidence limit, UCL: Upper 95% confidence limit
LOCF: Last observation carried forward

Source: ISE, Appendix 6.4, Figure 20

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See section 6.1.4 for the review of trial 1807, the phase 2 dose-ranging trial, which establishes the 3 mg dose as the appropriate dose for weight loss efficacy.

All trials utilized a dose escalation scheme of 0.6 mg/d weekly to the target dose of 3 mg in order to reduce gastrointestinal symptoms. This is the same titration scheme that is used for Victoza (1.2 and 1.8 mg doses).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Mean weight loss was generally observed until weeks 34-40 in the phase 3 trials, at which point it leveled off. The 12-week re-randomization period after the 56-week main treatment period in trial 1839 confirmed the continued efficacy with liraglutide with long-term treatment, as weight was regained when liraglutide was discontinued (lira/placebo re-randomized group).

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

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 and colorectal neoplasms.

  During the main treatment period (not including patients prematurely withdrawn), 7 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), 3 cases 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) meeting[23]. The Victoza application was under Agency review when the 2008 FDA guidance to evaluate CV risk in new anti-diabetic drug therapies[4] 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 2 Apr 2009 EMDAC meeting information for details). A post-marketing cardiovascular outcomes trial for Victoza is ongoing.

  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

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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.

- Hepatic Safety: Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 (0.15%) liraglutide-treated patients (two of whom had ALT greater than 20 and 40 times the upper limit of normal) compared with 1 (0.05%) placebo-treated patient during the clinical trials. Because clinical evaluation to exclude alternative causes of ALT and aspartate aminotransferase (AST) increases was not done in most cases, the relationship to liraglutide is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones). Two serious adverse events of hepatitis were reported; in one case the patient had a history of gallstones and alcohol abuse, and the second case was co-reported with pancreatitis. A case of “autoimmune hepatitis” associated with liraglutide has been reported in the literature.

- Renal Safety: In the post-marketing setting, renal failure has been reported, in some cases associated with gastrointestinal symptoms and hypovolemia. Two cases of renal failure were reported in the trials associated with liraglutide; one event appeared precipitated by gastrointestinal events, hypovolemia, and hypotension. An increase in the proportion of adverse events of increased serum creatinine in liraglutide-treated patients was reported; most increases were transient.

- 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 similar frequency in patients who were and were not 5% weight loss responders, suggesting these symptoms were not entirely responsible for weight loss with liraglutide.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The liraglutide program was designed to conform to the February 2007 FDA draft guidance for developing weight management drugs.[2] 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, 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 this section.

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 7.3.5.

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.

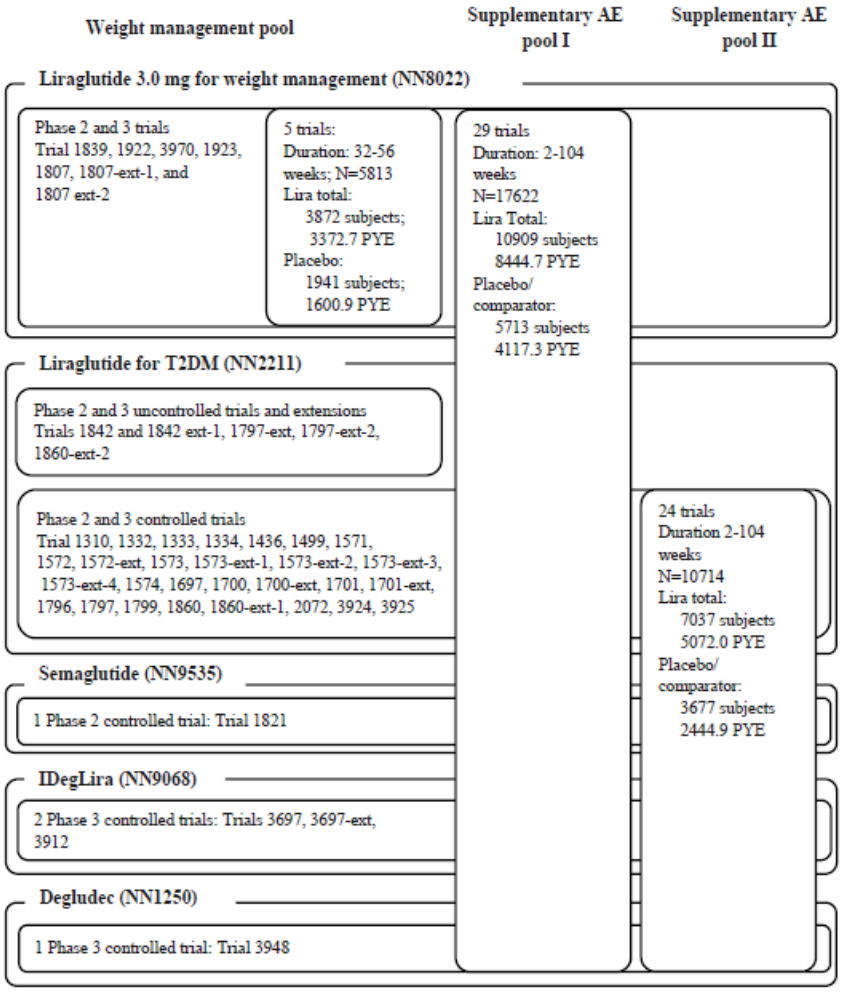
The Victoza clinical development program included 20 controlled phase 2 and 3 trials (including extensions) of up to 104 weeks duration as well as one uncontrolled trial and four uncontrolled trial extensions.

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



Source: Supplementary AE Report, Figure 1-1

7.1.2 Categorization of Adverse Events

The sponsor utilized MedDRA for coding and reporting of adverse events. The limitation of MedDRA coding was evident particularly when evaluating the data for neoplasms in non-adjudicated trials. MedDRA categories of neoplasms "malignant and unspecified" did not allow for appropriate categorization of the neoplasm data from non-adjudicated trials.

The sponsor compiled a number of MedDRA adverse event terms into "medical events of special interest" (MESIs). The known and potential adverse events associated with liraglutide and other GLP-1 agonists were explored in the weight management program using these compiled adverse events. In general, this is an effective way to describe

those particular safety issues. However, for those safety issues that were not labeled MESIs, the reviewer had to define which preferred terms were of interest for a particular safety issue. MedDRA High Group Level Terms and High Level Terms were useful for certain searches.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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 49. 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 50. 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

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

Table 51. 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

7.2.2 Explorations for Dose Response

Dose response was evaluated in trials 1807 and 1922 (see section 5.3). Certain adverse events were specifically explored for dose response and are described further in the relevant sections below.

7.2.3 Special Animal and/or In Vitro Testing

Pivotal nonclinical studies evaluating the safety of liraglutide were previously reviewed under NDA 22341.

7.2.4 Routine Clinical Testing

In general, routine clinical testing was adequate to characterize the safety of liraglutide.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable; no new data were presented in this NDA regarding the metabolism, clearance, and interaction of liraglutide. These data were provided and reviewed under NDA 22341.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Serious adverse events described or purportedly associated with other GLP-1 receptor agonists include medullary thyroid cancer, pancreatitis, pancreatic cancer, renal impairment, increased heart rate, and immunogenicity. All diabetes drugs, including GLP-1 receptor agonists, are associated with the risk for severe hypoglycemia, especially with insulin secretagogues. The sponsor adequately evaluated for these potential risks in the weight management program; in particular, in phase 3 the sponsor instituted a process of adjudication for neoplasms, pancreatitis, cardiovascular events, thyroid disease requiring thyroidectomy, and death. The sponsor also categorized

these events as MESI, allowing for dedicated assessment via specific case report form data collection and analysis.

7.3 Major Safety Results

7.3.1 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 52) includes patients prior to the data cut-offs for ongoing trials, and do not include patients in the follow-up phases. Table 53 and Table 54 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 52. 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

Clinical Pharmacology Trial

No deaths occurred in the clinical pharmacology trial 3630.

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 53. 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 54. 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
Liraglutide 1.8 mg					
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
Liraglutide 3.0 mg					
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
Placebo					
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.

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 the discussion of cardiovascular safety in section 7.3.5); one event occurred during the ongoing extension phase of trial 1839 and one event occurred during off-treatment follow-up.

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 55. 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 56 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 9.4).

Table 56. 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

7.3.2 Nonfatal Serious Adverse Events

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.

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 and neoplasms are discussed further below.

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

Table 57. 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
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 58) and the 120-day safety update (Table 59) are tabulated separately for completeness.

Table 58. 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)
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 59. 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

Diabetes Pool

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

Table 60. 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.

7.3.3 Dropouts and/or Discontinuations

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.

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 7.3.2), and one patient, randomized to placebo, was withdrawn due to a tooth infection.

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 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 7.4.1.

Other AEs more frequently leading to withdrawal with liraglutide 3 mg than with placebo were (by decreasing frequency) from the SOCs 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 7.3.5.

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 7.3.5.

Table 61. 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

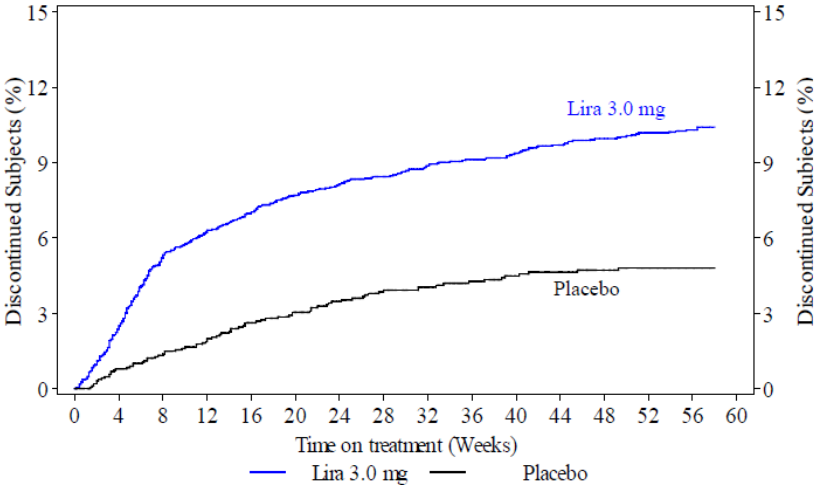
Hepatobiliary investigations¥	2 (<0.1)	<1	2 (<0.1)	<1	3 (0.2)	3
Neoplasms benign, malignant and unspecified	15 (0.4)	5	15 (0.4)	4	7 (0.4)	4
Skin and subcutaneous tissue disorders	13 (0.4)	5	15 (0.4)	5	7 (0.4)	6
Metabolism and nutrition disorders	11 (0.3)	4	12 (0.3)	4	5 (0.3)	3
Psychiatric disorders	9 (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

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.

7.3.4 Significant Adverse Events

Significant adverse events will be discussed in section 7.3.5, with a review of submission specific primary safety concerns.

7.3.5 Submission Specific Primary Safety Concerns

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.[8] 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)[24] and T2DM[25] 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.

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.

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’.

24 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.
25 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.

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.

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 64).

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 62. 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.[26]

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 63. 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)

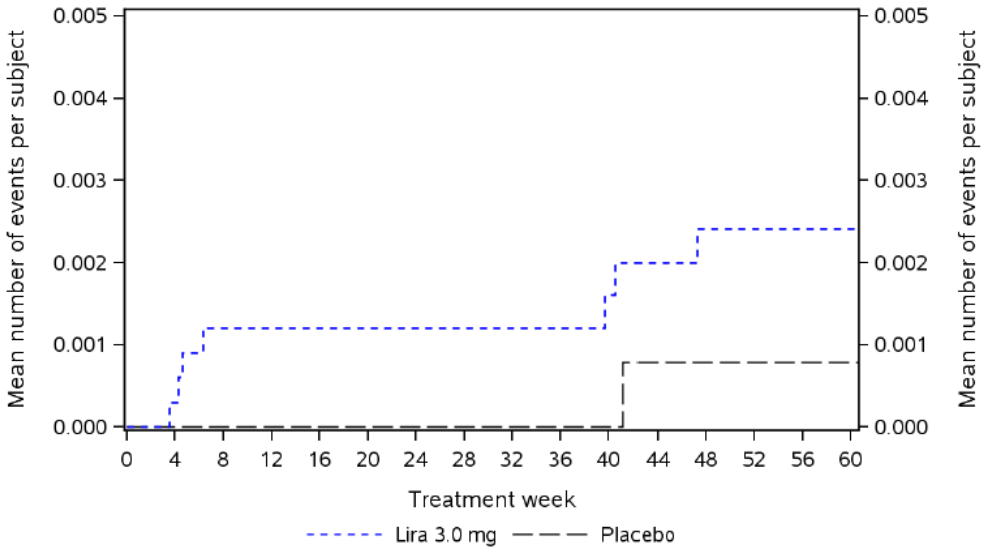
26 Parks M and Rosebraugh C. Weighing risks and benefits of liraglutide – the FDA's review of a new antidiabetic therapy. N Engl J Med 2010; 362:774-7.

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).

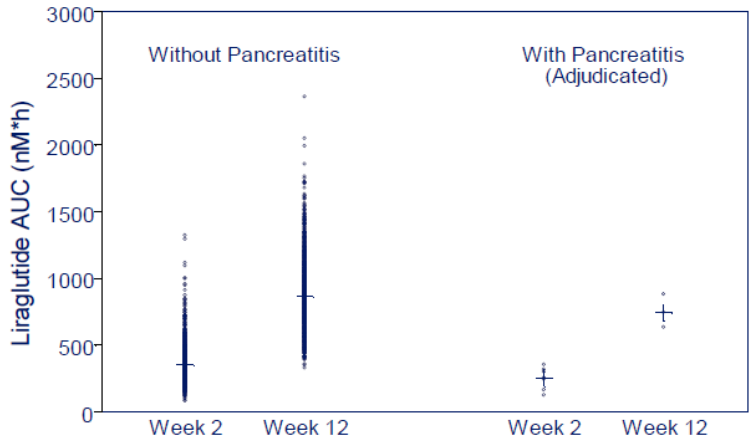
Figure 36. Mean Cumulative Event over Time Plot of Adjudicated Pancreatitis Events, Weight Management Pool



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)

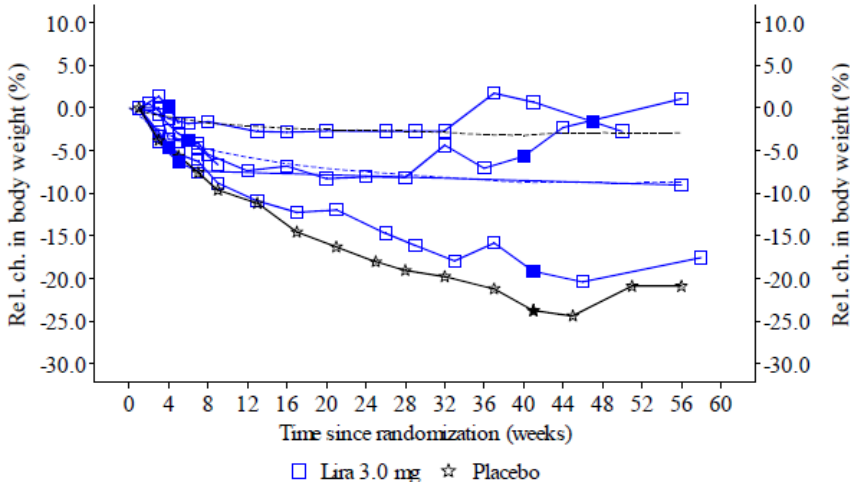


Source: ISS, Figure 2-41

Summaries of all AEs adjudicated as pancreatitis (or, for trial 1807, the one AE of pancreatitis by preferred term) are included in Table 64 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 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/m^2), 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 64. 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								
Liraglutide 3.0 mg								
409006/ trial 1839/ US/ M/52/62.9	Pancreatitis acute	Main	31/ 31days/ 4days	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/ 43days/ 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/ 283days/ 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.

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. Gatroduodenoscopy 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 phosphatise 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]
Placebo								
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 65. 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) (6) (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.
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]**
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

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× 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

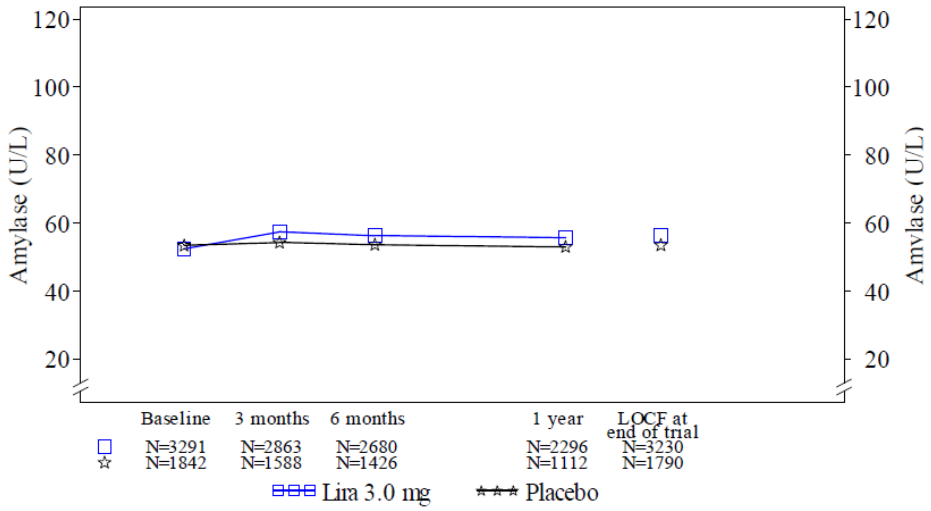


Figure is based on trials 1839, 1922, 3970 and 1923.
Note that trial 3970 is a 32 week trial.
Source: ISS, Figure 2-45

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× ULN. See Table 66 for enumeration of patients with amylase at least 3× ULN.

Table 66. 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 ≥ 3× 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

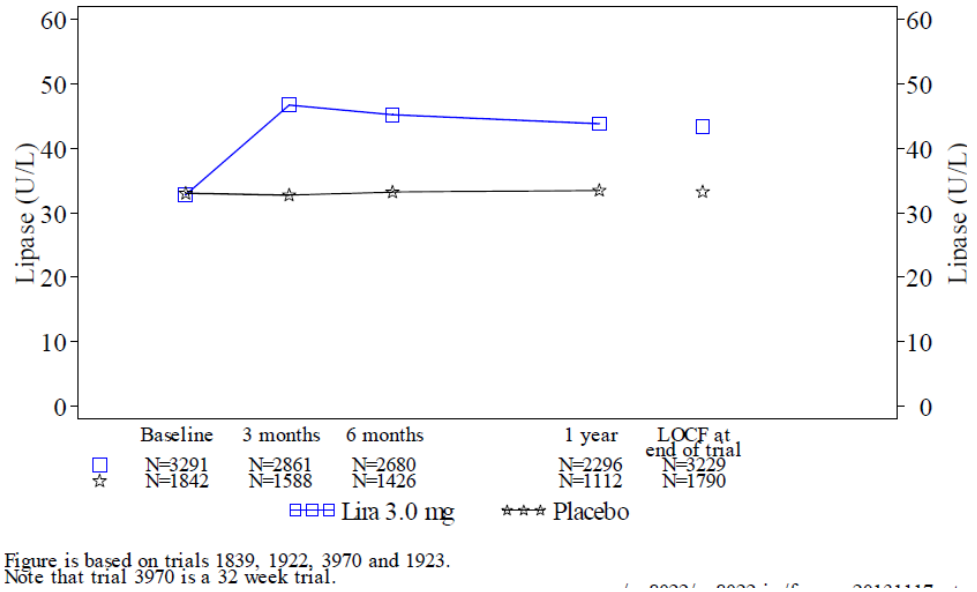


Figure is based on trials 1839, 1922, 3970 and 1923.
Note that trial 3970 is a 32 week trial.

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 67. 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 64, 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.

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 68. 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

Literature Reports

Six case reports of pancreatitis associated with liraglutide were identified in a literature review.[27,28, 29,30,31,32] One of these case reports was only available in Spanish and was therefore not reviewed;[29] the other five cases are summarized below.

27 Lee PH, et al. Acute pancreatitis associated with liraglutide. Ann Pharmacother. 2011; 45:e22
28 Knezevich E, et al. Liraglutide associated acute pancreatitis. Am J Health Syst Pharm. 2012; 69(5): 386-9.
29 Artero A, et al. [Acute pancreatitis in a patient treated with liraglutide.] Med Clin (Barc) 2013 Oct 19; 141(8): 368-9.
30 Bourezane H, et al. Late and severe acute necrotizing pancreatitis in a patient with liraglutide. Thérapie 2012; 67(6): 539-43.
31 Famularo G, et al. Pancreatitis during treatment with liraglutide. JOP 2012; 13(5): 540-1.
32 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.

- Lee, et al.[27] described the case of a 60-year-old female with T2DM treated with liraglutide 1.8 mg daily, metformin, pioglitazone, glimepiride, and insulin. The 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.[28] 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.[30] 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/µL. 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.[31] 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.[32] 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) 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.

Gallbladder Events

Obesity and rapid weight loss are associated with an increased risk for gallstone formation.[33] It has recently been suggested that exenatide, another GLP-1 receptor agonist, reduces cholecystokinin-induced gallbladder emptying compared with placebo in fasting healthy individuals.[34]

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.

Clinical Pharmacology Trial

No AEs related to the gallbladder were reported.

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 69). Approximately 75% of patients reporting events of cholelithiasis and cholecystitis had a cholecystectomy due to the events.

33 Stinton LM, et al. Epidemiology of gallstones. Gastroenterol Clin North Am 2010 Jun; 39(2): 157-69, vii.
34 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 69. '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 a kaline 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 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 70. 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.

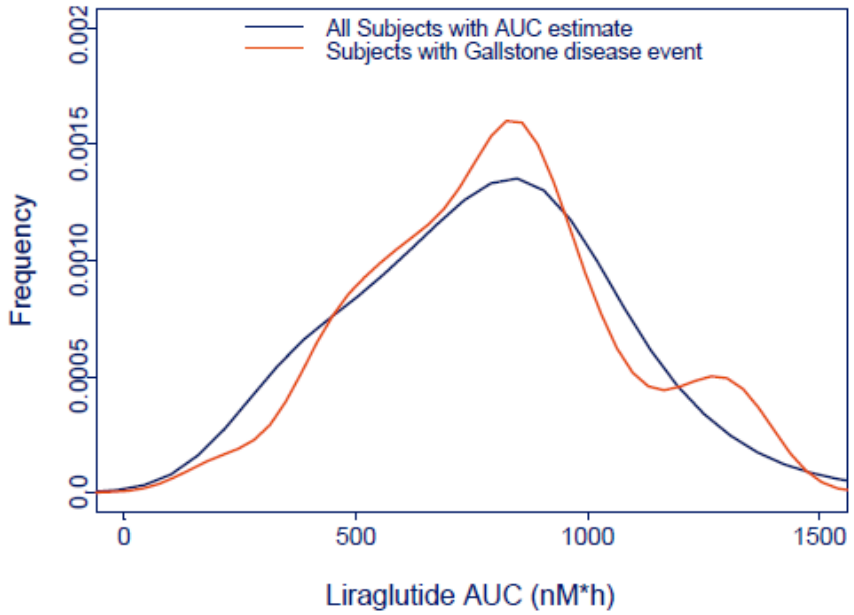
Table 71. Biliary Events, Trial 1922

	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 72. 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

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 73. 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

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%.35 Early diagnosis and treatment are associated with improved outcomes.[35] 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.[9] However, animal, observational, and clinical trial data reviewed by FDA to date have not supported a causal association.[8]

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

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

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 below for a discussion of calcitonin).

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 74). However, approximately twice as many patients experienced serious AEs of neoplasms in the liraglutide group as compared to those treated with placebo (Table 75). 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 74. 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
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 SOCs (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 75. 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
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

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

Event	Definitions, classifications and criteria	
Neoplasms, including thyroid neoplasms (if adjudicated as 'Neoplasm')	**Definitions:** - Neoplasm was defined as an abnormal growth of tissue **Classification:** Neoplasms were classified according to - tissue of origin/organ system - stage - malignancy status	**Stage:** - Stage 0: *in situ* - Stage I: localised - Stage II: locally advanced - Stage III: advanced - Stage IV: metastatic - Undetermined **Malignancy status:** - malignant - pre-malignant/carcinoma *in situ*/borderline - benign - unclassified
Thyroid neoplasms (if adjudicated as 'Thyroid Disorder requiring thyroidectomy')	**Definition** 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. **Classification:** Thyroid neoplasms were classified according to: - 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)	**Stage:** - Stage 0: *in situ* - Stage I: localised - Stage II: locally advanced - Stage III: advanced - Stage IV: metastatic - Undetermined **Malignancy status:** - malignant - pre-malignant/carcinoma *in situ*/borderline - benign - unclassified

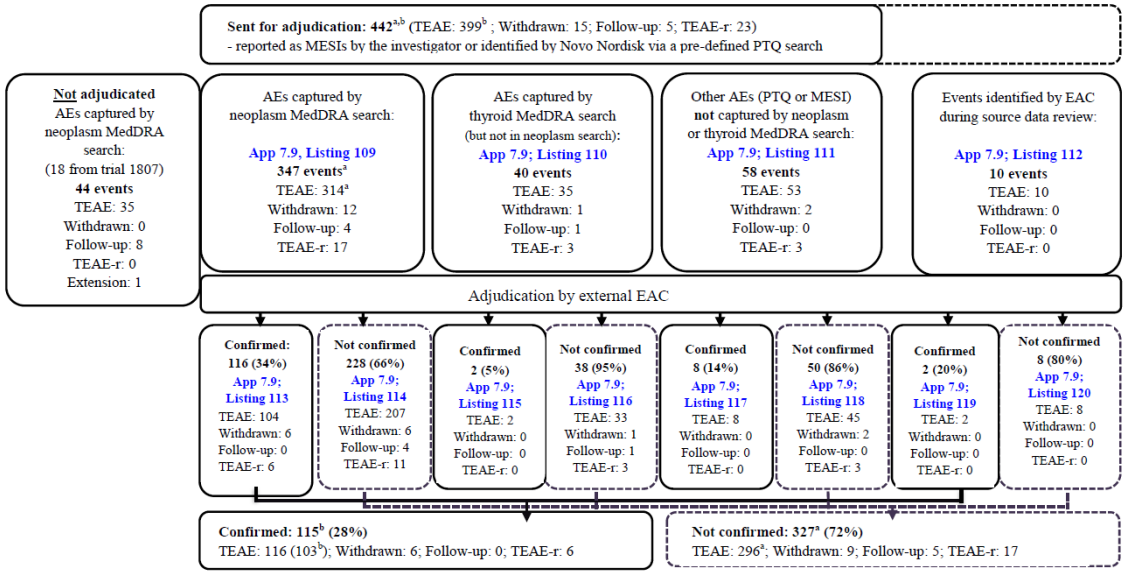
Source: ISS, Table 2-76

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. 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 77, Table 78, Table 79, and Table 80.

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 77, below.

