CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 206321/S-004

Trade Name:	SAXENDA
Generic or Proper Name:	Liraglutide injection
Sponsor:	Novo Nordisk, Inc.
Approval Date:	April 26, 2017
Indication:	An adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass (BMI) of at least 30kg/m² (obese) or at least 27 kg/m² (overweight) in the presence of at least 1 weight-related comorbid condition

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 206321/S-004

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206321/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206321/S-004
NDA 206321/S-006

SUPPLEMENT APPROVAL

Novo Nordisk, Inc.
Attention: Michelle Thompson
Senior Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. Thompson:

Please refer to your Supplemental New Drug Application (sNDA) and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Saxenda (liraglutide) injection for the following Prior Approval and Changes Being Effected supplements.

Supplement 004
This "Prior Approval" sNDA, dated June 24, 2016, and received June 27, 2016, provides for revisions of the prescribing information (PI) to include results from 160 weeks of treatment with Saxenda, followed by a 12-week off-drug period in Trial NN8022-1839.

Supplement 006
This "Changes Being Effected" sNDA, dated and received, January 12, 2017, provides for the following changes to the Medication Guide, Instructions for Use, and Carton and Container labeling to align with the currently approved Prescribing Information:

- "[rDNA origin]" removed;
- Patent string replaced with URL.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your April 24, 2017, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide, and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your January 12, 2017, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Martin White, M.S., Regulatory Project Manager, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling
Carton and Container Labeling

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

/s/

JAMES P SMITH
04/26/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206321/S-004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAXENDA® safely and effectively. See full prescribing information for SAXENDA.

SAXENDA (liraglutide) injection, for subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5 1)**.
- **Saxenda is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5 1, 13 1).**

·····RECENT MAJOR CHANGES·····-·····

Boxed Warning……..9/2016
Warnings and Precautions, Risk of Thyroid C-cell Tumors (5.1)....9/2016
Warnings and Precautions, Pancreatitis (5.2)……...5/2017
Warnings and Precautions, Acute Gallbladder Disease (5.3)……...5/2017
Warnings and Precautions, Suicidal Behavior and Ideation (5.8)…5/2017

·····INDICATIONS AND USAGE·····

Saxenda is a glucagon-like peptide-1 (GLP-1) receptor agonist 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) (1) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia) (1).

Limitations of Use:

- Saxenda is not indicated for the treatment of type 2 diabetes (1).
- Saxenda should not be used in combination with any other GLP-1 receptor agonist (1).
- Saxenda should not be used with insulin (1, 5.4).
- The effects of Saxenda on cardiovascular morbidity and mortality have not been established (1).
- The safety and efficacy of coadministration with other products for weight loss have not been established (1).
- Saxenda has not been studied in patients with a history of pancreatitis (1, 5.2).

·····DOSAGE AND ADMINISTRATION·····-·····

- Recommended dose of Saxenda is 3 mg daily. Administer at any time of day, without regard to the timing of meals (2).
- Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached (2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2).
- The injection site and timing can be changed without dose adjustment (2).

·····DOSAGE FORMS AND STRENGTHS·····-·····

- Injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg (6 mg/mL, 3 mL) (3).

·····CONTRAINDICATIONS·····

- Personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 (4, 5 1).
- Hypersensitivity to liraglutide or any product components (4, 5.7).
- Pregnancy (4, 8.1).

·····WARNINGS AND PRECAUTIONS·····-·····--·····

- Thyroid C-cell Tumors: See Boxed Warning (5.1).
- Acute Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.3).
- Serious Hypoglycemia: Can occur when Saxenda is used with an insulin secretagogue (e.g. a sulfonylurea). Consider lowering the dose of anti-diabetic drugs to reduce the risk of hypoglycemia (2, 5.4).
- Heart Rate Increase: Monitor heart rate at regular intervals (5.5).
- Renal Impairment: Has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of Saxenda in patients with renal impairment (5.6).
- Hypersensitivity Reactions: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue Saxenda and other suspect medications and promptly seek medical advice (5.7).
- Suicidal Behavior and Ideation: Monitor for depression or suicidal thoughts. Discontinue Saxenda if symptoms develop (5.8).

·····ADVERSE REACTIONS·····-·····

- Most common adverse reactions, reported in greater than or equal to 5% are: nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-844-363-4448 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Saxenda delays gastric emptying. May impact absorption of concomitantly administered oral medications. Use with caution (7).

·····USE IN SPECIFIC POPULATIONS·····-·····-·····

- Pediatric Use: Safety and effectiveness not established and use not recommended (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **Saxenda is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of Saxenda and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Saxenda *[see Contraindications (4), Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

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 comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)

Limitations of Use

- Saxenda is not indicated for the treatment of type 2 diabetes mellitus.
- Saxenda and Victoza® both contain the same active ingredient, liraglutide, and therefore should not be used together. Saxenda should not be used in combination with any other GLP-1 receptor agonist.
- Saxenda has not been studied in patients taking insulin. Saxenda and insulin should not be used together *[see Warnings and Precautions (5.4)]*.
- The effects of Saxenda on cardiovascular morbidity and mortality have not been established.
- The safety and effectiveness of Saxenda in combination with other products intended for weight loss, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.
- Saxenda has not been studied in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of Saxenda is 3 mg daily. The dose escalation schedule in Table 1 should be used to reduce the likelihood of gastrointestinal symptoms. If patients do not tolerate an increased dose during dose escalation, consider delaying dose escalation for approximately one additional week. Saxenda should be discontinued, however, if a patient cannot tolerate the 3 mg dose, as efficacy has not been established at lower doses (0.6, 1.2, 1.8, and 2.4 mg).

Table 1. Dose Escalation Schedule

Week	Daily Dose

1	0.6 mg
2	1.2 mg
3	1.8 mg
4	2.4 mg
5 and onward	3 mg

Saxenda should be taken once daily at any time of day, without regard to the timing of meals. Saxenda can be injected subcutaneously in the abdomen, thigh, or upper arm. The injection site and timing can be changed without dose adjustment. Saxenda must not be administered intravenously or intramuscularly.

When initiating Saxenda in patients taking insulin secretagogues (such as sulfonylureas), consider reducing the dose of the insulin secretagogue (for example, by one-half) to reduce the risk for hypoglycemia, and monitor blood glucose. Saxenda and insulin should not be used together *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*. Conversely, if discontinuing Saxenda in patients with type 2 diabetes, monitor for an increase in blood glucose.

Evaluate the change in body weight 16 weeks after initiating Saxenda and discontinue Saxenda if the patient has not lost at least 4% of baseline body weight, since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. An extra dose or increase in dose should not be taken to make up for the missed dose. If more than 3 days have elapsed since the last Saxenda dose, patients should reinitiate Saxenda at 0.6 mg daily and follow the dose escalation schedule in Table 1, which may reduce the occurrence of gastrointestinal symptoms associated with reinitiation of treatment.

Prior to initiation of Saxenda, patients should be trained by their healthcare professional on proper injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.

Saxenda solution should be inspected prior to each injection, and the solution should be used only if it is clear, colorless, and contains no particles.

BMI is calculated by dividing weight in (kilograms) by height (in meters) squared. A chart for determining BMI based on height and weight is provided in Table 2.

Table 2. BMI Conversion Chart

Weight	(lb)	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225
	(kg)	56. 8	59. 1	61. 4	63. 6	65. 9	68. 2	70. 5	72. 7	75. 0	77. 3	79. 5	81. 8	84. 1	86. 4	88. 6	90. 9	93. 2	95. 5	97. 7	100. 0	102. 3
Height																						
(in)	(cm)																					
58	147. 3	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47
59	149. 9	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	152. 4	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	154. 9	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	157. 5	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	160. 0	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	162. 6	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	165. 1	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	167. 6	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	170. 2	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	172. 7	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	175. 3	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	177. 8	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	180. 3	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	182. 9	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	185. 4	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	188. 0	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	190. 5	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	193. 0	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

3 DOSAGE FORMS AND STRENGTHS

Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg (6 mg/mL, 3 mL).

4 CONTRAINDICATIONS

Saxenda is contraindicated in:

- Patients with a personal or family history of medullary thyroid carcinoma (MTC) or patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Warnings and Precautions (5.1)]*
- Patients with a prior serious hypersensitivity reaction to liraglutide or to any of the product components *[see Warnings and Precautions (5.7)]*
- Pregnancy *[see Use in Specific Populations (8.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures in both genders of rats and mice *[see Nonclinical Toxicology (13.1)]*. Malignant thyroid C-cell carcinomas were detected in rats and mice. It is unknown whether Saxenda will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and liraglutide use in humans.

Saxenda is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of Saxenda and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Saxenda. Such monitoring may increase the risk of unnecessary procedures, due

to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC, and patients with MTC usually have calcitonin values greater than 50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Acute Pancreatitis

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide. After initiation of Saxenda, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Saxenda should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Saxenda should not be restarted.

In Saxenda clinical trials, acute pancreatitis was confirmed by adjudication in 9 (0.3%) of 3291 Saxenda-treated patients and 2 (0.1%) of 1843 placebo-treated patients. In addition, there were 2 cases of acute pancreatitis in Saxenda-treated patients who prematurely withdrew from these clinical trials, occurring 74 and 124 days after the last dose. There were 2 additional cases in Saxenda-treated patients, 1 during an off-treatment follow-up period within 2 weeks of discontinuing Saxenda, and 1 that occurred in a patient who completed treatment and was off-treatment for 106 days.

It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using Saxenda, since these patients were excluded from clinical trials.

5.3 Acute Gallbladder Disease

In Saxenda clinical trials, 2.2% of Saxenda-treated patients reported adverse events of cholelithiasis versus 0.8% of placebo-treated patients. The incidence of cholecystitis was 0.8% in Saxenda-treated patients versus 0.4% in placebo-treated patients. The majority of Saxenda-treated patients with adverse events of cholelithiasis and cholecystitis required cholecystectomy. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in Saxenda-treated patients than in placebo-treated patients even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

5.4 Risk for Hypoglycemia with Concomitant Use of Anti-Diabetic Therapy

The risk for serious hypoglycemia is increased when Saxenda is used in combination with insulin secretagogues (for example, sulfonylureas) in patients with type 2 diabetes mellitus. Therefore, patients may require a lower dose of sulfonylurea (or other concomitantly administered insulin secretagogues) in this setting *[see Dosage and Administration (2) and Adverse Reactions (6.1)]*. Saxenda should not be used in patients taking insulin.

Saxenda can lower blood glucose *[see Clinical Pharmacology (12.2)]*. Monitor blood glucose parameters prior to starting Saxenda and during Saxenda treatment in patients with type 2 diabetes. If needed, adjust co-administered anti-diabetic drugs based on glucose monitoring results and risk of hypoglycemia.

5.5 Heart Rate Increase

Mean increases in resting heart rate of 2 to 3 beats per minute (bpm) were observed with routine clinical monitoring in Saxenda-treated patients compared to placebo in clinical trials. More patients treated with Saxenda, compared with placebo, had changes from baseline at two consecutive visits of more than 10 bpm (34% versus 19%, respectively) and 20 bpm (5% versus 2%, respectively). At least one resting heart rate exceeding 100 bpm was recorded for 6% of Saxenda-treated patients compared with 4% of placebo-treated patients, with this occurring at two consecutive study visits for 0.9% and 0.3%, respectively. Tachycardia was reported as an adverse reaction in 0.6% of Saxenda-treated patients and in 0.1% of placebo-treated patients.

In a clinical pharmacology trial that monitored heart rate continuously for 24 hours, Saxenda treatment was associated with a heart rate that was 4 to 9 bpm higher than that observed with placebo.

The clinical significance of the heart rate elevation with Saxenda treatment is unclear, especially for patients with cardiac and cerebrovascular disease as a result of limited exposure in these patients in clinical trials.

Heart rate should be monitored at regular intervals consistent with usual clinical practice. Patients should inform health care providers of palpitations or feelings of a racing heartbeat while at rest during Saxenda treatment. For patients who experience a sustained increase in resting heart rate while taking Saxenda, Saxenda should be discontinued.

5.6 Renal Impairment

In patients treated with GLP-1 receptor agonists, including Saxenda, there have been reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis *[see Adverse Reactions (6.2)]*. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea leading to volume depletion. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or volume status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Use caution when initiating or escalating doses of Saxenda in patients with renal impairment *[see Use in Specific Populations (8.6)]*.

5.7 Hypersensitivity Reactions

There have been reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide *[see Adverse Reactions (6.1, 6.2)]*. If a hypersensitivity reaction occurs, the patient should discontinue Saxenda and other suspect medications and promptly seek medical advice.

Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Saxenda.

5.8 Suicidal Behavior and Ideation

In Saxenda clinical trials, 9 (0.3%) of 3384 Saxenda-treated patients and 2 (0.1%) of the 1941 placebo-treated patients reported suicidal ideation; one of these Saxenda-treated patients attempted suicide. Patients treated with Saxenda should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Saxenda in patients who experience suicidal thoughts or behaviors. Avoid Saxenda in patients with a history of suicidal attempts or active suicidal ideation.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-Cell Tumors *[see Warnings and Precautions (5.1)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.2)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.3)]*
- Risk for Hypoglycemia with Concomitant Use of Anti-Diabetic Therapy *[see Warnings and Precautions (5.4)]*
- Heart Rate Increase *[see Warnings and Precautions (5.5)]*
- Renal Impairment *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Saxenda was evaluated for safety in 5 double-blind, placebo controlled trials that included 3384 overweight or obese patients treated with Saxenda for a treatment period up to 56 weeks (3 trials), 52 weeks (1 trial), and 32 weeks (1 trial). All patients received study drug in addition to diet and exercise counseling. In these trials, patients received Saxenda for a mean treatment duration of 46 weeks (median, 56 weeks). Baseline characteristics included a mean age of 47 years, 71% women, 85% white, 39% with hypertension, 15% with type 2 diabetes, 34% with dyslipidemia, 29% with a BMI greater than 40 kg/m^2, and 9% with cardiovascular disease. In one of the 56-week trials, a subset of patients (with abnormal glucose measurements at randomization) *[see Clinical Studies (14)]* were enrolled for a placebo-controlled 160-week period instead, followed by a 12-week off-treatment follow-up. For those participating in this 160-week period, patients received Saxenda for a mean treatment duration of 110 weeks (median, 159 weeks). For all trials, dosing was initiated and increased weekly to reach the 3 mg dose.

In clinical trials, 9.8% of patients treated with Saxenda and 4.3% of patients treated with placebo prematurely discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (2.9% versus 0.2% for Saxenda and placebo, respectively), vomiting (1.7% versus less than 0.1%), and diarrhea (1.4% versus 0%).

Adverse reactions reported in greater than or equal to 2% of Saxenda-treated patients and more frequently than in placebo-treated patients are shown in Table 3.

Table 3. Adverse Reactions Reported in Greater Than or Equal to 2% of Saxenda-treated Patients and More Frequently than with Placebo*

	Placebo N = 1941 %	**Saxenda N = 3384 %**
Gastrointestinal Disorders		
Nausea	13.8	39.3
Diarrhea	9.9	20.9
Constipation	8.5	19.4
Vomiting	3.9	15.7
Dyspepsia	2.7	9.6
Abdominal Pain	3.1	5.4
Upper Abdominal Pain	2.7	5.1
Gastroesophageal Reflux Disease	1.7	4.7
Abdominal Distension	3.0	4.5
Eructation	0.2	4.5
Flatulence	2.5	4.0
Dry Mouth	1.0	2.3
Metabolism and Nutrition Disorders		
Hypoglycemia in T2DM[1]	12.7	23.0
Decreased Appetite	2.3	10.0
Nervous System Disorders		
Headache	12.6	13.6
Dizziness	5.0	6.9
General Disorders and Administration Site Conditions		
Fatigue	4.6	7.5

Injection Site Erythema	0.2	2.5
Injection Site Reaction	0.6	2.5
Asthenia	0.8	2.1
Infections and Infestations		
Gastroenteritis	3.2	4.7
Urinary Tract Infection	3.1	4.3
Viral Gastroenteritis	1.6	2.8
Investigations		
Increased Lipase	2.2	5.3
Psychiatric Disorders		
Insomnia	1.7	2.4
Anxiety	1.6	2.0

[1] Documented symptomatic (defined as documented symptoms of hypoglycemia in combination with a plasma glucose less than or equal to 70 mg/dL) in patients with type 2 diabetes (Study 2). See text below for further information regarding hypoglycemia in patients with and without type 2 diabetes. T2DM = type 2 diabetes mellitus

* Adverse reactions for trials with treatment period up to 56 weeks

Hypoglycemia

Saxenda can lower blood glucose. In a clinical trial involving patients with type 2 diabetes mellitus and overweight or obesity, severe hypoglycemia (defined as requiring the assistance of another person) occurred in 3 (0.7%) of 422 Saxenda-treated patients and in none of the 212 placebo-treated patients. Each of these 3 Saxenda-treated patients was also taking a sulfonylurea. In the same trial, among patients taking a sulfonylurea, documented symptomatic hypoglycemia (defined as documented symptoms of hypoglycemia in combination with a plasma glucose less than or equal to 70 mg/dL) occurred in 48 (43.6%) of 110 Saxenda-treated patients and 15 (27.3%) of 55 placebo-treated patients. The doses of sulfonylureas were reduced by 50% at the beginning of the trial per protocol. The frequency of hypoglycemia may be higher if the dose of sulfonylurea is not reduced. Among patients not taking a sulfonylurea, documented symptomatic hypoglycemia occurred in 49 (15.7%) of 312 Saxenda-treated patients and 12 (7.6%) of 157 placebo-treated patients.

In Saxenda clinical trials involving patients without type 2 diabetes mellitus, there was no systematic capturing or reporting of hypoglycemia, as patients were not provided with blood glucose meters or hypoglycemia diaries. Spontaneously reported symptomatic episodes of unconfirmed hypoglycemia were reported by 46 (1.6%) of 2962 Saxenda-treated patients and 19 (1.1%) of 1729 placebo-treated patients. Fasting plasma glucose values obtained at routine clinic visits less than or equal to 70 mg/dL, irrespective of hypoglycemic symptoms, were reported as “hypoglycemia” in 92 (3.1%) Saxenda-treated patients and 13 (0.8%) placebo-treated patients.

Gastrointestinal Adverse Reactions

In the clinical trials, approximately 68% of Saxenda-treated patients and 39% of placebo-treated patients reported gastrointestinal disorders; the most frequently reported was nausea (39% and 14% of patients treated with Saxenda and placebo, respectively). The percentage of patients reporting nausea declined as treatment continued. Other common adverse reactions that occurred at a higher incidence among Saxenda-treated patients included diarrhea, constipation, vomiting, dyspepsia, abdominal pain, dry mouth, gastritis, gastroesophageal reflux disease, flatulence, eructation and abdominal distension. Most episodes of gastrointestinal events were mild or moderate and did not lead to discontinuation of therapy (6.2% with Saxenda versus 0.8% with placebo discontinued treatment as a result of gastrointestinal adverse reactions). There have been reports of gastrointestinal adverse reactions, such as nausea, vomiting, and diarrhea, associated with volume depletion and renal impairment *[see Warnings and Precautions (5.6)]*.

Asthenia, Fatigue, Malaise, Dysgeusia and Dizziness

Events of asthenia, fatigue, malaise, dysgeusia and dizziness were mainly reported within the first 12 weeks of treatment with Saxenda and were often co-reported with gastrointestinal events such as nausea, vomiting, and diarrhea.

Immunogenicity

Patients treated with Saxenda may develop anti-liraglutide antibodies. Anti-liraglutide antibodies were detected in 42 (2.8%) of 1505 Saxenda-treated patients with a post-baseline assessment. Antibodies that had a neutralizing effect on liraglutide in an *in vitro* assay occurred in 18 (1.2%) of 1505 Saxenda-treated patients. Presence of antibodies may be associated with a higher incidence of injection site reactions and reports of low blood glucose. In clinical trials, these events were usually classified as mild and resolved while patients continued on treatment.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to Saxenda cannot be directly compared with the incidence of antibodies of other products.

Allergic Reactions

Urticaria was reported in 0.7% of Saxenda-treated patients and 0.5% of placebo-treated patients. Anaphylactic reactions, asthma, bronchial hyperreactivity, bronchospasm, oropharyngeal swelling, facial swelling, angioedema, pharyngeal edema, type IV hypersensitivity reactions have been reported in patients treated with liraglutide in clinical trials. Cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnea, and edema have been reported with marketed use of liraglutide. Anaphylactic reactions may potentially be life-threatening.

Injection Site Reactions

Injection site reactions were reported in approximately 13.9% of Saxenda-treated patients and 10.5% of placebo-treated patients. The most common reactions, each reported by 1% to 2.5% of Saxenda-treated patients and more commonly than by placebo-treated patients, included erythema, pruritus, and rash at the injection site. 0.6% of Saxenda-treated patients and 0.5% of placebo-treated patients discontinued treatment due to injection site reactions.

Breast Cancer

In Saxenda clinical trials, breast cancer confirmed by adjudication was reported in 17 (0.7%) of 2379 Saxenda-treated women compared with 3 (0.2%) of 1300 placebo-treated women, including invasive cancer (13 Saxenda- and 2 placebo-treated women) and ductal carcinoma *in situ* (4 Saxenda- and 1 placebo-treated woman). The majority of cancers were estrogen- and progesterone-receptor positive. There were too few cases to determine whether these cases were related to Saxenda. In addition, there are insufficient data to determine whether Saxenda has an effect on pre-existing breast neoplasia.

Papillary Thyroid Cancer

In Saxenda clinical trials, papillary thyroid carcinoma confirmed by adjudication was reported in 8 (0.2%) of 3291 Saxenda-treated patients compared with no cases among 1843 placebo-treated patients. Four of these papillary thyroid carcinomas were less than 1 cm in greatest diameter and 4 were diagnosed in surgical pathology specimens after thyroidectomy prompted by findings identified prior to treatment.