Because events in trial 1807 were not adjudicated, this trial is not included in Table 77 (events from 1807 are included in Table 74 and Table 75, above, which include neoplasms identified in the SMQ search).

Table 77. 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 78. 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 79. 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 80 demonstrates the distribution.

Table 80. 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 81. 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%).

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

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 77, 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 82. 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 82.

Table 82. Details on EAC Confirmed Thyroid Neoplasms, Weight Management Pool

Trial/subject/age/sex/BMI/country	Reported term	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/ Period	Details[b] and medical history
Liraglutide 3.0 mg					
1839/ 284003/ 27/M/38.7/ IL	Thyroid cancer (Reported term: Worsening of papillary carcinoma)	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 carcinomas (×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 carcinomas/	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.

Trial/subject/age/sex/BMI/country	Reported term	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/ Period	Details[b] and medical history
1922/ 406003/ 58/M/48.7/ DE	Thyroid cancer Lymphadenopathy	C-cell hyperplasia Papillary microcarcinoma	*In situ* Benign/ Stage: NA[c] Pre-malignant/ Stage 0/	-12/-11/ Screening 358/358/ Main treatment period	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
1922/ 109003/ 56/F/36.3/ FR	Thyroid adenoma Papillary microcarcinoma[a]	Follicular adenoma Papillary microcarcinoma[a].	Benign Stage: NA[c] Pre-malignant/ Stage 0/ *In situ*	51/51/ Main treatment period 137/137/ Withdrawn	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
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 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/L. Two weeks after starting liraglutide, his calcitonin value increased to 71.1 ng/L; see the table below for calcitonin values throughout the trial.

Table 83. Patient 406003 (Trial 1922), Calcitonin Values, ng/L

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/L). 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.[36] 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.[36]

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".

Although the sponsor reported in the ISS that no thyroid neoplasm events were reported in trial 1807, patient 121022 had AEs of increased blood calcitonin during the trial and thyroid neoplasm one month after stopping the drug. Baseline calcitonin was 28.2 ng/L and fluctuated between 21.6 and 37.9 ng/L during the trial. A biopsy of a thyroid nodule

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

apparently "was described to look like a colloid nodule without signs of medullar thyroid cancer. The full pathology report is not obtainable." This thyroid neoplasm was not adjudicated (events in trial 1807 were not adjudicated).

Reviewer comment: Baseline calcitonin was elevated and there was no report of C-cell neoplasia, although there was not enough information to fully assess the case.

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.[35] However, although measurement of serum calcitonin in the work-up of thyroid nodules might improve detection of MTC, there is controversy whether such monitoring improves patient outcomes.[37] The upper limit of normal for calcitonin in females is 5.0 ng/L and in males, 8.4 ng/L. Calcitonin values exceeding 30 to 50 ng/L increase the likelihood of, and values exceeding 100 ng/L are highly predictive of MTC.[38] 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.

37 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.
38 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.

Table 84. Calcitonin by Treatment Week and by Sex, Weight Management Pool

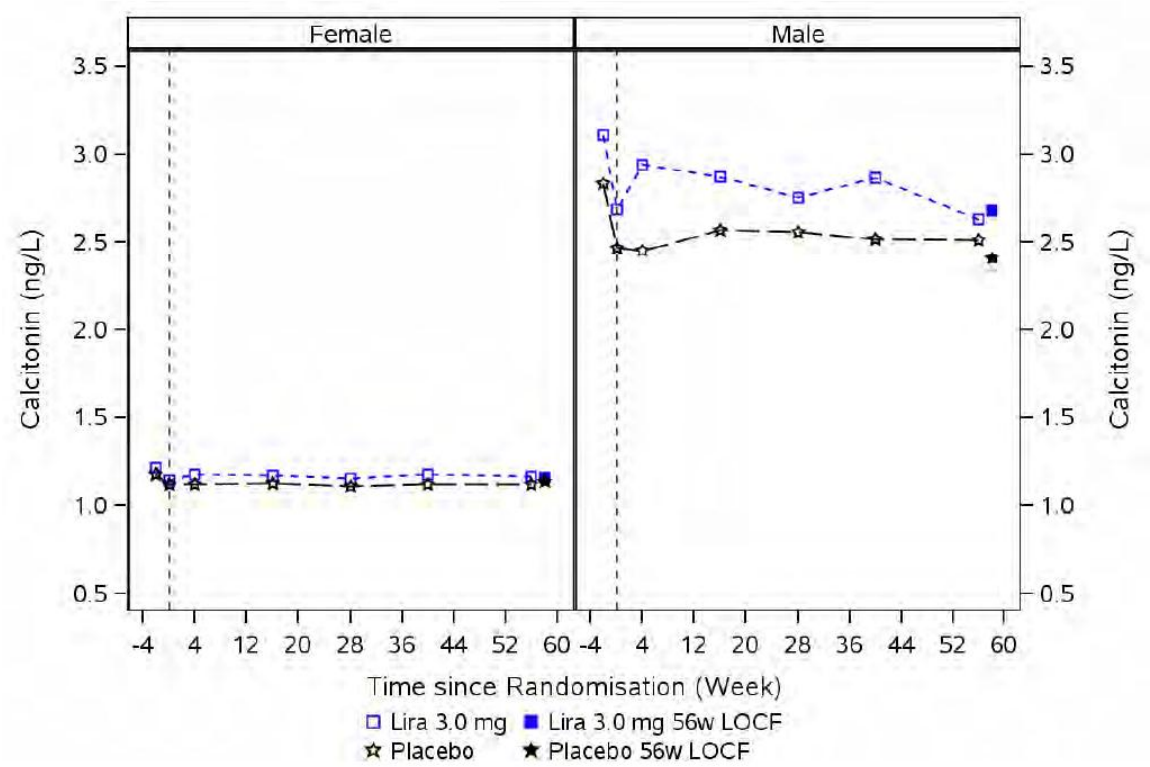
	Females		Males	
	Lira 3 mg N=2449	Placebo N=1374	Lira 3 mg N=935	Placebo N=567
Baseline				
Geometric mean (CV)	1.07 (100.3)	1.01 (120.5)	2.66 (120.5)	2.52 (107.5)
Min, Max	0.35, 15.5	0.35, 18.8	0.35, 68.9	0.35, 42.7
3 months*				
Geometric mean (CV)	1.11 (109.3)	1.03 (112.7)	2.75 (101.8)	2.60 (103.6)
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
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

Reviewer comment: It appears that there is a mean decrease in calcitonin in the placebo group; this effect is somewhat attenuated in the liraglutide group of unclear significance. This is shown in a dose-dependent fashion at week 20 in trial 1807:

Table 85. Repeated Measures Analysis of Calcitonin Comparison after 20 Weeks of Treatment

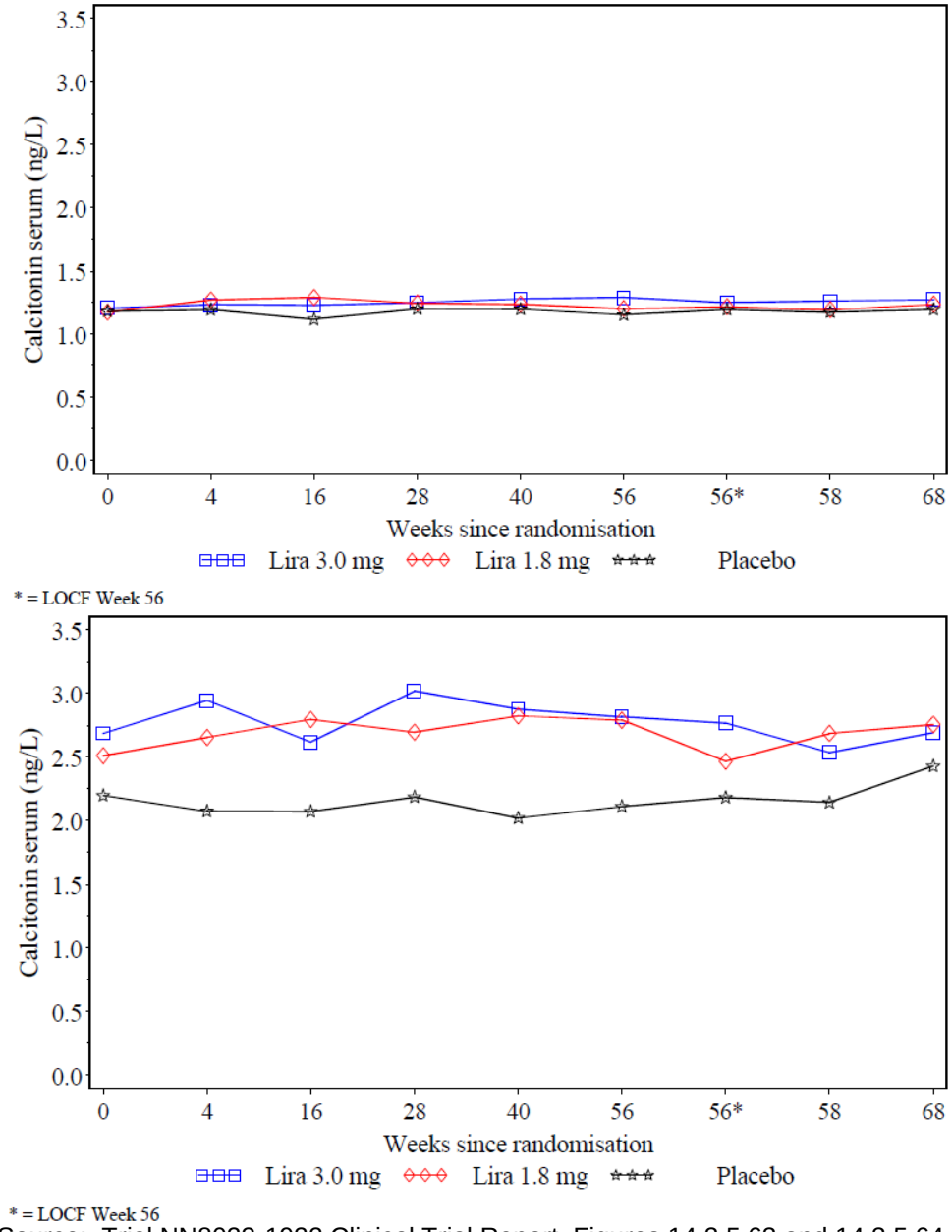
Treatment / Comparison	Estimates		P-value
Estimated increase in mean rel. to baseline mean # (%)			
Lira 1.2	-20.1	[-30.6;-7.90]	0.0020
Lira 1.8	-19.1	[-29.6;-7.18]	0.0026
Lira 2.4	-13.8	[-25.4;-0.37]	0.0444
Lira 3.0	-11.9	[-22.8; 0.56]	0.0605
Orlistat	-25.3	[-35.7;-13.1]	0.0002
Placebo	-21.6	[-32.2;-9.43]	0.0010
Estimated difference in mean rel. to comparator mean (%)			
Lira 1.2 vs. Placebo	1.98	[-16.6;24.72]	0.8482
Lira 1.8 vs. Placebo	3.14	[-15.5;25.85]	0.7603
Lira 2.4 vs. Placebo	9.98	[-10.3;34.80]	0.3587
Lira 3.0 vs. Placebo	12.37	[-7.53;36.57]	0.2404
Lira 1.2 vs. Orlistat	7.01	[-12.9;31.45]	0.5183
Lira 1.8 vs. Orlistat	8.22	[-11.7;32.64]	0.4460
Lira 2.4 vs. Orlistat	15.40	[-6.26;42.07]	0.1765
Lira 3.0 vs. Orlistat	17.91	[-3.42;43.96]	0.1055

Baseline means, males: 2.44 ng/L, females: 0.46 ng/L

Source: NN8022-1807 Clinical Trial Report, Table 14.3.5.29

Geometric mean calcitonin remains relatively stable over time and appeared similar by dose in trial 1922 (Figure 44).

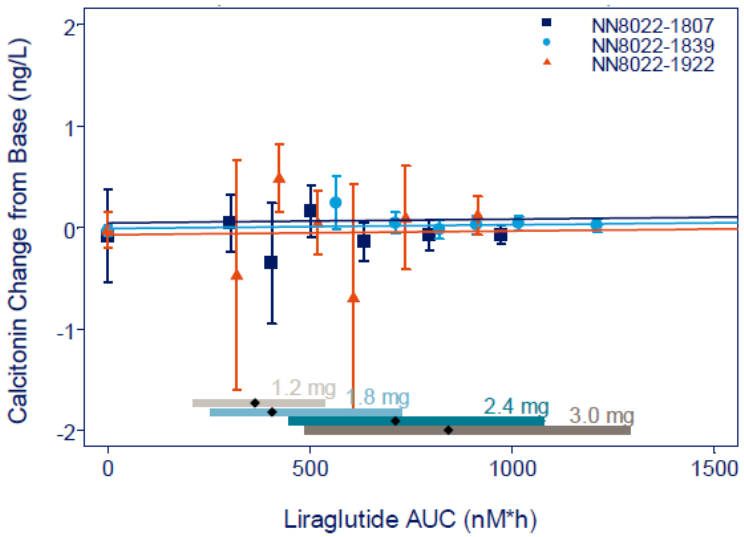
Figure 44. Calcitonin geometric mean (ng/L) by treatment group in females (top figure) and males (bottom figure), Trial 1922



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

There does not appear to be a clear exposure effect on calcitonin from an analysis of exposure-response (Figure 45).

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 86). 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 86. 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 ≥ 1.5× 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 ≥ 2× 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 ≥ 3× 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.

Table 87. Incidental Increase in Calcitonin at the End of the Trial, Weight Management Pool

	Lira 3.0 mg N	Lira 3.0 mg (%)	Lira All N	Lira All (%)	Placebo N	Placebo (%)	Total N	Total (%)
Number of subjects	3384		3872		1941		5813	
From < UNR to >= UNR	151	(4.46)	173	(4.47)	58	(2.99)	231	(3.97)
From < UNR to >= 1.5 UNR	31	(0.92)	33	(0.85)	11	(0.57)	44	(0.76)
From < UNR to >= 2 UNR	10	(0.30)	12	(0.31)	4	(0.21)	16	(0.28)
From < UNR to >= 3 UNR	4	(0.12)	4	(0.10)	1	(0.05)	5	(0.09)
From < UNR to >= 20 ng/L	5	(0.15)	6	(0.15)	1	(0.05)	7	(0.12)
From < UNR to >= 50 ng/L	0	(0.00)	0	(0.00)	1	(0.05)	1	(0.02)
From < 20 ng/L to >= 20 ng/L	16	(0.47)	17	(0.44)	7	(0.36)	24	(0.41)
From < 50 ng/L to >= 50 ng/L	1	(0.03)	2	(0.05)	2	(0.10)	4	(0.07)

N: Number of subjects, %: Percentages are based on total N
Incidental increase: Baseline calcitonin value below lower limit. At least one 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 Appendix 7.5, Table 174

More males treated with liraglutide 3 mg experienced persistent increases (defined as ≥ 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× 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 88. Persistent Increase in Calcitonin, Weight Management Pool

	Total				Females				Males			
	Lira 3.0 mg N	Lira 3.0 mg (%)	Placebo N	Placebo (%)	Lira 3.0 mg N	Lira 3.0 mg (%)	Placebo N	Placebo (%)	Lira 3.0 mg N	Lira 3.0 mg (%)	Placebo N	Placebo (%)
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/L 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.

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 89. 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 90. 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]
Liraglutide 3.0 mg						
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

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 *in situ*	Invasive breast adeno-carcinoma	Malignant/ Stage 1: Localised	249/258/ Main treatment period	No relevant	Ductal carcinoma *in situ*. 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

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 *in situ*	Breast ductal carcinoma *in situ*	Pre-malignant/ Stage 0: *In situ*	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 *in situ*	Ductal carcinoma *in situ*	Pre-malignant/ Stage 0: *In situ*	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 *in situ*	Ductal carcinoma *in situ*	Pre-malignant/ Stage 0: *In situ*	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.
Placebo						
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 *in situ*	Breast ductal carcinoma *in situ*	Pre-malignant/ Stage 0: *In situ*	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.[39] 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. Nevertheless, potential centrally-mediated mechanisms have been speculated (increases in luteinizing hormone).[40] Sex hormones were not measured in the clinical trials.

39 Jarow, J. (OHOP), consult for NDA 206321, dated 3 Jul 2014
40 Beak SA, et al. Glucagon-like peptide-1 stimulates luteinizing hormone-releasing secretion in a rodent

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 (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).

hypothalamic neuronal cell line. J Clin Invest. 1998; 101(6):1334-41.

Table 91. 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]
Liraglutide 3.0 mg						
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

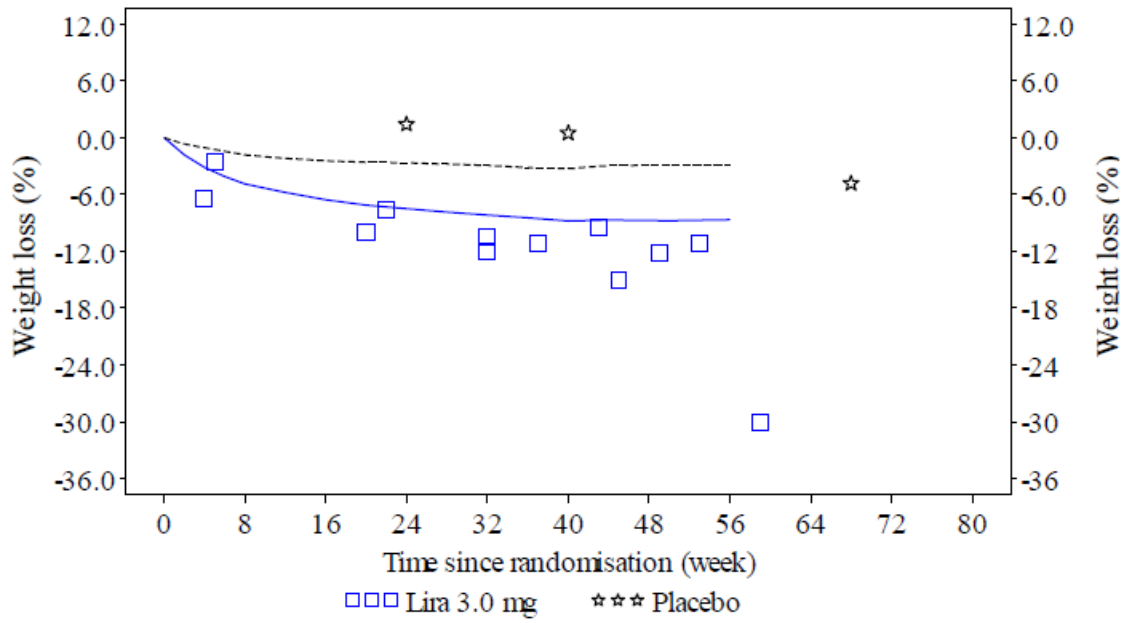


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).
Curves represent mean for subjects with no adjudicated breast neoplasms.
Events occured during re-randomisation period of 1839 is also included

Source: ISS, Appendix 7.2, Figure 256

Reviewer comments:

Note that this line reflects weight loss in the trials overall (men and women); however, women on average lost more weight than men.

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.

On 19 Sep 2014, FDA asked for a follow-up of adjudicated breast cancer cases from the ongoing phase 3 trial 1839, as well as a blinded tabulation of cases from the ongoing cardiovascular outcomes trial, LEADER. Neither trial supplied additional data that would add to the breast cancer concern; however, both trials are ongoing.

Table 92. Breast Cancer Cases in Ongoing Extension of Trial 1839 (after 120-Day Safety Update)

	Liraglutide 3.0 mg				Placebo			
	N	%	E	R	N	%	E	R
Number of women	643				277			
Patient years at risk[1] (PYR)	508.3				214.5			
Cases pending review by adjudication committee	1	0.16	1	0.20	1	0.36	1	0.47
Events sent for adjudication[2]	1	0.16	1	0.20	0	0	0	0
Positively adjudicated breast cancer[3]	0	0	0	0	0	0	0	0

[1]Includes time from November 12, 2013 through September 22, 2014 or last record for withdrawn patients
[2]Events included have undergone review by the EAC
[3]Only index event included
R: event rate per 100 patient years at risk
Number of women included in above table are the number of women as of November 12, 2013

Source: Response to FDA September 19, 2014 information request, Table 3

(b) (4)

[redacted]

Pancreas

As discussed above (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. [9] 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.[8]

Pancreatitis was discussed with regard to the liraglutide clinical program in a previous section, above.

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 reveled 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.

Colorectum

As noted in Table 77 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.

Two patients (0.06%) treated with liraglutide (and no placebo-treated patients) were reported to have malignant colorectal neoplasms; see details in Table 94.

Table 94. EAC-Confirmed Colorectal Neoplasms, 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]
Liraglutide 3.0 mg						
1922/402004/ 67/M/29.2/ DE	Rectal cancer	Rectal adenocarcinoma	Malignant/ Stage 1	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	Diverticulosis	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 diverticulitis	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

Trial/subject/ /age/sex/BMI/ Country	PT	EAC diagnosis	EAC malignancy 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	Diverticulosis 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
Placebo						
1839/132017/ 71/M/39.1/ IT	Colon adenoma	Colon adenoma	Benign	205/204/ Main treatment period	Polypectomy 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 95. 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]
Liraglutide 3.0 mg						
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.

Trial/ subject/ age/sex/BMI Country	PT	EAC diagnosis	EAC malignancy status	Inv onset, days/ EAC onset, days/	Medical history	Details[a]
Placebo						
1839-ext/ 106023/ 51/M/31.1/ DE	Neuro-endocrine tumor	Carcinoid tumor	Malignant	458 / 458	Resection of colon polyp in 2011 prior to entry into the trial. Immuno-histological examination showed well differentiated 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

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 97).

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 96. 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 97.

Table 97. 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

The imbalance in thyroid neoplasms in the diabetes trials is consistent with the original Victoza safety review.[41] (There was speculation by some advisory committee members at that time that the imbalance was potentially related to increased surveillance; i.e., ascertainment bias.[42])

Six (of nine) cases of 'thyroid cancer' from the diabetes program reported in this NDA were reviewed in the Victoza safety review,[41] 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

41 Mahoney KM. NDA 22341 Clinical Safety Review, signed 07 Aug 2009.
42 Parks M. Division Director's Memo for NDA 22341, 22 Jan 2010.

cells. On (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 98). 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. An additional case was reported in an uncontrolled trial (insulin degludec program); this event was reviewed in an efficacy supplement.[43] 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 (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.

43 Yanoff L. NDA 22341 S-009 / NDA 21536 S-0039. Signed 24 Feb 2012.

Table 98. 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).

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 96 (breast: liraglutide 0.1% vs. comparator <0.1%; pancreas: liraglutide <0.1% vs. comparator <0.1%; colorectal: liraglutide 0.1% vs. comparator 0.1%).

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 99. 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 HLGTs not available † Note that there was also one AE of neuroendocrine tumor of the pancreas 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 100. 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

Liver Events and Related Laboratory Data

Liver-Related Laboratory Data

Weight Management Program

The FDA Guidance for evaluating premarketing drug-induced liver injury[44] considers the best predictor for severe hepatotoxicity as transaminase elevation accompanied by

44 FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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 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 101), 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 101. 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	40 (1.2)	46 (1.2)	22 (1.1)
≥ 5x ULN	11 (0.3)	11 (0.2)	5 (0.3)
≥ 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)	13 (0.7)
≥ 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	4 (0.1)	5 (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)
≥ 2x ULN	6 (0.2)	6 (0.2)	3 (0.2)
≥ 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 25 Sep 2014, Appendix 1 Table 1

Table 102. 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 an 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 therafter 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 103. 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

One SAE of 'Alanine aminotransferase increased' was reported:

- Patient 210015 in trial 1839 (liraglutide 3 mg) was a 27-year-old male with a medical history of fatty liver, hypertension, and raised lipase and CPK at the start of the trial. Laboratory values during the trial were as follows:

Table 104. Laboratory Data, Patient 210015, Trial 1839

Week	-2	0	4	16	28	40	56	58	68
Serum albumin	4.9	4.9		5	4.8	4.7	4.6	5.1	4.6
ALT	57	57		399	87	51	42	49	41
Alkaline phosphatase	72	72		91	69	72	64	64	61
AST	34	34		159	38	37	31	45	28
Total bilirubin	0.53	0.53		0.41	0.58	0.29	0.70	0.82	0.29

Source: Reviewer created from NDA datasets

At week 16, the patient presented with elevated alanine aminotransferase (ALT). Laboratory data performed showed elevated ALT at 399 “with signs of inflamed liver”. No imaging tests were done at the time of the event.

Reviewer comment: The narrative does not specify what signs of inflamed liver were observed.

Approximately 1 week later, treatment with the trial drug was withdrawn temporarily; trial drug was reintroduced approximately 1 week later, and the patient was reported “recovered”. Approximately 3 weeks later, an ultrasound of the liver and biliary tree was performed. The ultrasound showed that the liver is not enlarged, normal appearance to all of the visual hepatic parenchyma, no evidence of focal or diffuse fatty infiltration, no focal parenchymal abnormality, normal gall bladder, no calculi, normal caliber common bile duct. By report, the patient lost a “considerable” amount of weight from 117.5 kg to 104.8 kg.

Reviewer comment: It is not clear why this event was reported as an SAE; it does not appear that the patient was hospitalized.

Diabetes Program

In a May 16, 2014 information request, the sponsor was asked to provide a “Hy’s law” analysis from the diabetes pool (NDA 223341, supplementary pool II). They provided information about 4 patients with ALT or AST ≥ 3x ULN with total bilirubin ≥ 2x ULN. Three of the cases were in patients treated with liraglutide and one with comparator. All 3 liraglutide cases are confounded (and thus, in my opinion not likely to be true Hy’s law cases), but are included here for completeness.

The first 3 cases were submitted to NDA 22341, and the 4th case (452002) was in an extension trial that was submitted to NDA 206321 [discussed in section 7.3.1 (deaths) and section 9.4 (narratives of deaths)].

Table 105. Patients with Transaminases Greater than 3 Times ULN and Bilirubin Greater than 2 Times ULN, Diabetes Pool

Trial #, Subject ID	Date	ALT, U/L	AST (SGOT), U/L	Bilirubin, umol/L	ALP, U/L
NN2211-1436, liraglutide 1.8mg +glimepiride, 579006	08MAR2007	262.0 (5.82x, ULN 45)	172.0 (4.41x, ULN 39)	114.8 (5.24x, ULN 21.9)	323.0 (2.63x, ULN 123)
NN2211-1697, glargine+glimepiride+metformin 761016	05SEP2006	270.0 (6.0x, ULN 45)	90.0 (2.31x, ULN 39)	133.5 (6.10x, ULN 21.9)	430.0 (3.50x,ULN 123)
NN221-2072, metformin+ liraglutide 0.045 mg 3708	29AUG2001	23 (0.51x, ULN 45)	109.0 (4.95x,ULN 22)	39.9 (2.12x, ULN 18.8)	74 (1.03x, ULN 72)
NN221-1860, liraglutide 1.8mg 452002	13AUG2009	129 (3.0x, ULN 43)	178 (4.81x, ULN 37)	244.0 (11.14x, ULN 21.9)	357.0 (3.03x, ULN 118)

Source: Response to FDA Request, dated Jun 18, 2014

The sponsor provided the following narratives; reviewer comments follow:

In Trial 1436, subject 579006 (liraglutide 1.8 mg+glimepiride) had greatly elevated blood AST, ALT, bilirubin and ALP. Although the subject had elevated AST, ALT and bilirubin, the subject did not fulfill the criteria of Hy's law as ALP was also demonstrated to be increased. This subject reported an adverse event in Week 26 of hepatobiliary disorders/acute cholecysitis (4 days off trial drug since the subject completed the study) with a 19-day duration. An abdominal ultrasound done on 14-MAR-2007 stated 'chronic calculus cholecystitis'. On the same date, the tests done for 'viral hepatitis' were reported negative. The adverse event was moderate, non-serious and was evaluated by the investigator to be unlikely related to trial products. The subject recovered.