Colorectal Neoplasms

In Saxenda clinical trials, benign colorectal neoplasms (mostly colon adenomas) confirmed by adjudication were reported in 20 (0.6%) of 3291 Saxenda-treated patients compared with 7 (0.4%) of 1843 placebo-treated patients. Six positively adjudicated cases of malignant colorectal neoplasms were reported in 5 Saxenda-treated patients (0.2%, mostly adenocarcinomas) and 1 in a placebo-treated patient (0.1%, neuroendocrine tumor of the rectum).

Cardiac Conduction Disorders

In Saxenda clinical trials, 11 (0.3%) of 3384 Saxenda-treated patients compared with none of the 1941 placebo-treated patients had a cardiac conduction disorder, reported as first degree atrioventricular block, right bundle branch block, or left bundle branch block.

Hypotension

Adverse reactions related to hypotension (that is, reports of hypotension, orthostatic hypotension, circulatory collapse, and decreased blood pressure) were reported more frequently with Saxenda (1.1%) compared with placebo (0.5%) in Saxenda clinical trials. Systolic blood pressure decreases to less than 80 mmHg were observed in 4 (0.1%) Saxenda-treated patients compared with no placebo-treated patients. One of the Saxenda-treated patients had hypotension associated with gastrointestinal adverse reactions and renal failure *[see Warnings and Precautions (5.6)]*.

Laboratory Abnormalities

Liver Enzymes

Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 (0.15%) Saxenda-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 Saxenda 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 Saxenda is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones).

Serum Calcitonin

Calcitonin, a biological marker of MTC, was measured throughout the clinical development program *[see Warnings and Precautions (5.1)]*. More patients treated with Saxenda in the clinical trials were observed to have high calcitonin values during treatment, compared with placebo. The proportion of patients with calcitonin greater than or equal to 2 times the upper limit of normal at the end of the trial was 1.2% in Saxenda-treated patients and 0.6% in placebo-treated patients. Calcitonin values greater than 20 ng/L at the end of the trial occurred in 0.5% of Saxenda-treated patients and 0.2% of placebo-treated patients; among patients with pre-treatment serum calcitonin less than 20 ng/L, none had calcitonin elevations to greater than 50 ng/L at the end of the trial.

Serum Lipase and Amylase

Serum lipase and amylase were routinely measured in the Saxenda clinical trials. Among Saxenda-treated patients, 2.1% had a lipase value at anytime during treatment of greater than or equal to 3 times the upper limit of normal compared with 1.0% of placebo-treated patients. 0.1% of Saxenda-treated patients had an amylase value at anytime in the trial of greater than or equal to 3 times the upper limit of normal versus 0.1% of placebo-treated patients. The clinical significance of elevations in lipase or amylase with Saxenda is unknown in the absence of other signs and symptoms of pancreatitis *[see Warnings and Precautions (5.2)]*.

6.2 Post-Marketing Experience

The following adverse reactions have been reported during post-approval use of liraglutide, the active ingredient of Saxenda. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neoplasms

Medullary thyroid carcinoma *[see Warnings and Precautions (5.1)]*

Gastrointestinal Disorders

Acute pancreatitis, hemorrhagic and necrotizing pancreatitis, sometimes resulting in death *[see Warnings and Precautions (5.2)]*

Metabolism and Nutrition Disorders

Dehydration resulting from nausea, vomiting and diarrhea *[see Adverse Reactions (6.1)]*

Renal and Urinary Disorders

Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis *[see Warnings and Precautions (5.6)]*

General Disorders and Administration Site Conditions

Allergic reactions: rash and pruritus *[see Adverse Reactions (6.1)]*

Immune System Disorders

Angioedema and anaphylactic reactions *[see Warnings and Precautions (5.7)]*

Hepatobiliary Disorders

Elevations of liver enzymes, hyperbilirubinemia, cholestasis and hepatitis *[see Adverse Reactions (6.1)]*

7 DRUG INTERACTIONS

7.1 Oral Medications

Saxenda causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, monitor for potential consequences of delayed absorption of oral medications concomitantly administered with Saxenda.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

SAXENDA is contraindicated during pregnancy because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm [*see Clinical Considerations*]. There are no available data with liraglutide in pregnant women to inform a drug associated risk for major birth defects and miscarriage. SAXENDA should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with SAXENDA should be discontinued.

Animal reproduction studies identified increased adverse embryofetal developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 3 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD *[see Animal Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

A minimum weight gain, and no weight loss, is recommended for all pregnant women, including those who are already overweight or obese, due to the necessary weight gain that occurs in maternal tissues during pregnancy.

Animal Data

Liraglutide has been shown to be teratogenic in rats at or above 0.8-times systemic exposures in obese humans resulting from the maximum recommended human dose (MRHD) of 3 mg/day based on plasma area under the time-concentration curve (AUC) comparison. Liraglutide has been shown to cause reduced growth and increased total major abnormalities in rabbits at systemic exposures below exposure in obese humans at the MRHD based on plasma AUC comparison.

Female rats given subcutaneous doses of 0.1, 0.25 and 1 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the exposure in obese humans at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1

mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the exposure in obese humans at the MRHD of 3 mg/day at all doses, based on plasma AUC comparison. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), greater than or equal to 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), greater than or equal to 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times exposure in obese humans at the MRHD of 3 mg/day, based on plasma AUC comparison. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F_2 generation rats descended from liraglutide-treated rats compared to F_2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.2 Lactation

Risk Summary

There are no data on the presence of liraglutide in human milk, the effects on the breastfed infant, or effects on milk production. Liraglutide was present in the milk of lactating rats (see *Data*).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SAXENDA and any potential adverse effects on the breastfed infant from SAXENDA or from the underlying maternal condition.

Data

In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

Safety and effectiveness of Saxenda have not been established in pediatric patients. Saxenda is not recommended for use in pediatric patients.

8.5 Geriatric Use

In the Saxenda clinical trials, 232 (6.9%) of the Saxenda-treated patients were 65 years of age and over, and 17 (0.5%) of the Saxenda-treated patients were 75 years of age and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
There is limited experience with Saxenda in patients with mild, moderate, and severe renal impairment, including end-stage renal disease. However, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure with liraglutide, which may sometimes require hemodialysis *[see Warnings and Precautions (5.6) and Adverse Reactions (6.2)]*. Saxenda should be used with caution in this patient population *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
There is limited experience in patients with mild, moderate, or severe hepatic impairment. Therefore, Saxenda should be used with caution in this patient population *[see Clinical Pharmacology (12.3)]*.

8.8 Gastroparesis
Saxenda slows gastric emptying. Saxenda has not been studied in patients with pre-existing gastroparesis.

10 OVERDOSAGE
Overdoses have been reported in clinical trials and post-marketing use of liraglutide. Effects have included severe nausea and severe vomiting. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

11 DESCRIPTION
Saxenda contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae*, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$ and the molecular weight is 3751.2 Daltons. The structural formula (Figure 1) is:

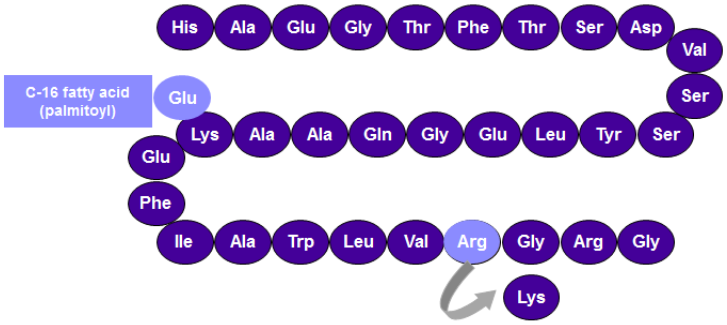


Figure 1. Structural Formula of liraglutide

Saxenda is a clear, colorless solution. Each 1 mL of Saxenda solution contains 6 mg of liraglutide and the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. Each pre-filled pen contains a 3 mL solution of Saxenda equivalent to 18 mg liraglutide (free-base, anhydrous).

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). Like endogenous GLP-1, liraglutide binds to and activates the GLP-1 receptor, a cell-surface receptor coupled to adenylyl cyclase activation through the stimulatory G-protein, Gs. Endogenous GLP-1 has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it

suitable for once-daily administration, is a result of self-association that delays absorption, plasma protein binding, and stability against metabolic degradation by DPP-4 and NEP.

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. Although liraglutide activated neurons in brain regions known to regulate appetite, specific brain regions mediating the effects of liraglutide on appetite were not identified in rats.

12.2 Pharmacodynamics

Liraglutide lowers body weight through decreased calorie intake. Liraglutide does not increase 24-hour energy expenditure.

As with other GLP-1 receptor agonists, liraglutide stimulates insulin secretion and reduces glucagon secretion in a glucose-dependent manner. These effects can lead to a reduction of blood glucose.

Cardiac Electrophysiology (QTc) in healthy volunteers

The effect of liraglutide on cardiac repolarization was tested in a QTc study. Liraglutide at steady-state concentrations after daily doses up to 1.8 mg did not produce QTc prolongation. The maximum liraglutide plasma concentration (C_{max}) in overweight and obese subjects treated with liraglutide 3 mg is similar to the C_{max} observed in the liraglutide QTc study in healthy volunteers.

12.3 Pharmacokinetics

Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 11 hours post dosing. The average liraglutide steady state concentration ($AUC_{\tau/24}$) reached approximately 116 ng/mL in obese (BMI 30-40 kg/m^2) subjects following administration of Saxenda. Liraglutide exposure increased proportionally in the dose range of 0.6 mg to 3 mg. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration. Liraglutide exposures were considered similar among three subcutaneous injection sites (upper arm, abdomen, and thigh). Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution - The mean apparent volume of distribution after subcutaneous administration of liraglutide 3 mg is 20-25 L (for a person weighing approximately 100 kg). The mean volume of distribution after intravenous administration of liraglutide is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (greater than 98%).

Metabolism - During the initial 24 hours following administration of a single [3H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination.

Elimination - Following a [3H]-liraglutide dose, intact liraglutide was not detected in urine or feces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or feces (6% and 5%, respectively). The majority of urine and feces radioactivity was excreted during the first 6-8 days. The mean apparent clearance following subcutaneous administration of a single dose of liraglutide is approximately 0.9-1.4 L/h with an elimination half-life of approximately 13 hours, making liraglutide suitable for once daily administration.

Specific Populations

Elderly - No dosage adjustment is required based on age. Age had no effect on the pharmacokinetics of liraglutide based on a pharmacokinetic study in healthy elderly subjects (65 to 83 years) and population

pharmacokinetic analyses of data from overweight and obese patients 18 to 82 years of age *[see Use in Specific Populations (8.5)]*.

Gender - Based on the results of population pharmacokinetic analyses, females have 24% lower weight adjusted clearance of Saxenda compared to males. Based on the exposure response data, no dose adjustment is necessary based on gender.

Race and Ethnicity - Race and ethnicity had no effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analyses that included overweight and obese patients of Caucasian, Black, Asian and Hispanic/Non-Hispanic groups.

Body Weight - Body weight significantly affects the pharmacokinetics of liraglutide based on results of population pharmacokinetic analyses conducted in patients with body weight range of 60-234 kg. The exposure of liraglutide decreases as baseline body weight increases.

Pediatric - Saxenda has not been studied in pediatric patients *[see Use in Specific Populations (8.4)]*.

Renal Impairment - The single-dose pharmacokinetics of liraglutide were evaluated in subjects with varying degrees of renal impairment. Subjects with mild (estimated creatinine clearance 50-80 mL/min) to severe (estimated creatinine clearance less than 30 mL/min) renal impairment and subjects with end-stage renal disease requiring dialysis were included in the trial. Compared to healthy subjects, liraglutide AUC in mild, moderate, and severe renal impairment and in end-stage renal disease was on average 35%, 19%, 29% and 30% lower, respectively *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment - The single-dose pharmacokinetics of liraglutide were evaluated in subjects with varying degrees of hepatic impairment. Subjects with mild (Child Pugh score 5-6) to severe (Child Pugh score greater than 9) hepatic impairment were included in the trial. Compared to healthy subjects, liraglutide AUC in subjects with mild, moderate and severe hepatic impairment was on average 11%, 14% and 42% lower, respectively *[see Use in Specific Populations (8.7)]*.

Drug Interactions
In vitro assessment of drug−drug interactions
Liraglutide has low potential for pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug−drug interactions
The drug-drug interaction studies were performed at steady state with liraglutide 1.8 mg/day. The effect on rate of gastric emptying was equivalent between liraglutide 1.8 mg and 3 mg (acetaminophen $AUC_{0\text{-}300min}$). Administration of the interacting drugs was timed so that C_{max} of liraglutide (8-12 h) would coincide with the absorption peak of the co-administered drugs.

Oral Contraceptives
A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide at steady state. Liraglutide lowered ethinylestradiol and levonorgestrel C_{max} by 12% and 13%, respectively. There was no effect of liraglutide on the overall exposure (AUC) of ethinylestradiol. Liraglutide increased the levonorgestrel $AUC_{0\text{-}\infty}$ by 18%. Liraglutide delayed T_{max} for both ethinylestradiol and levonorgestrel by 1.5 h.

Digoxin
A single dose of digoxin 1 mg was administered 7 hours after the dose of liraglutide at steady state. The concomitant administration with liraglutide resulted in a reduction of digoxin AUC by 16%; C_{max} decreased by 31%. Digoxin median time to maximal concentration (T_{max}) was delayed from 1 h to 1.5 h.

Lisinopril
A single dose of lisinopril 20 mg was administered 5 minutes after the dose of liraglutide at steady state. The co-administration with liraglutide resulted in a reduction of lisinopril AUC by 15%; C_{max} decreased by 27%. Lisinopril median T_{max} was delayed from 6 h to 8 h with liraglutide.

Atorvastatin
Liraglutide did not change the overall exposure (AUC) of atorvastatin following a single dose of atorvastatin 40 mg, administered 5 hours after the dose of liraglutide at steady state. Atorvastatin C_{max} was decreased by 38% and median T_{max} was delayed from 1 h to 3 h with liraglutide.

Acetaminophen
Liraglutide did not change the overall exposure (AUC) of acetaminophen following a single dose of acetaminophen 1000 mg, administered 8 hours after the dose of liraglutide at steady state. Acetaminophen C_{max} was decreased by 31% and median T_{max} was delayed up to 15 minutes.

Griseofulvin
Liraglutide did not change the overall exposure (AUC) of griseofulvin following co-administration of a single dose of griseofulvin 500 mg with liraglutide at steady state. Griseofulvin C_{max} increased by 37% while median T_{max} did not change.

Insulin Detemir
No pharmacokinetic interaction was observed between liraglutide and insulin detemir when separate subcutaneous injections of insulin detemir 0.5 Unit/kg (single-dose) and liraglutide 1.8 mg (steady state) were administered to patients with type 2 diabetes mellitus.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 104-week carcinogenicity study was conducted in male and female CD-1 mice at doses of 0.03, 0.2, 1, and 3 mg/kg/day liraglutide administered by bolus subcutaneous injection yielding systemic exposures 0.2-, 2-, 10- and 43-times the exposure in obese humans, respectively, at the maximum recommended human dose (MRHD) of 3 mg/day based on plasma AUC comparison. A dose-related increase in benign thyroid C-cell adenomas was seen in the 1 and the 3 mg/kg/day groups with incidences of 13% and 19% in males and 6% and 20% in females, respectively. C-cell adenomas did not occur in control groups or 0.03 and 0.2 mg/kg/day groups. Treatment-related malignant C-cell carcinomas occurred in 3% of females in the 3 mg/kg/day group. Thyroid C-cell tumors are rare findings during carcinogenicity testing in mice. A treatment-related increase in fibrosarcomas was seen on the dorsal skin and subcutis, the body surface used for drug injection, in males in the 3 mg/kg/day group. These fibrosarcomas were attributed to the high local concentration of drug near the injection site. The liraglutide concentration in the clinical formulation (6 mg/mL) is 10-times higher than the concentration in the formulation used to administer 3 mg/kg/day liraglutide to mice in the carcinogenicity study (0.6 mg/mL).

A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 7-times the exposure in obese humans, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was seen in males in 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats.

Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose *in vivo* micronucleus tests in rats.

In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1 mg/kg/day, a high dose yielding an estimated systemic exposure 11-times the exposure in obese humans at the MRHD, based on plasma AUC comparison. In female rats, an increase in early embryonic deaths occurred at 1 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1 mg/kg/day dose.

14 CLINICAL STUDIES

The safety and efficacy of Saxenda for chronic weight management in conjunction with reduced caloric intake and increased physical activity were studied in three 56-week, randomized, double-blind, placebo-controlled trials. In all studies, Saxenda was titrated to 3 mg daily during a 4-week period. All patients received instruction for a reduced calorie diet (approximately 500 kcal/day deficit) and exercise counseling (recommended increase in physical activity of minimum 150 mins/week) that began with the first dose of study medication or placebo and continued throughout the trial.

Study 1 enrolled 3731 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. Patients were randomized in a 2:1 ratio to either Saxenda or placebo. Patients were stratified based on the presence or absence of abnormal blood glucose measurements at randomization. All patients were treated for up to 56 weeks. Those patients with abnormal glucose measurements at randomization (2254 of the 3731 patients) were treated for a total of 160 weeks. At baseline, mean age was 45 years (range 18-78), 79% were women, 85% were Caucasian, 10% were African American, and 11% were Hispanic/Latino. Mean baseline body weight was 106.3 kg and mean BMI was 38.3 kg/m^2.

Study 2 was a 56-week trial that enrolled 635 patients with type 2 diabetes and with either overweight or obesity (as defined above). Patients were to have an HbA_{1c} of 7-10% and be treated with metformin, a sulfonylurea, or a glitazone as single agent or in any combination, or with diet and exercise alone. Patients were randomized in a 2:1 ratio to receive either Saxenda or placebo. The mean age was 55 years (range 18-82), 50% were women, 83% were Caucasian, 12% were African American, and 10% were Hispanic/Latino. Mean baseline body weight was 105.9 kg and mean BMI was 37.1 kg/m^2.

Study 3 was a 56-week trial that enrolled 422 patients with obesity (BMI greater than or equal to 30 kg/m^2) or with overweight (BMI 27-29.9 kg/m^2) and at least one weight-related comorbid condition such as treated or untreated dyslipidemia or hypertension; patients with type 2 diabetes mellitus were excluded. All patients were first treated with a low-calorie diet (total energy intake 1200-1400 kcal/day) in a run-in period lasting up to 12 weeks. Patients who lost at least 5% of their screening body weight after 4 to 12 weeks during the run-in were then randomized, with equal allocation, to receive either Saxenda or placebo for 56 weeks. The mean age was 46 years (range 18-73), 81% were women, 84% were Caucasian, 13% were African American, and 7% were Hispanic/Latino. Mean baseline body weight was 99.6 kg and mean BMI was 35.6 kg/m^2.

The proportions of patients who discontinued study drug in the 56-week trials were 27% for the Saxenda-treated group and 35% for the placebo-treated group, and in the 160-week trial the proportions of patients who discontinued were 47% and 55%, respectively. In the 56-week trials, approximately 10% of patients treated with Saxenda and 4% of patients treated with placebo discontinued treatment due to an adverse reaction *[see Adverse Reactions (6.1)]*. The majority of patients who discontinued Saxenda due to adverse reactions did so during the first few months of treatment. In the 160-week trial the proportions of patients who discontinued due to an adverse reaction was 13% and 6% for Saxenda- and placebo-treated patients, respectively.

Effect of Saxenda on Body Weight in 56-week Trials

For Study 1 and Study 2, the primary efficacy parameters were mean percent change in body weight and the percentages of patients achieving greater than or equal to 5% and 10% weight loss from baseline to week 56. For Study 3, the primary efficacy parameters were mean percent change in body weight from randomization to week 56, the percentage of patients not gaining more than 0.5% body weight from randomization (i.e., after run-in) to week 56, and the percentage of patients achieving greater than or equal to 5% weight loss from randomization to week 56. Because losing at least 5% of fasting body weight through lifestyle intervention during the 4- to 12-week run-in was a condition for their continued participation in the randomized treatment period, the results may not reflect those expected in the general population.

Table 4 presents the results for the changes in weight observed in Studies 1, 2, and 3. After 56 weeks, treatment with Saxenda resulted in a statistically significant reduction in weight compared with placebo. Statistically significantly greater proportions of patients treated with Saxenda achieved 5% and 10% weight loss than those treated with placebo. In Study 3, statistically significantly more patients randomized to Saxenda than placebo had not gained more than 0.5% of body weight from randomization to week 56.

Table 4. Changes in Weight at Week 56 for Studies 1, 2, and 3

	Study 1 (Obesity or overweight with comorbidity)		**Study 2 (Type 2 diabetes with obesity or overweight)**		**Study 3 (Obesity or overweight with comorbidity following at least 5% weight loss with diet)**	
	Saxenda N=2487	**Placebo N=1244**	**Saxenda N=423**	**Placebo N=212**	**Saxenda N=212**	**Placebo N=210**
Weight						
Baseline mean (SD) (kg)	106.2 (21.2)	106.2 (21.7)	105.7 (21.9)	106.5 (21.3)	100.4 (20.8)	98.7 (21.2)
Percent change from baseline (LSMean)	-7.4	-3.0	-5.4	-1.7	-4.9	0.3
Difference from placebo (LSMean) (95% CI)	-4.5* (-5.2;-3.8)		-3.7* (-4.7;-2.7)		-5.2* (-6.8;-3.5)	
% of Patients losing greater than or equal to 5% body weight	62.3%	34.4%	49.0%	16.4%	44.2%	21.7%
Difference from placebo (LSMean) (95% CI)	27.9* (23.9;31.9)		32.6* (25.1;40.1)		22.6* (13.9;31.3)	
% of Patients losing greater than 10% body weight	33.9%	15.4%	22.4%	5.5%	25.4%	6.9%
Difference from placebo (LSMean) (95% CI)	18.5* (15.2;21.7)		16.9* (11.7;22.1)		18.5* (11.7;25.3)	

SD = Standard Deviation; CI = Confidence Interval

* $p < 0.0001$ compared to placebo. Type 1 error was controlled across the three endpoints.

Includes all randomized subjects who had a baseline body weight measurement. All available body weight data during the 56 week treatment period are included in the analysis. In Studies 1 and 2 missing values for week 56 were handled using multiple imputations analysis. In Study 3 missing values for week 56 were handled using weighted regression analysis.

The cumulative frequency distributions of change in body weight from baseline to week 56 are shown in Figure 2 for Studies 1 and 2. One way to interpret this figure is to select a change in body weight of interest on the horizontal axis and note the corresponding proportions of patients (vertical axis) in each treatment group who achieved at least that degree of weight loss. For example, note that the vertical line arising from -10% in Study 1 intersects the Saxenda and placebo curves at approximately 34% and 15%, respectively, which correspond to the values shown in Table 4.

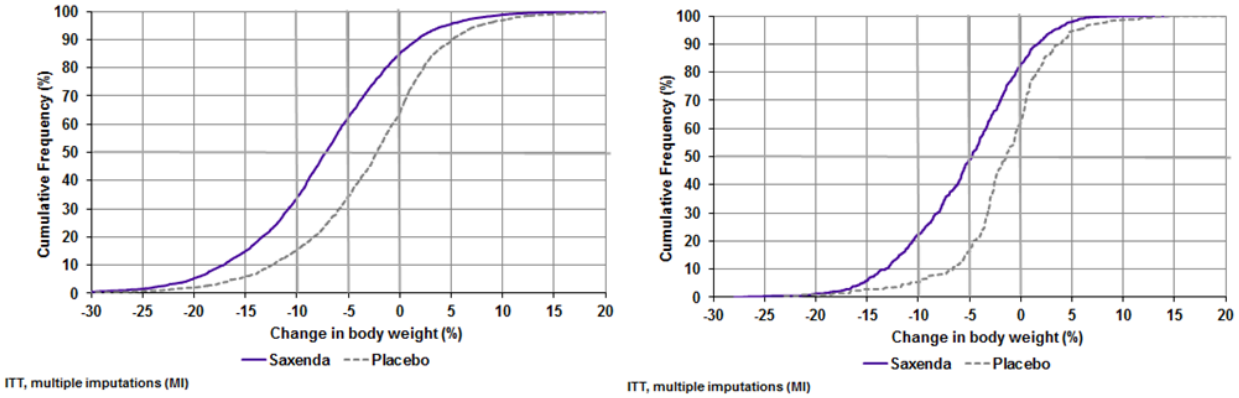


Figure 2. Change in body weight (%) from baseline to week 56 (Study 1 on left and Study 2 on right)

The time courses of weight loss with Saxenda and placebo from baseline through week 56 are depicted in Figures 3 and 4.

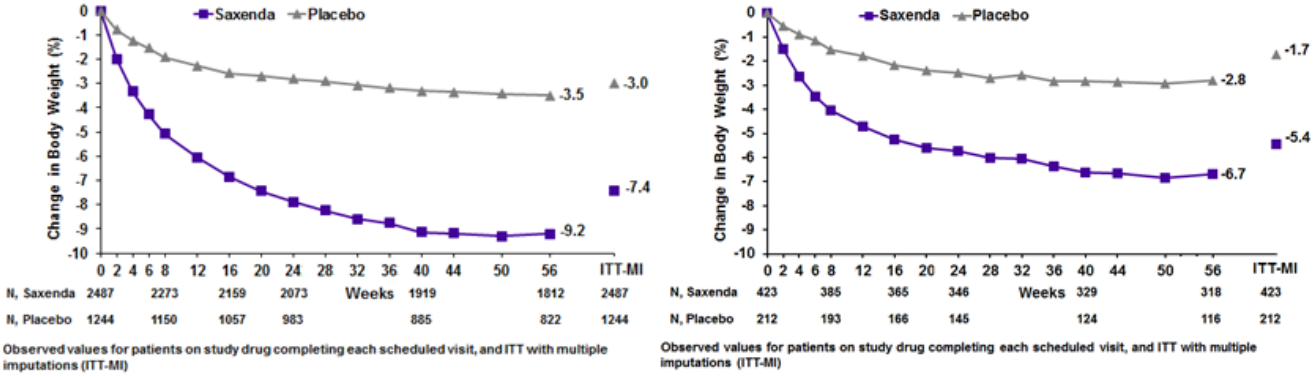
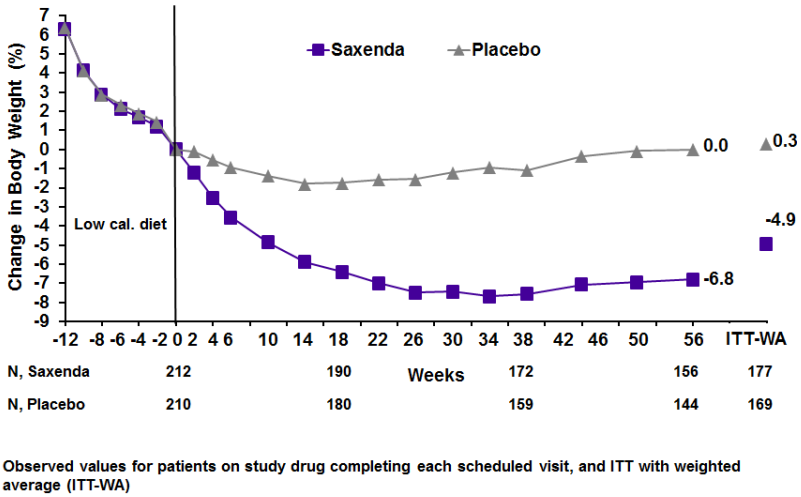


Figure 3. Change from baseline (%) in body weight (Study 1 on left and Study 2 on right)



Observed values for patients on study drug completing each scheduled visit, and ITT with weighted average (ITT-WA)

Figure 4. Change from baseline (%) in body weight during Study 3

Effect of Saxenda on Body Weight in a 160-week Trial (Study 1, Subset of Patients with Abnormal Blood Glucose at Randomization)

The numbers and percentages of patients known to have lost greater than or equal to 5% body weight at week 56 and/or week 160 in Study 1 (patients with abnormal glucose at randomization only) are summarized in Table 5 for descriptive purposes.

Table 5. Changes in Weight at Week 56 and Week 160 for Study 1 (Subset of Patients with Abnormal Blood Glucose at Randomization)

	Saxenda N=1505	**Placebo N=749**
Baseline mean body weight (SD) (kg)	107.5 (21.6)	107.9 (21.8)
Number (%) of patients known to lose greater than or equal to 5% body weight at 56 weeks	817 (56%)	182 (25%)
Number (%) of patients known to lose greater than or equal to 5% body weight at 160 weeks	424 (28%)	102 (14%)
Number (%) of patients known to lose greater than or equal to 5% body weight at both 56 weeks and 160 weeks	391 (26%)	74 (10%)
Number (%) of patients with weight assessment at 160 weeks	747 (50%)	322 (43%)

SD = Standard Deviation

Includes all randomized subjects who had a baseline body weight measurement. All available body weight data at 56 and 160 weeks are included in the analysis.

Effect of Saxenda on Anthropometry and Cardiometabolic Parameters in 56-week Trials

Changes in waist circumference and cardiometabolic parameters with Saxenda are shown in Table 6 for Study 1 (patients without diabetes mellitus) and Table 7 for Study 2 (patients with type 2 diabetes). Results from Study 3, which also enrolled patients without diabetes mellitus, were similar to Study 1.

Table 6. Mean Changes in Anthropometry and Cardiometabolic Parameters in Study 1 (Patients without Diabetes)

	Saxenda N = 2487		Placebo N = 1244		
	Baseline	**Change from Baseline (LSMean[1])**	**Baseline**	**Change from Baseline (LSMean[1])**	**Saxenda minus Placebo (LSMean)**
Waist Circumference (cm)	115.0	-8.2	114.5	-4.0	-4.2
Systolic Blood Pressure (mmHg)	123.0	-4.3	123.3	-1.5	-2.8
Diastolic Blood Pressure (mmHg)	78.7	-2.7	78.9	-1.8	-0.9
Heart Rate (bpm)	71.4	2.6	71.3	0.1	2.5
	Baseline	**% Change from Baseline (LSMean[1])**	**Baseline**	**% Change from Baseline (LSMean[1])**	**Relative Difference of Saxenda to Placebo (LSMean)**
Total Cholesterol (mg/dL)*	193.8	-3.2	194.4	-0.9	-2.3
LDL Cholesterol (mg/dL)*	111.8	-3.1	112.3	-0.7	-2.4
HDL Cholesterol (mg/dL)*	51.4	2.3	50.9	0.5	1.9
Triglycerides (mg/dL)†	125.7	-13.0	128.3	-4.1	-7.1

Based on last observation carried forward method while on study drug

[1] Least squares mean adjusted for treatment, country, sex, pre-diabetes status at screening, baseline BMI stratum and an interaction between pre-diabetes status at screening and BMI stratum as fixed factors, and the baseline value as covariate.

* Baseline value is the geometric mean

†Values are baseline median, median % change, and the Hodges-Lehmann estimate of the median treatment difference.

Table 7. Mean Changes in Anthropometry and Cardiometabolic Parameters in Study 2 (Patients with Diabetes Mellitus)

	Saxenda N = 423		Placebo N = 212		
	Baseline	**Change from Baseline (LSMean[1])**	**Baseline**	**Change from Baseline (LSMean[1])**	**Saxenda minus Placebo (LSMean)**
Waist Circumference (cm)	118.1	-6.0	117.3	-2.8	-3.2
Systolic Blood Pressure (mmHg)	128.9	-3.0	129.2	-0.4	-2.6
Diastolic Blood Pressure (mmHg)	79.0	-1.0	79.3	-0.6	-0.4
Heart Rate (bpm)	74.0	2.0	74.0	-1.5	3.4
	Baseline	**% Change from Baseline (LSMean[1])**	**Baseline**	**% Change from Baseline (LSMean[1])**	**Relative Difference of Saxenda to Placebo (LSMean)**
Total Cholesterol (mg/dL)*	171.0	-1.4	169.4	2.4	-3.7
LDL Cholesterol (mg/dL)*	86.4	0.9	85.2	3.3	-2.3
HDL Cholesterol (mg/dL)*	45.2	4.8	45.4	1.9	2.9
Triglycerides (mg/dL)†	156.2	-14.5	155.8	-0.7	-13.5

Based on last observation carried forward method while on study drug

[1] Least squares mean adjusted for treatment, country, sex, background treatment, baseline HbA_{1c} stratum and an interaction between background treatment and HbA_{1c} stratum as fixed factors, and the baseline value as covariate.
* Baseline value is the geometric mean
†Values are baseline median, median % change, and the Hodges-Lehmann estimate of the median treatment difference.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Saxenda is available in the following package sizes containing disposable, pre-filled, multi-dose pens. Each individual pen delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg or 3 mg (6 mg/mL, 3 mL).

3 x Saxenda pen NDC 0169-2800-13
5 x Saxenda pen NDC 0169-2800-15

Each Saxenda pen is for use by a single patient. A Saxenda pen should never be shared between patients, even if the needle is changed.

16.2 Recommended Storage

Prior to first use, Saxenda should be stored in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC) (Table 8). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze Saxenda and do not use Saxenda if it has been frozen.

After initial use of the Saxenda pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Saxenda should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the Saxenda pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy.

Table 8. Recommended Storage Conditions for Saxenda

Prior to first use	After first use	
Refrigerated 36°F to 46°F (2°C to 8°C)	Room Temperature 59°F to 86°F (15°C to 30°C)	Refrigerated 36°F to 46°F (2°C to 8°C)
Until expiration date	30 days	

17 PATIENT COUNSELING INFORMATION

FDA-Approved Medication Guide
Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Instructions
Saxenda is indicated for chronic weight management in conjunction with a reduced-calorie diet and increased physical activity.

Advise patients to take Saxenda exactly as prescribed. Patients should be instructed to follow the dose escalation schedule and not to take more than the recommended dose of Saxenda.

Instruct patients to discontinue use of Saxenda if they have not achieved 4% weight loss by 16 weeks of treatment.

Risk of Thyroid C-cell Tumors
Inform patients that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia or dyspnea) to their physician *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Acute Pancreatitis
Patients should be informed of the potential risk for acute pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue Saxenda promptly and contact their physician if persistent severe abdominal pain occurs.

Acute Gallbladder Disease
Patients should be informed that substantial or rapid weight loss can increase the risk of cholelithiasis. Cholelithiasis may also occur in the absence of substantial or rapid weight loss. Patients should be instructed to contact their physician if cholelithiasis is suspected for appropriate clinical follow-up.

Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Anti-Diabetic Therapy
Patients with type 2 diabetes mellitus on anti-diabetic therapy should be advised to monitor their blood glucose levels and report symptoms of hypoglycemia to their physician.

Heart Rate Increase
Patients should be informed to report symptoms of sustained periods of heart pounding or racing while at rest to their physician. For patients who experience a sustained increase in resting heart rate while taking Saxenda, Saxenda should be discontinued.

Dehydration and Renal Impairment
Patients treated with Saxenda should be advised of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Patients should be informed of the potential risk for worsening renal function, which in some cases may require dialysis.

Hypersensitivity Reactions
Patients should be informed that serious hypersensitivity reactions have been reported during use of liraglutide. If symptoms of hypersensitivity reactions occur, patients must stop taking Saxenda and seek medical advice promptly.

Suicidal Behavior and Ideation
Patients treated with Saxenda should be advised to report emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Patients should be informed that if they experience suicidal thoughts or behaviors, Saxenda should be discontinued.

Jaundice and Hepatitis
Inform patients that jaundice and hepatitis have been reported during postmarketing use of liraglutide. Instruct patients to contact their physician if they develop jaundice.

Never Share a Saxenda Pen Between Patients
Patients should be informed that they should never share a Saxenda pen with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.

Version: 4

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PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For information about Saxenda contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

1-844-363-4448

MEDICATION GUIDE

Saxenda (sax-end-ah)
(liraglutide) injection
solution for subcutaneous use

What is the most important information I should know about Saxenda?
Serious side effects may happen in people who take Saxenda, including:

Possible thyroid tumors, including cancer. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, Saxenda and medicines that work like Saxenda caused thyroid tumors, including thyroid cancer. It is not known if Saxenda will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.

Do not use Saxenda if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is Saxenda?

Saxenda is an injectable prescription medicine that may help some obese or overweight adults who also have weight related medical problems lose weight and keep the weight off.

- Saxenda should be used with a reduced calorie diet and increased physical activity.
- Saxenda is not for the treatment of type 2 diabetes mellitus.
- Saxenda and Victoza have the same active ingredient, liraglutide.
- Saxenda and Victoza should not be used together.
- Saxenda should not be used with other GLP-1 receptor agonist medicines.
- Saxenda and insulin should not be used together.
- It is not known if Saxenda is safe and effective when taken with other prescription, over-the-counter, or herbal weight loss products.
- It is not known if Saxenda changes your risk of heart problems or stroke or of death due to heart problems or stroke.
- It is not known if Saxenda can be used safely in people who have had pancreatitis.
- It is not known if Saxenda is safe and effective in children under 18 years of age. Saxenda is not recommended for use in children.

Who should not use Saxenda?

Do not use Saxenda if:

- you or any of your family have a history of medullary thyroid carcinoma.
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). This is a disease where people have tumors in more than one gland in their body.
- you are allergic to liraglutide or any of the ingredients in Saxenda. See the end of this Medication Guide for a complete list of ingredients in Saxenda.
    - Symptoms of a serious allergic reaction may include:
        - swelling of your face, lips, tongue, or throat
        - fainting or feeling dizzy
        - very rapid heartbeat
        - problems breathing or swallowing
        - severe rash or itching

Talk with your healthcare provider if you are not sure if you have any of these conditions.

- are pregnant or planning to become pregnant. Saxenda may harm your unborn baby.

Before taking Saxenda, tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions listed in the section “What is the most important information I should know about Saxenda?”
- are taking certain medications called GLP-1 receptor agonists.
- are allergic to liraglutide or any of the other ingredients in Saxenda. See the end of this Medication Guide for a list of ingredients in Saxenda.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- have or have had problems with your pancreas, kidneys or liver.
- have or have had depression or suicidal thoughts.
- are pregnant or plan to become pregnant. Saxenda may harm your unborn baby. Tell your healthcare provider if you become pregnant while taking Saxenda. If you are pregnant you should stop using Saxenda.
- are breastfeeding or plan to breastfeed. It is not known if Saxenda passes into your breast milk. You and your healthcare provider should decide if you will take Saxenda or breastfeed. You should not do both without talking with your healthcare provider first.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements. Saxenda slows stomach emptying and can affect medicines that need to pass through the stomach quickly. Saxenda may affect the way some medicines work and some other medicines may affect the way Saxenda works. Tell your healthcare provider if you take diabetes medicines, especially sulfonylurea medicines or insulin.

How should I use Saxenda?

- Use Saxenda exactly as prescribed by your healthcare provider. Your dose should be increased after using Saxenda for 1 week until you reach the 3 mg dose. After that, do not change your dose unless your healthcare provider tells you to.
- Saxenda is injected 1 time each day, at any time during the day.
- You can take Saxenda with or without food.
- Your healthcare provider should start you on a diet and exercise program when you start taking Saxenda. Stay on this program while you are taking Saxenda.
- Saxenda comes in a prefilled pen.
- Your healthcare provider must teach you how to inject Saxenda before you use it for the first time. If you have questions or do not understand the instructions, talk to your healthcare provider or pharmacist. Read the Patient Instructions for Use that come with this Medication Guide for detailed information about the right way to use your Saxenda pen.
- Pen needles are not included. Use the Saxenda pen with Novo Nordisk disposable needles. You may need a prescription to get pen needles from your pharmacist. Ask your healthcare provider which needle size is best for you.
- When starting a new prefilled Saxenda pen, you must follow the "Check the Saxenda flow with each new pen" (see the detailed Patient Instructions for Use that comes with this Medication Guide). You only need to do this 1 time with each new pen. You should also do this if you drop your pen. If you do the "Check the Saxenda flow with each new pen" before each injection, you will run out of medicine too soon.
- Inject your dose of Saxenda under the skin (subcutaneous injection) in your stomach area (abdomen), upper leg (thigh), or upper arm, as instructed by your healthcare provider. **Do not inject into a vein or muscle.**
- If you take too much Saxenda, call your healthcare provider right away. Too much Saxenda may cause severe nausea and vomiting.
- If you miss your daily dose of Saxenda, use Saxenda as soon as you remember. Then take your next daily dose as usual on the following day. Do not take an extra dose of Saxenda or increase your dose on the following day to make up for your missed dose. If you miss your dose of Saxenda for **3 days or more**, call your healthcare provider to talk about how to restart your treatment.
- Never share your Saxenda pen or needles with another person. You may give an infection to them, or get an infection from them.

What are the possible side effects of Saxenda?

- **Saxenda may cause serious side effects, including:possible thyroid tumors, including cancer.** See "What is the most important information I should know about Saxenda?"
- **inflammation of the pancreas** (**pancreatitis).** Stop using Saxenda and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **gallbladder problems.** Saxenda may cause gallbladder problems including gallstones. Some gallbladder problems need surgery. Call your healthcare provider if you have any of the following symptoms:
  - pain in your upper stomach (abdomen)
  - fever
  - yellowing of your skin or eyes (jaundice)
  - clay-colored stools
- **low blood sugar (hypoglycemia) in people with type 2 diabetes mellitus who also take medicines to treat type 2 diabetes mellitus.** Saxenda can cause low blood sugar in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus (such as sulfonylureas). In some people, the blood sugar may get so low that they need another person to help them. If you take a sulfonylurea medicine, the dose may need to be lowered while you use Saxenda. Signs and symptoms of low blood sugar may include:
  - shakiness
  - sweating
  - headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heartbeat
  - feeling jittery

Talk to your healthcare provider about how to recognize and treat low blood sugar. Make sure that your family and other people who are around you a lot know how to recognize and treat low blood sugar. You should check your blood sugar before you start taking Saxenda and while you take Saxenda.

- **increased heart rate.** Saxenda can increase your heart rate while you are at rest. Your healthcare provider should check your heart rate while you take Saxenda. Tell your healthcare provider if you feel your heart racing or pounding in your chest and it lasts for several minutes when taking Saxenda.
- **kidney problems (kidney failure).** Saxenda may cause nausea, vomiting or diarrhea leading to loss of fluids (dehydration). Dehydration may cause kidney failure which can lead to the need for dialysis. This can happen in people who have never had kidney problems before. Drinking plenty of fluids may reduce your chance of dehydration.

Call your healthcare provider right away if you have nausea, vomiting, or diarrhea that does not go away, or if you cannot drink liquids by mouth.

- **serious allergic reactions.** Serious allergic reactions can happen with Saxenda. Stop using Saxenda, and get medical help right away if you have any symptoms of a serious allergic reaction. See " **Who should not use Saxenda**".
- **depression or thoughts of suicide.** You should pay attention to any mental changes, especially sudden changes, in your mood, behaviors, thoughts, or feelings. Call your healthcare provider right away if you have any mental changes that are new, worse, or worry you.