Reviewer comment: The diagnosis of chronic calculus cholecystitis was made 1 week after the abnormal laboratory values, and is likely the explanation for the laboratory findings.

In Trial 1697, subject 761016 (glargine+glimepiride+metformin) had greatly elevated blood ALT, and bilirubin, however, ALP was also increased and the AST value was about 2 times the normal upper range. Therefore, the subject did not meet the criteria of Hy's law. No adverse event, which could explain or elaborate on the finding, was recorded for this subject.

Reviewer comment: This is a comparator case.

In Trial 2072, at week 4, subject 3708 (metformin+liraglutide 0.045 mg) had greatly elevated AST, and bilirubin, with normal ALT, however ALP was also increased above the ULN, therefore the subject did not meet Hy's law. At the same study visit, this subject reported persistent hyperglycemia, and for this reason he was withdrawn from the trial. Furthermore, the subject reported past history of alcohol abuse at baseline, and in increase in alcohol consumption in the days prior to the study visit, as well as increased concomitant atorvastatin from 40mg to 60mg per day. Additional laboratory parameters at the visit included FPG 308 mg/dl and triglycerides of 1080 mg/dl (409 mg/dl 2 weeks prior). Patient was advised to discontinue atorvastatin and to follow up in one week. At the follow-up, all hepatobiliary laboratory parameters were normal.

Additional data from the investigator was provided. The patient reportedly was diagnosed with type 2 diabetes in 1996 (5 years prior) during a hospitalization for a "pancreatic seizure" secondary to heavy alcohol use (possible episode of acute pancreatitis). Six months prior to enrollment (11/15/2000), his medical history and relevant labs were as follows:

Table 106. Medical History, Patient 3708, Diabetes Trial NN2211-2072

Patient Medical History/Current Conditions	Onset Date/End Date	Con Meds	Current State	Relevant Labs
Type 2 Diabetes	1996	Glucophage 850mg TID	Ongoing/Stable HbA1c 7.0%	ALT – 21, AST – 85, GGT – 128 (u/L))
Hyperlipidemia	1998	Lipitor 40mg QD	Ongoing – managed by PCP	Bilirubin, total – 1.5mg/dL
Hypertension	1998	Vasotec 20mg BID	Ongoing – managed by PCP	Albumin Creatinine Ratio – 26.471
History of Alcohol Abuse	1986/1996	Currently drinks 1 equivalent per week		

Source: Response to FDA Request, dated Jun 18, 2014

On 4/12/2001, this patient was screened for participation in the Novo Nordisk NN2211-2072 and was assigned #3708. The patient's medical history had not changed since the prior visit noted above. However, the patient's diabetes had improved with a HbA1c of 6.4%. His other relevant labs were ALT – 11, AST – 48 (both mU/mL) and his Bilirubin, total was 0.95 mg/dL.

Visit Week 4 occurred on 4/26/2001. The patient was advised to switch to Metformin 1000mg BID per protocol. No Labs drawn. No changes in medical conditions reported.

Visit Week 8 occurred on 5/31/2001. The patient reported and adverse event of Poison Ivy starting on 5/27/2001 and was being treated with Cortaid Lotion, Kenalog Cream 1%, and Atarax 25 mg each day. Again, no labs drawn per protocol.

Randomization Visit occurred on 7/26/2001. The patient reported additional therapy of Atenolol 50mg QD initiated by the treating PCP. The blood pressure did improve with this added therapy. Labs resulted as FPG – 166 mg/dL, Tot Bili – 1.30, ALT – 13, AST – 60, Tot Chol – 238, Trigs – 676, HDL – 62, LDL – unable to calc.

On 8/9/2001 our site conducted a phone call with patient. Patient reported "moderate nausea, vomiting and diarrhea" as well as fatigue since 8/7/2001. No con meds have been taken for this Adverse Event. Patient was instructed by Principal Investigator to discontinue study drug. Patient had already dosed on 8/9/2001, so he did not dose on 8/10/2001.

Subsequent visit occurred on 8/14/2001. Patient only missed one dose of study drug on 8/10/2001. Moderate nausea, vomiting and diarrhea resolved on 8/11/2001 and patient stated that a "stomach virus" was going around his office and attributes feeling bad to this recollection. Patient reported an increase in fasting glucose results. Labs resulted as the following; FPG – 242 mg/dL, Tot Bili – 1.49, ALT – 15, AST – 68, Tot Chol – 172, Trigs – 409, HDL – 58, LDL – unable to calc.

The patient's next follow up visit occurred on 8/29/2001. Patient reported consistent hyperglycemia with fasting reading of 200-300mg/dL. Patient also reported an adverse event of a sore throat started on 8/28/2001 (no concomitant medications) as well as mild diarrhea starting 8/19/2001, no medications necessary. Patient's PCP was contacted and discussed patient's participation. **It was agreed that patient should be withdrawn from the study secondary to persistent hyperglycemia. Last dose of trial medication was on 8/28/2001.** Patient was instructed to resume Metformin 750mg TID, and was advised to increase Lipitor to 60mg QD.
Labs results were as follows: Fasting plasma glucose confirmed the hyperglycemia concern resulting in 308 mg/dL. In addition, the patient's lipid control deteriorated with labs resulting in; Tot Chol – 230, Trigs – 1080, HDL – 38, LDL – unable to calc. Other labs were Tot Bili – 2.33, ALT – 23, AST – 109

On 9/4/2001, the patient was contacted regarding the lab results from 8/29/2001. Patient noted the resolution of sore throat on 9/4/2001. Patient also reported an increase in ETOH consumption in the days prior to the visit. Patient advised to discontinue Lipitor and to follow up in one week. PCP also contacted regarding care and will resume follow up. Retest labs were scheduled for the following day (9/5/2001), resulting in the following: HbA1c of 9.1%, FPG – 233 mg/dL, Tot Bili – 1.43, ALT – 18, AST – 71.

9/26/2001 – Follow up visit
Glucose much improved, patient reported BGs in 130-180 range, continuing on Metformin 850mg, TID. Patient admits to continued struggle with ETOH consumption.
Labs resulted in the following: FPG – 249 mg/dL, Tot Bili – 0.9, ALT – 20, AST – 78, Tot Chol – 350, Trigs – 1750, HDL – 56, LDL – unable to calc. Liver function tests were back to baseline and patient was advised to resume Lipitor 40mg QD. Patient agreed to continue follow up with PCP.

This patient has not been seen in our office since 9/26/2001. Contact information is no longer current.

Reviewer comment: I do not agree that the alkaline phosphatase (1.03x ULN) is consistent with the case not meeting Hy's law as stated by the sponsor. However, this case is confounded by alcohol use +/- a recent viral illness, and the laboratory data appear consistent with this. He did have a prior history of elevated AST (80 U/L) and total bilirubin (1.5 mg/dL) in Nov 2000.

In Trial 1860, subject 452002 (liraglutide 1.8mg) had greatly elevated ALT, AST, bilirubin, as well as ALP (> 3x ULN), and therefore the subject did not meet Hy's Law. The subject had a past medical history of stenosis of ductus hepatocholodochus and cholecystectomy with stent implant was done 3 years prior to the trial. During the trial,

the patient had recurrent AE reports of bile duct/common hepatic duct stenosis with jaundice and acute cholangitis. The subject also had multiple related endoscopic procedures, and dysfunctional endoprotheses were replaced twice. The subject was noted as not recovered from the AE of hepatic duct stenosis, and this was the probable explanation for the elevated hepatobiliary liver parameters during the trial. The causality of liraglutide was noted as unlikely and no action was taken to trial drug.

Reviewer comment: This patient had several events of abnormal liver tests associated with bile duct stenosis. Ultimately, the patient was diagnosed with and died of bile duct cancer (see listing in section 7.3.1 and narrative in section 9.4).

Adverse Events of Hepatitis or Liver Injury

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 107. 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 dipyrone). 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, as described in the pancreatitis section of this review.

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.

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.[45] 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 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.

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.

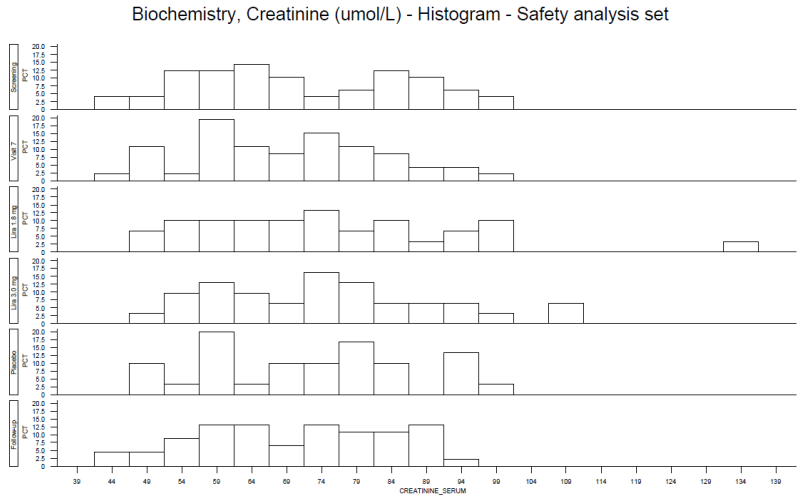
Clinical Pharmacology Trial

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):

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

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.

Weight Management Program

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 108. 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 109. 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]
Liraglutide 3.0 mg					
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) 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 110. 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

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.[46]

As noted in Table 108 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 111. 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 109 above for a description of this event.

46 Levey AS, et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009; 150:604-612.

Estimated glomerular filtration rate demonstrated a mean decrease from baseline in both treatment groups with an increase thereafter; see the following figure.

Figure 48. Change in Estimated Glomerular Filtration Rate (CKD-EPI Equation), Weight Management Pool

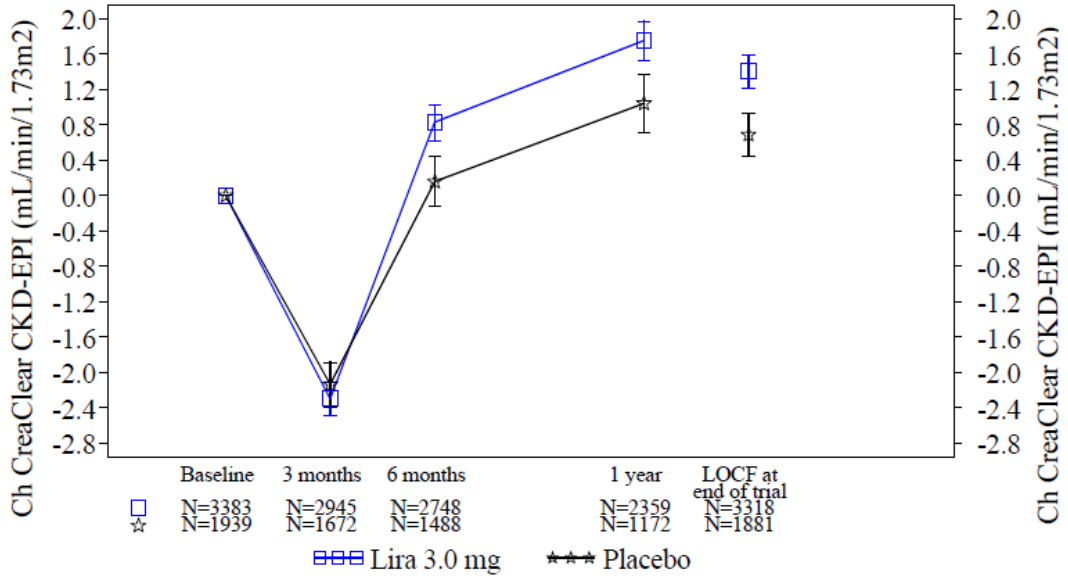


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

Source: ISS, Appendix 7.5, Figure 56

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 112. 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)

Source: Supplementary AE Report, Appendix 1, Table 75

Literature Reports

Two recent literature reports regarding liraglutide and acute kidney injury include a case of acute interstitial nephritis[47] and a case of acute tubular necrosis.[48]

- Gariani, et al.[47] 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.[48] 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

47 Gariani K, et al. Acute interstitial nephritis after treatment with liraglutide. Am J Kidney Dis. 2014; 63(2): 346-8.
48 Kaakeh Y, et al. Liraglutide-induced acute kidney injury. Pharmacotherapy. 2012; 32(1): e7-11.

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 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).

Cardiovascular Safety

In 2008, FDA published a guidance regarding CV risk assessment in drugs to treat T2DM,[4] 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 2.6) 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, it was recommended 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 below, as are hypotension and heart failure-related events.

Blood pressure and lipid changes were reported in section 6.1.5 (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%).

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 7.3.1).

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 113. 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.

Weight Management Analysis

The primary analysis[49] 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.

49 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.

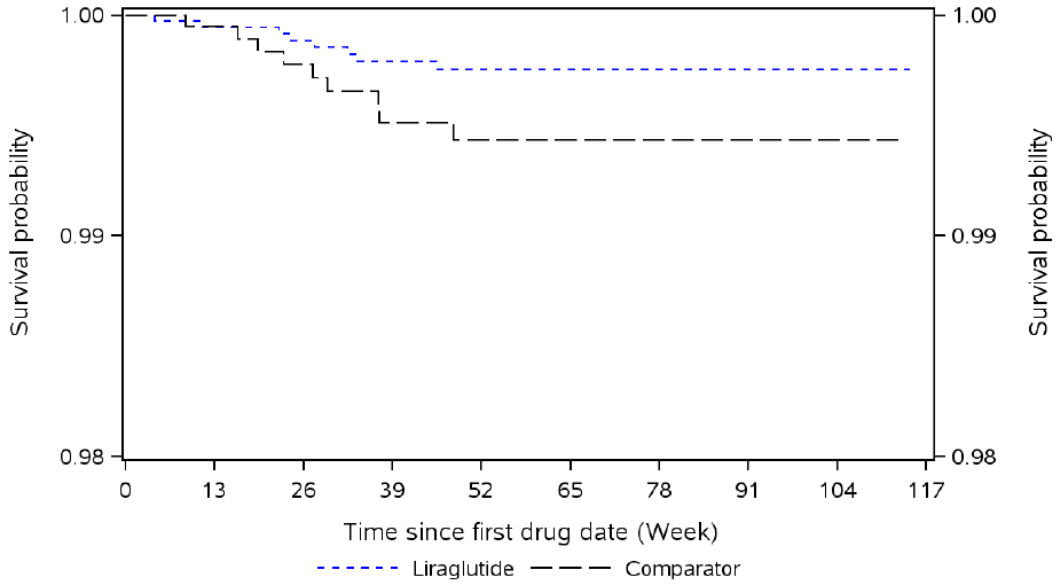
Table 114. Adjudicated MACE, Weight Management Pool

	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

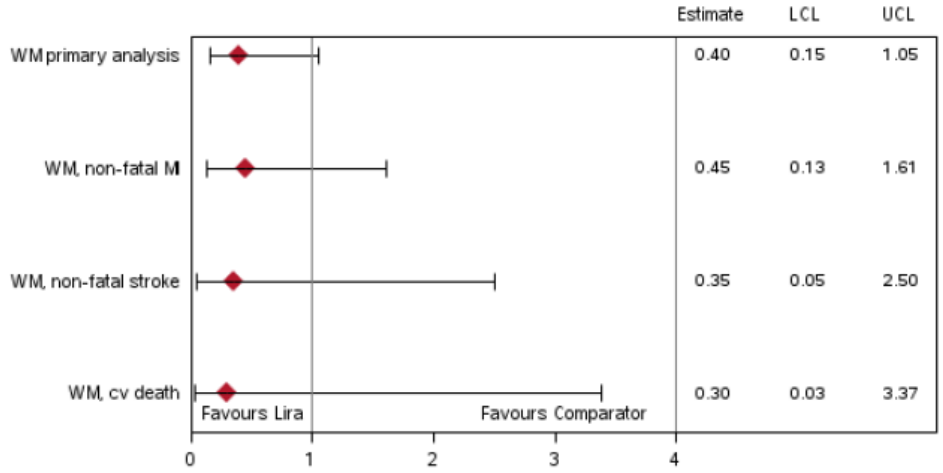
The estimated hazard ratio for the primary endpoint of time to first MACE for liraglutide (8 events) versus comparators (9 events) was 0.40 (95% CI: 0.15; 1.05); the Kaplan-Meier plot is shown below. Point estimates for the hazard ratios of the MACE components were consistent with the composite, as shown in Figure 50.

Figure 49. Time to First MACE, Weight Management Pool



Source: CV Meta-analysis Report, Figure 6-1

Figure 50. 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).

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).

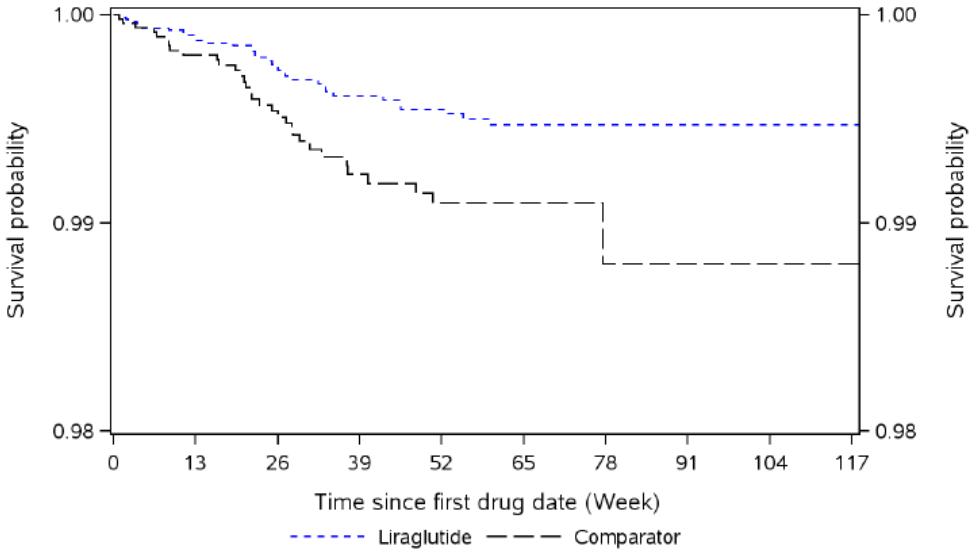
Table 115. Adjudicated MACE, Weight Management and Diabetes Pools, Combined

	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

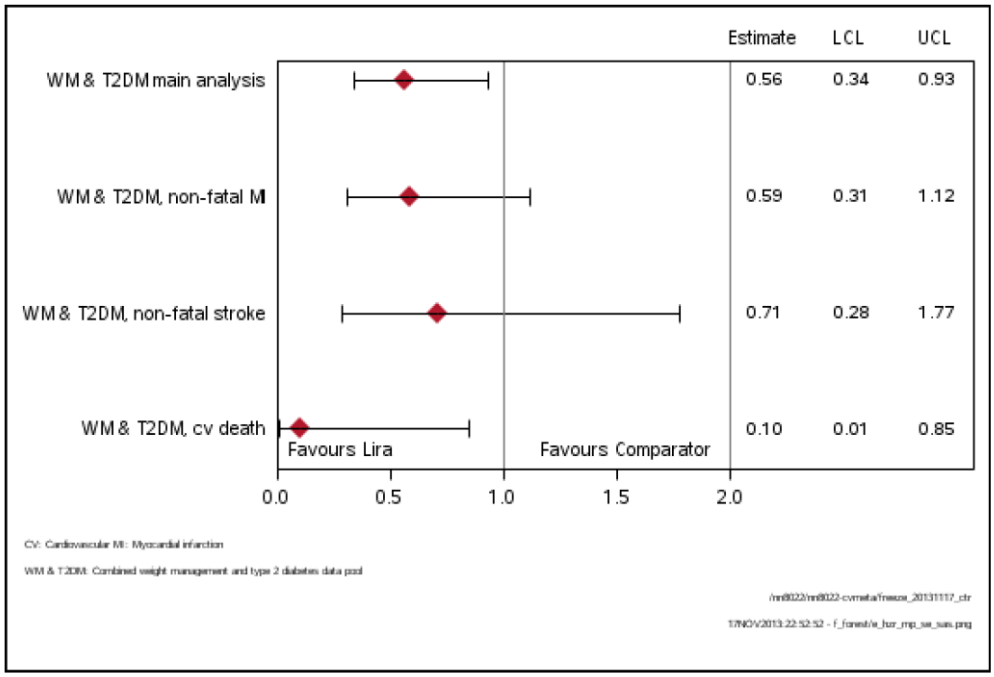
See Figure 51 for a Kaplan-Meier plot of the time to first MACE in the combined weight management and diabetes programs on-treatment analysis population, and Figure 52 for a plot of the main analysis of the MACE composite and the individual components.

Figure 51. Time to First MACE, Combined Weight Management and Type 2 Diabetes Pool



Source: CV Meta-analysis Report, Figure 6-5

Figure 52. Estimated Hazard Ratios for MACE Composite and MACE Components, Weight Management + Diabetes Pools



Source: CV Meta-analysis Report, Appendix 1, Figure 78

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%).

Increased Heart Rate and Arrhythmias

Heart Rate

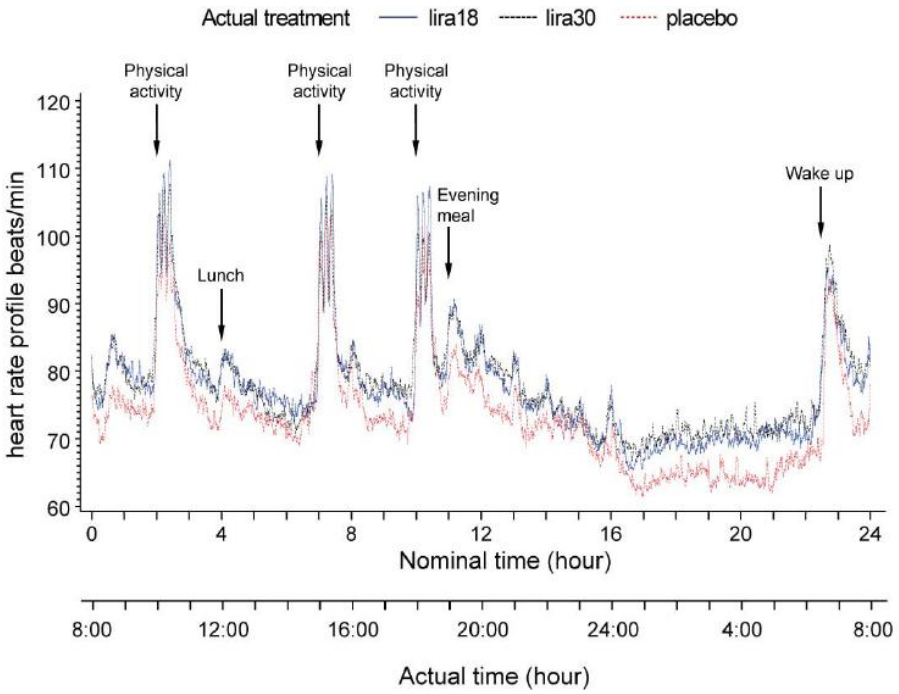
As noted in the Victoza label, mean increases from baseline in heart rate (HR) of 2 to 3 beats per minute (bpm) were observed with liraglutide compared to placebo in the T2DM program. Although the clinical consequences of drug-induced increases in HR in the setting of unchanged or decreased blood pressure 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 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 53 and Table 116. 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 53. Mean HR Profile during 24-hr Respiratory Chamber by Treatment, Trial 3630



Source: NN8022-3630 Clinical Trial Report, Figure 12-1

Table 116. Heart Rate during 24-hr Respiratory Chamber by Treatment, Trial 3630

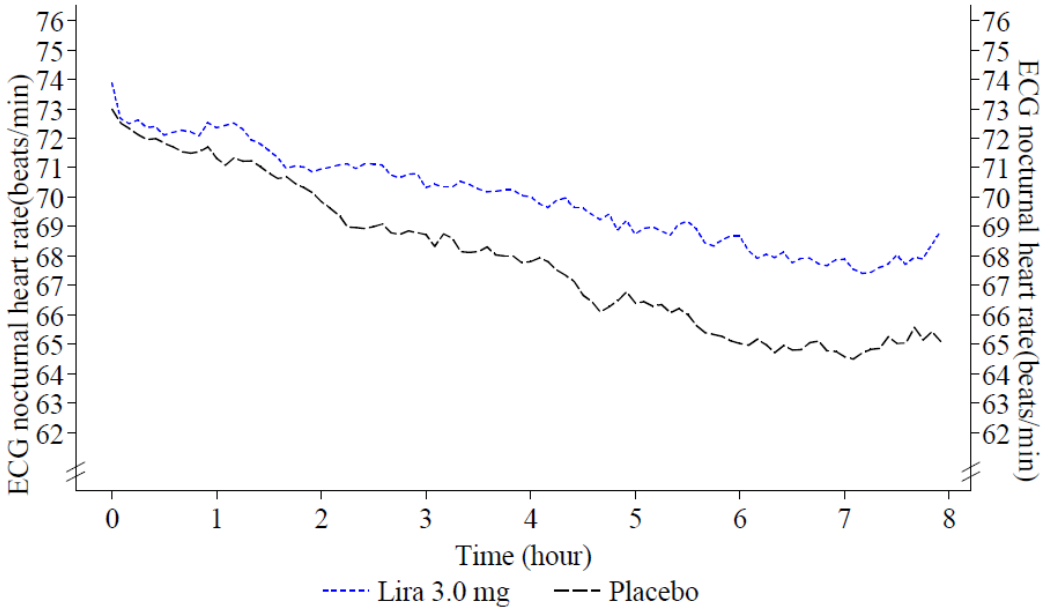
	Estimated LS Mean			Estimated Difference (95% CI)		
	Lira 3mg	Lira 1.8mg	Pbo	3mg vs Pbo	1.8mg vs Pbo	3mg vs 1.8mg
24-hr HR, bpm	78.20	77.26	71.59	6.61 (4.02, 9.19)	5.67 (3.20, 8.13)	0.94 (-1.63, 3.52)
9-hr daytime HR, bpm	80.23	80.59	75.95	4.28 (0.98, 7.57)	4.63 (1.40, 7.87)	-0.36 (-3.70, 2.98)
3-hr 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 54. 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 55). 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 56 presents the pooled and by trial (range: 1 to 5 bpm) treatment differences.