The most common side effects of Saxenda include:

- nausea
- diarrhea
- constipation
- headache
- vomiting
- low blood sugar (hypoglycemia)
- decreased appetite
- upset stomach
- tiredness
- dizziness
- stomach pain
- change in enzyme (lipase) levels in your blood

Nausea is most common when first starting Saxenda, but decreases over time in most people as their body gets used to the medicine.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Saxenda. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Keep your Saxenda pen, pen needles, and all medicines out of the reach of children.

General information about the safe and effective use of Saxenda.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Saxenda for a condition for which it was not prescribed. Do not give Saxenda to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about Saxenda that is written for health professionals.

What are the ingredients in Saxenda?

Active ingredient: liraglutide

Inactive ingredients: disodium phosphate dihydrate, propylene glycol, phenol and water for injection

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

For information about Saxenda contact: Novo Nordisk Inc. 800 Scudders Mill Road, Plainsboro, NJ 08536 1-844-363-4448

Saxenda®, Victoza®, NovoFine®, and NovoTwist® are registered trademarks of Novo Nordisk A/S.

PATENT Information: http://novonordisk-us.com/patients/products/product-patents.html

For more information, go to saxenda.com or call 1-844-363-4448.

This Medication Guide has been approved by the U.S. Food and Drug Administration **Revised: SEPTEMBER 2016, VERSION 2**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206321/S-004

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	*See electronic stamp*
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	206321 / S-004
Applicant	Novo Nordisk Inc.
Date of Submission	27 June 2016
PDUFA Goal Date	27 April 2017
Proprietary Name / Established (USAN) names	Saxenda / liraglutide
Dosage forms / Strength	Solution for injection (6 mg/mL) / 3 mg subcut. daily
Proposed Indication	No Change
Recommended:	Approval

Material Reviewed/Consulted & Primary Reviewer(s)		
Medical Officer Review	19 Apr 2017	Julie Golden, MD
Statistical Review	31 Mar 2017	Alexander Cambon, PhD
Pharm/Tox Review	17 Feb 2017	Anthony Parola, PhD
OPDP Labeling Consult	28 Mar 2017	Ankur Kalola, PharmD

OPDP: Office of Prescription Drug Promotion

This memo summarizes the Division's regulatory action for a supplemental NDA that proposes addition of clinical trial data to Section 14 of Saxenda labeling. I am not aware of disagreements among the review team with respect to the final labeling, to which the applicant has agreed.

The basis for this submission is results from the pre-specified stratum of patients with pre-diabetes at randomization who were enrolled into a 3-year treatment phase of Trial 1839. The first year of this trial, during which change in weight was the primary endpoint, is already described in labeling since it was a pivotal trial for the initial approval of Saxenda. In the present submission, although the applicant did not propose a new indication for Saxenda, (b) (4)

Dr. Golden's clinical review and Dr. Cambon's statistical review are thorough, and I agree with their conclusions. Thus, I will only highlight very briefly the primary discussion points of this submission.

Patients with pre-diabetes at baseline were randomly assigned 2:1 to Saxenda or placebo. Pre-diabetes was defined as 1 or more of the following: HbA1c 5.7-6.4% and/or fasting plasma glucose (FPG) 100-125 mg/dL (inclusive) and/or oral glucose tolerance test (OGTT) with plasma glucose 140-199 mg/dL (inclusive) at 2 hours after challenge. Patients were treated with study drug for 160 weeks followed by a 12-week observational follow-up period, for a total trial duration of 172 weeks. Study drug was initiated at 0.6 mg daily and escalated by 0.6 mg every 7 days until the target 3 mg daily was reached. All patients had to be at the target dose of 3 mg daily by 35 days after randomization, at which time dose and dosing frequency was not to be changed at any time during the treatment period.

The primary endpoint was the proportion of patients with onset of T2DM at 160 weeks, defined as either HbA1c ≥6.5% and/or FPG ≥126 mg/dL, and/or OGTT 2-hour post-challenge PG ≥200 mg/dL. All assessments were to be confirmed by repeat measurements within 4 weeks. As discussed in Dr. Golden's review, the Division had disagreed with this endpoint in 2008 (pre-IND/EOP2 meeting), with

communications highlighting that it would be required to establish whether liraglutide delays, prevents, or simply masks the development of T2DM in patients with pre-diabetes.

In this subset of trial 1839, 2254 patients were randomized: 1505 to Saxenda and 749 to placebo. The mean age was ~47 years, 76% were women, 84% were white, 10% were black, 9% were Hispanic, mean fasting body weight was 108 kg, and mean BMI was 39 kg/m^2.

The proportion of patients withdrawn from the trial prior to week 160 was 47% for Saxenda and 55% for placebo. Unfortunately, patients who discontinued treatment prematurely and withdrew from the trial did not return for a landmark visit at week 160; therefore, analyses that consider measurements from retrieved dropouts could not be performed. The sponsor's primary and secondary analyses, excerpted from the statistical review below, suggest superiority of Saxenda over placebo with respect to time to T2DM onset and weight loss, but Dr. Cambon states that "[b]ecause of the high number of censored observations (50% of subjects were censored and were not assessed at the three-year landmark visit), results obtained from sensitivity analysis attempting to address this large a proportion of missing data may be questionable." Dr. Cambon notes that even at year 2, there was missing data with respect to weight loss for 41% and 50% of patients assigned to Saxenda and placebo, respectively (see Table 7, statistical review).

Table 6: Description of Sponsor Primary and Secondary Analysis Results

Endpoint	Arms	Analysis* Method	Treatment Ratio/Difference	UCL	LCL	P-Value
Time-to-T2DM Onset	Ratio Saxenda vs. placebo	Weibull	2.68	1.86	3.87	<.0001
% Weight Loss	Saxenda – Placebo	ANCOVA	4.32 %	3.70	4.94	<.0001
5% Weight Loss	Saxenda – Placebo		25.9%			<.0001

* All analyses in table are sponsor analyses. Because of the high amount of missing/censored data (~50%), methods to address missing data may be questionable. I therefore did not perform alternative sensitivity analysis. Note that sponsor analysis is based on FAS- all randomized subjects exposed to at least one dose of the trial product and with at least one post baseline assessment of any endpoint. We do not agree with this analysis population. All our efficacy analyses are based on all randomized subjects. Table 7 below shows descriptive statistics for 5% weight loss for 1, 2, and 3years, including missing data.

Dr. Golden notes that 26 (12.8%) of 1472 Saxenda-treated patients and 46 (6.2%) of 738 placebo-treated patients were diagnosed with T2DM up to 160 weeks.[1] She states, "The clinical significance of converting from pre-diabetes to diabetes based on biomarkers alone is unclear. It is also unclear if Saxenda is preventing or treating (underlying, masked) diabetes…." Later, she notes that during the 12-week off-treatment period, an additional 5 patients on Saxenda (31 vs. 26) and 1 patient on placebo (47 vs. 46) were diagnosed with T2DM, adding, "The increase in the number of patients who developed T2DM on Saxenda in just this short period of time off-drug (12 weeks) raises the question whether Saxenda is merely masking the development of T2DM, and whether the difference observed between groups is durable."

Given the degree of missingness, there was considerable discussion regarding whether any of the 3-year data would be acceptable for labeling. The statistical reviewers, including Division of Biometrics II management, favored only including descriptive categorical weight data, since one could assume that patients who discontinue early and do not have weight measurements at later time points are "non-responders." With respect to weight loss as a continuous variable, however, the statistical reviewers stated that the change in body weight cannot be reliably estimated over the 160-week period given the large amount of missing values; this would affect both tables and figures that present mean changes in weight over time. Thus, the following table was suggested for labeling by DB2:

[1] Denominators are the applicant's Full Analysis Set, i.e., randomized patients who received at least one dose of study drug and had at least one follow-up value. The statistical review team disagrees with this analysis population, favoring analyses that use all randomized patients.

Table 5: Changes in Weight at Week 56 and Week 160 (b) (4) for Study 1 ((b) (4) Patients with Abnormal Glucose at Baseline)

	Saxenda N=1505	Placebo N=749
Baseline mean body weight (SD) (kg)	107.5 (21.6)	107.9 (21.8)
Number (%) of patients known to lose greater than or equal to 5% body weight at 56 weeks	817 (56%)	182 (25%)
Number (%) of patients known to lose greater than or equal to 5% body weight at 160 weeks	424 (28%)	102 (14%)
Number (%) of patients known to lose greater than or equal to 5% body weight at both 56 weeks and 160 weeks	391 (26%)	74 (10%)
Number (%) of patients with weight assessment (b) (4) at 160 weeks	(b) (4)	

SD = Standard Deviation; Includes all randomized subjects who had a baseline body weight measurement. All available body weight data at 56 and 160 weeks are included in the analysis.

Source: Statistical Review, Section 5.2.

(b) (4)

Dr. Golden's review provides a thorough discussion of the safety of Saxenda in this 3-year stratum of trial 1839. She concludes that no new safety findings were identified in this review. She specifically discusses the following ongoing safety considerations: pancreatitis, acute gallstone disease, hypoglycemia, acute renal failure, psychiatric events, gastrointestinal events, cardiovascular events, and neoplasms. See her review for details; I concur with her conclusions. Labeling will be updated with appropriate safety information from this trial.

Taken together, Dr. Golden recommends (b) (4) She notes that the endpoint reflects changes in biomarkers for which the clinical relevance is uncertain in this population. "Because liraglutide is a glucose-lowering drug, and the diagnosis of diabetes is based on glucose/HbA1c thresholds, fewer patients taking liraglutide who reach these thresholds is expected. However, whether these changes can be expected to ultimately change the natural history of disease in these patients, particularly the micro- and macrovascular complications of diabetes over a long-term period, is unknown." Given this consideration as well as the limitations imposed by ~50% missingness at the end of the trial, I concur with her recommendations. Because the review team is amenable to including descriptive categorical data regarding weight loss from this trial, however, the supplement can be approved with the revised labeling as negotiated with the applicant.

Recommended Regulatory Action: Approval

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

/s/

JAMES P SMITH
04/25/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206321/S-004

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA SE8
Application Number	206321
Priority or Standard	Standard
Submit Date	June 24, 2016
Received Date	June 27, 2016
PDUFA Goal Date	April 27, 2017
Division / Office	DMEP/ODE II
Reviewer Name	Julie Golden, M.D.
Review Completion Date	March 24, 2017
Established Name	Liraglutide
Trade Name	Saxenda
Therapeutic Class	GLP-1 analog
Applicant	Novo Nordisk, Inc.
Formulation	Injection
Dosing Regimen	Daily
Indication	Chronic weight management
Intended Populations	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 that (b) (4)

1.2 Risk Benefit Assessment

The primary outcome of this trial was for the prevention or delay of type 2 diabetes mellitus in patients with overweight/obesity and pre-diabetes. The benefits of this outcome (above and beyond the benefits of weight loss) cannot be weighed against the risks for the following reasons:

- The endpoint reflects changes in biomarkers (blood glucose, HbA1c) for which the clinical relevance is uncertain in this population. Because liraglutide is a glucose-lowering drug, and the diagnosis of diabetes is based on glucose/HbA1c thresholds, fewer patients taking liraglutide who reach these thresholds is expected. However, whether these changes can be expected to ultimately change the natural history of disease in these patients, particularly the micro- and macrovascular complications of diabetes over a long-term period, is unknown.

- It is unclear if treatment with Saxenda is preventing or rather masking the development of diabetes in patients with pre-diabetes. It is noted that upon a relatively short period of drug discontinuation, more patients on Saxenda reverted to diabetes, which suggests the latter.

- The substantial amount of missing data in this trial (approximately 50 percent of patients prematurely discontinued prior to the 160 week endpoint measurement) suggests that the trial findings are unreliable. Patients who complete the trial are likely different than those who drop-out, with respect to both measured and unmeasured variables. In addition, these populations (completers and drop-out) are likely different among treatment groups. Therefore, the ability to conduct a randomized comparison is lost (e.g., comparison of completers in each group). The impact of missing data on the interpretation of trial results has been a particular focus of the Agency over the past several years since the National Academy of Science's publication of *The Prevention and Treatment of Missing Data in Clinical Trials* (2010).

(b) (4)

(b) (4)

The sponsor has not proposed a new indication for Saxenda.

I recommend that some descriptive data be included in Section 14 of the label regarding long-term weight changes, acknowledging that the degree of missing data does not allow for a confident assessment of the true treatment effect after 1 year.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Liraglutide is an analog of human GLP-1 and acts as a GLP-1 receptor agonist. It is approved in the U.S. at doses of 1.2 mg and 1.8 mg for the management of diabetes mellitus (Victoza) and at a dose of 3 mg for the management of obesity (Saxenda). Saxenda is presented as a solution for injection. Each pre-filled pen contains a 3 mL solution equivalent to 18 mg liraglutide.

2.2 Tables of Currently Available Treatments for Proposed Indications

See the original clinical NDA review; information is unchanged.

2.3 Availability of Proposed Active Ingredient in the United States

See Section 2.1, Product Information.

2.4 Important Safety Issues With Consideration to Related Drugs

See discussion in the original clinical NDA review. To my knowledge, no new safety issues have arisen in the GLP-1 receptor agonist class generally, or with liraglutide specifically, since the Saxenda approval.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- At the pre-IND/End-of-Phase 2 (EOP2) meeting March 10, 2008, the following question was asked by the sponsor:

  Is the approach and trial design of the NN8022-1839 trial, as is described in this briefing package, adequate and sufficient in scope, to yield data for the prospectively defined endpoints and profiles, (b) (4)

  FDA responded in pre-meeting comments:

  (b) (4)

(b) (4)

Data from the 1-year trial from 1839 was submitted to the original NDA in support of the approval of Saxenda for weight management. This included patients who had normoglycemia and who had pre-diabetes (only the patients with pre-diabetes continued in the extension trial).

- The following post-marketing requirement (PMR) based on the 1839 extension trial was agreed to at the time of Saxenda approval:

  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.

2.6 Other Relevant Background Information

(b) (4)

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, this submission was of good quality. Items that were not provided in the original submission – such as efficacy and safety by demographic subgroup – were provided upon request in a reasonable timeframe.

2 Aggregate microvascular disease is defined as the average prevalence of 3 components: (1) retinopathy measured by photography (ETDRS of 20 or greater); (2) neuropathy detected by Semmes Weinstein 10 gram monofilament, and (3) nephropathy based on eGFR by CKD-Epi (<45 ml/min, confirmed) and albumin-to-creatinine ratio in spot urine (> 30mg/gm, confirmed)
3 Aroda VR Edelstein SL Goldberg RB Knowler WC Marcovina SM Orchard TJ Bray GA Schade DS Temprosa MG White NH Crandall JP Diabetes Prevention Program Research Group. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. *J Clin Endocrinol Metab.* 2016;101(4):1754-61.

3.2 Compliance with Good Clinical Practices

The trial was conducted in accordance with Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice. The 21 Code of Federal Regulations (CFR), parts 312, 50, and 56 were followed, and the trial was conducted in accordance with FDA 21 CFR 312.120.

The protocol, protocol amendments, consent forms, subject information sheets and other materials handed out to patients were reviewed and approved according to local regulations by appropriate health authorities. They were also reviewed and approved by an independent ethics committee (IEC)/institutional review board (IRB).

Although the trial was double-blinded, it is noted that the sponsor was unblinded after the 1-year portion of the trial.

Additionally, for 16 patients with pre-diabetes stratified to 3 years of treatment, potential unblinding occurred because the central laboratory released the PK profile reports to the sites and it could not be ruled out whether the information was disclosed to the affected patients. Potential unblinding also occurred for 9 patients with pre-diabetes who were enrolled at site 469 where the principal investigator was signatory investigator of the clinical study report (CSR) for the 1-year part of the trial. The signatory investigator received the CSR including appendices (which include patient details and treatment allocation) for review and it could not be ruled out whether the information was disclosed to the affected patients.

Some patients were randomized to the wrong stratum in the trial. This caused patients without pre-diabetes to be stratified to 160 weeks of treatment and patients with pre-diabetes to inclusion into the re-randomized trial period after 56 weeks of treatment (1-year part of the trial). The vast majority (approximately 90%) of the incorrect stratifications were corrected by re-stratification to the correct stratum before visit 17 (week 56) was completed. However, 6 patients without pre-diabetes participated in the 3-year part of the trial and 37 patients with pre-diabetes were re-randomized and included in the report for the 1-year part of the trial. The sponsor conducted a sensitivity analysis that included the 37 patients who were re-randomized and excluded the 6 patients without pre-diabetes.

3.3 Financial Disclosures

Out of 73 investigators, 6 had disclosable financial interests (8.2%). All 6 investigators were from the U.S. (out of 43 U.S. investigators total, 14.0%). These 6 investigators contributed 133 out of 2254 randomized patients (5.9%).

Table 1. Financial Disclosure Form

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 73		
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): 6		
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: 6 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)

Source: Financial Disclosure Summary Table and FDA Form 3455 (US)

Table 2. Investigators with Financial Interest Disclosures

Site No.	Name of Investigator	Role	No. Patients Screened	No. Patients Randomized	Disclosable Financial Interest		
					Explanation	Amount	Date
[redacted]							

(b) (6)

Source: FDA Form 3455 (US), Table for Financial Disclosure Review and Table Significant Payments Other Sorts

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new chemistry, clinical microbiology, nonclinical, or clinical pharmacology information was provided in this supplement.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3. Tabular Listing of Clinical Trials

Trial ID Country	Type of study	Trial design; Type of control	Test drugs and route of administration	Number of exposed subjects (males/females randomised)	Type of subjects	Treatment duration	Study status Type of report Location
NN8022-1839 AT, AU, BE, BR, CA, CH, DE, DK, ES, FI, FR, GB, HK, HU, IE, IL, IN, IT, MX, NL, NO, PL, RS, RU, TR, US, ZA	Efficacy and safety	Multi-centre, multi-national, randomised, double-blind, parallel-group trial Placebo control	Liraglutide: once-daily s.c. doses of 3.0 mg, dose-escalated in weekly increments of 0.6 mg	3723 (803/2928) **1-year part (56 weeks)** Liraglutide 3.0 mg: 2481 Placebo:1242 **Re-randomised period (12 weeks)** Cont. liraglutide 3.0 mg: 351 Cont. placebo:304 Switched from liraglutide 3.0 mg to placebo: 350	Obese, overweight with co-morbidities	56 weeks + 12-week re-randomised period	Complete; Full; seq 00, M 5.3.5.1
				3-year part (160 weeks) Liraglutide 3.0 mg: 1505 Placebo:749	Pre-diabetic, obese, overweight with co-morbidities	160 weeks	Complete; Full; M 5.3.5.1

Source: Tabular listing of all clinical studies

5.2 Review Strategy

This supplement review focuses primarily on the results in the pre-diabetes population from the 3-year part of study 1839. See Section 7.1.1 for more details on additional data reviewed to support Saxenda safety.

5.3 Discussion of Individual Studies/Clinical Trials

The efficacy supplement is based on the results of the 3-year part of study 1839. Sections 6 and 7 of this review discuss the efficacy and safety results from that trial in detail.

6 Review of Efficacy

Efficacy Summary

This supplement [redacted] (b) (4) was based on a single 3-year/160-week trial that evaluated a stratified subset of patients with pre-diabetes from an original, larger trial (1839, see the original NDA review). The primary endpoint was the proportion of Saxenda- vs. placebo-treated patients with onset of T2DM at 160 weeks. Secondary endpoints [redacted] (b) (4)

At screening or baseline, the average age of the trial population was 47.5 years, 76.0% were women, mean fasting body weight was 107.6 kg, mean BMI was 38.8 kg/m^2, 83.6% were white, 9.6% were black, 5.1% were Asian, 9.4% were Hispanic, and 41.7% were residents of the United States.

A total of 2254 patients were randomized to 160 weeks of treatment; 1505 to Saxenda and 749 to placebo. The proportion of patients withdrawn prior to week 160 was 47.4% in the Saxenda group and 55.0% in the placebo group.

[The efficacy results in this document are taken from the sponsor's submission; please see the statistical review (Dr. Cambon) for FDA analyses and discussion of statistical issues.]

At week 160, 26 (1.8%) patients treated with Saxenda and 46 (6.2%) patients treated with placebo met the primary endpoint of development of T2DM. During the 12-week off-treatment period (172-week time point), an additional 5 patients on Saxenda (31 vs. 26) and 1 patient on placebo (47 vs. 46) were diagnosed with T2DM.

Patients randomized to Saxenda lost an average of 4.8% body weight and those randomized to placebo 2.6% [treatment difference (95% CI) -2.2% (-3.13, -1.27)]. The proportion of patients with ≥ 5% weight loss at week 160 was 47% for Saxenda-treated patients and 35% for placebo-treated patients, and with ≥ 10% weight loss, 25% and 17%, respectively.

Placebo-subtracted mean change (95% CI) in HDL-cholesterol was +1.0% (-0.6, +2.7), in LDL-C -2.0% (-4.3, +0.4), and in total cholesterol -1.8% (-3.3, -0.2). Placebo-subtracted median percent change (95% CI) in triglycerides was -5.0% (-8.3, -1.8).

6.1 Indication

The sponsor has not proposed any change to the currently approved weight management indication. [redacted] (b) (4)

(b) (4)

6.1.1 Methods

Trial 1839 was a randomized, double-blind (investigators and patients were blinded; Novo Nordisk was unblinded after 1 year), placebo-controlled, parallel-group, multicenter, multinational trial in patients with obesity or overweight with co-morbidities; patients enrolled in the 3-year portion of the trial were diagnosed with pre-diabetes at randomization. See the original clinical NDA review for a discussion of the main 1839 trial design, including patients with and without pre-diabetes.

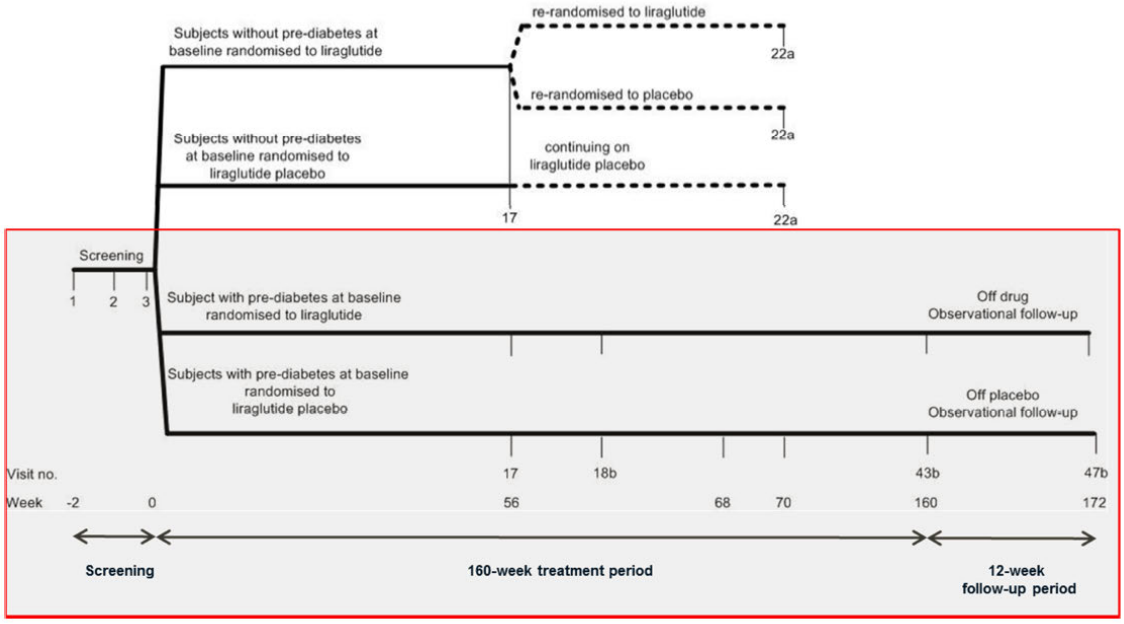
Patients were randomized in a 2:1 manner to treatment with Saxenda or placebo, and the randomization was stratified based on screening pre-diabetes status and baseline body mass index (BMI) (≥ 30 kg/m^2, < 30 kg/m^2).

Pre-diabetes was diagnosed if 1 of the following was true:

- HbA1c 5.7−6.4% and/or
- Fasting plasma glucose (FPG) ≥ 100 mg/dL and ≤ 125 mg/dL and/or
- Oral glucose tolerance test (OGTT) PG at 2-hour post-challenge ≥ 140 mg/dL and ≤ 199 mg/dL

Patients classified at screening as having pre-diabetes were randomized to receive either Saxenda or placebo for 160 weeks, followed by a 12-week off-drug/placebo observational follow-up period, for a total trial duration of 172 weeks. Patients consented to the 3-year part of the trial at randomization.

Figure 1. Trial Design



Note: In the figure liraglutide is liraglutide 3.0 mg and liraglutide placebo is placebo.

This report covers the 3-year part of the trial and the 12-week off drug-placebo observational period for subjects with pre-diabetes at randomisation (highlighted in red box).

Data for all subjects (with or without pre-diabetes at randomisation) up to week 56 as well as from the re-randomised period (subjects without pre-diabetes) were covered in the CTR for the 1-year part of the trial.

Source: 1839-3y CSR, Figure 9-1

In order to reduce dose-related gastrointestinal side effects, patients followed a fixed dose escalation. The dose was gradually escalated to 3 mg starting with 0.6 mg and 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 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 was not to be changed at any time during the treatment period. If any dose was missed by the patient up to and including 3 consecutive days, it was to be documented in the medical record and the investigator discussed the importance of treatment compliance with the patient. After a potential trial drug discontinuation of up to 3 days, the patient was to re-initiate trial drug at the target dose. Missed doses for more than 3 consecutive days were discussed with the sponsor and it was up to the investigator's judgment if the patient could continue on the target dose or was to be withdrawn.

If the investigator suspected acute pancreatitis, all suspected drugs were to be discontinued until confirmatory tests had been conducted. If tests revealed that a

patient did not have acute pancreatitis, the patient could remain in the trial with re-initiation of titration until the target dose was reached.

Rescue criteria applied to patients who developed T2DM during the trial. If a self-measured FPG on 3 consecutive days/occasions or measured in the central laboratory exceeded the limits set below, the patient was to contact the investigator and attend an unscheduled visit as soon as possible:

- From baseline to week 6: FPG > 270 mg/dL
- From week 7 to week 12: FPG > 240 mg/dL
- From week 13 to week 160: FPG > 200 mg/dL (or HbA1c > 8% if measured in the central laboratory)

A new FPG was to be obtained and analyzed by the central laboratory and if this value exceeded the limits, then the background medication was initially to be escalated to the maximum approved dose. If this was insufficient to achieve glycemic control, then 1 of the other allowed anti-diabetic treatments was to be added.

Assessment of Efficacy

The primary endpoint was the proportion of patients with onset of T2DM at 160 weeks. Patients were diagnosed with T2DM based on the following criteria:

- $HbA_{1c} \geq 6.5\%$ and/or
- FPG ≥ 126 mg/dL and/or
- OGTT 2-hour post-challenge PG ≥ 200 mg/dL

All assessments were to be confirmed by repeated measurements within 4 weeks. The date of diagnosis was to be filled out on the Diabetes Diagnosis Information form in the eCRF.

No subsequent OGTTs were to be performed for patients with confirmed diagnosis of T2DM, however FPG, fasting insulin, and fasting C-peptide were to be taken at pre-specified visits as a regular laboratory visit sample.

The pre-specified endpoints are shown in Table 4. (b) (4) Pre-specified analyses using last observation carried forward (LOCF) were presented in the clinical study report. For the most part, the efficacy review focuses on the analyses presented in the SCE; these analyses are discussed further in Sections 6.1.4, 6.1.5, and 6.1.6.

Table 4. Pre-specified Efficacy Endpoints in Trial 1839 (3-year)

Endpoints	Week 160	Week 172	(b) (4)
Onset of T2DM			
Time to onset of T2DM	X (primary)	X	
Proportion of patients with T2DM (yes/no)	X	X	
Proportion of patients with normoglycemia	X		
Body weight-related			
Absolute and relative change from baseline in fasting body weight	X	X	
Proportion of patients losing ≥ 5% of baseline fasting body weight	X		
Proportion of patients losing > 10% pf baseline fasting body weight	X		
Absolute change from baseline in waist circumference	X	X	
Absolute change from baseline in BMI	X		
Relative change from baseline in excess body weight (BMI -25)	X		
Glycemic control parameters			
Absolute change from baseline in HbA1c	X	X	
Absolute change from baseline in FPG	X		
Change from baseline in AUC of plasma glucose during OGTT	X		
Change from baseline in AUC of incremental plasma glucose during OGTT	X		
Relative change from baseline in AUC of C-peptide during OGTT	X		
Relative change from baseline in AUC of incremental C-peptide during OGTT	X		
Relative change from baseline in AUC of insulin during OGTT	X		
Relative change from baseline in AUC of incremental insulin during OGTT	X		
Fasting insulin	X		
Fasting C-peptide	X		
Beta-cell function (HOMA)	X		
Insulin resistance (HOMA)	X		
Vital signs			
Absolute change from baseline in SBP	X	X	
Absolute change from baseline in DBP	X	X	
Cardiovascular biomarkers			
Relative change from baseline in hsCRP	X		
Relative change from baseline in adiponectin	X		
Relative change from baseline in fibrinogen at wk 160	X		
PAI-1	X		
Lipid-related endpoints			
Relative change from baseline in total cholesterol	X		
Relative change from baseline in LDL-cholesterol	X		
Relative change from baseline in HDL-C	X		
Relative change from baseline in VLDL-C	X		
Relative change from baseline in triglycerides	X		
Relative change from baseline in FFA	X		
UACR			
Relative change from baseline in UACR	X	X	
PRO			
Absolute change from baseline in sub & total score of IWQOL-Lite	X		
Absolute change from baseline in sub & total score of SF-36	X		
Sub-scores and total score of TRIM-W	X		
Concomitant medication			
Change from baseline in anti-hypertensive drugs	X		
Change from baseline in lipid-lowering drugs	X		
Change from baseline in oral anti-diabetic drugs	X		

Source: Summary of Clinical Efficacy, Table 1-2

6.1.2 Demographics

Overall, the Saxenda and placebo groups were well matched with respect to demographic and baseline characteristics. The average age of all patients was 47.5 years; 66.5% were 40-65 years of age and 26.5% were 18-40 years of age; 76.0% of all patients were women.

At screening, the mean fasting body weight was 107.6 kg and the mean BMI was 38.8 kg/m^2, with 2.8% of patients with BMI 27.0-29.9 kg/m^2, 27.7% BMI 30.0-34.9 kg/m^2, 32.7% BMI 35.0-39.9 kg/m^2, and 36.9% BMI >40 kg/m^2.

None of the patients had T2DM at randomization based on the diagnostic criteria, although maximum HbA1c and FPG values within the diabetes range are noted (Table 5). All patients had pre-diabetes at screening, except 6 patients who were normoglycemic and randomized in error. Baseline HbA1c and FPG were similar between groups.

Most (83.6%) of the trial population was white, 9.6% were black or African American, 5.1% Asian, 0.3% American Indian or Alaskan native, <0.1% Native Hawaiians or other Pacific Islanders, and 1.3% 'Other'. A total of 9.4% of patients were Hispanic or Latino and 41.7% were residents of the United States.

At baseline, no major differences between the 2 treatment groups were observed for history of dyslipidemia, hypertension, history of gallbladder disease, cardiovascular disease, or history of psychiatric disorders.

Table 5. Demographics and Baseline Characteristics

	Lira 3.0 mg	Placebo	Total
Number of subjects	1505	749	2254
Age (yrs)			
N	1505	749	2254
Mean (SD)	47.5 (11.7)	47.3 (11.8)	47.5 (11.7)
Median	48.0	48.0	48.0
Min; Max	18.0 ; 78.0	18.0 ; 77.0	18.0 ; 78.0
Height (m)			
N	1505	749	2254
Mean (SD)	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)
Median	1.65	1.65	1.65
Min; Max	1.34 ; 2.03	1.44 ; 1.93	1.34 ; 2.03
HbA1c (%)			
N	1504	749	2253
Mean (SD)	5.8 (0.3)	5.7 (0.3)	5.7 (0.3)
Median	5.7	5.7	5.7
Min; Max	4.5 ; 6.8	4.2 ; 6.8	4.2 ; 6.8
Fasting BW (kg)			
N	1499	745	2244
Mean (SD)	107.5 (21.6)	107.9 (21.8)	107.6 (21.6)
Median	104.5	104.0	104.4
Min; Max	65.2 ; 234.3	62.9 ; 197.9	62.9 ; 234.3
BMI (kg/^m2)			
N	1505	749	2254
Mean (SD)	38.8 (6.4)	39.0 (6.3)	38.8 (6.4)
Median	37.8	38.2	37.9
Min; Max	27.0 ; 77.2	27.3 ; 60.0	27.0 ; 77.2
FPG (mmol/L)			
N	1505	749	2254
Mean (SD)	5.5 (0.6)	5.5 (0.5)	5.5 (0.6)
Median	5.4	5.4	5.4
Min; Max	4.1 ; 10.6	3.7 ; 7.7	3.7 ; 10.6
Fasting Plasma Glucose (mg/dL)			
N	1505	749	2254
Mean (SD)	99.1 (11.1)	98.4 (9.8)	98.8 (10.7)
Median	97.3	97.3	97.3
Min; Max	73.9 ; 191.0	66.7 ; 138.7	66.7 ; 191.0

	Lira 3.0 mg N	(%)	Placebo N	(%)	Total N	(%)
Number of subjects	1505		749		2254	
Age group						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
18-40yrs	395	(26.2)	202	(27.0)	597	(26.5)
40-65yrs	1005	(66.8)	493	(65.8)	1498	(66.5)
65-75yrs	99	(6.6)	53	(7.1)	152	(6.7)
>75yrs	6	(0.4)	1	(0.1)	7	(0.3)
Sex						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Female	1141	(75.8)	573	(76.5)	1714	(76.0)
Male	364	(24.2)	176	(23.5)	540	(24.0)
Ethnicity						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Hispanic or Latino	143	(9.5)	70	(9.3)	213	(9.4)
Not Hispanic or Latino	1362	(90.5)	679	(90.7)	2041	(90.6)
Race						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
White	1256	(83.5)	628	(83.8)	1884	(83.6)
Black or African American	146	(9.7)	71	(9.5)	217	(9.6)
Asian	75	(5.0)	39	(5.2)	114	(5.1)
American Indian or Alaska Native	5	(0.3)	2	(0.3)	7	(0.3)
Native Hawaiian or Oth. Pacific Islander	1	(<0.1)	1	(0.1)	2	(<0.1)
Other	22	(1.5)	8	(1.1)	30	(1.3)
Smoker status						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Current Smoker	217	(14.4)	124	(16.6)	341	(15.1)
Never Smoked	886	(58.9)	432	(57.7)	1318	(58.5)
Previous Smoker	402	(26.7)	193	(25.8)	595	(26.4)
BMI (kg/m^2)						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
27.0-29.9 kg/m2 - Overweight	39	(2.6)	23	(3.1)	62	(2.8)
30.0-34.9 kg/m2 - Obesity class I	427	(28.4)	197	(26.3)	624	(27.7)
35.0-39.9 kg/m2 - Obesity class II	492	(32.7)	245	(32.7)	737	(32.7)
≥40.0 kg/m2 - Obesity class III	547	(36.3)	284	(37.9)	831	(36.9)
History of CV disease (eCRF)						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Yes	682	(45.3)	336	(44.9)	1018	(45.2)
No	793	(52.7)	393	(52.5)	1186	(52.6)
Not Known	29	(1.9)	20	(2.7)	49	(2.2)
Not Applicable	1	(<0.1)	0	(0.0)	1	(<0.1)
History of CV disease (SMQ search)						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Yes	191	(12.7)	99	(13.2)	290	(12.9)
No	1314	(87.3)	650	(86.8)	1964	(87.1)

	Lira 3.0 mg N	(%)	Placebo N	(%)	Total N	(%)
History of gallbladder disease						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Yes	208	(13.8)	112	(15.0)	320	(14.2)
No	1286	(85.4)	632	(84.4)	1918	(85.1)
Not Known	11	(0.7)	4	(0.5)	15	(0.7)
Not Applicable	0	(0.0)	1	(0.1)	1	(<0.1)
Dyslipidaemia						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Yes	499	(33.2)	249	(33.2)	748	(33.2)
No	1006	(66.8)	500	(66.8)	1506	(66.8)
Hypertension						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Yes	635	(42.2)	312	(41.7)	947	(42.0)
No	870	(57.8)	437	(58.3)	1307	(58.0)
Both dyslipidaemia and hypertension						
N	1505	(100.0)	749	(100.0)	2254	(100.0)
Yes	317	(21.1)	156	(20.8)	473	(21.0)
No	1188	(78.9)	593	(79.2)	1781	(79.0)

N: Number of subjects, %: Percentages are based on N, BMI: Body mass index
History of CV disease is based on the eCRF form history of concomitant cardiovascular disease and by SMQ search of the medical history including Ischaemic heart disease, Cardiac failure, Central nervous system haemorrhages, Cerebovascular conditions and Embolic and thrombotic events. History of gallbladder disease is based on the eCRF form history of gallbladder disease. Dyslipidaemia is found by SMQ search of the medical history. Hypertension is found by SMQ search of the medical history.
Percentages less than 0.09 are displayed as <0.1.

Source: 1839-3y CSR, Tables 10-2 and 10-3

6.1.3 Subject Disposition

A total of 2254 patients were randomized to 160 weeks of treatment; 1505 to Saxenda and 749 to placebo. Of these, 1501 patients were exposed to Saxenda and 747 were exposed to placebo.

A total of 1128 (50.0%) patients completed 160 weeks of treatment and 1110 (49.2%) completed 172 weeks of the trial (including the 12 week follow-up period).

Table 6. Disposition of Trial 1839, Summary

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Total Randomised*	2487	1244	3731
Randomised (without pre-diabetes)**	959	487	1446
Randomised (with pre-diabetes)	1528	757	2285
Randomised, 3 year report population***	1505 (100.0)	749 (100.0)	2254 (100.0)
Exposed	1501 (99.7)	747 (99.7)	2248 (99.7)
Completer week 56****	1086 (72.2)	497 (66.4)	1583 (70.2)
Completer week 160	791 (52.6)	337 (45.0)	1128 (50.0)
Full analysis set week 160	1472 (97.8)	738 (98.5)	2210 (98.0)
Safety analysis set week 160	1501 (99.7)	747 (99.7)	2248 (99.7)
Entered off drug period	787 (52.3)	336 (44.9)	1123 (49.8)
Completer week 172	783 (52.0)	327 (43.7)	1110 (49.2)
Full analysis set follow-up	783 (52.0)	326 (43.5)	1109 (49.2)

* Includes patients with and without pre-diabetes at randomisation.
** Per the protocol, patients without pre-diabetes at randomisation were only eligible for the 56 week period of the trial. The disposition for these patients was included in the 1-year clinical trial report.
*** Randomised subjects with pre-diabetes, except the 37 subjects with pre-diabetes that went into the re-randomised period of the 1-year part and 6 subjects with normoglycaemia who entered the 3-year part.
**** Subjects with pre-diabetes that continued in the three year part after completion of the first year.
N: Number of subjects, %: Percentages are based on total N in 3 year report population
Table is based on trial 1839 (1-year and 3-year part).

Source: ISE, Table 1

Table 7. Reasons for Premature Withdrawal

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Randomised	1505 (100.0)	749 (100.0)	2254 (100.0)
Exposed	1501 (99.7)	747 (99.7)	2248 (99.7)
Completer w160	791 (52.6)	337 (45.0)	1128 (50.0)
Withdrawn before w160	714 (47.4)	412 (55.0)	1126 (50.0)
Adverse event	191 (12.7)	43 (5.7)	234 (10.4)
Ineffective therapy	29 (1.9)	36 (4.8)	65 (2.9)
Non-compliance with protocol	73 (4.9)	34 (4.5)	107 (4.7)
Withdrawal criteria	360 (23.9)	249 (33.2)	609 (27.0)
Withdrawn consent	324 (21.5)	233 (31.1)	557 (24.7)
Target dose not tolerated	1 (0.1)	0 (0.0)	1 (0.0)
Pregnancy or pregnancy intent	31 (2.1)	12 (1.6)	43 (1.9)
Use of insulin, GLP1RA or DPP4i	0 (0.0)	2 (0.3)	2 (0.1)
Acute pancreatitis	7 (0.5)	1 (0.1)	8 (0.4)
Psychiatric disorder (INV/MHP opinion)	1 (0.1)	2 (0.3)	3 (0.1)
Calcitonin >=50 ng/L (France)	0 (0.0)	0 (0.0)	0 (0.0)
AE withdrawals total w160	200 (13.3)	46 (6.1)	246 (10.9)
Other	60 (4.0)	50 (6.7)	110 (4.9)
Missing reason for disc.	1 (0.1)	0 (0.0)	1 (0.0)
Full analysis set w160	1472 (97.8)	738 (98.5)	2210 (98.0)
Safety analysis set w160	1501 (99.7)	747 (99.7)	2248 (99.7)
Entered off drug period	787 (52.3)	336 (44.9)	1123 (49.8)
Completer w172	783 (52.0)	327 (43.7)	1110 (49.2)
Withdrawn before w172	722 (48.0)	422 (56.3)	1144 (50.8)
Adverse event	191 (12.7)	43 (5.7)	234 (10.4)
Ineffective therapy	29 (1.9)	36 (4.8)	65 (2.9)
Non-compliance with protocol	76 (5.0)	36 (4.8)	112 (5.0)
Withdrawal criteria	364 (24.2)	256 (34.2)	620 (27.5)
Withdrawn consent	328 (21.8)	240 (32.0)	568 (25.2)
Target dose not tolerated	1 (0.1)	0 (0.0)	1 (0.0)
Pregnancy or pregnancy intent	31 (2.1)	12 (1.6)	43 (1.9)
Use of insulin, GLP1RA or DPP4i	0 (0.0)	2 (0.3)	2 (0.1)
Acute pancreatitis	7 (0.5)	1 (0.1)	8 (0.4)
Psychiatric disorder (INV/MHP opinion)	1 (0.1)	2 (0.3)	3 (0.1)
Calcitonin >=50 ng/L (France)	0 (0.0)	0 (0.0)	0 (0.0)
AE withdrawals total w172	200 (13.3)	46 (6.1)	246 (10.9)
Other	61 (4.1)	51 (6.8)	112 (5.0)
Missing reason for disc.	1 (0.1)	0 (0.0)	1 (0.0)
Full analysis set follow-up	783 (52.0)	326 (43.5)	1109 (49.2)

AE: Adverse event, INV: Investigator, MHP: Mental health professional, N: Number of subjects, %: Proportion of randomised subjects.
The tabulated reason for withdrawal is the primary reason for withdrawal registered in the eCRF. AE withdrawals (total) include subjects withdrawn due to adverse events or target dose not tolerated, or the withdrawal criteria for acute pancreatitis or psychiatric disorder.
A subject can have more than one reason for withdrawal.

Source: 1839-3y CSR, Table 10-1

6.1.4 Analysis of Primary Endpoint

The primary endpoint was the proportion of patients with onset of T2DM at week 160, assessed as time to onset of T2DM. At week 160, 26 patients treated with Saxenda and 46 patients treated with placebo had developed T2DM; see Table 8 and the Kaplan-Meier curve in Figure 2.