Figure 55. Mean Change in Resting Heart Rate by Visit, Weight Management Pool

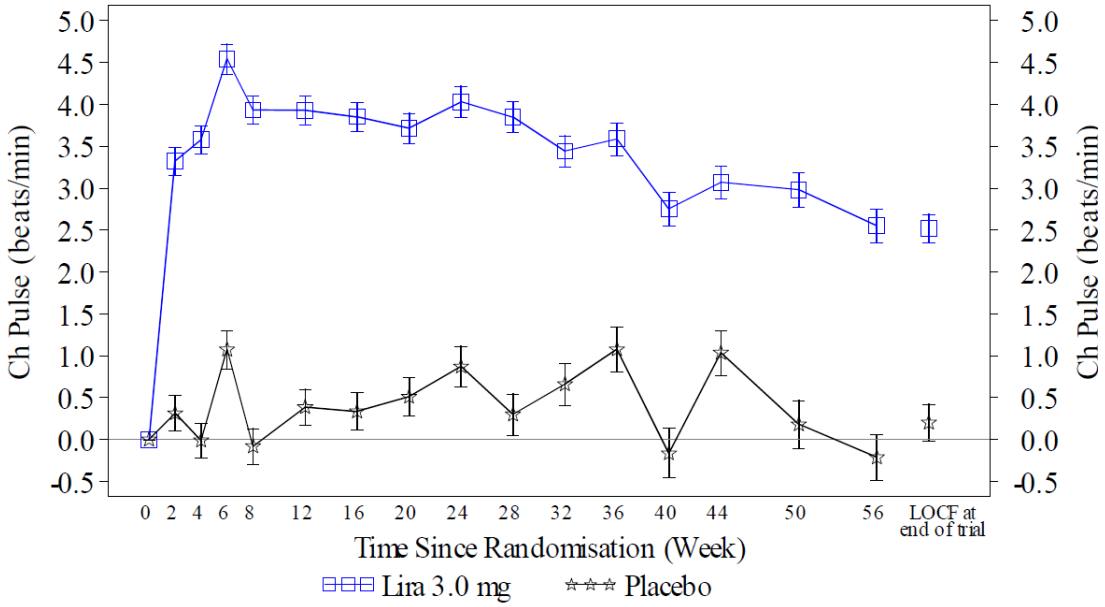
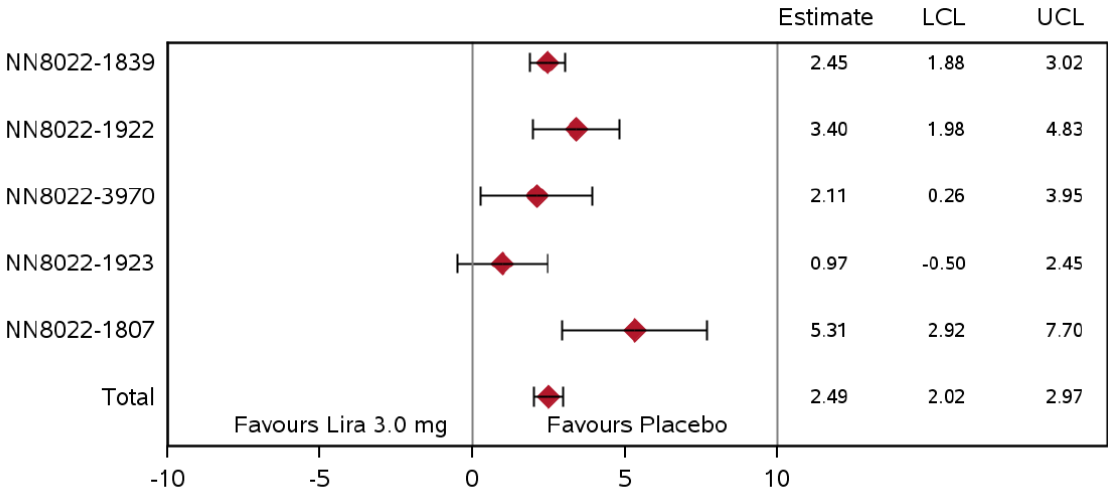


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).
Source: ISS, Figure 2-35

Figure 56. Mean Change in Resting Heart Rate at End-of-Treatment, by Trial and Pooled

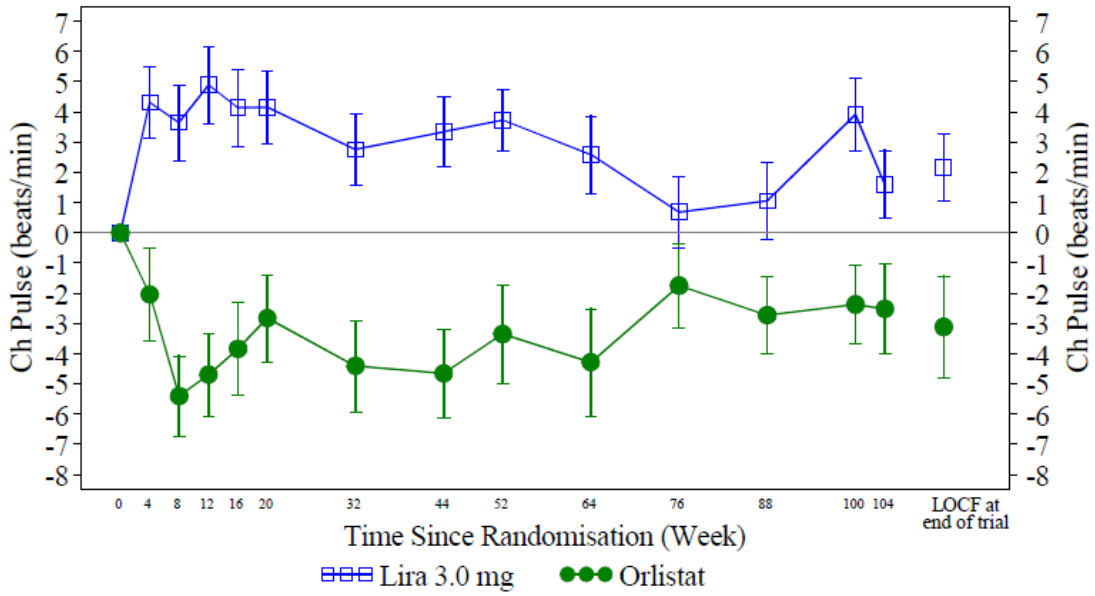


P-value for interaction: 0.0256.
LCL: Lower 95% confidence limit, UCL: Upper 95% confidence limit
Source: ISS, Figure 2-34

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.

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 57. 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 117. Maximum HR and HR Change, Weight Management Pool

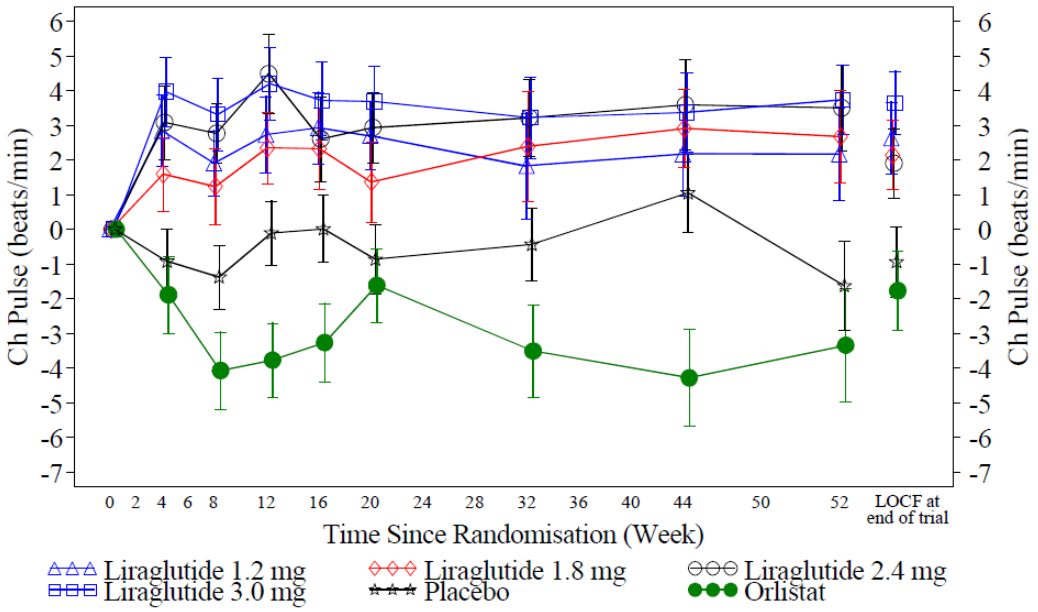
	Lira 3 mg N=3384 n (%)	**Placebo N=1941 n (%)**
Change from baseline to max > 0 bpm	3065 (90.6)	1665 (85.8)
Change from baseline to max > 5 bpm	2723 (80.5)	1355 (69.8)
Change from baseline to max > 10 bpm	2056 (60.8)	907 (46.7)
Change from baseline to max > 15 bpm	1364 (40.3)	512 (26.4)
Change from baseline 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

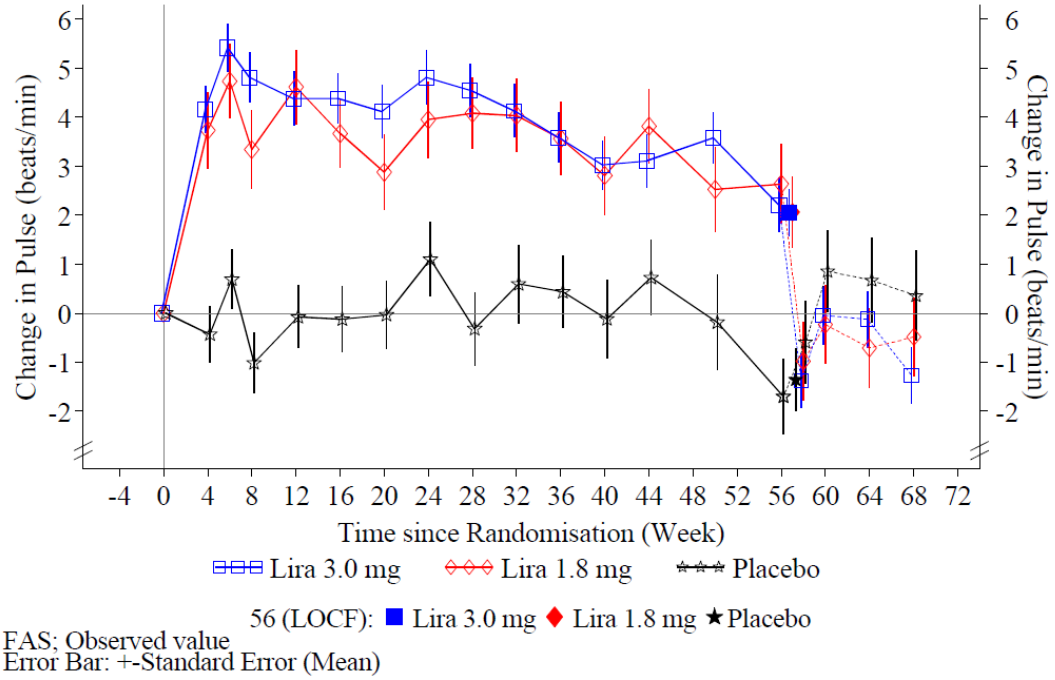
There was no clear indication of a liraglutide dose-response, based on a within-dose comparison of change in mean resting HR at end of treatment in the 2 trials that included lower doses of liraglutide. Mean change in HR by liraglutide dose in trials 1807 and 1922 is illustrated in Figure 58 and Figure 59, respectively.

Figure 58. 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 59. Mean Change in Heart Rate by Visit, Trial 1922



FAS; Observed value
Error Bar: +-Standard Error (Mean)

Source: NN8022-1922 Clinical Trial Report, Figure 12-14

In trial 1922 (Figure 59, 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 118).

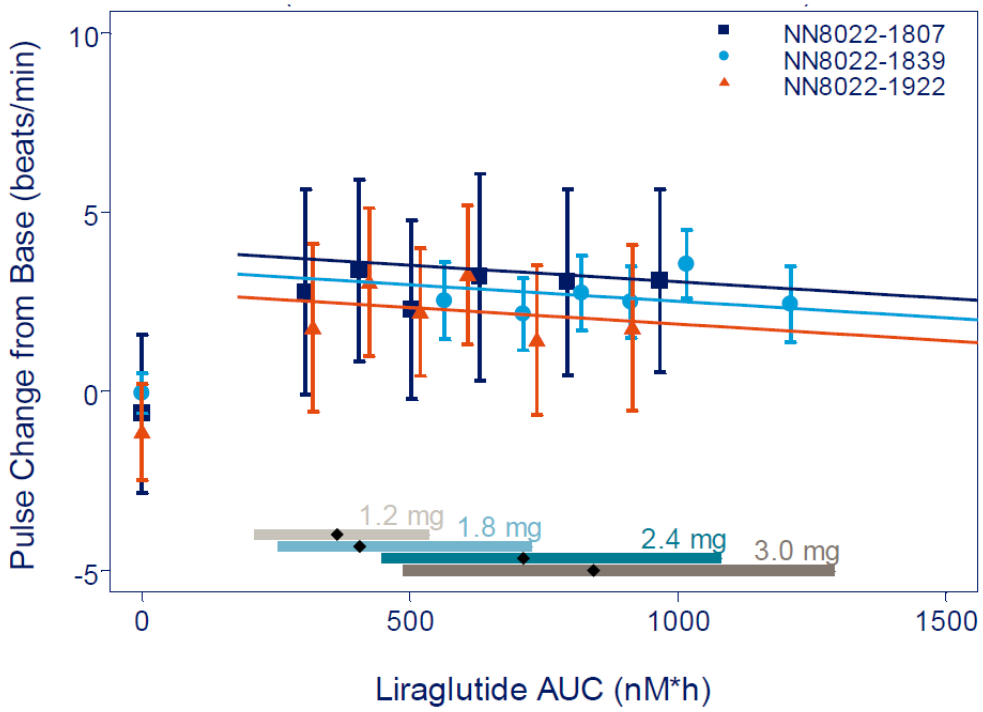
Table 118. Categories for HR Increase from Baseline until Week 56, Trial 1922

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 60. 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 61).

Figure 61. Change in Heart Rate by Visit in 5% Weight Loss Non-Responders (Top) and Responders (Bottom)

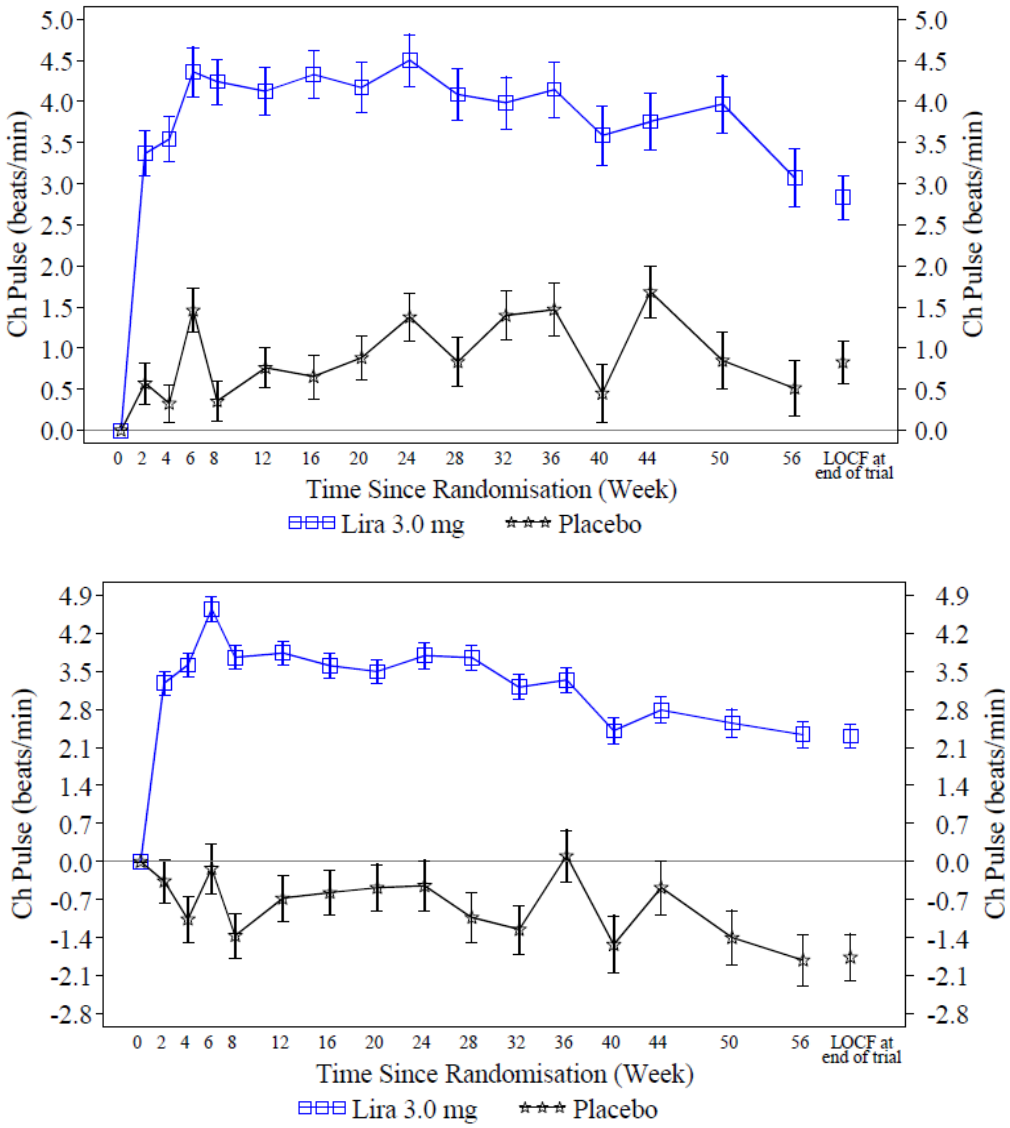


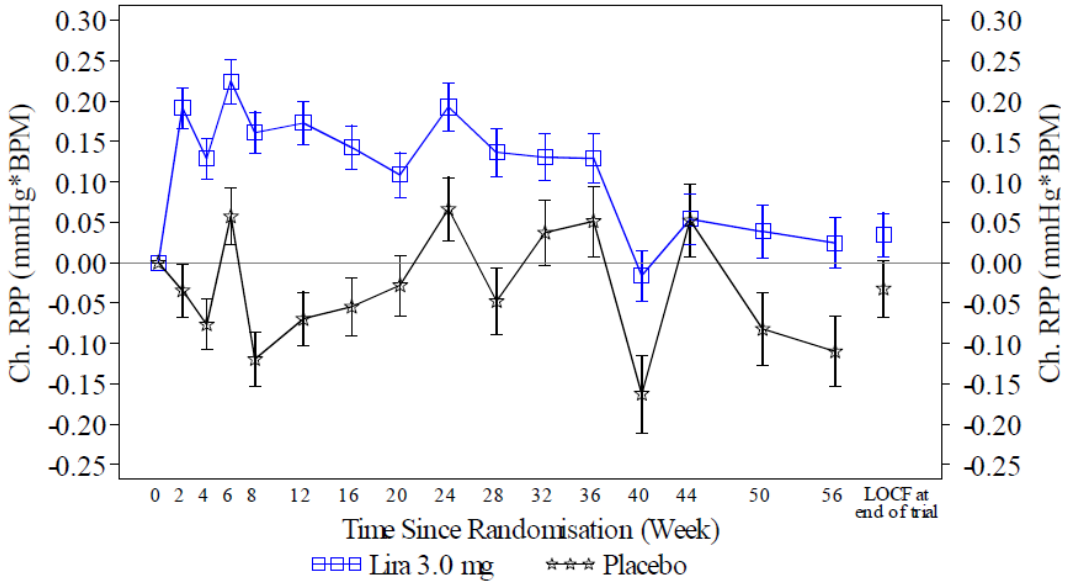
Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

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 62. Change in Rate-Pressure Product by Visit, Weight Management Pool



Source: ISS, Figure 2-39

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.[12]

Table 119. 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 120 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 120. '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’ HLGT 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 7.3.1).

Hypotension

Liraglutide is associated with blood pressure decreases, as described in section 6.1.5 (efficacy results). It has been speculated that GLP-1 receptor agonists may exert blood pressure lowering effects via natriuresis and/or vasodilatory action.[50,51,52]

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 6.1.5) 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

50 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.
51 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.
52 Ussher JR and Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res. 2014; 114(11): 1788-803.

and 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).

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 121. 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.

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.[53,54,55,56] 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

53 Egan A. FDA Clinical Review of NDA 21888 (rimonabant), EMDAC 13 Jun 2007.
54 Golden J. FDA Clinical Review of NDA 22529 (lorcaserin), EMDAC 16 Sep 2010 and 10 May 2012.
55 Roberts M. FDA Clinical Review of NDA 22580 (phentermine/topiramate), EMDAC 15 July 2010 and 22 Dec 2012.
56 Craig E. FDA Clinical review of NDA 200063 (naltrexone/bupropion), EMDAC 7 Dec 2010.

any suicidal behavior or any suicidal ideation of type 4 (active suicidal ideation with 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).[57] 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.[57]

57 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.[58] 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

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 122. 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.

58 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 123 and most common PTs in the SMQ are shown in Figure 63. 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 123). In patients treated with liraglutide 3 mg, 5 SAEs in 4 patients were: 'anxiety', 'panic attack', 'depression suicidal' (see narrative 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 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.

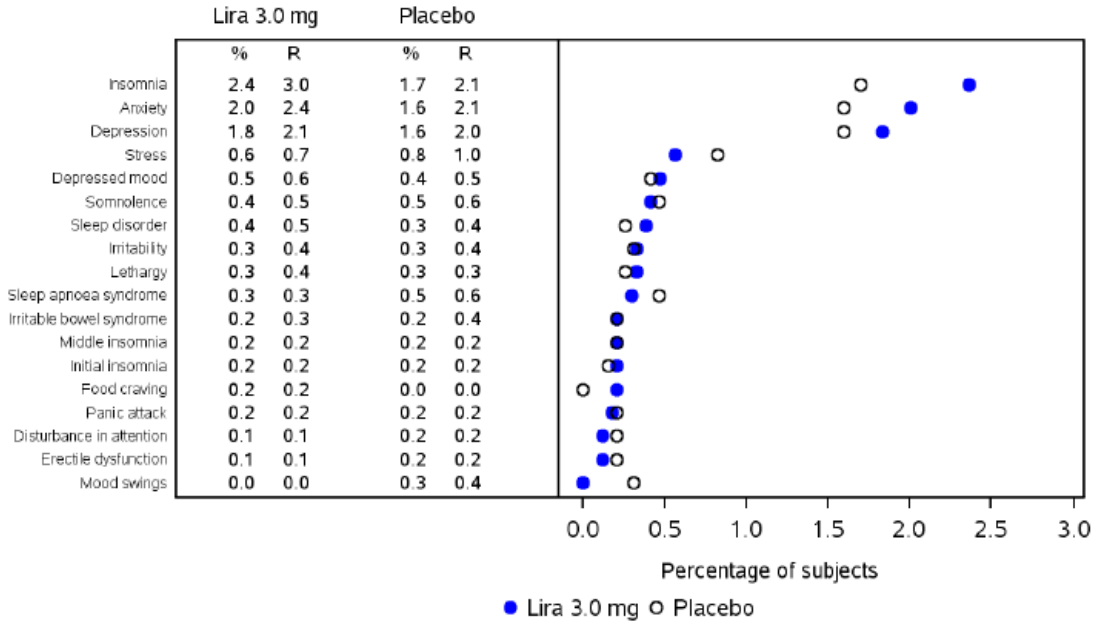
Table 123. Psychiatric Disorders, Weight Management Pool

	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 63. 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

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 123, 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 below, in discussion of the C-SSRS.

Insomnia

As shown in Figure 63, 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 64. Cumulative Event over Time Plot of Insomnia, Weight Management Pool

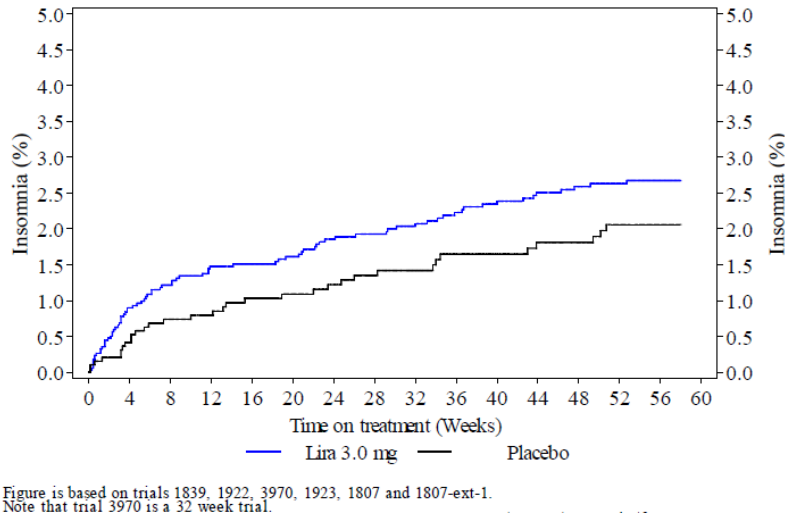


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial 3970 is a 32 week trial.

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%).

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 HLGTs 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 124. 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 SOCs						
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

Mental Health Questionnaires

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 125 and Table 126.

Table 125. 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 126. 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 127. 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

C-SSRS

C-SSRS post-baseline results are summarized in the table below.

Table 128. 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).

As seen in Table 128, 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 above) that for unclear reasons was not captured in the C-SSRS.

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.

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 129). 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 129. 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

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.

Spontaneously reported events are events which are not reported on the same day as a plasma glucose value.

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.

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.

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 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 130).