Table 8. Patients Diagnosed with T2DM up to 160 weeks

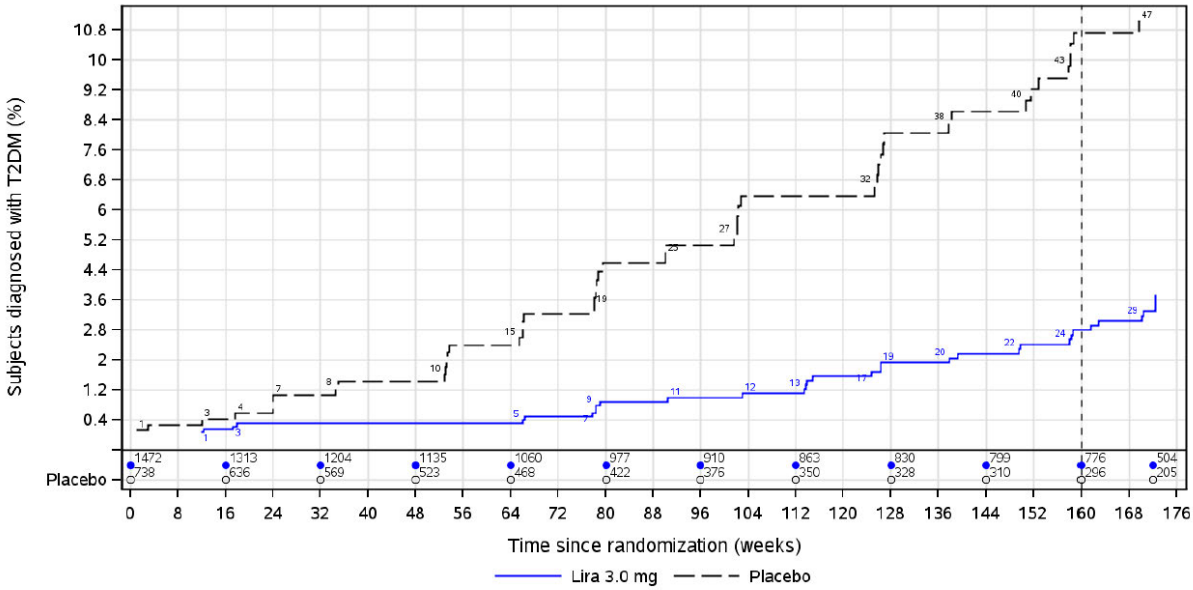
	Lira 3.0 mg			Placebo		
	N	%	R	N	%	R
Full analysis set	1472			738		
Subjects developing T2DM (0 - 160 weeks)	26	1.8	0.8	46	6.2	3.2

FAS: full analysis set, T2DM: Type 2 diabetes mellitus, N: Number of subjects fulfilling T2DM criteria, %: Percentage of subjects fulfilling T2DM criteria, R: T2DM incidence rate per 100 years of exposure

Source: Trial 1839-3y, Table 11-1

Reviewer comment: The clinical significance of converting from pre-diabetes to diabetes based on biomarkers alone is unclear. It is also unclear if Saxenda is preventing or treating (underlying, masked) diabetes; see Section 6.1.9, Discussion of Persistence of Efficacy and/or Tolerance Effects for further discussion. See Dr. Cambon's statistical review for further discussion of the statistical issues.

Figure 2. Time to Onset of T2DM, Kaplan-Meier Curve



Note: Numbers in the figure corresponds to the accumulated number of diagnosed subjects

Source: Trial 1839-3y CSR, Figure 11-1

6.1.5 Analysis of Secondary Endpoints

Body Weight

At week 160, patients randomized to Saxenda lost an average of 4.8% body weight and those randomized to placebo 2.6%, for a treatment difference of -2.2% (Table 9).

Table 9. Percent Mean Change in Body Weight at Week 160

	FAS	N	Baseline	Estimate	95% CI	P-value
LSMeans						
Lira 3.0 mg	1472	1467	107.64 kg	-4.82		
Placebo	738	734	107.96 kg	-2.62		
Treatment difference						
Lira 3.0 mg - Placebo				-2.20	[-3.13 ; -1.27]	<.0001

FAS: Number of subjects in full analysis set, N: Number of subjects contributing to analysis, Baseline: Arithmetic mean, CI: Confidence Interval. Missing values at week 160 are imputed using copy-from-placebo (non-sequential). The P-value corresponds to a two-sided test of no difference. The endpoint is analysed using an ANCOVA model with treatment, country, sex, baseline BMI-stratum as fixed factors, and the baseline value as covariate.
Output presents data for subjects with pre-diabetes at baseline and includes 6 subjects who did not have pre-diabetes at baseline, but participated in the 3-year part of the trial.
Table is based on trial 1839 (3-year data)
Source: ISE, Table 2

The proportion of patients with ≥ 5% weight loss at week 160 was 47% for Saxenda-treated patients and 35% for placebo-treated patients, and with ≥ 10% weight loss, 25% and 17%, respectively.

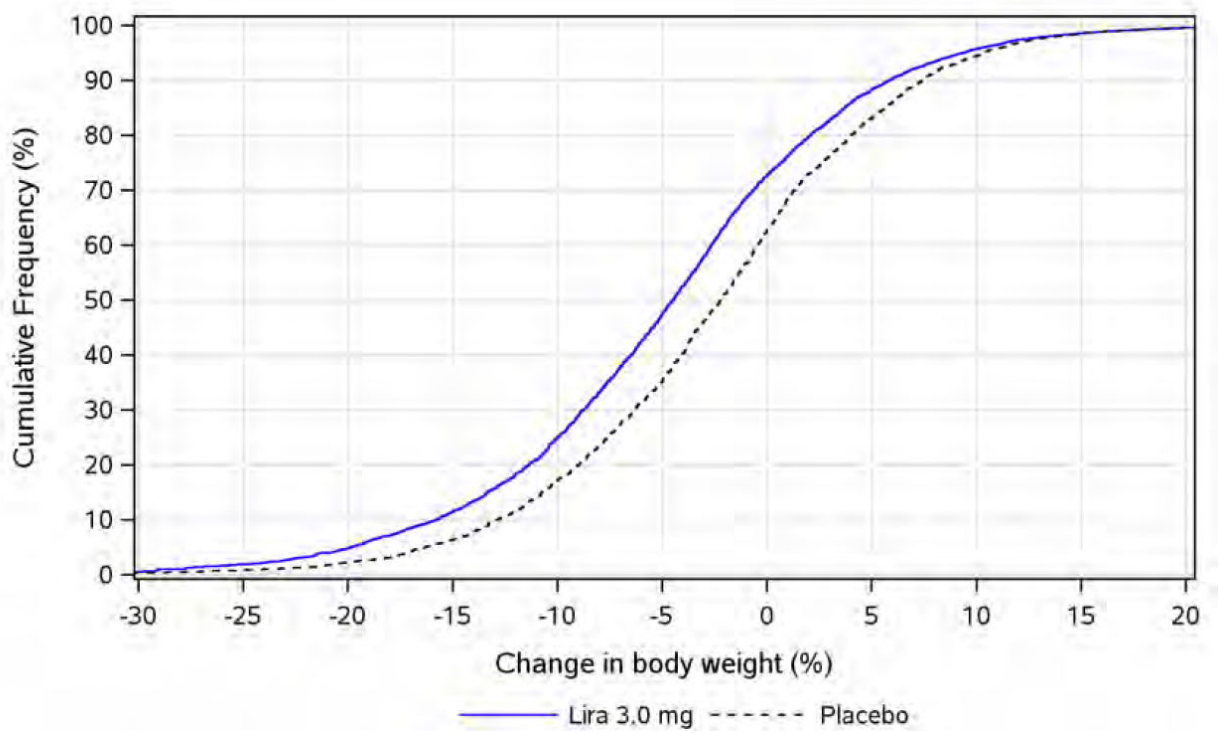
Table 10. Proportions of Patients with ≥ 5% and > 10% Weight Loss at Week 160

	FAS	N	%	95% CI	P-value
Subjects losing ≥5% of baseline fasting body weight after 160 weeks of treatment					
Estimated proportion					
Lira 3.0 mg	1472	1467	47.42		
Placebo	738	734	35.48		
Risk difference					
Lira 3.0 mg - Placebo			11.94	[6.66, 17.22]	<.0001
Subjects losing > 10% of baseline fasting body weight after 160 weeks of treatment					
Estimated proportion					
Lira 3.0 mg	1472	1467	25.08		
Placebo	738	734	17.45		
Risk difference					
Lira 3.0 mg - Placebo			7.63	[3.38, 11.87]	0.0004

FAS: Number of subjects in full analysis set, N: Number of subjects contributing to analysis, %: Percentages are based on total N, CI: Confidence Interval
Missing values post-baseline are imputed by multiple imputation (copy-from-placebo, non-sequential). The binary endpoint is analysed by a logistic regression model with an identity link and treatment, sex and BMI strata as fixed factors and baseline value as covariate.
Source: SCE, Table 2-6

Reviewer comment: Although Saxenda was shown to meet the weight loss requirements of an obesity drug after 1 year of treatment in the original NDA, this effect appears to attenuate over time, such that the weight loss, while statistically significantly different than placebo at the end of the 3-year study, does not meet the 5% mean or categorical clinical criteria as outlined in the FDA draft weight management guidance[4] (notwithstanding the missing data issues). See Dr. Cambon's statistical review for further discussion of the statistical issues.

Figure 3. Percent Mean Change in Body Weight, Cumulative Distribution Plot



Source: ISE, Figure 5

6.1.6 Other Endpoints

Glycemia

Favorable mean changes observed in HbA1c and FPG at week 160 were small (as the population was non-diabetic) in the Saxenda- vs. placebo-treated group:

4 Draft Guidance for Industry: Developing Products for Weight Management, February 2007

Table 11. Changes in HbA1c and FPG, Week 160

	Baseline		Change from Baseline		Treatment Estimate		
	Saxenda	Placebo	Saxenda	Placebo	Est. Treatment Difference	95% CI	p-value
HbA1c (%)	5.75	5.74	-0.35	-0.14	-0.21	-0.24, -0.18	<0.0001
FPG (mg/dL)	99.06	98.39	-6.61	0.75	-7.36	-8.26, -6.47	<0.0001

Source: SCE, Table 2-8

As expected with a glucose-lowering drug, the proportion of patients with normoglycemia at week 160, defined as 2-hour plasma glucose during OGTT as < 140 mg/dL, FPG < 100 mg/dL, and HbA1c < 5.7%, was higher in the Saxenda group as compared to the placebo group:

Table 12. Patients with Normoglycemia at Week 160

	FAS	N	Estimate	95% CI	P-value
LS-Means, Frequencies					
Lira 3.0 mg	1472	1472	66.64%		
Placebo	738	738	35.44%		
Treatment Odds Ratio					
Lira 3.0 mg / Placebo			3.639	[3.010, 4.399]	<.0001

Normoglycaemia: Normoglycaemia is defined as having fasting plasma glucose < 5.6 mmol/L (100 mg/dL) and 2 hour post-challenge glucose <7.8 mmol/L (140 mg/dL) and HbA1c <5.7%.
FAS: Number of subjects in full analysis set, N: Number of subjects contributing to analysis,
CI: Confidence Interval
Frequencies and odds: The probability of status as without pre-diabetes at week 160
Missing data are imputed using last observation carried forward.
The binary endpoint is analysed in a logistic regression model using a logit link. The model includes treatment, country, sex, and BMI stratum as fixed factors.

Source: SCE, Table 2-7

Lipids

Small changes were observed after 160 weeks in lipids, with no evidence for a treatment difference for LDL-C or HDL-C (Table 13 and Table 14).

Table 13. Percent Mean Change in HDL-C, LDL-C, and Total-C at Week 160

	FAS	N	Baseline*	Estimate	95% CI	P-value
HDL						
LSMeans						
Lira 3.0 mg	1472	1253	50.05 mg/dL	104.91% (4.91)		
Placebo	738	605	50.09 mg/dL	103.85% (3.85)		
Treatment Ratio						
Lira 3.0 mg / Placebo				1.010	[0.99;1.03]	0.2297
Relative Difference						
Lira 3.0 mg to Placebo				1.0%	[-0.6%; 2.7%]	
LDL						
LSMeans						
Lira 3.0 mg	1472	1252	110.85 mg/dL	95.42% (-4.58)		
Placebo	738	605	114.18 mg/dL	97.37% (-2.63)		
Treatment Ratio						
Lira 3.0 mg / Placebo				0.980	[0.96;1.00]	0.0962
Relative Difference						
Lira 3.0 mg to Placebo				-2.0%	[-4.3%; 0.4%]	
Total Cholesterol						
LSMeans						
Lira 3.0 mg	1472	1253	192.69 mg/dL	97.08% (-2.92)		
Placebo	738	606	196.69 mg/dL	98.83% (-1.17)		
Treatment Ratio						
Lira 3.0 mg / Placebo				0.982	[0.97;1.00]	0.0274
Relative Difference						
Lira 3.0 mg to Placebo				-1.8%	[-3.3%;-0.2%]	

FAS: Number of subjects in full analysis set, N: Number of subjects contributing to analysis,
CI: Confidence Interval, Baseline*: Geometric mean.
Relative difference is calculated as (treatment ratio-1)*100.
Missing values post-baseline are imputed using last observation carried forward.
The P-value corresponds to a two-sided test of no difference.
The endpoint is analysed using an ANCOVA model with treatment, country, sex, and baseline BMI stratum as fixed factors, and the baseline value of the endpoint as covariate.

Source: SCE, Table 2-9

Table 14. Percent Median Change in TG at Week 160

	Lira 3.0 mg	Placebo
N at week 0	1469	738
Median week 0 (1st quartile, 3rd quartile) (mg/dL)	132.7 (97.3, 175.2)	135.4 (99.1, 178.8)
N at week 160	1253	606
Median percent change after week 160	-10.7	-4.5
Location shift estimate - Lira vs Placebo (95%CIs)	-5.0 (-1.8, -8.3)	

Location shift estimated by Hodges-Lehmann.
N: Number of subjects contributing to analysis.

Source: SCE, Table 2-9

Blood Pressure

Nominally statistically significantly greater decreases from baseline to week 160 were seen with Saxenda compared with placebo for systolic blood pressure (SBP). No

evidence for a treatment difference between Saxenda and placebo was seen in change in diastolic blood pressure (DBP) from baseline to week 160.

Table 15. Changes in Blood Pressure, Week 160

	Baseline		Change from Baseline		Treatment Estimate		
	Saxenda	Placebo	Saxenda	Placebo	Est. Treatment Difference	95% CI	p-value
SBP (mmHg)	124.80	125.01	-3.24	-0.44	-2.80	-3.81, -1.79	<0.0001
DBP (mmHg)	79.40	79.83	-2.36	-1.74	-0.62	-1.33, 0.09	0.0866

Source: SCE, Table 2-8

6.1.7 Subpopulations

The sponsor evaluated the primary endpoint by age, race, geographical region, and sex; Saxenda was numerically favorable vs. placebo for all the subgroups below:

Table 16. Patients with T2DM by Age

	Lira 3.0 mg				Placebo			
	N	%	R	E	N	%	R	E
Subjects in full analysis set								
< 65 years	1368				685			
>= 65 years	104				53			
Subjects developing T2DM (0 - 160 weeks)								
< 65 years	26	1.9	0.9	2929	40	5.8	3.0	1324
>= 65 years	0	0.0	0.0	232	6	11.3	5.1	117

Source: Response to IR 15 Sep 2016, Table 1

Table 17. Patients with T2DM by Race

	Lira 3.0 mg				Placebo			
	N	%	R	E	N	%	R	E
Subjects in full analysis set								
Black	143				70			
White	1230				620			
Other	99				48			
Subjects developing T2DM (0 - 160 weeks)								
Black	3	2.1	1.0	289	3	4.3	2.6	116
White	18	1.5	0.7	2653	38	6.1	3.1	1230
Other	5	5.1	2.3	218	5	10.4	5.3	95

Source: Response to IR 15 Sep 2016, Table 4

Table 18. Patients with T2DM by Geographical Region

	Lira 3.0 mg				Placebo			
	N	%	R	E	N	%	R	E
Subjects in full analysis set								
US	612				310			
non US	860				428			
Subjects developing T2DM (0 - 160 weeks)								
US	7	1.1	0.6	1205	23	7.4	4.1	563
non US	19	2.2	1.0	1956	23	5.4	2.6	878

Source: Response to IR 15 Sep 2016, Table 6

Table 19. Patients with T2DM by Sex

	Lira 3.0 mg				Placebo			
	N	%	R	E	N	%	R	E
Subjects in full analysis set								
Female	1110				565			
Male	362				173			
Subjects developing T2DM (0 - 160 weeks)								
Female	13	1.2	0.5	2372	33	5.8	3.0	1085
Male	13	3.6	1.6	788	13	7.5	3.6	357

Source: Response to IR 15 Sep 2016, Table 8

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable; only the 3 mg dose was studied.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Development of T2DM

During the 12-week off-treatment period (172-week time point), an additional 5 patients on Saxenda (31 vs. 26) and 1 patient on placebo (47 vs. 46) were diagnosed with T2DM:

Table 20. Patients Diagnosed with T2DM up to 172 Weeks

	FAS	Number of events	Estimate	95% CI	P-value
Lira 3.0 mg	1472	31			
Placebo	738	47			
Treatment estimate					
Lira 3.0 mg / Placebo			2.444	[1.741, 3.431]	<.0001
Treatment Hazard Ratio					
Lira 3.0 mg / Placebo			0.243		

T2DM: Type 2 diabetes mellitus, FAS: Number of subjects in full analysis set, CI: Confidence Interval
Missing data are imputed using last observation carried forward.
The time of onset of type 2 diabetes is set in between the first of the two required registrations of elevated HbA1c, FPG or 2h OGTT plasma glucose, and the diabetes assessment visit prior to the first registration.
The endpoint is analysed in a Weibull model that includes treatment, sex and BMI stratification factor as fixed factors and baseline FPG will be included as a covariate.
The treatment estimate is the factor that the time to event is multiplied with for lira compared to placebo.
Subjects were off-drug in the observational follow-up period (weeks 160 to 172).
Output presents data for subjects with pre-diabetes at baseline and includes 6 subjects who did not have pre-diabetes at baseline, but participated in the extension period of the trial.

Source: Trial 1839-3y CSR, Table 14.2.17

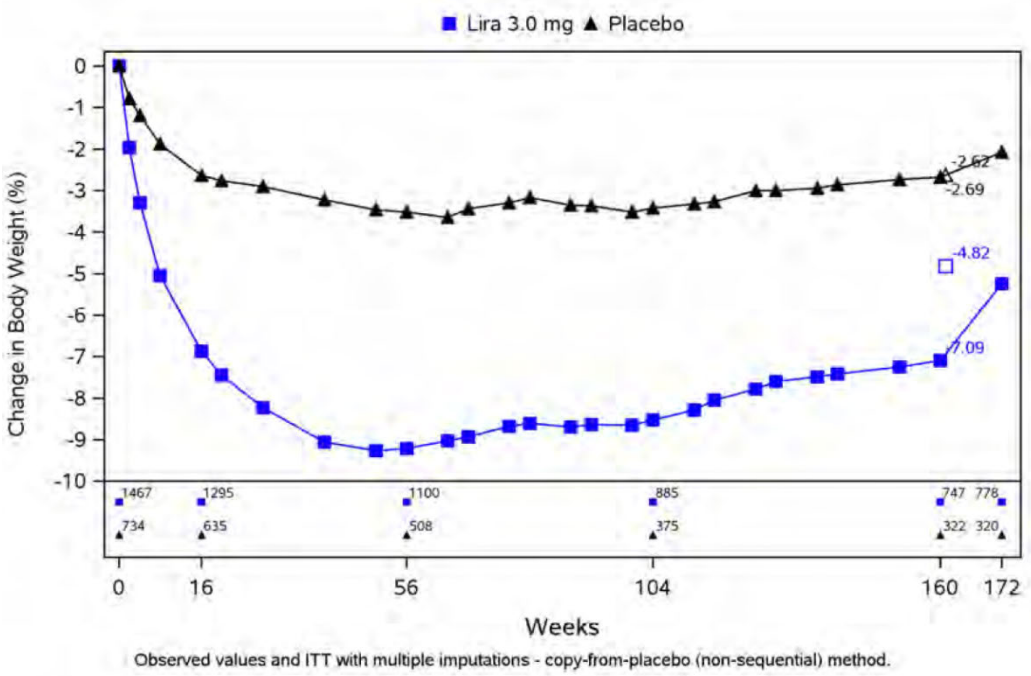
Reviewer comment: The increase in the number of patients who developed T2DM on Saxenda in just this short period of time off-drug (12 weeks) raises the question whether Saxenda is merely masking the development of T2DM, and whether the difference observed between groups is durable.

Weight Change

As shown in Figure 4, mean peak weight loss in the Saxenda-treated patients occurred at approximately 1 year (end of the main study) then gradually increased over time, with an attenuated placebo-subtracted weight loss (-2.2%) at week 160. This pattern has been observed with other chronic weight management drugs studied over 2 to 4 years.[5, 6] Furthermore, the figure illustrates that after 12 weeks off-drug, weight regain appears to be occurring in both treatment groups, and more rapidly on average in the Saxenda group. Again, this pattern of weight regain after drug discontinuation has been seen with other drugs.[5,6]

5 Xenical (orlistat) PI
6 Belviq/Belviq XR (lorcaserin) PI

Figure 4. Percent Mean Change in Body Weight, Baseline to 172 weeks



Source: ISE, Figure 4

6.1.10 Additional Efficacy Issues/Analyses

Issues related to the acceptability of the primary endpoint for a labeling claim are addressed in Sections 2.5 and 2.6 of this review.