Table 130. Fasting Plasma Glucose Values in Patients with Hypoglycemia AEs Reported at FPG Visits, Weight Management Pool, Patients without T2DM Only (Excluding Trial 1922)

		Lira 3.0 mg			Placebo		
	Criteria	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 131. 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 132. 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 N	%	E	Placebo 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:

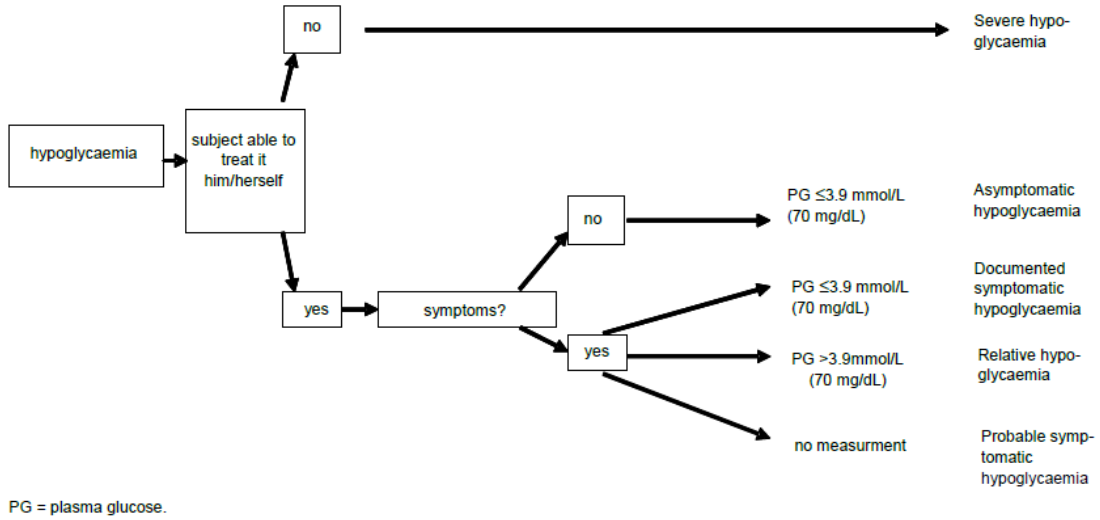
- In patients without pre-diabetes :
  - Liraglutide 3 mg: 16 (1.4%) reported 28 AEs
  - Placebo: 4 (0.6%) reported 5 AEs

- In patients with pre-diabetes:
  - Liraglutide 3 mg: 12 (0.7%) reported 13 AEs
  - Placebo: 3 (0.3%) reported 3 AEs

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 65. American Diabetes Association (ADA) Definition of a Hypoglycemic Episode



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 133. 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 133. Hypoglycemic Episodes by Classification, Trial 1922

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

Source: ISS, Table 2-24

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 134 – 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 134. 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.

Thyroid Disorders

This section addresses non-neoplasm- and non-calcitonin-related thyroid disorders. For a discussion of thyroid neoplasms and calcitonin, see the neoplasms section, above.

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 135. 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 (<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. However, mean TSH decreased over the duration of the trial, of unclear clinical significance. By the end of the trial, mean change in TSH was similar between treatment groups.

Figure 66. Thyroid Stimulating Hormone, Change from Baseline, Weight Management Pool

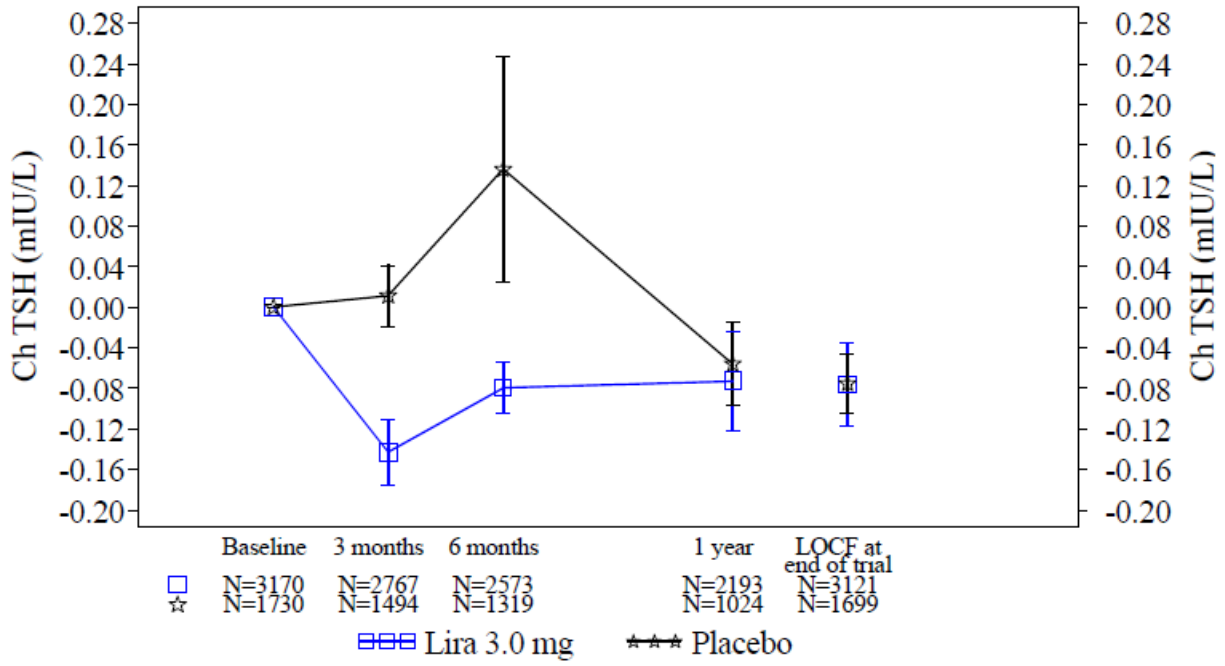


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).
Source: ISS Appendix 7.5, Figure 74

- 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 by individual preferred terms occurred at a similar incidence in liraglutide- and comparator-treated patients.

Table 136. 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

7.4 Supportive Safety Results

7.4.1 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 137. 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 129 and Table 133)
* Excluding preferred terms reported more frequently with placebo

Source: Proposed PI, Table 3; ISS Appendix 7.2, Table 10

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:

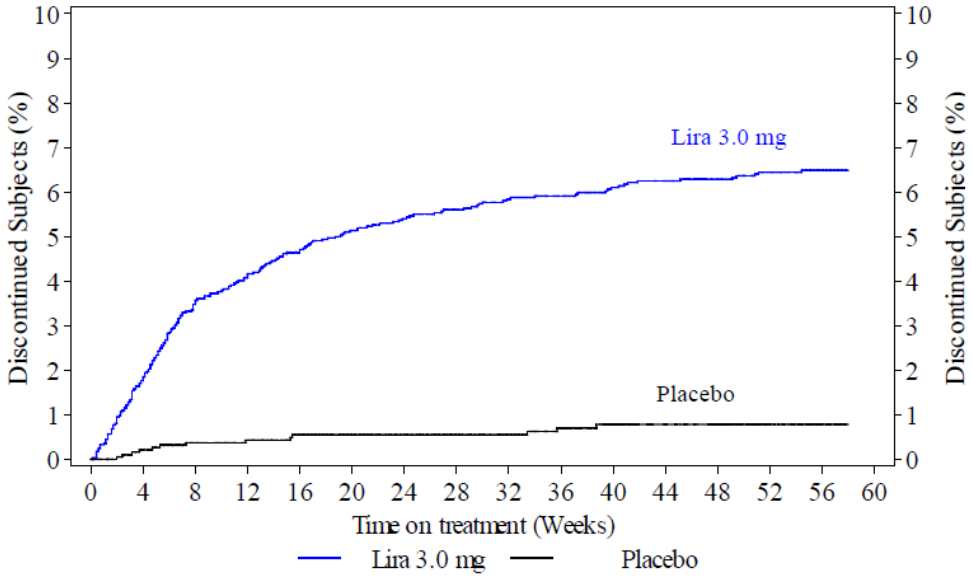
In the five double-blind clinical trials of 26 weeks duration or longer, gastrointestinal adverse reactions were reported in 41% of Victoza-treated patients and were dose-related. Gastrointestinal adverse reactions occurred in 17% of comparator-treated patients. Common adverse reactions that occurred 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 67. Time to Discontinuation due to Gastrointestinal Disorders, Weight Management Pool



Source: ISS, Figure 2-5

Nausea and Vomiting

GLP-1 slows gastric emptying in a dose-dependent fashion.[59] Therefore, nausea is an expected side effect of GLP-1 receptor agonists, and has been shown to occur with liraglutide in the T2DM population.[5] (Although 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.

59 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 138. 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 7.3.5 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 7.3.5 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

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 68 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 68. Percentage of Patients with Nausea (Top) and Vomiting (Bottom) by Week and Treatment, Weight Management Pool

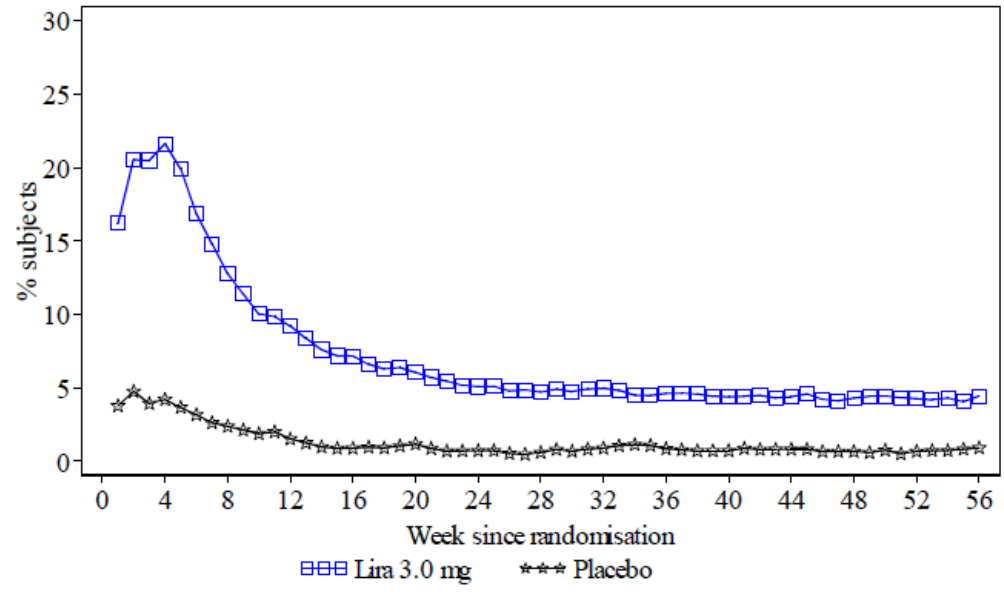


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

/nn8022/nn8022-iss/freeze_20131117_ctr
19NOV2013:10:56:30 - f_perc_eventsasle_percent_nausea_sas.cgm

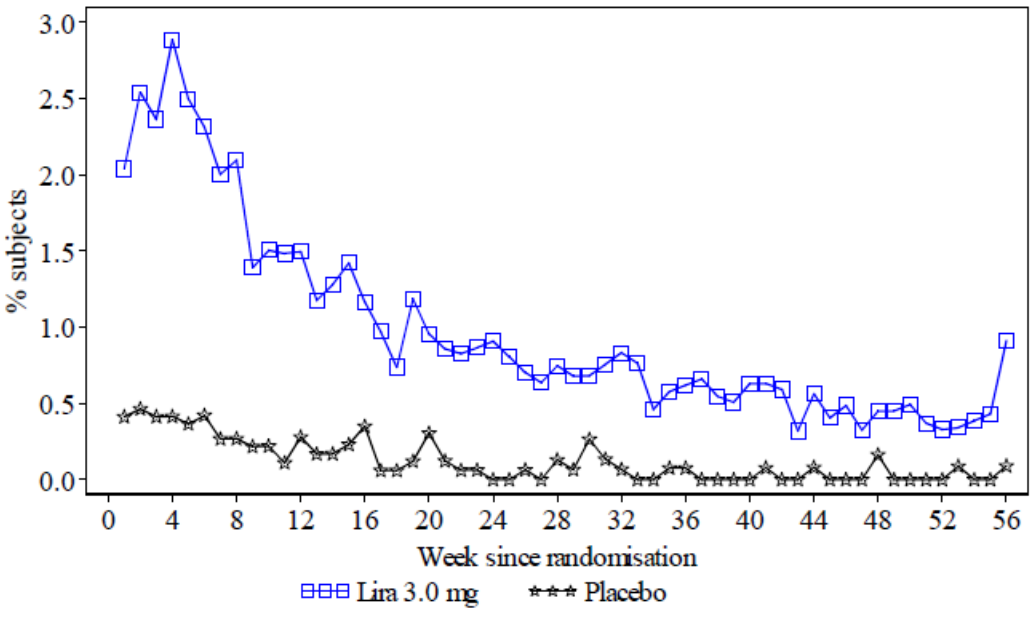


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

/nn8022/nn8022-iss/freeze_20131117_ctr
19NOV2013:10:56:47 - f_perc_eventsasle_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 139. 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 similar frequency in patients who were and were not 5% weight loss responders, suggesting that weight loss was not entirely due to these symptoms.

Table 140. 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

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 141. 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

7.4.2 Laboratory Findings

Biochemistry

The proportion of patients with abnormal laboratory findings related to the liver and kidney are presented in section 7.3.5 (submission specific primary safety concerns). Calcitonin and amylase and lipase are discussed with the review of thyroid neoplasms and pancreatitis, respectively, also in section 7.3.5. Blood glucose was discussed with hypoglycemia in section 7.3.5. TSH was discussed with thyroid disorders in section 7.3.5.

Central Tendencies

Mean decreases were seen in ALT, albumin, alkaline phosphatase, AST, total calcium, serum creatinine, and serum urea were seen with liraglutide-treated patients as compared to placebo-treated patients during the trial and/or at the end of the trial. However, in general mean values were similar between treatment groups at each visit.

Outliers

Outlier analyses were requested by the sponsor and are presented in this section if not in other sections of the review.

Table 142. Abnormally High or Low Biochemistry Parameters, Weight Management Pool

	Lira 3 mg N=3384	All lira N=3872	Placebo N=1941
CK			
> 5x ULN	12 (0.4)	12 (0.3)	10 (0.6)
> 10x ULN	4 (0.1)	4 (0.1)	3 (0.2)
Serum Calcium			
> 11.5 mg/dL	15 (0.4)	16 (0.4)	3 (0.2)
> 12.5 mg/dL	1 (<0.1)	1 (<0.1)	0
> 13.5 mg/dL	0	0	0
< 7 mg/dL	16 (0.5)	20 (0.5)	5 (0.3)
< 6 mg/dL	5 (0.1)	7 (0.2)	2 (0.1)
Serum Potassium			
> 6 mmol/L	26 (0.8)	33 (0.9)	15 (0.8)
> 7 mmol/L	0	2 (0.1)	2 (0.1)
< 3 mmol/L	4 (0.1)	5 (0.1)	1 (0.1)
< 2 mmol/L	0	0	0
Serum Sodium			
> 150 mmol/L	491 (14.5)	547 (14.1)	214 (11.0)
> 160 mmol/L	11 (0.3)	12 (0.3)	5 (0.3)
< 130 mmol/L	4 (0.1)	4 (0.1)	1 (0.1)
< 120 mmol/L	0	0	0
Serum Albumin			
< 3 g/dL	2 (0.1)	2 (0.1)	0
< 2 g/dL	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

The majority of the elevations in serum calcium were transient. CK elevations were typically associated with increases in physical activity and were not associated with muscle symptoms or renal dysfunction.

Hematology

Central Tendencies

Mean increases were observed in serum leukocytes and percent neutrophils and mean decreases were seen in percent lymphocytes, percent basophils (not shown), and percent monocytes in liraglutide-patients as compared with placebo. The clinical significance is unclear. Adverse events related to infections were not different between groups and mean values were within the normal range and remained similar between groups for the duration of the trials.

Figure 69. Mean Change in White Blood Cell Parameters, Weight Management Pool

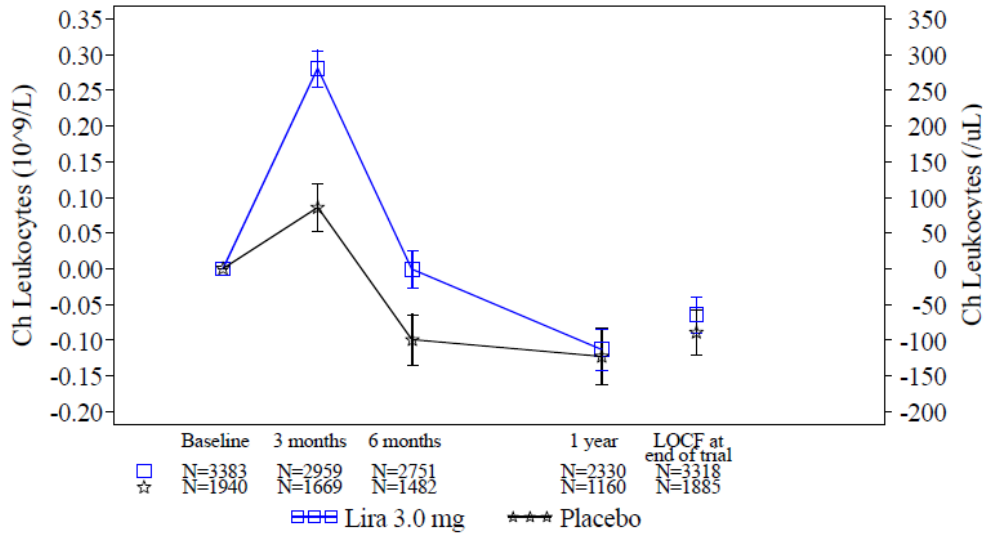


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

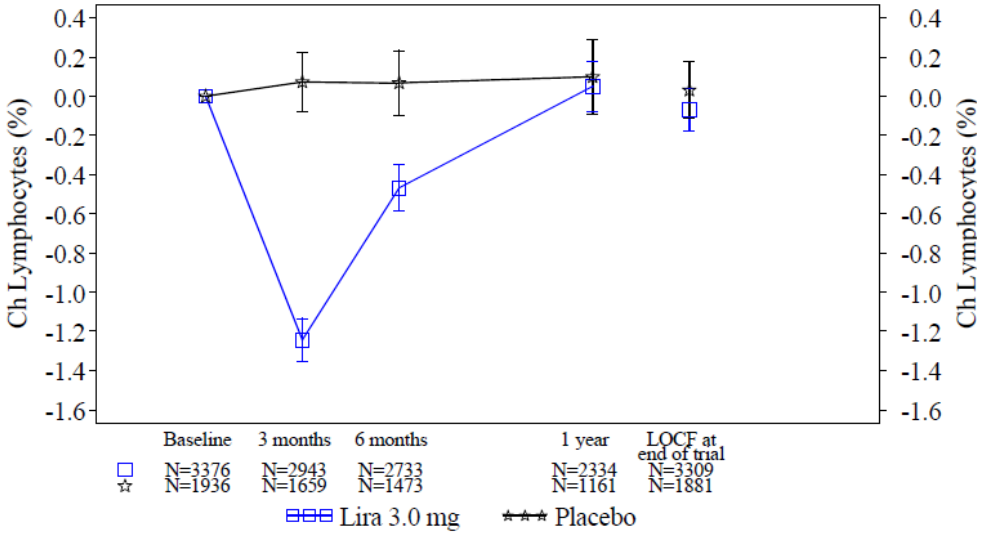


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

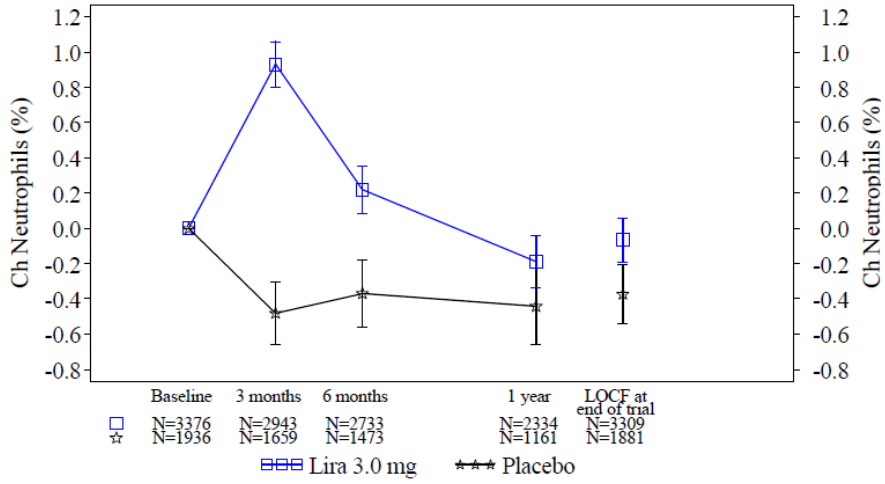


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Note that trial duration was 32 weeks for 3970 and 52 weeks for 1807 (including ext-1).

Source: ISS Appendix 7.5, Figures 220, 226, 232, and 238

Table 143. Abnormally High or Low Hematology Parameters, Weight Management Pool

	Lira 3 mg N=3384	All lira N=3872	Placebo N=1941
Hb			
< 8 g/dL	5 (0.1)	5 (0.1)	4 (0.2)
> 2 g/dL above ULN	0	5 (0.1)	1 (0.1)
> 4 g/dL above ULN	0	3 (0.1)	1 (0.1)
WBC count			
< 3000/mm^3	27 (0.8)	29 (0.7)	13 (0.7)
< 1000/mm^3	3 (0.1)	3 (0.1)	1 (0.1)
< 500/mm^3	0	0	0
Neutrophil count			
< 1500/mm^3	101 (3.0)	109 (2.8)	41 (2.1)
< 1000/mm^3	18 (0.5)	23 (0.6)	4 (0.2)
< 500/mm^3	8 (0.2)	11 (0.3)	2 (0.1)
Lymphocyte count			
< 800/mm^3	33 (1.0)	37 (1.0)	21 (1.1)
< 500/mm^3	7 (0.2)	7 (0.2)	5 (0.3)
< 200/mm^3	0	0	0
> 4000/mm^3	64 (1.9)	71 (1.8)	26 (1.3)
> 20000/mm^3	0	0	0
Platelet count			
< 75000/mm^3	1 (0.1)	1 (0.1)	3 (0.2)
< 50000/mm^3	0	0	3 (0.2)
< 25000/mm^3	0	0	2 (0.1)

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

7.4.3 Vital Signs

Blood pressure as an efficacy parameter is discussed in section 6.1.5. Blood pressure and heart rate as safety parameters are discussed as part of cardiovascular safety in section 7.3.5.

7.4.4 Electrocardiograms (ECGs)

In all the phase 2 and 3 trials, a 12-lead ECG was performed at screening and at end-of treatment. In trials 1922 and 1839, an additional ECG was performed at week 28 and at follow-up, and in trial 1923 ECGs were performed at baseline.

The ECG recordings were evaluated by the investigators and rated as 'normal', 'abnormal, not clinically significant' or 'abnormal, clinically significant'. Any new findings or deterioration of previous findings observed during the trial were to be recorded as AEs/SAEs if they fulfilled the criteria for AEs/SAEs.

In addition, all ECGs obtained in trials 1839, 1922, and 3970 were assessed centrally by cardiologists from (b) (4) for evidence of myocardial ischemia, silent MI, arrhythmia or other electrocardiographic abnormalities, as well as for confirmation of the machine read heart rate via measurement of the R-R interval between a minimum of 3 QRS complexes.

The cardiologist was to categorize the ECG findings as follows (either at screening or during the trial, as new findings):

- Normal ECG/ECG with clinically insignificant findings
- ECG findings suggestive of MI
- ECG with other significant abnormal findings

The effect of liraglutide 3 mg on the QT interval has not been investigated in the liraglutide weight management program. FDA agreed that the results obtained in the clinical pharmacology trial investigating the effect of liraglutide on QTc performed as part of the liraglutide in T2DM development program (trial NN2211-1644) at doses up to 1.8 mg can be extrapolated to the 3 mg dose used in the obese population, based on an exposure overlap between the populations and absence of an exposure-related QT finding.

Results
At screening, 29.5% of liraglutide 3 mg and 30.6% of placebo-treated patients were reported to have abnormal ECGs (1.1% and 0.5%, respectively, were considered clinically significant).

The proportion of patients with abnormal ECG findings reported by the investigator with onset during the treatment period was similar between groups at 6 months (liraglutide 3 mg 25.5%, placebo 27.0%), 1 year (liraglutide 3 mg 25.1%, placebo 28.4%) and at the end of trial LOCF (liraglutide 3 mg 25.5%, placebo 28.5%). Abnormal clinically significant ECG findings were reported by 1.1% and 0.9%; 0.8% and 0.6%; and 0.7% and 0.7% of liraglutide- and placebo-treated patients at the above time points, respectively. The proportion of patients shifting to a worse ECG category from screening to end-of-treatment was similar between treatment groups.

Reviewer comment: A slight imbalance, not in favor of liraglutide is noted for changes suggestive of myocardial infarction (MI). Note that ECGs indicating new ischemia / infarction since last ECG reading were adjudicated by the Event Adjudication Committee (EAC) to determine whether the event was 'acute coronary syndrome' (i.e., MI or hospitalization of unstable angina).

Table 144. Investigator-Interpreted ECGs, Screening to End-of-Trial, LOCF, Weight Management Pool

	End of trial including LOCF&				
Screening	Normal N (%)	Abnormal, NCS N (%)	Abnormal, CS N (%)	Not done N (%)	Missing N (%)
Lira 3.0 mg (N=3384)					
Normal	1883 (55.6)	302 (8.9)	8 (0.2)	78 (2.3)	114 (3.4)
Abnormal, NCS	413 (12.2)	486 (14.4)	5 (0.1)	18 (0.5)	38 (1.1)
Abnormal, CS	10 (0.3)	15 (0.4)	9 (0.3)	2 (0.1)	2 (0.1)
Not done	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Placebo (N=1941)					
Normal	988 (50.9)	186 (9.6)	5 (0.3)	66 (3.4)	103 (5.3)
Abnormal, NCS	200 (10.3)	307 (15.8)	5 (0.3)	24 (1.2)	49 (2.5)
Abnormal, CS	0 (0.0)	4 (0.2)	3 (0.2)	1 (0.1)	0 (0.0)
Not done	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N: Number of subjects, %: Percentages are based on total N
NCS: Non clinically significant, CS: Clinically significant
Table is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1
&: Week 32 for trial 3970, week 52 for trial 1807-ext-1 and week 56 for trials 1839, 1922 and 1923.
Source: ISS, Table 2-58

In trials 1839, 1922, and 3970, in which ECGs were centrally read, new findings at 6 months (28/32 weeks), one year (56 weeks), and at any time were generally similar between groups:

Table 145. Centrally Read ECG, Week 28/32, Weight Management Pool

	Lira 3.0 mg N (%)	Placebo N (%)
Number of Subjects	3079	1633
Does ECG indicate the following	2532 (100.0)	1262 (100.0)
New ischemia since prior ECG	9 (0.4)	4 (0.3)
New infarction since prior ECG	10 (0.4)	3 (0.2)
Anterior	4 (0.2)	2 (0.2)
Lateral	1 (<0.1)	0 (0.0)
LBB and cannot assess location of infarction	0 (0.0)	0 (0.0)
Inferior	5 (0.2)	1 (<0.1)
Posterior	0 (0.0)	0 (0.0)
New left bundle branch block since prior ECG	0 (0.0)	1 (<0.1)
None of the above	2513 (99.2)	1254 (99.4)
Other abnormalities	2532 (100.0)	1262 (100.0)
Yes	38 (1.5)	14 (1.1)
New arrhythmia	10 (0.4)	4 (0.3)
New LVH	0 (0.0)	1 (<0.1)
Other	28 (1.1)	9 (0.7)
No	2494 (98.5)	1248 (98.9)
Overall conclusion	2532 (100.0)	1262 (100.0)
Normal ECG or non significant changes	2489 (98.3)	1244 (98.6)
New finding suggestive of MI	10 (0.4)	4 (0.3)
Other new significant abnormal ECG findings	33 (1.3)	14 (1.1)

ECG: Electrocardiogram, N: Number of subjects, %: Percentage of subjects
Table is based on trials 1839, 1922 and 3970.
Measurements at week 28 (1839 and 1922) and week 32 (3970) are used.

Source: ISS, Appendix 74, Table 219

Table 146. Centrally Read ECG, Week 56, Weight Management Pool

	Lira 3.0 mg N (%)	Placebo N (%)
Number of Subjects	2903	1454
Does ECG indicate the following	2582 (100.0)	1197 (100.0)
New ischemia since prior ECG	3 (0.1)	4 (0.3)
New infarction since prior ECG	12 (0.5)	3 (0.3)
Anterior	5 (0.2)	1 (<0.1)
Lateral	1 (<0.1)	0 (0.0)
LBB and cannot assess location of infarction	0 (0.0)	0 (0.0)
Inferior	7 (0.3)	2 (0.2)
Posterior	0 (0.0)	0 (0.0)
New left bundle branch block since prior ECG	2 (<0.1)	0 (0.0)
None of the above	2565 (99.3)	1190 (99.4)
Other abnormalities	2582 (100.0)	1197 (100.0)
Yes	22 (0.9)	14 (1.2)
New arrhythmia	3 (0.1)	4 (0.3)
New LVH	0 (0.0)	1 (<0.1)
Other	19 (0.7)	10 (0.8)
No	2560 (99.1)	1183 (98.8)
Overall conclusion	2582 (100.0)	1197 (100.0)
Normal ECG or non significant changes	2553 (98.9)	1182 (98.7)
New finding suggestive of MI	13 (0.5)	3 (0.3)
Other new significant abnormal ECG findings	16 (0.6)	12 (1.0)

ECG: Electrocardiogram, N: Number of subjects, %: Percentage of subjects
Table is based on trials 1839 and 1922.

Source: ISS, Appendix 7.4, Table 220

Table 147. Centrally Read ECG, Any Finding During Treatment Period, Weight Management Pool

	Lira 3.0 mg N (%)	Placebo N (%)
Number of Subjects	3079	1633
Does ECG indicate the following	2867 (100.0)	1441 (100.0)
New ischemia since prior ECG	12 (0.4)	8 (0.6)
New infarction since prior ECG	22 (0.8)	6 (0.4)
Anterior	9 (0.3)	3 (0.2)
Lateral	2 (<0.1)	0 (0.0)
LBB and cannot assess location of infarction	0 (0.0)	0 (0.0)
Inferior	12 (0.4)	3 (0.2)
Posterior	0 (0.0)	0 (0.0)
New left bundle branch block since prior ECG	2 (<0.1)	1 (<0.1)
None of the above	2864 (99.9)	1440 (99.9)
Other abnormalities	2867 (100.0)	1441 (100.0)
Yes	60 (2.1)	27 (1.9)
New arrhythmia	13 (0.5)	8 (0.6)
New LVH	0 (0.0)	2 (0.1)
Other	47 (1.6)	18 (1.2)
No	2859 (99.7)	1428 (99.1)
Overall conclusion	2867 (100.0)	1441 (100.0)
Normal ECG or non significant changes	2858 (99.7)	1430 (99.2)
New finding suggestive of MI	23 (0.8)	7 (0.5)
Other new significant abnormal ECG findings	49 (1.7)	25 (1.7)

ECG: Electrocardiogram, N: Number of subjects, %: Percentage of subjects
Table is based on trials 1839, 1922 and 3970.
Measurements at week 28/56 (1839 and 1922) and week 32 (3970) are used.

Source: ISS, Appendix 7.4, Table 221

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 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.[60] 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

60 Porter, B. (DPARP), consult for NDA 22341, dated 7 May 2010

delaying sample collection (dataset was incomplete).[60] 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 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.

Allergic Reactions

A predefined search was based on the SMQs and preferred terms presented in the following table.

Table 148. 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 hypersensivity
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.

Weight Management

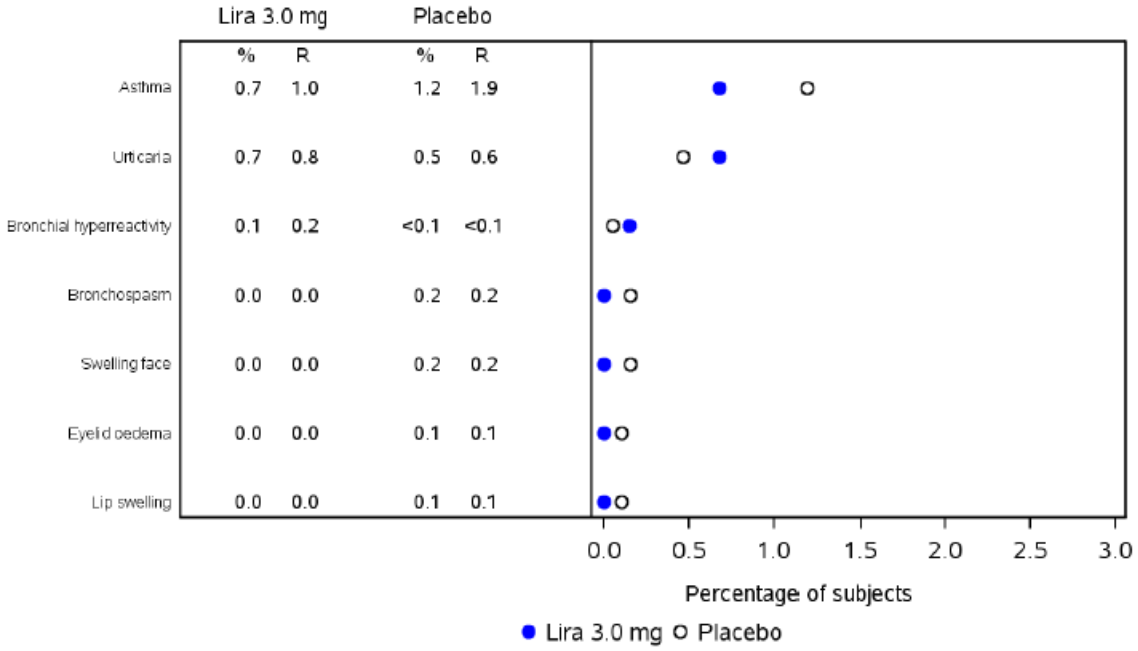
Upon suspicion of acute severe hypersensitivity in trials 1839, 1922, and 3970, a sample for drug-specific IgE antibodies was to be drawn and analyzed. Tryptase measurement was recommended in trial 1839. (No samples for tryptase measurement were actually taken.)

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 collapse[61] 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

61 'Circulatory collapse' AEs did not appear to be due to allergic reactions.

with placebo. The most frequently reported allergic events were asthma and urticaria (Figure 70).

Figure 70. 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 whith 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.

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 149. 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

Injection Site Reactions

The sponsor conducted a search of pre-defined terms related to injection site reactions using the MedDRA high level terms (HLTs) listed below.

Table 150. MedDRA Terms Used in the Injection Site Reactions Search

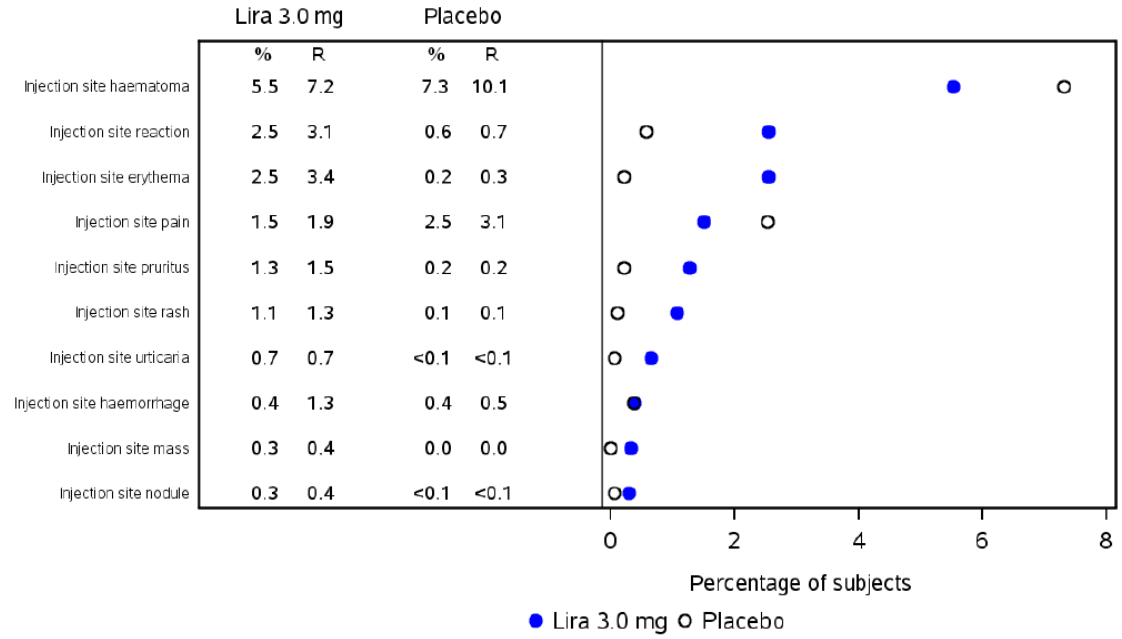
HLTs	
Administration site reactions NEC	Lipodystrophies
Application and instillation site reactions	Injection site reactions
Infusion site reactions	

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 71, below, illustrates the most common injection site reaction AEs by preferred term in the weight management trials (liraglutide 3 mg versus placebo).

Figure 71. 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 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 151. 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 152. 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

Immune Complex Disease

The following terms were used to identify potential AEs of immune complex disease.

Table 153. MedDRA Terms Used in the Immune Complex Disease Search

SMQs (narrow scope)	Preferred terms
Systemic lupus erythematous	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’.

Immune-Mediated AEs

The potential for immune-mediated AEs has been raised in two recent published case reports. A case of autoimmune hepatitis[45] is discussed in the section that reviews liver events, and a case of interstitial nephritis[47] is discussed in the section that reviews renal events. 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 report[27] discussed in the section that reviews 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 nephritis[47]) reported a recent switch from exenatide to liraglutide.

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 154. 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 overall the proportion of patients reporting AEs were similar for patients with and without ADA (anti-drug antibodies). Common AEs (at least 20% incidence) with an imbalance not in favor of the patients with ADA include administration site reactions and hypoglycemia:

Table 155. Adverse Events with Liraglutide by ADA Status, Weight Management Pool

	With Abs	Without Abs
N	**42**	**1463**
Total AEs	40 (95.2)	1375 (94.0)
Blood and Lymphatic System Disorders	1 (2.4)	33 (2.3)
Cardiac Disorders	2 (4.8)	47 (3.2)
Congenital, Familial, and Genetic Disorders	0	3 (0.2)
Ear and Labyrinth Disorders	1 (2.4)	29 (2.0)
Endocrine Disorders	0	21 (1.4)
Eye Disorders	1 (2.4)	63 (4.3)
Gastrointestinal Disorders	30 (71.4)	1019 (69.7)
General Disorders and Administration Site Conditions	13 (31.0)	450 (30.8)
Administration site reactions	9 (21.4)	216 (14.8)
Injection site pruritus	2 (4.8)	17 (1.2)
Injection site reaction	2 (4.8)	37 (2.5)
Injection site erythema	1 (2.4)	31 (2.1)
Injection site rash	1 (2.4)	19 (1.3)
Injection site urticaria	1 (2.4)	10 (0.7)
Hepatobiliary Disorders	0	40 (2.7)
Immune system disorders	1 (2.4)	27 (1.8)
Hypersensitivity	1 (2.4)	10 (0.7)
Infections and Infestations	16 (38.1)	803 (54.9)
Injury, Poisoning, and Procedural Complications	7 (16.7)	214 (14.6)
Investigations	8 (19.0)	254 (17.4)
Metabolism and Nutrition Disorders	16 (38.1)	491 (33.6)
Hypoglycemia	13 (31.0)	326 (22.3)
Musculoskeletal and Connective Tissue Disorders	11 (26.2)	384 (26.2)
Neoplasms Benign, Malignant, and Unspecified	1 (2.4)	51 (3.5)
Nervous System Disorders	8 (19.0)	396 (27.1)
Psychiatric Disorders	1 (2.4)	135 (9.2)
Renal and Urinary Disorders	0	64 (4.4)
Reproductive System and Breast Disorders	2 (4.8)	76 (5.2)
Respiratory, Thoracic, and Mediastinal Disorders	3 (7.1)	169 (11.6)
Skin and Subcutaneous Tissue Disorders	5 (11.9)	177 (12.1)
Social Circumstances	0	3 (0.2)
Surgical and Medical Procedures	3 (7.1)*	12 (0.8)
Vascular Disorders	4 (9.5)	79 (5.4)
Vascular hypertensive disorders	2 (4.8)	34 (2.3)

* 2 dental procedures and 1 angioplasty

Source: Response to FDA Request, dated 15 October 2014

An additional question with the development of ADA is whether they impact liraglutide efficacy. This was explored in trial 1839:

Table 156. 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 157. 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 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The majority of patients treated with liraglutide in the phase 3 trials were exposed to 3 mg. Liraglutide 1.2, 1.8, 2.4, and 3 mg were tested in the phase 2 trial 1807 and liraglutide 1.8 mg was tested in the T2DM trial 1922. Adverse events by dose were presented for selected AEs (gastrointestinal, hypoglycemia, heart rate, acute gallstone disease, and psychiatric disorders) and discussed elsewhere in the review. A dose-response was observed for gastrointestinal AEs.

Table 158. AEs by Liraglutide Dose, Trial 1807 (52 weeks)

	Lira 1.2 mg			Lira 1.8 mg			Lira 2.4 mg			Lira 3.0 mg		
	N (%)	E	R	N (%)	E	R	N (%)	E	R	N (%)	E	R
Subjects	95			90			93			93		
Withdrawn	17 (17.9)			20 (22.2)			27 (29.0)			18 (19.4)		
All AEs	88 (92.6)	365	500.4	85 (94.4)	438	662.3	88 (94.6)	88	700.6	89 (95.7)	498	657.6
Severity												
Severe	11 (11.6)	12	16.5	9 (10.0)	11	16.6	16 (17.2)	18	25.8	12 (12.9)	16	21.1
Moderate	59 (62.1)	112	153.5	60 (66.7)	156	235.9	65 (69.9)	153	219.6	64 (68.8)	141	186.2
Mild	80 (84.2)	241	330.4	74 (82.2)	271	409.8	80 (86.0)	316	453.7	85 (91.4)	341	450.3
Missing	0 (0.0)	0	0.0	0 (0.0)	0	0.0	1 (1.1)	1	1.4	0 (0.0)	0	0.0
Relationship												
Probable	23 (24.2)	32	43.9	22 (24.4)	31	46.9	28 (30.1)	62	89.0	36 (38.7)	49	64.7
Possible	46 (48.4)	90	123.4	56 (62.2)	129	195.1	65 (69.9)	157	225.4	73 (78.5)	185	244.3
Unlikely	78 (82.1)	243	333.1	74 (82.2)	278	420.3	69 (74.2)	269	386.2	77 (82.8)	264	348.6
SAEs	4 (4.2)	4	5.5	7 (7.8)	7	10.6	4 (4.3)	6	8.6	7 (7.5)	10	13.2
AE withdrawal	6 (6.3)	13	17.8	9 (10.0)	13	19.7	12 (12.9)	20	28.7	7 (7.5)	12	15.8

N: Number of subjects, %: Percentages are based on total N, E: Number of events
R: Event rate per 100 years of exposure

Source: ISS, Table 2-119

Table 159. AEs by Liraglutide Dose, Trial 1922

	Placebo				Lira 1.8 mg				Lira 3.0 mg			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	212				210				422			
Withdrawn	72	(34.0)			47	(22.3)			99	(23.4)		
All AEs	182	(85.8)	1039	578	190	(90.5)	1662	876	392	(92.9)	3725	981
Severity												
Severe	21	(9.9)	30	17	29	(13.8)	56	30	52	(12.3)	83	22
Moderate	105	(49.5)	289	161	118	(56.2)	381	201	239	(56.6)	742	195
Mild	169	(79.7)	720	401	176	(83.8)	1224	645	366	(86.7)	2900	763
Missing	0	(0.0)	0	0	1	(0.5)	1	1	0	(0.0)	0	0
Relation												
Probably	43	(20.3)	93	52	83	(39.5)	195	103	195	(46.2)	734	193
Possibly	76	(35.8)	187	104	109	(51.9)	390	206	235	(55.7)	988	260
Unlikely	169	(79.7)	749	417	171	(81.4)	1066	562	357	(84.6)	1978	521
Missing	8	(3.8)	10	6	9	(4.3)	11	6	19	(4.5)	25	7
SAEs	13	(6.1)	20	11	18	(8.6)	22	12	37	(8.8)	50	13
AE withdrawal	7	(3.3)	7	4	18	(8.6)	25	13	39	(9.2)	51	13

N: Number of subjects; %: Percentage of subjects; E: Number of events;
R: Event rate per 100 patient years of exposure;
Source: ISS, Table 2-120

Exposure-response was also explored by the sponsor based on exposure-response modelling data for heart rate, calcitonin, pancreatitis, and hepatobiliary disorders. See the relevant sections of this review for those findings.

7.5.2 Time Dependency for Adverse Events

Time dependency was explored for gastrointestinal AEs in section 7.4.1. A higher proportion of patients withdrew due to gastrointestinal disorders with liraglutide 3 mg (6.2%) than with placebo (0.8%), mainly during the first few months of treatment. A decrease in reports of nausea and vomiting occurred after that period (see Figure 68). Since most patients with symptoms did not discontinue, it can be assumed that patients had better tolerability as time went on.

Table 160. Adverse Events by Time on Treatment, Weight Management Pool

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
0-3 months	3384				1941			
3-6 months	3003				1715			
6-9 months	2798				1524			
>9 months	2531				1271			
>3 months	3003				1715			
Years of exposure								
0-3 months	792.8				459.0			
3-6 months	724.1				401.8			
6-9 months	663.5				347.0			
>9 months	793.9				393.0			
>3 months	2181.5				1141.9			
Adverse events								
0-3 months	2742	(81.0)	10153	1280.7	1309	(67.4)	3503	763.1
3-6 months	1675	(55.8)	3599	497.0	883	(51.5)	1740	433.0
6-9 months	1504	(53.8)	3159	476.1	763	(50.1)	1450	417.9
>9 months	1502	(59.3)	3333	419.8	685	(53.9)	1422	361.8
>3 months	2411	(80.3)	10091	462.6	1263	(73.6)	4613	404.0
AE withdrawals								
0-3 months	240	(7.1)	370	46.7	48	(2.5)	74	16.1
3-6 months	50	(1.7)	61	8.4	19	(1.1)	20	5.0
6-9 months	28	(1.0)	43	6.5	10	(0.7)	13	3.7
>9 months	20	(0.8)	25	3.1	6	(0.5)	9	2.3
>3 months	96	(3.2)	129	5.9	35	(2.0)	42	3.7
Serious adverse events								
0-3 months	75	(2.2)	83	10.5	20	(1.0)	22	4.8
3-6 months	43	(1.4)	59	8.1	28	(1.6)	34	8.5
6-9 months	55	(2.0)	68	10.2	24	(1.6)	27	7.8
>9 months	55	(2.2)	67	8.4	23	(1.8)	29	7.4
>3 months	142	(4.7)	194	8.9	72	(4.2)	91	8.0

N: Number of subjects, %: Percentages are based on total N, E: Number of events
R: Event rate per 100 years of exposure. Treatment emergent adverse events in the safety summary are those events that were treatment emergent and belonged to the main treatment period of each of the individual trials. Table is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1

Source: ISS, Table 5-11

Figure 72. Most Frequently Reported AEs (≥ 5%) by Time on Treatment, Weight Management Pool

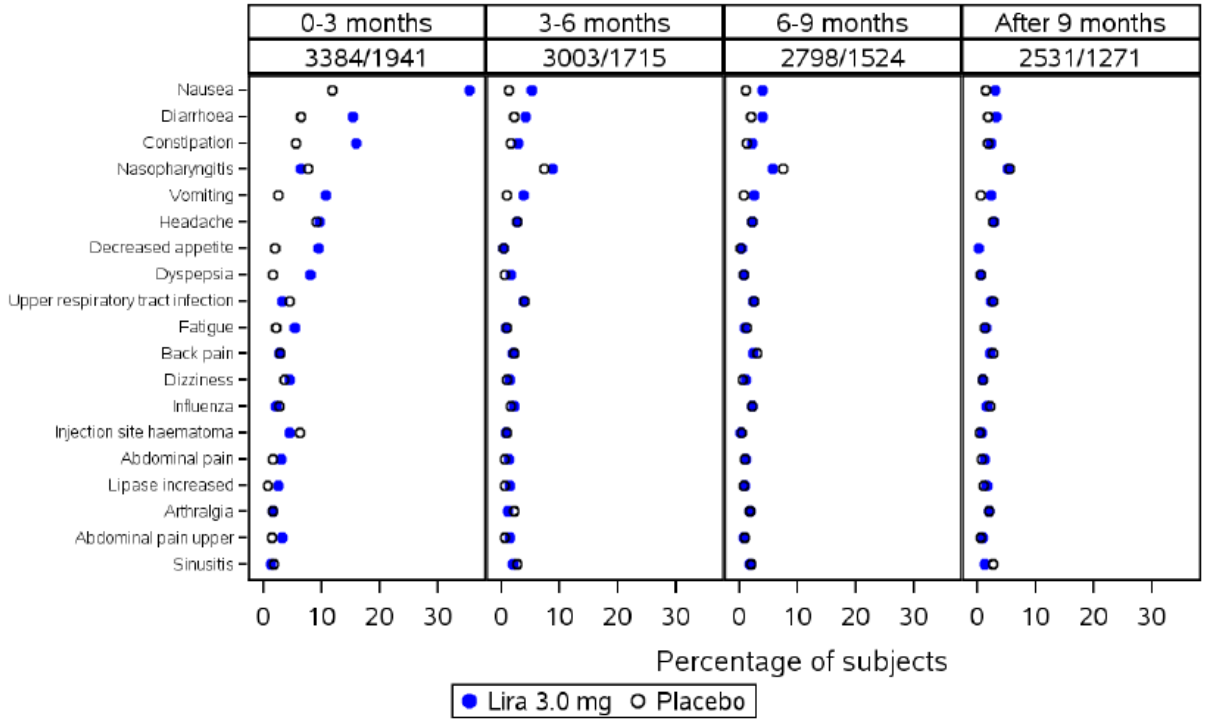


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.
Source: ISS, Figure 5-21

7.5.3 Drug-Demographic Interactions

Sex

Overall, the proportion of AE, AEs leading to withdrawal, and SAEs were similar for liraglutide-treated patients in men and women; however, men in the placebo group tended to report more AEs leading to withdrawal and SAEs (suggesting an imbalance in women).

Table 161. Adverse Events by Sex, Weight Management Pool

	Lira 3.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects								
Females	2449				1374			
Males	935				567			
Years of exposure								
Females	2172.2				1155.7			
Males	802.1				445.2			
Adverse events								
Females	2257	(92.2)	15046	692.7	1167	(84.9)	6150	532.2
Males	844	(90.3)	5214	650.0	455	(80.2)	1968	442.0
AEs leading to withdrawal								
Females	238	(9.7)	369	17.0	54	(3.9)	77	6.7
Males	93	(9.9)	131	16.3	29	(5.1)	39	8.8
Serious adverse events								
Females	152	(6.2)	192	8.8	54	(3.9)	68	5.9
Males	61	(6.5)	85	10.6	35	(6.2)	45	10.1

N: Number of subjects, %: Percentages are based on total N, E: Number of events
R: Event rate per 100 years of exposure. Treatment emergent adverse events in the safety summary are those events that were treatment emergent and belonged to the main treatment period of each of the individual trials. Table is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1

Source: ISS, Table 5-1

Differences between men and women were seen for the following events:

Hepatobiliary disorders: The proportion of patients reporting AEs was higher for liraglutide-treated women than liraglutide-treated men (driven by AEs in the HLGT 'gallbladder disorders'), whereas in the placebo group, no differences between women and men were observed.

Investigations: The proportion of patients reporting AEs was higher for men than for women in both treatment groups (higher with liraglutide 3 mg than with placebo), mainly driven by events of 'lipase increased', 'amylase increased' and 'blood calcitonin increased'.

Age

More patients 65 years and older treated with liraglutide withdrew from the trial due to adverse events.

	Liraglutide 3 mg N (%)	**Placebo N (%)**
Number of Patients		
Patients aged < 65 years	3152	1825
Patients aged ≥ 65 years	232	116
Adverse Events		
Patients aged < 65 years	2883 (91.5)	1520 (83.3)

Patients aged ≥ 65 years	218 (94.0)	102 (87.9)
AEs Leading to Withdrawal		
Patients aged < 65 years	291 (9.2)	80 (4.4)
Patients aged ≥ 65 years	40 (17.2)	3 (2.9)
SAEs		
Patients aged < 65 years	188 (6.0)	77 (4.2)
Patients aged ≥ 65 years	25 (10.8)	12 (10.3)

Source: ISS, Table 5-2

Preferred terms reported more frequently with liraglutide in patients ≥ 65 years included diarrhea, constipation, fatigue, and dizziness. Note that the sponsor separated out the ≥ 75 year old subgroup in the figure below; however, there were 17 patients treated with liraglutide and only 3 treated with placebo in this subgroup, making the findings difficult to interpret.