7 Review of Safety

Safety Summary

No new safety findings were identified in this review. Ongoing safety considerations include:

- Pancreatitis: Of the 12 EAC-confirmed events of acute pancreatitis, 10 events (0.7%) occurred in patients on Saxenda and 2 events (0.3%) occurred in patients on placebo (2 events in Saxenda-treated patients were non-TEAEs that occurred in patients who discontinued Saxenda during the first year). Five patients treated with Saxenda and 1 patient treated with placebo had imaging or elevations in ALT suggestive of gallstones. One additional pancreatitis event was identified after the 172-week trial completion in a patient previously treated with Saxenda.

- Acute gallstone disease: A pre-defined MedDRA search to identify events potentially related to acute gallstone disease was performed The search identified

93 acute gallstone disease AEs in 74 (4.9%) patients treated with Saxenda and 18 events in 13 (1.7%) patients treated with placebo. In the Saxenda group, 2.3% of patients had events that were serious and 1.2% severe compared with 0.8% and 0.3%, respectively, for placebo. None of the events were fatal. Events that led to withdrawal occurred in 0.3% of patients treated with Saxenda vs. no patients treated with placebo. Cholecystectomy was performed in the majority of Saxenda-treated patients with adverse events of cholelthiasis or cholecystitis. There was generally a greater weight loss among Saxenda-treated patients with gallstone AEs than in the overall Saxenda population; this pattern was not evident with placebo.

- Hypoglycemia: During the trial, no severe hypoglycemic episodes by ADA criteria (requiring assistance of another person) were reported. The majority of AEs of "hypoglycemia" (19.9% Saxenda, 4.7% placebo) occurred during the OGTT visit, based on a biochemical value (symptoms were not systematically collected). Spontaneously reported hypoglycemia in patients without T2DM (i.e., symptoms without confirmatory blood glucose measurements) occurred in 3.4% Saxenda-treated patients and 1.7% placebo-treated patients. None of the hypoglycemia events were serious, reported as a medical event of special interest (MESI) by the investigator, or led to discontinuation of treatment.

- Acute renal failure: A total of 26 events in 20 patients (1.3%) treated with Saxenda and 14 events in 11 patients (1.5%) treated with placebo were identified in a pre-defined search of AEs. The majority of preferred terms in the Saxenda group were of 'blood creatinine increased'. SAEs included 4 events reported by 3 patients with Saxenda (renal failure acute (2 events) and renal impairment (2 events)) and 3 events in 3 patients with placebo (renal failure acute (2 events) and oliguria (1 event)). One SAE of acute renal failure in the Saxenda group was co-reported with gastrointestinal AEs.

- Psychiatric AEs: The proportions of patients with psychiatric AEs were similar between Saxenda-treated patients and placebo-treated patients, as were the proportions of patients with SAEs. No psychiatric events were fatal. The majority of events were captured within the HLGTs sleep disorders and disturbances, depressed mood disorders and disturbances, and anxiety disorders and symptoms. Psychiatric SAEs reported for Saxenda were suicidal ideation, suicide attempt, and sleep apnea syndrome (2 events), and for placebo, suicide attempt and depression. Mean PHQ-9 scores at the end-of-treatment and total scores above designated cut-off during the trial were similar in the Saxenda and placebo groups, as were the categorical shifts to maximum scores. During the trial, no patients reported suicidal behavior on the C-SSRS; however, 2 suicide attempt AEs were reported without being captured on the C-SSRS (1 in each group). A total of 19 patients (1.3%) treated with Saxenda and 12 patients (1.6%) treated with placebo reported suicidal ideation on the C-SSRS.

- Gastrointestinal AEs: The proportions of patients with AEs within the 'gastrointestinal disorders' SOC and the rates of events were higher with Saxenda (73.6%, 124.4 events per 100 patient years of observation, PYO) than with placebo (50.2%, 62.4 events per 100 PYO). The most frequently reported gastrointestinal AEs were nausea, diarrhea, constipation, vomiting, and dyspepsia. Gastrointestinal AEs were the most frequently reported event types leading to permanent treatment discontinuation (Saxenda 7.9% vs. placebo 1.5%).

- Cardiovascular events: Overall, the proportions of patients with adjudication-confirmed treatment-emergent cardiovascular events and rates of events were similar with Saxenda (0.80%, 0.56 events per 100 PYO) and placebo (0.80%, 0.54 events per 100 PYO). As there were only 18 first events (26 total events) in this trial, no conclusion can be drawn regarding the cardiovascular risk of Saxenda.

- Neoplasms: For EAC-confirmed neoplasms overall, the proportions of patients with events and rates of events were 4.40% (2.16 events per 100 PYO) for Saxenda and 3.75% (2.35 events per 100 PYO) for placebo. For malignant neoplasms, the proportions of patients with EAC-confirmed neoplasms and rates of events were 1.87% (0.92 events per 100 PYO) for Saxenda and 1.47% (0.89 events per 100 PYO) for placebo.

    - Thyroid: Three patients (0.2%) on Saxenda and no patients on placebo had adjudication-confirmed thyroid neoplasms. All 3 events were identified after thyroidectomies performed due to worsening of pre-existing thyroid disease or during evaluation for nodular goiter or hyperparathyroidism. One case was classified as malignant and 2 cases were pre-malignant. One of the events was a non-TEAE, reported 236 days after last day of Saxenda treatment. All events were papillary microcarcinomas and no cases of medullary thyroid cancer or C-cell hyperplasia were identified during the trial.

    - Pancreas: One Saxenda-treated patient had an EAC-confirmed pancreatic neoplasm, described as a pseudopapillary tumor of the pancreas. Although one patient in the placebo group apparently died of pancreatic cancer, this event was not confirmed as a pancreatic neoplasm event by the EAC.

    - Colorectal: Overall, a similar proportion of patients in the Saxenda and placebo groups had events of colorectal neoplasms (1.1%); 4 events in 3 patients were malignant in Saxenda-treated patients (0.2%) vs. 1 event in 1 placebo-treated patient (0.1%). One pre-malignant case occurred in a Saxenda-treated patient.

    - Breast: Malignant breast neoplasms were reported more frequently in the Saxenda vs. placebo group (6 patients, 0.4% vs. 0 patients, respectively). Considering breast cancer data from all Saxenda clinical trials presented in the post-marketing requirement (PMR) study report, it was noted that the observed

number of cases in the Saxenda group was numerically (but not statistically significantly) higher than expected and the number in the placebo group was numerically (but not statistically significantly) lower than expected; women with events in the Saxenda group tended to have greater absolute breast cancer risk compared to the general population; and women with events in the Saxenda group had greater than average weight loss, raising the possibility for detection bias. However, a breast cancer risk with Saxenda cannot be excluded.

- Data from clinical trials, literature, and postmarketing pregnancy experience were provided as part of the Pregnancy and Lactation Labeling Rule (PLLR) conversion. In Saxenda trials, 41 pregnancies were reported with available fetal outcome: 22 were reported as live birth without congenital anomaly, 13 were reported as fetal loss (2 with ectopic pregnancy and 11 spontaneous abortion in the first trimester of pregnancy), and 6 cases were reported as termination (1 case without fetal defect, 1 with Down's syndrome, other 4 not described). An assessment of updated clinical trial data, including comparator data for the PLLR review, does not allow for a determination of drug-associated risk in pregnancy. Saxenda is contraindicated in pregnancy, as are all weight management drugs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Although the sponsor has included a summary of clinical safety in the supplement with analyses of pooled safety data from the controlled parts of the 5 phase 2 and 3 trials [trials 1807, 1839 (1-year and 3-year data), 1922, 3970 and 1923], these data (with the exception of the 3-year part of 1839) have already been fully reviewed in the original NDA. Therefore, this safety review will focus on the results in the pre-diabetes population from the 3-year part of study 1839. Note that some of the events in trial 1839 have previously been reviewed with the original NDA – specifically, the 1-year main part of 1839 in patients with and without pre-diabetes. This review will generally not separate out events that have been previously reviewed from newly reported events. Some events reported in this review are a subset of those that were presented in the original NDA (i.e., pre-diabetes patients are a subset of the entire obesity population), and some events are newly reported events (i.e., the additional 2 years of the 1839 trial; the first year data were presented in the original NDA).

Additional data reviewed for this supplement include the findings from the breast cancer PMR (see Section 7.6.1, Human Carcinogenicity) and pregnancies from liraglutide programs (see Section 7.6.2, Human Reproduction and Pregnancy Data).

7.1.2 Categorization of Adverse Events

MedDRA version 15.1 was used to code adverse events. I assessed the categorization of events by comparing the verbatim terms used by investigators to the preferred terms, focusing on events that led to discontinuation of treatment. Based on this evaluation, I believe that AEs were generally categorized appropriately.

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

Since this supplement is based on the 3-year part of trial 1839, the single trial is being used to assess safety.

7.2 Adequacy of Safety Assessments

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

In the trial safety database,[7] 1501 patients were exposed to at least 1 dose of Saxenda: 1123 patients were exposed for at least 12 months, 896 patients for at least 24 months, and 793 patients were exposed for at least 36 months.

Table 21. Cumulative Exposure in the Treatment Period

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	1501	747	2248
Subjects with >= 1 month exposure	1429 (95.2)	724 (96.9)	2153 (95.8)
Subjects with >= 3 months exposure	1333 (88.8)	667 (89.3)	2000 (89.0)
Subjects with >= 6 months exposure	1246 (83.0)	598 (80.1)	1844 (82.0)
Subjects with >= 9 months exposure	1185 (78.9)	553 (74.0)	1738 (77.3)
Subjects with >= 12 months exposure	1123 (74.8)	516 (69.1)	1639 (72.9)
Subjects with >= 18 months exposure	997 (66.4)	447 (59.8)	1444 (64.2)
Subjects with >= 24 months exposure	896 (59.7)	383 (51.3)	1279 (56.9)
Subjects with >= 30 months exposure	843 (56.2)	360 (48.2)	1203 (53.5)
Subjects with >= 36 months exposure	793 (52.8)	338 (45.2)	1131 (50.3)

N: Number of subjects, %: Percentages are based on total N, SAS: safety analysis set.
Source: Trial 1839-3y CSR, Table 12-1

7 Including 6 patients who did not have pre-diabetes at baseline but nevertheless participated in the 3-year part of the trial, and excluding 37 patients with pre-diabetes who were randomized to the 1-year part of the trial

7.2.2 Explorations for Dose Response

The 3 mg dose used in this trial is the approved dose for the weight management indication; see the original clinical NDA review for further discussion of dose response.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing in trial 1839 was determined adequate in the clinical review of the original NDA.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable; no new data were presented in this supplement regarding the metabolism, clearance, or interactions of liraglutide.

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

The evaluation for potential AEs was adequate.

Medical Events of Special Interest (MESI) were pre-defined in the protocol, and in the event of a MESI, specific forms were to be filled out according to the investigator's judgment. In addition, certain MESIs underwent adjudication by an external independent event adjudication committee (EAC); see Table 22. MESIs were selected based on the known and potential risks of GLP-1 receptor agonists, previous experience with liraglutide in patients with T2DM, and requirements from regulatory agencies for the development of drugs for weight management.

The majority of MESIs are discussed in Section 7.3.5, Submission Specific Primary Safety Concerns. Withdrawals due to AEs are discussed in Section 7.3.3, Dropouts and/or Discontinuations, and medication errors are discussed in Section 7.6.4, Overdose, Drug Abuse Potential, Withdrawal and Rebound. There were no events of suspected transmission of an infectious agent via trial product (all AEs identified by pre-specified MedDRA search were of food poisoning).

Table 22. Medical Events of Special Interest

Type of MESI	Adjudication (Y/N)
Death (if not already reported as a cardiovascular MESI)	Y
Cardiovascular events	
-Acute coronary syndrome (myocardial infarction or hospitalisation for unstable angina pectoris)	Y
-Cerebrovascular event (stroke or transient ischemic attack)	Y
-Heart failure (clinical manifestation of new episode or worsening of existing heart failure)	Y[a]
-Stent thrombosis	Y
-Revascularisation procedure	Y[b]
-Hospitalisation for cardiac arrhythmia	N
Pancreatitis or acute, severe, persistent abdominal pain leading to a suspicion of pancreatitis	Y
Acute gallstone disease (biliary colic or acute cholecystitis)	N
Elevated lipase or amylase ≥3xUNR[c]	N
Neoplasms (all types)[d]	Y
Thyroid disease	Y[e]
Any confirmed episode of calcitonin value ≥20 ng/L (from visit 3 and onwards)	N
Acute renal failure	N
Severe hypoglycaemic events	N
Immunogenicity event (allergic reactions including allergic reactions at injection sites, or immune-complex disease)	N
Psychiatric Disorders (including psychiatric disorders diagnosed by C-SSRS and PHQ-9 questionnaires)	N
AEs leading to withdrawal (if not already reported as any of the listed MESIs)	N
Medication errors concerning trial products - administration of wrong drug or use of wrong device - wrong route of administration, such as intramuscular instead of subcutaneous - administration of an accidental overdose, i.e. dose which may have led to significant health consequences, as judged by the investigator, irrespective of whether the SAE criteria were fulfilled or not - administration of a high dose with the intention to cause harm, e.g. suicide attempt	N
Suspected transmission of an infectious agent via a trial product	N

Abbreviations: C-SSRS = Columbia suicidality severity rating scale; MESI = medical event of special interest; N = no; PHQ-9 = patient health questionnaire-9; UNR = upper limit of normal range; Y = yes.
[a] If required hospitalisation for at least 12 hours. [b] Only coronary revascularisation procedures.
[c] Events reported as result of protocol-scheduled visits were always to be reported as separate MESIs, even if followed by diagnosis of pancreatitis (i.e. event/diagnosis not to be updated, new event to be filed). [d] If thyroid neoplasm, thyroid disease MESI was to be selected. [e] Only those requiring thyroidectomy and thyroid neoplasms.

Source: Trial 1839-3y CSR, Table 9-5

In the original clinical NDA review of Saxenda, a novel finding of increased breast cancer events associated with liraglutide was noted. PMR 2802-8 was therefore required upon approval:

To assess the risk of breast cancer associated with liraglutide in Trial 1839. To assess this risk, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the trial, 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.

This PMR was completed by the sponsor and the results are reviewed as part of this supplement (Section 7.6.1).

7.3 Major Safety Results

7.3.1 Deaths

Four patients had 5 events with fatal outcomes during the 3-year trial: 3 events in 2 patients treated with Saxenda (cardiorespiratory arrest, ventricular fibrillation, and bile duct cancer) and 2 events in 2 patients treated with placebo (cardiorespiratory arrest and pancreatic carcinoma metastatic); see Table 23 for details.

Table 23. Deaths

Subject ID Age[a]/Sex/ BMI[a]	Preferred term/ EAC cause of death (EAC diagnosis)	Onset of fatal AE (trial day)	Comments including relevant medical history	Causality (investigator/ sponsor)
Liraglutide 3.0 mg				
(b) (6) 65/M/33.3	Cardio-respiratory arrest & Ventricular fibrillation/ CV death (cardiac arrest)	579	Medical history: coronary artery disease with multiple stent placements, sleep apnoea, hypertension, hyperlipidaemia. The subject suddenly collapsed at home and was taken to the hospital in full cardiac arrest. He was administered advanced cardiovascular life support without recovery and died with the diagnosis of fatal acute arrest due to ventricular fibrillation. Previously the subject had experienced 2 SAEs: acute coronary syndrome causing syncope (day 319, EAC-confirmed NSTEMI), and coronary revascularisation (day 321, EAC-confirmed event of coronary revascularisation).	Possibly/ unlikely

Subject ID Age[a]/Sex/ BMI[a]	Preferred term/ EAC cause of death (EAC diagnosis)	Onset of fatal AE (trial day)	Comments including relevant medical history	Causality (investigator/ sponsor)
(b) (6) 59/F/34.7	Bile duct cancer/ Non-CV death (metastatic cholangiocarcinoma)	966	Medical history: hypertension. On day 371, the subject reported stage I sqauamous cell carcinoma on (left hand); EAC-confirmed malignant neoplasm event. Later, the subject was diagnosed with chronic cholecystitis (non-serious) based on intermittent abdominal pain, and underwent cholecystectomy (day 966). Based on pathology report, the subject was diagnosed with gallbladder adenocarcinoma stage III (histologic grade moderately-poorly differentiated) and died approximately 70 days after onset of the event.	Unlikely/ unlikely
Placebo				
(b) (6) 59/M/57.6	Cardiorespiratory arrest/ Non-CV death (pulmonary failure with lung white-out leading to PEA arrest)	112	Medical history: morbid obesity, sleep apnoea. The subject went to his primary care physician due to chest pain and shortness of breath. He later passed out and developed asystoli. CPR was performed and the subject was hospitalised and treated with intensive care and broad-spectrum antibiotics for possible pneumonia. He rapidly deteriorated and died later the same day.	Unlikely/ unlikely
(b) (6) 77/F/51.7	Pancreatic carcinoma metastatic/ Non-CV death (death due to cancer)	894	Medical history: gallstone disease, cholecystectomy. The subject complained of anorexia on day 894, and had lost approximately 45 pounds during the last year. Accordingly a CT scan of the abdomen and pelvis was performed and demonstrated metastatic disease. Paracentesis and omentum needle core biopsy confirmed metastatic adenocarcinoma. Final diagnosis reported was pancreatico-biliary carcinoma. Chemotherapy was planned as treatment. Trial drug was discontinued and the subject was withdrawn. The subject died approximately 4 months after onset.	Unlikely/ unlikely

Note: Comments are based on information in case narratives from the safety database in Section 14.3.3.

Abbreviations: AE = adverse event; BMI = body mass index; CPR = cardiopulmonary resuscitation; CT = computerised tomography; CV = cardiovascular; EAC = event adjudication committee; F = female; M = male; NSTEMI = Non-ST-elevation myocardial infarction; SAE = serious adverse event; SAS = safety analysis set.

[a] Baseline value.

Source: 1839-3y CSR, Table 12-12

Additional information regarding the fatal AE of "bile duct cancer" follows:

This clinical trial case from the United States was reported as "metastatic cholangiocarcinoma" and concerned a 62-year-old female patient. The patient was treated with Saxenda from (b) (6). Medical history included

obesity, osteoarthritis, fibromyalgia, hypertension, indigestion, colitis, fibroid tumor of uterus, peripheral neuropathy, environmental allergies and contact dermatitis rash/episodic.

The patient had a recent history of abdominal pain for over a week that was intermittent, for which she saw her primary care physician (b) (6). Diagnostic tests revealed cholecystitis (non-serious event), and she underwent a successful cholecystectomy on (b) (6) The patient subsequently contacted the site and reported she had gallbladder cancer and was advised to see an oncologist. The final pathologic diagnosis from the gallbladder cholecystectomy was adenocarcinoma. Histologic grade was moderately-poorly differentiated (grade II-III). The extent of tumor was that it involved the entire gallbladder, mainly in the body and widely infiltrated the gallbladder muscular wall as glandular structures and as single cells. The tumor infiltrated into perimuscular connective tissue, and was present at the serosa and at the plane of resection from the hepatic fossa. Margins of resection showed that the tumor was present at the non-peritonealized surface (liver bed), serosa, and cyst duct margin. Additional tumor features included lymphovascular invasion and perineural invasion. Additional findings included high-grade dysplasia (carcinoma *in situ*) and intestinal/goblet metaplasia. It was also noted that the patient had chronic cholecystitis with cholelithiasis.

On (b) (6), the patient underwent liver resection. Anterior common duct lymph node revealed metastatic adenocarcinoma with focal acute inflammation, stage pT3 N1. Segment of the liver was poorly differentiated adenocarcinoma in bile duct wall and adjacent soft tissue. Surgical margins of resection were free of tumor.

There were no signs or symptoms present at trial start and this event was not a recurrence or a metastasis of a pre-existing neoplasm.

The outcome of the event was fatal (b) (6). An autopsy was not performed. The primary cause of death was reported as gallbladder cancer.

Reviewer comment: Cholelithiasis, a labeled adverse event with Saxenda, is a risk factor for adenocarcinoma of the gallbladder.[8] The relationship of Saxenda to this fatal event therefore cannot be confirmed or excluded.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were reported at a higher incidence in patients treated with Saxenda (15.1%) as compared to placebo (12.9%). In addition, more SAEs were considered severe, probably or possibly related to drug, and not recovered in the

8 Stinton LM and Shaffer EA. Epidemiology of Gallbladder Disease: Cholelithiasis and Cancer. Gut Liver (2012); 6(2): 172-87.

Saxenda group; although overall, the numbers of events meeting these descriptions were small (Table 24).

Table 24. Treatment-Emergent SAEs

	Lira 3.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1501				747			
Years of observation time	3218.9				1470.2			
All SAEs	227	(15.1)	350	10.9	96	(12.9)	143	9.7
Severity								
Severe	117	(7.8)	159	4.9	39	(5.2)	49	3.3
Moderate	90	(6.0)	131	4.1	53	(7.1)	68	4.6
Mild	50	(3.3)	60	1.9	21	(2.8)	26	1.8
Relationship to investigational product								
Probable	10	(0.7)	12	0.4	0	(0.0)	0	0.0
Possible	42	(2.8)	52	1.6	13	(1.7)	16	1.1
Unlikely	191	(12.7)	286	8.9	86	(11.5)	127	8.6
Outcome								
Recovered	202	(13.5)	305	9.5	88	(11.8)	129	8.8
Fatal	2	(0.1)	3	0.1	2	(0.3)	2	0.1
Recovering	7	(0.5)	7	0.2	4	(0.5)	4	0.3
Recovered with sequelae	5	(0.3)	5	0.2	1	(0.1)	1	<0.1
Not recovered	26	(1.7)	27	0.8	5	(0.7)	6	0.4
Unknown	3	(0.2)	3	0.1	1	(0.1)	1	<0.1
SAEs leading to withdrawal	38	(2.5)	43	1.3	10	(1.3)	11	0.7

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 years of observation time, TE: treatment emergent, SAE: serious adverse event, SAS: safety analysis set. A TE adverse event is defined as an event that has onset date on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment.