Figure 73. Most Frequently Reported AEs (≥ 5%) by Age Group, Weight Management Pool

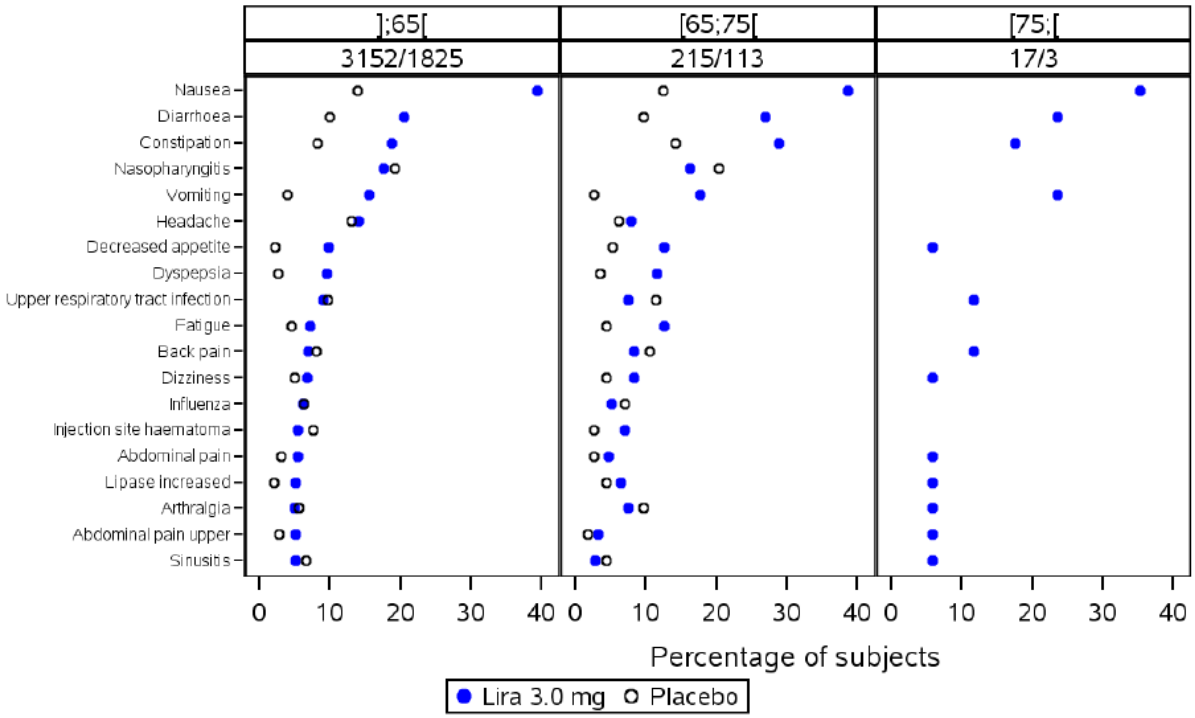


Figure is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.

Source: ISS, Figure 5-4

7.5.4 Drug-Disease Interactions

Information is available for background diabetes status, renal function, and CV history.

Type 2 Diabetes

The proportions of patients reporting AEs were similar for patients with different baseline glycemic category (normoglycemic, pre-diabetes, diabetes) with liraglutide 3 mg and placebo, although there appeared to be a tendency for higher rates of AEs and SAEs in patients with T2DM, both with liraglutide 3 mg and placebo.

Table 162 Adverse Events by Baseline Glycemic Status, Weight Management Pool

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
normo-glycaemic	1129				676			
pre-diabetes	1833				1053			
diabetes	422				212			
Years of exposure								
normo-glycaemic	984.0				546.2			
pre-diabetes	1610.4				875.0			
diabetes	379.9				179.7			
Adverse events								
normo-glycaemic	1041	(92.2)	6323	642.6	552	(81.7)	2603	476.5
pre-diabetes	1668	(91.0)	10212	634.1	888	(84.3)	4477	511.7
diabetes	392	(92.9)	3725	980.6	182	(85.8)	1039	578.1
AEs leading to withdrawal								
normo-glycaemic	103	(9.1)	164	16.7	24	(3.6)	37	6.8
pre-diabetes	189	(10.3)	285	17.7	52	(4.9)	72	8.2
diabetes	39	(9.2)	51	13.4	7	(3.3)	7	3.9
Serious adverse events								
normo-glycaemic	59	(5.2)	75	7.6	22	(3.3)	28	5.1
pre-diabetes	117	(6.4)	152	9.4	54	(5.1)	65	7.4
diabetes	37	(8.8)	50	13.2	13	(6.1)	20	11.1

N: Number of subjects, %: Percentages are based on total N, E: Number of events
R: Event rate per 100 years of exposure. Treatment emergent adverse events in the safety summary are those events that were treatment emergent and belonged to the main treatment period of each of the individual trials. Table is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1. Diabetes status has been defined according to Standards of medical care in diabetes published in Diabetes Care 2010.

Source: ISS, Table 5-7

Common adverse events (preferred terms) that appeared more frequently in patients with diabetes with liraglutide were dizziness and abdominal pain. Hypoglycemia was reviewed separately; see section 7.3.5.

Renal Impairment

Baseline renal function was classified as normal (≥ 90 mL/min/1.73 m^2), mild (60−89 mL/min/1.73 m^2), moderate (30−59 mL/min/1.73 m^2], or severe (15–29 mL/min/1.73 m^2), based on estimated creatinine clearance according to the CKD-EPI equation. There is limited experience in patients with severe renal impairment.

Table 163. Adverse Events by Renal Function, Weight Management Pool

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects								
Normal	1758				1044			
Mild impairment	1461				830			
Moderate impairment	161				63			
Severe impairment	3				2			
Years of exposure								
Normal	1543.9				853.7			
Mild impairment	1284.8				692.2			
Moderate impairment	142.4				50.7			
Severe impairment	2.2				2.1			
Adverse events								
Normal	1605	(91.3)	10288	666.4	858	(82.2)	4347	509.2
Mild impairment	1339	(91.6)	8783	683.6	709	(85.4)	3459	499.7
Moderate impairment	153	(95.0)	1145	804.3	51	(81.0)	302	595.2
Severe impairment	3	(100.0)	40	1781.7	2	(100.0)	6	280.6
AE withdrawals								
Normal	154	(8.8)	254	16.5	50	(4.8)	74	8.7
Mild impairment	152	(10.4)	206	16.0	33	(4.0)	42	6.1
Moderate impairment	24	(14.9)	39	27.4	0	(0.0)	0	0.0
Severe impairment	1	(33.3)	1	44.5	0	(0.0)	0	0.0
Serious adverse events								
Normal	108	(6.1)	139	9.0	43	(4.1)	48	5.6
Mild impairment	92	(6.3)	115	9.0	37	(4.5)	54	7.8
Moderate impairment	12	(7.5)	22	15.5	9	(14.3)	11	21.7
Severe impairment	1	(33.3)	1	44.5	0	(0.0)	0	0.0

N: Number of subjects, %: Percentages are based on total N, E: Number of events
R: Event rate per 100 years of exposure. Treatment emergent adverse events in the safety summary are those events that were treatment emergent and belonged to the main treatment period of each of the individual trials. Renal function is based on estimated creatinine clearance according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation: normal,[90 mL/min per 1.73 m^2 or above],mild [60-89 mL/min per 1.73 m^2], moderate [30-59 mL/min per 1.73 m^2], or severe renal impairment [15-29 mL/min per 1.73 m^2]. MedDRA version 15.1. Table is based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1.

Source: ISS, Table 5-9

Common adverse events of fatigue, dizziness, and increased lipase with liraglutide appeared increased with moderate renal impairment. In addition, AEs with liraglutide in the HLGT ‘renal and urinary tract investigations and urinalysis’ and the HLGT ‘water electrolyte and mineral investigations’ were higher with increasing degree of renal impairment.

CV History

The frequency of events within the SOC 'cardiac disorders' was higher in patients with a history of CV disease than in patients without a history of CV disease in both treatment groups, but without a striking imbalance between treatment groups. There are too few events to draw firm conclusions. See section 7.3.5 for a discussion of adjudicated CV events.

Table 164. Cardiac Adverse Events by High Level Group Term, by CV History, Weight Management Pool

	With CV History		Without CV History	
	Lira 3 mg N=311	Placebo N=172	Lira 3 mg N=3073	Placebo N=1769
Adverse Events	299 (96.1)	155 (90.1)	2802 (91.2)	1467 (82.9)
Cardiac disorders	19 (6.1)	8 (4.7)	87 (2.8)	48 (2.7)
Cardiac arrhythmias	7 (2.3)	3 (1.7)	51 (1.7)	21 (1.2)
Coronary artery disorders	7 (2.3)	3 (1.7)	12 (0.4)	6 (0.3)
Cardiac disorder signs and symptoms	5 (1.6)	1 (0.6)	22 (0.7)	18 (1.0)
Myocardial disorders	2 (0.6)	1 (0.6)	6 (0.2)	6 (0.3)
Cardiac valve disorders	1 (0.3)	0	1 (<0.1)	2 (0.1)
Pericardial disorders	1 (0.3)	0	0	0
Heart failures	0	0	0	1 (<0.1)

Source: ISS, Appendix 7.2, Tables 555 and 556

7.5.5 Drug-Drug Interactions

Pharmacokinetic drug-drug interactions were characterized with Victoza, and are described in labeling. In the clinical pharmacology trial 3630, equivalence was demonstrated with respect to 5-hour gastric emptying between liraglutide 3 mg and 1.8 mg, assessed as paracetamol (acetaminophen) $AUC_{(0-300min)}$. This may impact absorption of orally administered medications and should be labeled.

In addition, it was noted in the review of hypoglycemia adverse events in patients with T2DM that severe hypoglycemia was seen only in patients on liraglutide plus a sulfonylurea. It is expected that the risk of severe hypoglycemia might increase in the presence of an insulin secretagogue (or insulin, which was not studied). Information about adjusting concomitant insulin secretagogues should be included in labeling.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Adverse events related to cancer are presented in section 7.3.5.

7.6.2 Human Reproduction and Pregnancy Data

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 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 165. 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. continued…

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 166. 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

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. Although pediatric studies are underway, no data in children was submitted with this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

According to the ISS, "From clinical trials and marketed use in subjects with T2DM, overdoses with liraglutide have been reported at doses up to 40 times (72 mg) the recommended maintenance dose. Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycemia. All subjects recovered without complications."

In the weight management program, 3 events of overdose and 2 events of accidental overdose were reported with liraglutide 3 mg:

- Patient 251016 in trial 1839 injected liraglutide twice within 24 hours in error. No other AEs were reported following the overdose.

- Patient 254002 in trial 1839 forgot to administer liraglutide and on the following day administered the dose twice to compensate and experienced nausea.

- Patient 441003 in trial 1839 administered liraglutide 3.6 mg/day for 28 days and experienced 2 non-serious events of vomiting and nausea. The overdose event was evaluated as moderate.

- Patient 469016 in trial 1839 reported moderate accidental overdose. The patient administered liraglutide 3 mg in the morning and again 10 hours late in an attempt to change the dosing schedule. On the following day, only one dose was administered. The patient reported non-serious events of nausea, vomiting, diarrhea, heartburn and flatulence which all resolved.

- Patient 296028 in trial 1839 reported mild accidental overdose on day 194, on the following day an AE of 'appetite decreased' was reported. The event of accidental overdose lasted 29 days and was not reported as a MESI by the investigator, therefore no further information is available.

During year 2 of trial 1807, 2 non-serious mild events of overdose were reported with liraglutide:

- Patient 171016 forgot to take liraglutide 2.4 mg dose on 2 consecutive days, and therefore took 3 doses (a total of 7.2 mg liraglutide) the next day. During the following night and morning, the patient experienced severe vomiting; there were no other symptoms.

- Patient 113012 by mistake administered 3.6 mg of liraglutide instead of 3 mg. No symptoms were reported following this event. Both subjects recovered from the events and no changes in liraglutide dose were recorded.

Abuse Potential

The Controlled Substance Staff confirmed in an advice letter to the company dated 14 Sep 2012 that studies to evaluate the abuse potential of liraglutide is not required. There were no additional events (aside from the "overdose" AEs described above) that qualified for a predefined "drug abuse" search (PTs: "accidental overdose", "intentional overdose", and "overdose"). An additional search conducted by this reviewer for

preferred terms containing “abuse”, “dependence”, or “misuse” did not uncover any additional events in patients treated with liraglutide.

Withdrawal and Rebound

Potential withdrawal and rebound effects were primarily evaluated from follow-up data for the 1006 patients without pre-diabetes at randomization who were treated with liraglutide 3 mg in the main treatment period of the 1839 trial, and who were re-randomized to liraglutide 3 mg (liraglutide/liraglutide group) or placebo (liraglutide/placebo group) treatment for an additional 12 weeks.

Table 167. Summary of AEs in the Re-randomization Period (Weeks 56 to 68), Trial 1839

	Lira / Lira			Lira / Placebo			Placebo		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of Subjects	351			350			304		
Events	208 (59.3)	421	525.0	179 (51.1)	357	454.1	163 (53.6)	312	457.4
Serious									
Yes	6 (1.7)	6	7.5	7 (2.0)	11	14.0	3 (1.0)	3	4.4
No	205 (58.4)	415	517.5	178 (50.9)	346	440.1	162 (53.3)	309	453.0
Severity									
Severe	10 (2.8)	10	12.5	8 (2.3)	16	20.3	5 (1.6)	6	8.8
Moderate	77 (21.9)	122	152.1	61 (17.4)	95	120.8	67 (22.0)	93	136.3
Mild	163 (46.4)	289	360.4	145 (41.4)	246	312.9	132 (43.4)	213	312.2
Outcome									
Recovered	180 (51.3)	342	426.5	162 (46.3)	273	347.2	139 (45.7)	239	350.4
Fatal									
Recovering	11 (3.1)	13	16.2	10 (2.9)	14	17.8	5 (1.6)	6	8.8
Recovered With Sequelae									
Not Recovered	52 (14.8)	65	81.1	53 (15.1)	67	85.2	47 (15.5)	65	95.3
Unknown	1 (0.3)	1	1.2	3 (0.9)	3	3.8	2 (0.7)	2	2.9

N: Number of Subjects, %: Percentage of subjects, E: Number of Events R: Event rate per 100 exposure years

Source: ISS, Table 5-19

Few psychiatric disorders were reported in the first 2 weeks of re-randomization, with lira/lira: 0.3%, lira/placebo: 0.3%, and placebo: no events. Over the entire re-randomized period, ‘Psychiatric disorders’ were reported similarly with lira/lira (2.8%) and lira/placebo (3.1%); 1.3% of patients treated with placebo reported events. These numbers were mainly attributed to ‘insomnia’ (0.3%, 1.1%, and none for placebo) and ‘depression’ (1.4%, 1.1%, and 0.7%). One patient in the lira/lira group (0.3%) and 1 patient in the lira/placebo group (0.3%) reported suicidal ideation on the C-SSRS during the re-randomization period. No patients reported suicidal ideation on the C-SSRS in the placebo-treated group during the re-randomization period.

The proportion of patients treated with lira/lira who reported 'increased appetite' in the first 2 weeks after re-randomization was 0.6%, compared with 1.1% in subjects treated with lira/placebo; 0.3% reported this event with placebo. No increase in the reporting of binge eating was observed with lira/placebo in the re-randomized period.

Table 168. Binge Eating Scale: Moderate and Severe Binge Eating, Trial 1839 Re-Randomized Period

	Lira / Lira			Lira / Placebo			Placebo		
	N	n	(%)	N	n	(%)	N	n	(%)
Safety analysis set	351			350			304		
Moderate binge eating (BES > 17)									
Week 56	287	32	(11.1)	292	25	(8.6)	254	42	(16.5)
Week 58	290	32	(11.0)	294	22	(7.5)	255	36	(14.1)
Week 58 (LOCF)	290	32	(11.0)	294	22	(7.5)	255	36	(14.1)
Severe binge eating (BES >= 27)									
Week 56	287	1	(0.3)	292	5	(1.7)	254	6	(2.4)
Week 58	290	2	(0.7)	294	2	(0.7)	255	7	(2.7)
Week 58 (LOCF)	290	2	(0.7)	294	2	(0.7)	255	7	(2.7)

N: Number of subjects, n: Number of subjects fulfilling criteria, %: Percentage of N

Source: ISS, Table 5-21

7.7 Additional Submissions / Safety Issues

All safety information, including data from the 120-day safety update, was included in sections above.

8 Postmarket Experience

Liraglutide was approved for the treatment of type 2 diabetes in 2010. In collaboration with the Division, the Office of Surveillance and Epidemiology has been actively monitoring the safety of liraglutide and other incretin mimetics. Renal and immunogenicity events were added to liraglutide labeling after a 915 review. Both offices (OND and OSE) responded to a citizen's petition regarding the safety of liraglutide. Incretin mimetics have had media attention for a series of articles that implicated the drugs in a number of pancreatic safety signals, including pancreatitis and pancreatic cancer. This is discussed in other sections of this review.

In preparation for the advisory committee meeting, DMEP consulted the Division of Pharmacovigilance I and the Division of Epidemiology in OSE to update the post-marketing information of liraglutide. Both divisions presented their findings to the EMDAC, and the reader is referred to Dr. Debra Ryan and Dr. Christian Hampp's reviews for further information. An important new finding was the detection of 13 cases of MTC associated with liraglutide reported in FAERS. Dr. Marina Zemskova reviewed the 9 cases with clinical information, but could not draw a firm conclusion regarding causality to liraglutide. Please see her review for further details.

9 Appendices

9.1 Literature Review/References

Medical and scientific literature is referenced throughout the document.

9.2 Labeling Recommendations

A complete labeling review was conducted separately and incorporated into the draft label sent to the applicant on 30 Sep 2014. Major recommendations included:

- Limitations of use should state that liraglutide 3 mg is not indicated for the treatment of diabetes and should not be used with other GLP-1 receptor agonists
- Pregnancy should be a contraindication
- Acute gallbladder disease and suicidality should be included in Warnings and Precautions
- Adverse Reactions should include those with incidence ≥ 2%
- Other adverse reactions that should be described further include: breast cancer, papillary thyroid cancer, colorectal neoplasms, cardiac conduction disorders, hypotension, liver enzyme increases, and serum calcitonin increases
- Pregnancy (b) (4) Category X
- (b) (4) should be removed from Clinical Pharmacology
- (b) (4) should be removed from Clinical Studies

9.3 Advisory Committee Meeting

An Endocrinologic and Metabolic Drugs Advisory Committee meeting was held on 11 Sep 2014. FDA reviewers presented clinical safety and efficacy data (J. Golden, Division of Metabolism and Endocrinology; this reviewer); statistical analyses of weight loss in the three weight management phase 3 trials that addressed missing data (B. McEvoy, Division of Biometrics 2); neoplasm incidence in the clinical trials and review of epidemiological studies with Victoza (C. Hampp, Division of Epidemiology); review of post-marketing safety of Victoza from FAERS (D. Ryan, Division of Pharmacovigilance); and review of post-marketing cases of medullary thyroid carcinoma associated with Victoza (M. Zemskova, DMEP). The following questions were posed to the committee; a summary of the discussion / vote follows:

1. **DISCUSSION:** Please comment on whether the sponsor has provided adequate evidence to establish the efficacy of liraglutide 3 mg per day for chronic weight management. In your discussion, comment on the extent to which the observed

effects on endpoints related to weight-related comorbidities factor into your assessment of the benefits of liraglutide for the proposed population.

In general, committee members agreed that liraglutide 3 mg met the standard for efficacy of a weight management product, even given updated statistical analyses demonstrating an attenuated effect on weight loss after accounting for missing data in a more robust fashion.

Dr. Hiatt commented that weight is a surrogate and that endpoints such as progression to diabetes and quality of life (physical domain) were important in the risk benefit calculus. He and Dr. Cooke commented that the results of the Look AHEAD trial were problematic when considering cardiometabolic benefits in the long-term.

Dr. Everett noted that the 95% confidence intervals of the primary and FDA's efficacy analyses overlapped substantially, and that either analysis was an acceptable approach. He noted that 33% of patients treated with liraglutide in 1839 lost at least 10% of body weight, which is a substantial response.

2. **DISCUSSION:** Discuss the safety profile of liraglutide for chronic weight management. 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

Dr. Kelsen raised a number of issues regarding the observed increase in breast cancer incidence. He noted that an increased risk of malignancy, even if small, becomes substantial on the population level. If there is a lead-time bias, then the placebo group should "catch-up" in terms of breast cancer incidence, which would be less concerning. Because it is unknown if liraglutide could act as a tumor promotor for certain kinds of cancer, the committee felt that patients with a personal history of malignancy, especially breast cancer and pancreatic cancer, should be counseled. Dr. Heckberg noted that once something (e.g., breast cancer warning) is placed in the label, there will be a detection bias. Dr. Yanovski noted that obesity is a risk factor for cancer and that a similar issue was raised prior to the approval of orlistat. Most of the committee members agreed that there is concern regarding medullary thyroid cancer and that information related to this should be placed in the package insert.

There was a consensus by the committee that gallbladder-related events are increased with use of liraglutide, and some committee members commented that pancreatitis related events appear to increase with use of liraglutide.

There was a consensus by the committee that the cardiovascular safety of liraglutide needs to be studied further as it is not clear what effects the small increase in pulse rate would have on clinical outcomes. There are too few events to date in the clinical trials to be confident of the risk. Dr. Hiatt and Dr. Everett agreed that not all drugs with a cardiovascular risk will work through the same mechanism. While MACE might not be increased, other AEs, such as congestive heart failure, pulmonary embolus, or arrhythmia should be considered.

Some committee members commented that from the data there appears to be an increased risk of suicidal ideation with the use of liraglutide.

There was a consensus among the committee that liraglutide should not be used in pregnant women or women trying to get pregnant. The committee also discussed concern over an increased incidence of colon polyps with use of liraglutide and that this finding should be looked into further.

3. **DISCUSSION:** Discuss the safety database for liraglutide 3 mg per day for chronic weight management, given the extent of clinical trial and post-marketing experience with liraglutide for diabetes mellitus with doses up to 1.8 mg per day.

a. How does the experience with liraglutide for diabetes mellitus inform the safety profile of liraglutide 3 mg per day for chronic weight management, given the different patient populations and doses?

b. Labeling for Victoza (liraglutide up to 1.8 mg per day), which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, states that Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the thyroid C-cell tumor findings identified in rodents. If the current application were approved as proposed, it would be presumed that there would be no recommendation against using liraglutide 3 mg per day as initial therapy, for weight management, for patients with diabetes mellitus with BMI 27 kg/m^2 or greater. Discuss the implications of this overlap in populations and any concerns it may raise.

c. There is an ongoing cardiovascular outcomes trial to assess the CV risk of liraglutide in type 2 diabetes mellitus. The maximum dose of liraglutide in this trial is 1.8 mg per day. Discuss whether this trial would be sufficient to characterize the CV risk of liraglutide 3 mg per day for weight management.

In general, the committee agreed that the safety profile of liraglutide 3 mg appears relatively similar to liraglutide for diabetes mellitus. However, it was expressed that the safety data in diabetes is informative but uncertainty still exists due to the difference in dosing and the limitations characteristic of spontaneous reporting that limit the ability to use post-marketing reports to further our understanding of particular events. It was discussed that hypoglycemia could be more of a concern with the 3 mg dose, especially among patients using sulfonylureas.

The majority of the committee was not concerned about the possibility of using liraglutide as a first-line agent for obese diabetic patients. There was discussion regarding whether the labels needed to be consistent for both indications (i.e., type 2 diabetes versus weight management), with some citing that consistency should be a goal and others citing that there are differences between the two indications that provide rationale for inconsistency (e.g., numbers and safety profiles of drugs available for type 2 diabetes compared with obesity; availability of comparative effectiveness data).

The majority of the committee members agreed that the ongoing cardiovascular outcomes trial to assess the CV risk of liraglutide in type 2 diabetes mellitus is sufficient to characterize the CV risk of liraglutide 3 mg per day for weight management.

4. **VOTE:** Considering the currently available data and the proposed Risk Evaluation and Mitigation Strategy (REMS), is the overall benefit-risk assessment of liraglutide 3 mg per day favorable to support its approval for chronic weight management in individuals with a BMI 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity?

    a. If voting YES, please provide your rationale and whether you recommend any additional studies post-approval.

    b. If voting NO, please provide your rationale and discuss what additional data would be necessary prior to approval to address your concerns.

Vote Result: Yes – 14 No – 1 Abstain – 0

The majority of the committee agreed that the overall benefit-risk assessment of liraglutide 3 mg per day is favorable to support its approval for chronic weight management in individuals with a BMI 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least one weight-related comorbidity. Of the committee members who voted "Yes", the following recommendations were made for post approval.

- *Further studies conducted on the incidence of MTC and C-cell hyperplasia*
- *Longer-term safety studies with the inclusion of more diverse patient populations*
- *Specific guidelines should be provided for long-term use*
- *Follow-up studies on gallbladder disease and risk of spontaneous abortion*

- *Label should include the discontinuation of therapy for patients not achieving weight loss after 12 weeks on a full dose*
- *Label should inform the patient to receive regular mammograms*
- *The data related to sleep apnea were not recommended for labeling because of uncertain clinical benefit*
- *Label could include a range of weight loss parameters*
- *Label should include patient reported outcomes*
- *Label should include a precaution against sulfonylurea use with liraglutide*

The one committee member who voted "No" stated that currently there is not enough information to mitigate the risks of malignancy, and that the following additional data would be necessary prior to approval to address concerns:

- *The sponsor should look at the placebo-controlled arms in the studies already conducted to determine whether or not there is a lead-time bias as it relates to malignancies*
- *FDA should address high-risk populations in the label*

9.4 Narratives of Deaths from the 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/m^2). 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? urospepsis?), 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 liragluitde 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 endoprothesis was done (b) (6). The patient developed 'acute cholangitis' and sepsis on (b) (6) and five days later a new endoprothesis 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 endobilliary prothesis. On (b) (6) 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 endobiliary 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/m^2 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.

9.5 Financial Disclosure Information

Covered Clinical Study (Name and/or Number): NN8022-3630

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 2		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from

		applicant)

Covered Clinical Study (Name and/or Number): NN8022-1807

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 78		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): NN8022-1922

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 622		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced		

by the outcome of the study: 0 Significant payments of other sorts: 13 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): NN8022-1923

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 134		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): NN8022-1839

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 989		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 13		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): NN8022-3970

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 225		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts:		

Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

JULIE K GOLDEN
10/18/2014

JAMES P SMITH
10/18/2014

STUDY ENDPOINT CONSULT REVIEW

Template version: August 6, 2014

STUDY ENDPOINTS TRACKING NUMBER	AT 2014-32
IND/NDA/BLA NUMBER	NDA 206321
LETTER DATE/SUBMISSION NUMBER	
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	March 10, 2014
REVIEW DIVISION	DMEP
MEDICAL REVIEWER	Julie Golden
REVIEW DIVISION PM	Pat Madara
STUDY ENDPOINTS REVIEWER(S)	Sarrit Kovacs, PhD
ASSOCIATE DIRECTOR, STUDY ENDPOINTS (ACTING)	Elektra J. Papadopoulos, MD, MPH
REVIEW COMPLETION DATE	September 9, 2014
ESTABLISHED NAME	liraglutide
TRADE NAME	
APPLICANT	Novo Nordisk
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
ENDPOINT(S) CONCEPT(S)	Obesity-specific quality of life (IWQoL-Lite) Generic health status (SF-36)
MEASURE(S)	Impact of Weight on Quality of Life-Lite (IWQoL-Lite) 36-item Short Form Health Survey (SF-36)
INDICATION	"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."
INTENDED POPULATION(S)	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

A. EXECUTIVE SUMMARY

This Study Endpoints review is provided as a response to a request for consultation by the Division of Metabolic and Endocrine Products (DMEP) regarding NDA 206321 for liraglutide. The applicant has included the patient-reported outcome (PRO) instruments, Impact of Weight on Quality of Life-Lite (IWQoL-Lite) and 36-item Short Form Health Survey (SF-36), for the measurement of obesity-specific quality of life as secondary endpoints in a phase 3a clinical trial 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.

The applicant's briefing document for the advisory committee (AC) meeting includes an efficacy conclusion on page 117 stating the following:

"Finally, liraglutide 3.0 mg was associated with clinically meaningful improvements in quality of life, with statistically significant increases in the IWQoL-Lite total scores in each of the trials in which the questionnaire was used. The improvement in IWQoL-Lite scores was mainly driven by improvements in physical function. Significant increases in overall physical and mental health domains of the SF-36 questionnaire were also observed in trial 1839. Quality of life generally improved with weight loss and the effect was enhanced with the greater weight loss achieved with liraglutide 3.0 mg treatment."

This review concludes (b) (4)

See detailed comments in Section B below.

(b) (4)

B. COMMENTS REGARDING THE APPLICANT'S SUBMISSION

Please find our proposed comments in response to the applicant's briefing document for the AC meeting below. Given that the applicant's briefing document focuses only on the PRO instrument results related to Trial 1839, the comments below are focused solely on the IWQoL-Lite, SF-36, and their inclusion Trial 1839.

17 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SARRIT M KOVACS
10/03/2014

ELEKTRA J PAPADOPOULOS
10/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 25, 2014

FROM: Marina Zemskova, MD, Medical Officer, Division of Metabolism and Endocrinology Products

To: File (NDA 206321, Saxenda)

SUBJECT: Postmarketing cases of medullary thyroid carcinoma in patients treated with liraglutide

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Summary
This review summarizes the cases of medullary thyroid cancer in patients treated with liraglutide that were received by the Agency in postmarketing period.

Liraglutide (Victoza, Novo Nordisk, 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. The Victoza label carries a boxed warning regarding 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.*.". However, the relevance of animal findings to humans remains unknown up to date.

Currently, the FDA is reviewing an NDA for Saxenda (NDA 206321), a higher dose version of liraglutide proposed for use as a weight-loss agent. In order to ensure that the benefits of liraglutide continue to outweigh any risks, the Agency reviewed all cases of medullary thyroid cancer associated with use of liraglutide reported to the FDA Adverse Event Reporting System (FAERS) database since approval of Victoza on January 25, 2010.

Results
In the postmarketing period, the Agency received a total of 13 case reports of MTC.
Nine cases were reported from United States, 2 cases were reported from Europe and 1 case was reported from Canada.
Of the 13 patients with MTC, the majority of patients were older than 50 years (age range 43-66 years), 4 were males and 9 were females.
Duration of exposure was reported in 10 out of 13 patients (including one patient with no other clinical information available). Six out of 10 patients had duration of exposure of less than 12 months; 4 patients had exposure duration between 18 to 43 months.

In 4/13 cases no clinical information other than a diagnosis of MTC and duration of exposure was available. Thus, only the 9 cases with clinical information will be discussed further (Table 1).

Table 1. Postmarketing MTC cases

Age/Sex, Country	Time from first exposure to diagnosis (months)	Reason for Workup	MTC diagnosis				Surgical Pathology
			Ultrasound report	FNA report	Preop*. calcitonin level, pg/ml	RET testing	
63/M, Belgium	15	Evaluation of liver, bone, lung metastasis	Left thyroid and paratracheal masses	MTC (lymph nodes, bones)	265	Negative	MTC
60/F, France	6	Palpable thyroid nodule	Unknown	MTC	1500	Unknown	Not done
49/F, US	43	Palpable thyroid nodule	3.1 cm thyroid nodule	MTC	926	Not done	MTC 2.1cm
43/F, US	41	Palpable thyroid nodule	Thyroid nodule (1.6 cm by CT scan)	MTC	345	Unknown	Not done
56 /M, US	11	Ultrasound for hyperparathyroidism	Unknown	Suspicious		Unknown	MTC 0.1cm PTC 0.1 cm
62/F, US	8	CT scan for unknown reason	1.6 cm thyroid nodule	MTC	170	Negative	MTC; "tiny" focus of PTC
66/M, US	33	CT scan for colon cancer	4.4 cm thyroid nodule	Done, no results reported		Negative	MTC 4.4cm
56/M, France	11	Presence of goiter prior to the onset of treatment with liraglutide	1 cm thyroid nodule	Not done	Not done	Not done	MTC 0.3cm
62/F, US	2	None, incidental finding during the surgery	Unknown	Not done		Negative	MTC 0.3cm PTC 0.1 cm

*Preop= preoperative; MTC= medullary thyroid carcinoma

Evaluation prior to liraglutide exposure:

Of these 9 cases, none of the patients had had an ultrasound or FNA immediately prior to initiation of treatment with liraglutide. Two of 9 patients had a remote history of goiter. One of these 2 patients had had an FNA which revealed a benign thyroid nodule in the past. None of these patients had baseline calcitonin levels reported or had RET genetic testing. Information regarding prior exposure to other GLP-1 agonists was not available except for one patient. This patient was on exenatide therapy for 4 years prior to initiation of liraglutide therapy.

Initial presentation and work-up

The majority of patients were asymptomatic at presentation.

In 3/9 patients a palpable thyroid nodule prompted further investigation. In 3 other patients, a work up was initiated after thyroid nodules were discovered incidentally by imaging. Two other patients were already being followed for a long-standing history of goiter which resulted in total thyroidectomy and a microscopic focus of MTC was an incidental finding on the final pathology report for both of these patients.

The only patient who presented with symptoms was a 63 years old male who complained of retrosternal pain, lack of energy, anorexia and weight loss that prompted further imaging studies. CT scan demonstrated extensive lung, bone and liver metastasis and left thyroidal mass.

In the majority of patients thyroid abnormalities were further evaluated by a thyroid ultrasound and fine needle aspiration (FNA). The diagnosis of MTC was established by FNA in 6 out of 9 patients and confirmed by elevated calcitonin levels in 5 of these 6 patients. In 3 patients with microscopic disease**,** MTC was not detected prior to total thyroidectomy for thyroid nodule or goiter. Microscopic MTCs were incidental findings on final pathology report. Lastly, 4 out of 9 patients underwent RET mutation testing after the diagnosis of MTC was established. Of note, based on the information provided in the reports, it is unknown whether this RET mutation testing refers to germline or somatic RET mutations.

Surgical outcome

Only 7 out of 9 patients underwent surgery. The disease was unifocal in all patients. Tumor size was reported in 5/7 patients and ranged from 0. 1 cm to 4.4 cm. Of these 5 patients, three patients had microcarcinoma (tumor size < 1 cm). One patient had regional lymph node metastasis at time of surgery, and 1 patient had widely metastatic disease. Lastly, 3/7 patients had concomitant incidental findings of papillary microcarcinoma. Overall, surgical findings appear consistent with what is expected in general population.

Conclusion

In conclusion, a causality assessment between MTC and liraglutide is complicated by low number of reported cases and relatively short duration of exposure prior to diagnosis. Clinical presentation of MTC in the reported cases appears to be consistent with what is expected in the general population. Lastly, important clinical Information such as baseline assessment for thyroid disorder, family and past medical history, RET genetic testing and staging information is missing from all case reports.

Thus, no firm conclusion regarding causal relationship of MTC with liraglutide can be drawn from these cases.

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/s/

MARINA ZEMSKOVA
09/26/2014

Medical Officer Consult
Division of Oncology Drug Products 1

Consult Request	Julie Golden DMEP/ODE2
NDA/IND	206,321/61040
NDA Sponsor	Novo Nordisk Inc.
Product Name	Liraglutide
Intended Use	Chronic weight management
Primary Reviewer	Jonathan P Jarow
Team Leader	V. Ellen Maher
Date Logged in:	June 17, 2014
Desired Completion Date:	July 17, 2014
Review Completed:	June 24, 2014

Executive Summary

There is concern regarding a potential neoplasm imbalance observed in the clinical development program of liraglutide, a drug currently approved for type 2 diabetes and seeking a new indication in weight management. Nonclinical studies showed an association with thyroid c-cell neoplasia and the current labeling has a boxed warning. Review of the safety database does not reveal an imbalance in exposure-adjusted neoplasia in either the weight management development program or the type 2 diabetes program. Adjudication was performed using an acceptable algorithm in four of the five randomized trials in the weight management development program. There was no imbalance in the exposure-adjusted total malignant neoplasia category for the adjudicated events, however, there was an increase in the incidence of malignant breast cancer. Review of the case narratives for the patients with breast cancer and the timing of onset does not support or deny the potential role of liraglutide in cancer promotion or progression. Examination of the postmarketing adverse event reporting for liraglutide does not reveal a signal for breast cancer but did reveal a significant signal for pancreatic and thyroid cancer. It is not clear whether the observed imbalance in breast cancer incidence in the clinical trial database is due to chance or an association. Nevertheless, the discrepancy between the clinical trial database and the postmarketing data for both thyroid and pancreatic cancer is concerning. Further investigation of the postmarketing data by OSE is warranted.

Questions

1. In the development program for weight management, the applicant identified neoplasms as medical events of special interest that they identified and adjudicated. Please comment on your assessment of the adequacy of their methods used to search for potential cases and their adjudication procedures. Are there any important limitations to their methods that could affect the interpretation of the results obtained in the clinical development program?

2. What is your clinical interpretation of the numerical imbalances observed in breast, colorectal, thyroid, and pancreatic neoplasms identified in the clinical trials? Please comment on whether there are features of the reported cases (or aggregate data) that strengthen or weaken the possibility that liraglutide promotes the development or progression of malignancy.

Background

Liraglutide is a human glucagon-like peptide-1 (GLP-1) analogue that is administered by subcutaneous injection. The NDA (22341) for liraglutide (Victoza) was approved with an indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus" in January 2010. Liraglutide stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. The current product labeling has a boxed warning regarding the thyroid C-cell tumors in rodents and that liraglutide is contraindicated in patients with either a personal or family history of either medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

Nonclinical

There was no evidence of mutagenicity or genotoxicity of liraglutide in nonclinical studies. The two year carcinogenicity study demonstrated that liraglutide causes a dose and duration dependent thyroid C-cell neoplasms, both benign and malignant, in rodents. Of note, the clinical program has had only one occurrence of medullary thyroid cancer and that was in a placebo-treated patient. GLP-1 receptors are expressed in a variety of tissues but their role in carcinogenesis or promotion is unknown. GLP-1 receptor expression has been reported in medullary thyroid carcinoma but not in breast carcinoma.

Methods: Safety population(s) and methods of adjudication

The primary safety evaluation of liraglutide in weight management is based on the pooled analysis of five phase 2 and 3 trials (trials 1807, 1839, 1922, 3970, and 1923). Using a cutoff date of July 2, 2013, there were a total of 3,872 liraglutide-treated patients with 3,372.7 patient years of exposure versus 1,941 placebo-treated patients with 1,600.9 patient years of exposure in the weight management safety database. The sponsor also created supplemental safety databases that incorporated the safety events from 24 phase 2 and 3 trials in type 2 diabetic patients that had duration of exposure ranging from 2 to 104 weeks. The number of liraglutide-treated patients was 7,037 (5,072 patient years of exposure) and comparator-treated was 3,677 (2,444.9 patient years of exposure). The comparator includes both placebo and active controls. Safety data obtained from all completed (as of July 2, 2013) randomized, controlled phase 2 and 3 clinical trials in type 2 diabetes development program is included as a supplementary database and labeled by the sponsor as "supplementary pool I".

Neoplasms were defined as medical events of special interest as the weight management program was underway and were subject to independent adjudication by an external committee. Because of timing, the first of the five weight management trials did not undergo the adjudication process. A predefined MedDRA search was utilized to identify all neoplasm events in the safety populations. In addition a MedDRA search for thyroid disorders not captured by the neoplasm search was added. Finally, investigators could

also identify events independent of the MedDRA searches. Detailed case narratives were provided and reviewed by the external committee to confirm the diagnosis and date of onset. A total of 435 treatment-emergent events were sent for adjudication of which 314 were identified by the MedDRA search. The overall confirmation rate for these events was quite low at about 25%. The confirmation rate for events captured under the neoplasm SOC was the highest at more than 50%.

The external independent adjudication of neoplasm events was performed by (b) (4) (b) (4) In addition to neoplasms, the committee also adjudicated the following types of adverse events in four (trials 1839, 1922, 1923 and 3970) of the five weight management trials; death, coronary and cerebrovascular events, pancreatitis, and thyroid disease. The events from trial 1923 were adjudicated *post hoc*. Events from trial 1807 were not adjudicated and the events from the extension of trial 1837 are currently being adjudicated. The subcommittee that adjudicated the neoplasm events was comprised of two medical oncologists and an endocrinologist. The materials reviewed included the medical records, laboratory results, pathology reports and if the patient died, the autopsy and death certificate. The methods of adjudication employed by (b) (4) are similar to that utilized in the collection of data for the SEER database.

The sponsor presented the following analyses in their integrated summary of safety:

- All neoplasms, benign and malignant, identified by MedDRA in weight management trials (5 trials plus an extension) but not adjudicated.
- Neoplasm events, benign and malignant, confirmed by external adjudication in four weight management trials
- Selected types (breast, colorectal, pancreas, and thyroid) of confirmed neoplasms in the weight management trials

Analyses of the larger safety populations that include patients in the type 2 diabetes in addition to the weight management program were also performed and the results of which were presented in tabular format without discussion in the "Supplementary AE report."

Materials reviewed

Integrated Summary of Safety
Supplementary AE Report
Event Adjudication Committee Charter
Patient narratives
FAERS database using Empirica

Comments

Question 1. Are there any important limitations to their methods that could affect the interpretation of the results obtained in the clinical development program?

No. The Sponsor utilized two methods to identify "events". The first was a MedDRA search using pre-defined terms of the entire safety database which includes the weight management program as well as the type 2 diabetes development program. The second method was external adjudication of events of special interest that included four of the

five trials in the weight management development program. Both of these methods have their advantages and disadvantages but however imperfect they are, they are standard and are acceptable for the purpose. The major advantage of the MedDRA search queries is that it covers a larger population which helps with more precise measurement of event rates of low incidence. The main disadvantage for this method of analysis is the significant over estimation of event rates, particularly for benign neoplasms, as demonstrated by the results of the adjudication process performed in the four selected trials. There are well known detection biases in the estimation of neoplasm incidence rates in clinical trials, however, these should be balanced between arms if the trials were well blinded. There may also be unknown confounders that may affect observed neoplasm rates. For instance, weight loss may result in an ascertainment bias for detection of malignancies in patients being regularly screened.

Question 2. What are your interpretation of the numerical imbalances and the observed features of the reported cases?

There does not appear to be a large cancer signal in the clinical trial database. The best safety population to utilize for describing the cancer risk for this specific indication, weight management, is the adjudicated events from the four weight management trials. The advantage of using the larger data set that includes the type 2 diabetes management development program trials is the greater power to detect imbalances in adverse effects with low event rates. However, as demonstrated by the adjudication process, the reliability of the categorization of events, particularly of the benign neoplasms, is in doubt. Moreover, there is the possibility that the events rates may vary in different patient populations, for instance diabetic patients may have a greater risk for pancreatic tumors.

The exposure-adjusted event rate, rather than raw incidence, is the best parameter to use for comparison of the drug versus placebo since the treatment arms varied in number and duration of exposure. Therefore, from the oncological perspective, the primary analysis for this application would be the exposure adjusted rates of the adjudicated events from the weight management program. As seen in Table 1, there is no imbalance of the exposure adjusted rates for all neoplasms and specifically malignant neoplasms. Amongst the individual malignant neoplasms, there does appear to be a numeric imbalance favoring placebo for breast cancer with a similar pattern observed in the entire population using a MedDRA SMQ search for the high level group term of breast neoplasm malignant. For the purposes of comparison, the SEER database reports an incidence of breast cancer of 0.125 per 100 patients per year for the general population.

Table 1. Incidence of neoplasms in safety populations.

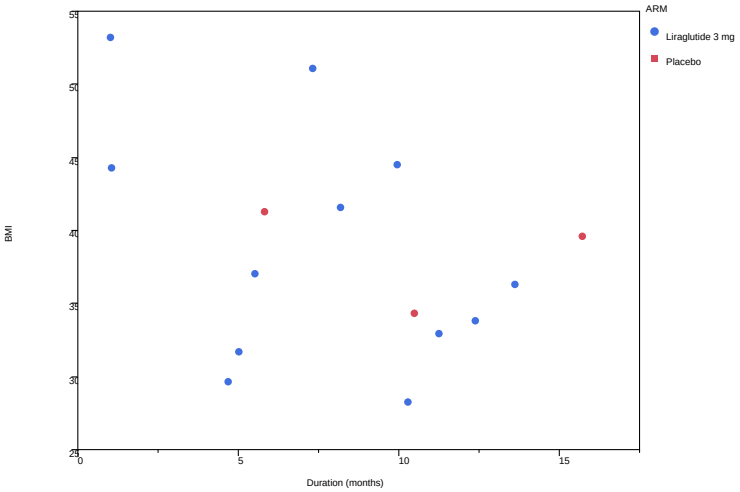
	Adjudicated Events[1]		MedDRA SMQ Search[2]	
	Weight Management		Weight Management plus Type 2 Diabetes	
	Liraglutide 3 mg N = 3,291 % (per 100 PYE)	Placebo N = 1,843 % (per 100 PYE)	Liraglutide N = 10,909 % (per 100 PYE)	Comparator N = 5,713 % (per 100 PYE)
All Neoplasms	1.9 (2.3)	1.5 (2.2)	3.8 (5.7)	3.3 (5.6)

	Adjudicated Events[1]		MedDRA SMQ Search[2]	
	Weight Management		Weight Management plus Type 2 Diabetes	
	Liraglutide 3 mg N = 3,291 % (per 100 PYE)	Placebo N = 1,843 % (per 100 PYE)	Liraglutide N = 10,909 % (per 100 PYE)	Comparator N = 5,713 % (per 100 PYE)
Malignant Neoplasms	0.8 (0.9)	0.7 (0.9)	---	---
Breast[4]	0.2 (0.3)	<0.1 (<0.1)	0.2 (0.2)	< 0.1 (< 0.1)
Skin[5]	0.2 (0.2)	0.3 (0.4)	0.1 (0.2)	0.1 (0.2)
Colorectal[6]	<0.1 (<0.1)	0 (0)	0.1 (0.2)	< 0.1 (0.1)
Pancreatic[7]	<0.1 (<0.1)	0 (0)	<0.1 (<0.1)	0 (0)
Thyroid[8]	<0.1 (0.1)	<0.1 (<0.1)	< 0.1 (0.1)	< 0.1 (< 0.1)

1 Table 277 in appendix 7.2 of ISS
2 Table 54 in appendix 1 of the supplementary AE report
3 Comparator includes both placebo and active controls
4. HLGT breast neoplasm malignant and unspecified (incl. nipple)
5. HLGT skin neoplasms malignant and unspecified
6. HLGT gastrointestinal neoplasms malignant and unspecified
7. Preferred term pancreatic carcinoma
8. Preferred term thyroid cancer

Malignant breast cancer was reported in twelve liraglutide-treated patients and only in three placebo-treated patients. All of these breast cancer events are significant based on review of the narratives. There was no distinct pattern in the timing of these events or an association with baseline BMI (Figure 1). One half of the patients had no relevant risk factors, two had received prior hormonal replacement therapy, and one had a prior history of breast cancer. It is reasonable to assume that these confounders were balanced between arms since these were all large randomized studies. There is nothing in the case narratives to support or deny a role of liraglutide in the promotion or progression of breast cancer.

Figure 1. Time of onset of adjudicated breast cancer events by treatment and baseline BMI.



The clinical trial safety database did not reveal a significant imbalance in exposure-adjusted incidence of either pancreatic or thyroid malignancies. A search of the postmarketing safety database was performed using Emprica® signal in order to check on the breast cancer signal raised in the clinical trial safety database. The results of the Emprica® signal search (b) (4) (b) (4) (Figure 2). The discrepancy between the clinical trial and postmarketing findings raise concerns about the adequacy of the clinical trials to detect a signal. The imbalance observed in postmarketing data may be an artifact of reporting bias or real and possibly due to longer duration of exposures. Other potential explanations for this discrepancy include insufficient numbers in the clinical trial database to detect a signal or a difference in the populations treated. We recommend further investigation of the postmarketing experience.

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/s/

JONATHAN P JAROW
07/02/2014

VIRGINIA E MAHER
07/03/2014

CLINICAL FILING CHECKLIST FOR NDA

NDA/BLA Number: 206321 **Applicant: Novo Nordisk, Inc.** **Stamp Date: 12/20/2013**

Drug Name: Liraglutide **NDA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Module 5.3.5.3.: ISS (trials from the weight management program); supplementary AE report (trials from diabetes and weight management programs); CV meta-analysis report
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Represented by Summary of Clinical Efficacy (Module 2.7.3); appendices are provided in Module 5.3.5.3.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview (Module 2.5), section 6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product	X			

	Content Parameter	Yes	No	NA	Comment
	(*i.e.*, appropriately designed dose-ranging studies)? • **Study Number: NN8022-1807** Study Title: Effect of liraglutide on body weight in obese subjects without diabetes: a 20-week randomised, double-blind, placebo-controlled, six-armed parallel-group, multi-centre, multinational trial with an open label orlistat comparator arm. Sample Size: 564 Arms: 6 Location in submission: Module 5.3.5.1 • **Study Number: NN8022-1922** Study Title: Effect of liraglutide on body weight in overweight or obese subjects with type 2 diabetes - A 56 week randomised, double-blind, placebo-controlled, three armed parallel group, multi-centre, multinational trial with a 12 week observational follow-up period Sample Size: 846 Arms: 3 Location in submission: Module 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? • **Pivotal Study #: NN8022-1839** • **Pivotal Study #2: NN8022-1922** • **Pivotal Study #3: NN8022-1923**	X			All 3 pivotal trials were conducted in support of a weight management indication The sponsor has also submitted the phase 2 trial NN8022-1807 (+ extension) and sleep apnea trial NN8022-3970; however, because of reasons of study design, these studies will only be considered supportive for efficacy
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			With the caveat regarding the other 2 trials listed above
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			FDA requested 2 co-primary endpoints: change from baseline in body wt at wk 56 and proportion of pts losing ≥ 5% body wt

	Content Parameter	Yes	No	NA	Comment
					at wk 56; in trials -1807 and -1922 sponsor also included a third co-primary endpoint of proportion of pts losing ≥ 10% body wt at wk 56, presumably to conform with other regulatory authorities' requests; in -1923 (with diet run-in) the 3 co-primary endpoints reflect the study design: % body wt loss; percentage of pts who maintain run-in wt loss after 56 wks; proportion of pts who lose ≥ 5% of baseline body wt after 56 wks
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Trials were conducted in multiple foreign sites
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			The sponsor conducted a thorough QT study under the diabetes IND (NN2211-1644); the QT-IRT has determined that this trial is adequate to address the arrhythmogenic potential of the 3 mg dose (see memo to IND 73206, dated 10/20/2011)
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			This appears to be adequately addressed in Module 5.3.6 (PSUR/PBRER)
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Obesity guidance recommends 3000 patients randomized to drug, 1500 to placebo

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
					in trials of at least 1 year duration; in 3 pivotal trials: lira 3 mg N=3115, lira 1.8 mg N=210, pbo N=1664 (with larger database for supportive safety; e.g., lira 1.8 mg in diabetes population)
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			Verbatim terms included in ISS AE dataset (S_RPTERM); MedDRA v10 (trial 1807), v15.1 (trials 1839, 1922, 1923, and 3970)
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			ISS includes adverse events of medical interest; the adequacy is a review issue
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		Trial 1807/1807 ext: adverse dropout narratives were not included. It is noted that the preNDA meeting stated: *An appendix to the NDA, Summary 2.7.4 Summary of Clinical Safety will include hyperlinks to all of the narratives in the submission, according to category (deaths, serious adverse events, withdrawals due to adverse event, and non-serious adverse events of special interest).* However, the narratives were not organized according to category. This makes it difficult to confirm

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
					which narratives were included.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		The sponsor did not provide justification with relevant literature for the inclusion of any comparator other than placebo in the CV meta-analysis.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			PSP included. Requesting waiver for children < 6yo and deferral for children 6-18yo.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Trials were conducted in multiple foreign sites
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		X		CV datasets differ somewhat from statistics request at preNDA meeting – will need confirmation regarding acceptability
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			However, CRFs indicate some AEs were deleted and not included in datasets for unclear reasons
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Audit trail in eCRF forms uninterpretable Some AEs were found to have been "deleted" for unclear reasons
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			Missing 1 CRF: Trial 1923, patient 210011

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
					In some trials, CRFs for MESI or pregnancies were included
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. We acknowledge your submission dated 14 Feb 2014. Data validity will continue to be a review issue. We request the following information that you offered to provide:

    a. The sensitivity analysis for body weight by excluding the sites with unusual data pattern for body weight

    b. Information regarding the collection of 100% SDV for partial SDV subjects in trial NN8022-1839

    c. Ongoing information regarding protocol violations

2. We acknowledge your submission dated 13 Feb 2014. The adequacy of the safety reporting in the eCRFs will continue to be a review issue. Provide a list of treatment-emergent AEs that were deleted from the CRFs and the reason for each deletion. Some general comments regarding the examples presented:

    a. For example 1 (subject 101018 in trial 1839, “cardiac arrhythmia”), it appears that the patient was feeling ill, so an AE of a pre-existing condition was reported. When it was determined that this was not worsening of the pre-existing condition, the AE was deleted rather than clarification / addition of a new AE (e.g., “feeling ill”). The reason, “changed information” does not adequately explain the rationale.

    b. For example 2 (subject 508022 in trial 1922, “anxiety”), it appears that the AE was a pre-existing condition, so it was deleted due to “transcription error”. However, it is not clear from the query and reason provided if anxiety could be considered worsened.

c. For example 4 (subject 105019 in trial 1923, "anemia"), the description of the events are not clarified by the information in the audit trail. As with other AE deletion reasons, "transcription error" in this case is uninformative.

3. Provide an assessment of patients with laboratory results that are considered clinically significantly abnormal. For example, patient 133039 in trial 1807 (ALT 955 U/L) and patient 490007 in trial 1839 (ALT 1523 U/L). This should be done for all laboratory parameters, with an explanation of how 'clinically significantly abnormal' was determined, and a summary of the sponsor's impression of these cases should be provided, including any work-up conducted.

4. It is noted that the preNDA meeting stated: *An appendix to the NDA, Summary 2.7.4 Summary of Clinical Safety will include hyperlinks to all of the narratives in the submission, according to category (deaths, serious adverse events, withdrawals due to adverse event, and non-serious adverse events of special interest).* However, it does not appear that the narratives were organized according to category. Provide a table of contents of narratives by category that includes the location in the NDA. Provide narratives for adverse withdrawals for trial 1807, which do not appear to be included.

5. Provide justification with relevant literature for the inclusion of any comparator other than placebo in the CV meta-analysis.

6. Provide missing CRF: Trial 1923, patient 210011 (adverse withdrawal).

7. Provide a rationale for assuming the applicability of foreign data to U.S. population / practice of medicine in the submission. If already provided in the NDA, provide the location.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

JULIE K GOLDEN
02/26/2014

JAMES P SMITH
02/26/2014