Source: 1839-3y CSR, Table 12-13

The most frequently reported SAEs with Saxenda were within the SOCs 'hepatobiliary disorders', 'infections and infestations', 'musculoskeletal and connective tissue disorders', 'gastrointestinal disorders', and 'neoplasms benign, malignant and unspecified'. The proportions of patients with events and rates of events were higher with Saxenda than with placebo (incidence >2x) for hepatobiliary disorders and neoplasms. The most frequent SAEs by SOC and PT with PT incidence greater than placebo are enumerated in Table 25. Discussion of SAEs and AEs of special interest are discussed in Section 7.3.5.

Table 25. SAEs with Incidence Greater than Placebo

	Saxenda N=1501	**Placebo N=747**
Hepatobiliary disorders	37 (2.5)	6 (0.8)
Cholelithiasis	20 (1.3)	6 (0.8)
Cholecystitis acute	9 (0.6)	1 (0.1)
Cholecystitis	6 (0.4)	0
Bile duct stone	3 (0.2)	0

Biliary colic	2 (0.1)	0
Infections and infestations	34 (2.3)	17 (2.3)
Appendicitis	4 (0.3)	0
Gastroenteritis	4 (0.3)	0
Diverticulitis	3 (0.2)	1 (0.1)
Urosepsis	3 (0.2)	0
Arthritis bacterial	2 (0.1)	0
Urinary tract infection	2 (0.1)	0
Musculoskeletal and connective tissue disorders	33 (2.2)	15 (2.0)
Osteoarthritis	12 (0.8)	5 (0.7)
Intervertebral disc protrusion	6 (0.4)	1 (0.1)
Lumbar spinal stenosis	2 (0.1)	0
Gastrointestinal disorders	33 (2.2)	12 (1.6)
Hiatus hernia	4 (0.3)	0
Pancreatitis acute	3 (0.2)	1 (0.1)
Abdominal hernia	3 (0.2)	0
Abdominal pain	3 (0.2)	0
Abdominal pain upper	2 (0.1)	0
Gastritis	2 (0.1)	0
Hemorrhoids	2 (0.1)	0
Pancreatitis	2 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	31 (2.1)	7 (0.9)
Breast cancer	5 (0.3)	0
Chronic myeloid leukemia	2 (0.1)	0
Colon adenoma	2 (0.1)	0
Thyroid cancer	2 (0.1)	0
Injury, poisoning and procedural complications	23 (1.5)	11 (1.5)
Ankle fracture	3 (0.2)	0
Humerus fracture	2 (0.1)	0
Joint dislocation	2 (0.1)	0
Post procedural hemorrhage	2 (0.1)	0
Tibia fracture	2 (0.1)	0
Wound	2 (0.1)	0
Cardiac disorders	15 (1.0)	8 (1.1)
Acute coronary syndrome	2 (0.1)	0
Pericarditis	2 (0.1)	0
Reproductive system and breast disorders	13 (0.9)	3 (0.4)
Menorrhagia	3 (0.2)	0
Endometrial hyperplasia	2 (0.1)	0
Nervous system disorders	12 (0.8)	8 (1.1)
Syncope	3 (0.2)	1 (0.1)
Surgical and medical procedures	12 (0.8)	6 (0.8)
Coronary revascularization	3 (0.2)	1 (0.1)
General disorders and administration site conditions	12 (0.8)	5 (0.7)
Non-cardiac chest pain	5 (0.3)	1 (0.1)
Medical device complication	2 (0.1)	0
Respiratory, thoracic and mediastinal disorders	11 (0.7)	2 (0.3)
Nasal septum deviation	3 (0.2)	0
Sleep apnea syndrome	2 (0.1)	0

Renal and urinary disorders	8 (0.5)	8 (1.1)
Nephrolithiasis	4 (0.3)	1 (0.1)
Renal impairment	2 (0.1)	0
Vascular disorders	7 (0.5)	4 (0.5)
Orthostatic hypotension	2 (0.1)	0
Skin and subcutaneous tissue disorders	5 (0.3)	2 (0.3)
Excessive skin	2 (0.1)	0
Investigations	4 (0.3)	2 (0.3)
Lipase increased	2 (0.1)	0
Pregnancy, puerperium and perinatal conditions	4 (0.3)	2 (0.3)
Abortion spontaneous	2 (0.1)	0
Eye disorders	2 (0.1)	1 (0.1)
Retinal detachment	2 (0.1)	0
Immune system disorders	2 (0.1)	0
PTs with greater than 1 patient in the Saxenda group and incidence greater than placebo included.		

Source: Reviewer created from 1839-3y datasets

As shown in Table 26, the proportions of patients treated with Saxenda with SAEs within the SOCs of 'hepatobiliary disorders' were higher in year 1 than in years 2 and 3, although the imbalance versus placebo persisted throughout the 3-year trial. The rate of neoplasms increased in the third year of the trial in the Saxenda group as compared to the rate in the placebo group.

Table 26. Most Frequent SAEs by SOC and by Year of Onset

SOC	Year 1 [weeks 0 to 56]		Year 2 [weeks 57 to 108]		Year 3 [weeks 109 to 160]	
	Lira 3.0 mg (%) R	Placebo (%) R	Lira 3.0 mg (%) R	Placebo (%) R	Lira 3.0 mg (%) R	Placebo (%) R
All SAEs	(7.3) 10.3	(6.3) 8.3	(8.2) 11.8	(6.8) 10.7	(7.3) 10.8	(8.2) 11.1
Most frequent SOCs:						
Hepatobiliary disorders	(1.4) 1.8	(0.5) 0.6	(0.8) 0.9	(0.2) 0.5	(0.9) 1.3	(0.3) 0.3
Musculoskeletal and connective tissue disorders	(1.1) 1.3	(0.7) 0.8	(1.3) 1.6	(1.4) 1.8	(0.3) 0.3	(1.1) 1.1
Gastrointestinal disorders	(1.0) 1.2	(0.9) 1.2	(0.8) 1.0	(0.6) 0.7	(1.0) 1.2	(0.8) 0.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	(1.0) 1.1	(0.5) 0.6	(0.6) 1.1	(0.4) 0.5	(1.2) 1.4	(0.3) 0.3
Infections and infestations	(0.8) 0.9	(1.2) 1.5	(1.1) 1.4	(1.0) 1.4	(1.1) 1.3	(1.1) 1.1
Injury, poisoning and procedural complications	(0.7) 1.0	(0.4) 0.5	(0.7) 0.9	(0.8) 0.9	(0.5) 0.6	(1.1) 1.1
Cardiac disorders	(0.3) 0.4	(0.5) 0.6	(0.5) 0.7	(0.2) 0.2	(0.8) 1.2	(0.8) 1.6
Renal and urinary disorders	(0.2) 0.2	(0.3) 0.3	(0.5) 0.6	(0.6) 0.7	(0.1) 0.1	(0.8) 0.8
Nervous system disorders	(0.2) 0.2	(0.5) 0.8	(0.6) 0.7	(0.8) 0.9	(0.3) 0.3	(0.3) 0.3

Abbreviations: R = rate of events (per 100 patient years of observation time); SAE = serious adverse event; SAS = safety analysis set; SOC = system organ class; TE = treatment-emergent.

Source: Trail 1839-3y CSR, Table 12-15

Not shown in Table 25 were 2 SAEs of hepatitis in the Saxenda group, which were reported under separate preferred terms: 'hepatitis acute' and 'hepatitis'. Narratives follow:

- [redacted] (b) (6) ('hepatitis acute') was a 54-year-old female treated with Saxenda for 4 months prior to the event. Medical history included presbyopia, nephrolithiasis, renal tuberculosis, dermoid cyst of the ovary, fibromyalgia, hypothyroidism, major depressive disease, alcohol abuse, skin lesion and impaired memory and concentration. The patient complained of severe epigastric pain and laboratory tests showed ALT 672 U/L (ref. < 31), AST 494 U/L (ref. < 31), GGT 480 U/L (ref. 5-36), alkaline phosphatase 210 U/L (ref. 35-104), and total bilirubin 0.44 mg/dL (ref 0.20-1.00). The patient stopped all medications. Three days later, gallstones were diagnosed by ultrasound with no dilatation of the biliary ducts. Laboratory tests showed ALT 229 U/L, AST 38 U/L, GGT 317 U/L, and alkaline phosphatase 170

U/L. No viral hepatitis serologies were performed. One month later, the patient recovered with normal transaminases.

Reviewer comment: Although the time course and positive dechallenge is suggestive of a drug etiology, this case is confounded by the finding of gallstones and the history of alcohol abuse.

- (b) (6) ('hepatitis') was a 52-year-old male patient who was treated with Saxenda for 1 month prior to the event. Medical history included morbid obesity, obstructive sleep apnea, increased blood pressure, gastroesophageal reflux disease, intermittent edema, pyloroplasty, and knee pain. The patient was admitted to the hospital for abdominal pain, amylase 833 U/L, and lipase 690 U/L. ALT was 255 U/L (ref. < 63), AST 335 U/L (ref. < 41), and serum bilirubin 1.8 mg/dL (ref. 0.1-1.4). ALT increased over several days to 367 U/L. The patient was diagnosed with acute pancreatitis (EAC-confirmed, see Table 32 in Section 7.3.5) and hepatitis. He recovered and discontinued from the drug. An ultrasound conducted 2 months later demonstrated a mildly prominent common bile duct with no gallstones.

Reviewer comment: The relationship of Saxenda to these events is possible, but whether it may be due to a direct drug effect or indirect (via gallstones) is unclear. Acute pancreatitis is discussed further in Section 7.3.5.

7.3.3 Dropouts and/or Discontinuations

The reason for withdrawal recorded on the end-of-trial forms included pre-specified criteria such as 'withdrawal criteria' (see below), AEs, and other reasons.

If patients did not tolerate the 3 mg target dose within 35 days after randomization, they were to be withdrawn from the trial.

Acute pancreatitis and psychiatric disorders were specific 'withdrawal criteria' in this trial; these events that led to discontinuation were recorded as discontinuation due to fulfillment of withdrawal criteria in the eCRF and not as withdrawals due to AEs. However, to capture all types of AEs leading to discontinuation in the trial, patients discontinuing due to fulfillment of withdrawal criteria were also considered as AEs leading to withdrawal. A summary of reasons for withdrawal can be found in Section 6.1.3, Subject Disposition, in Table 7.

Permanent treatment discontinuation due to AEs was observed in higher proportions of patients in the Saxenda group than in the placebo group:

- 200 patients (~13%) treated with Saxenda discontinued from the trial due to AEs:
  - 191 with 'AE' as reason for withdrawal
  - 7 with the withdrawal criterion 'acute pancreatitis' as reason
  - 1 with the withdrawal criterion 'psychiatric disorders' as reason

  - 1 with the withdrawal criterion 'target dose not tolerated' as reason[9]
- 46 patients (~6%) treated with placebo discontinued from the trial due to AEs:
  - 43 with 'AE' as reason for withdrawal
  - 2 with the withdrawal criterion 'psychiatric disorders' as reason
  - 1 with the withdrawal criterion 'acute pancreatitis' as reason

The most frequently reported AEs leading to permanent treatment discontinuation during the treatment period in either group were within the SOCs 'gastrointestinal disorders', 'general disorders and administration site conditions', 'nervous system disorders', 'investigations', 'neoplasms benign, malignant and unspecified' and 'psychiatric disorders'.

Gastrointestinal disorders and neoplasms led to permanent treatment discontinuation by higher proportions of patients and at higher rates with Saxenda than with placebo. Gastrointestinal disorders accounted for ~60% and ~20% of events leading to permanent treatment discontinuation with Saxenda (168 of 287 events) and placebo (14 of 66 events), respectively.

Table 27. AEs Leading to Discontinuation

	Saxenda	**Placebo**
	N=1501	**N=747**
Gastrointestinal disorders	118 (7.9)	11 (1.5)
Nausea	52 (3.5)	5 (0.7)
Vomiting	37 (2.5)	0
Diarrhea	20 (1.3)	1 (0.1)
Abdominal pain	13 (0.9)	1 (0.1)
Constipation	10 (0.7)	0
Gastroesophageal reflux disease	6 (0.4)	0
Dyspepsia	5 (0.3)	1 (0.1)
Abdominal distension	4 (0.3)	1 (0.1)
Pancreatitis acute	4 (0.3)	1 (0.1)
Pancreatitis	3 (0.2)	1 (0.1)
Abdominal pain upper	2 (0.1)	0
Flatulence	2 (0.1)	0
Pancreatic disorder	2 (0.1)	0
General disorders and administration site conditions	17 (1.1)	6 (0.8)
Fatigue	9 (0.6)	1 (0.1)
Injection site reaction	2 (0.1)	0
Injection site urticaria	2 (0.1)	0
Nervous system disorders	13 (0.9)	5 (0.7)
Dizziness	6 (0.4)	0
Investigations	12 (0.8)	5 (0.7)

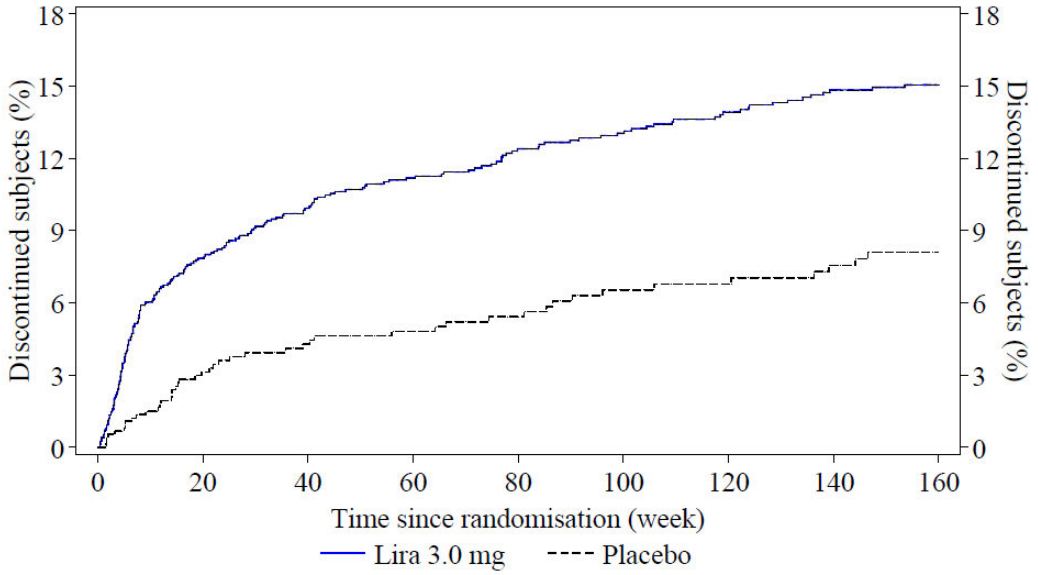
9 For the patient in the Saxenda group (b) (6) who withdrew due to 'target dose not tolerated', a corresponding AE was not reported and this patient does therefore not contribute to the summaries of AEs leading to withdrawal.

Lipase increased	11 (0.7)	2 (0.3)
Amylase increased	3 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (0.7)	2 (0.3)
Breast cancer	3 (0.2)	0
Psychiatric disorders	9 (0.6)	8 (1.1)
Skin and subcutaneous tissue disorders	8 (0.5)	1 (0.1)
Rash	2 (0.1)	0
Urticaria	2 (0.1)	0
Infections and infestations	6 (0.4)	2 (0.3)
Hepatobiliary disorders	5 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders	5 (0.3)	0
Muscle spasms	3 (0.2)	0
Ear and labyrinth disorders	3 (0.2)	1 (0.1)
Vertigo	3 (0.2)	0
Metabolism and nutrition disorders	3 (0.2)	1 (0.1)
Cardiac disorders	2 (0.1)	3 (0.4)
Injury, poisoning and procedural complications	2 (0.1)	1 (0.1)
Surgical and medical procedures	2 (0.1)	1 (0.1)
Reproductive system and breast disorders	2 (0.1)	0
PTs with greater than 1 patient in the Saxenda group and incidence greater than placebo included.		

Source: Reviewer created from 1839-3y datasets

Approximately 80% of the TEAEs leading to permanent treatment discontinuation had an onset during year 1 in both treatment groups. The higher frequency of AEs leading to permanent treatment discontinuation with Saxenda was primarily due to the higher rates of gastrointestinal events seen during year 1, especially during the first ~10-12 weeks of the treatment period.

Figure 5. Time to Discontinuation, Primary Reason for Discontinuation was AEs



Note: AE withdrawals (total) include subjects withdrawn due to adverse events or target dose not tolerated, or the withdrawal critera for acute pancreatitis or psychiatric disorder

Source: Trial 1839-3y CSR, Figure 10-2

The proportions of patients with serious AEs leading to permanent treatment discontinuation were higher with Saxenda (2.5%) than with placebo (1.3%). This difference was primarily driven by imbalances in the SOCs 'neoplasms benign, malignant and unspecified', 'gastrointestinal disorders', and 'hepatobiliary disorders'. The most frequent SAEs by PT leading to permanent treatment discontinuation were breast cancer (Saxenda 3 events, placebo 0 events), pancreatitis acute (Saxenda 3 events, placebo 1 event), and pancreatitis (Saxenda 2 events, placebo 0 events).

Adverse events with 'dose reduction' recorded as action taken to trial product occurred in a greater proportion of patients treated with Saxenda (1.7%) vs. placebo (0.3%). The most frequent AEs leading to dose reduction were gastrointestinal disorders (1.2% Saxenda vs. 0.3% placebo), and included events of nausea, diarrhea, and abdominal pain. Events leading to dose reduction primarily occurred during dose escalation.

Adverse events with temporary discontinuation of trial drug occurred in a greater proportion of patients treated with Saxenda (12.5%) vs. placebo (6.7%). Gastrointestinal disorder AEs were the most frequent event types leading to temporary discontinuation of trial drug with both treatments (Saxenda 5.2%, placebo 2.0%): vomiting (1.9% vs. 0.3%), nausea (1.7% vs. 0.3%), and diarrhea (1.3% vs. 0.3%) were reported at a greater incidence with Saxenda than placebo. Lipase increased (1.3% vs. 0.3%) and gastritis (0.5% vs. 0) also more commonly led to temporary discontinuation of trial drug with Saxenda than with placebo. Other events occurred less frequently.

7.3.4 Significant Adverse Events

Generalized Hypersensitivity Reactions

The Warnings and Precautions section of the Saxenda label includes the following information about hypersensitivity reactions:

There have been reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with liraglutide …. If a hypersensitivity reaction occurs, the patient should discontinue Saxenda and other suspect medications and promptly seek medical advice.

Angioedema has also been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to angioedema with Saxenda.

A pre-defined MedDRA search was conducted to identify potential allergic reactions; the terms utilized in the search are listed below:

Table 28. Allergic Reaction Terms

Included terms
SMQ Anaphylactic reaction (narrow scope)
SMQ Anaphylactic/anaphylactoid shock conditions (narrow scope)
SMQ Angioedema (narrow scope)
SMQ Severe cutaneous adverse reactions (narrow scope)
SMQ Asthma/bronchospasm (narrow scope)
PTs: Documented hypersensitivity to administered drug, Type II hypersensitivity, Type IV hypersensitivity reaction

Abbreviations: PT: preferred term; SMQ = standardised MedDRA query.

Source: Trial 1839-3y CSR, Table 12-53

Reviewer comment: These terms/SMQs missed the PT 'drug hypersensitivity' for which there were 9 events (0.6%) in the Saxenda group and 2 events (0.3%) in the placebo group. In each case, the verbatim terms indicated that the suspect drug was not study drug.

Overall, the proportion of allergic events was 3.9% in the Saxenda group and 3.5% in the placebo group (Table 29). More patients on Saxenda than placebo experienced urticaria (1.3% vs. 0.4%). Of the patients with urticaria AEs, 3 patients treated with Saxenda discontinued trial drug temporarily and 2 patients treated with Saxenda permanently discontinued treatment due to urticaria; all these patients recovered from the urticaria events after discontinuation of treatment (temporary or permanent).

Table 29. Allergic Reaction AEs

	Saxenda N=1501	**Placebo N=747**
Allergic events	58 (3.9)	26 (3.5)
Asthma	21 (1.4)	19 (2.5)
Urticaria	19 (1.3)	3 (0.4)
Bronchial hyperreactivity	4 (0.3)	1 (0.1)
Bronchospasm	2 (0.1)	1 (0.1)
Swelling face	2 (0.1)	1 (0.1)
Anaphylactic reaction	2 (0.1)	0
Circulatory collapse	2 (0.1)	0
Lip swelling	2 (0.1)	0
Type IV hypersensitivity reaction	2 (0.1)	0
Angioedema	1 (0.1)	1 (0.1)
Eye swelling	1 (0.1)	0
Face edema	1 (0.1)	0
Pharyngeal edema	1 (0.1)	0
Urticaria chronic	1 (0.1)	0
Gingival swelling	0	1 (0.1)

Source: Trial 1839-3y CSR, Table 12-55

None of the allergic events were fatal. Three SAEs were reported by 3 patients treated with Saxenda (anaphylactic reaction, asthma, and circulatory collapse), and 1 event in one patient on placebo (angioedema). Narratives of the SAEs are as follows:

- Saxenda – anaphylactic reaction: Patient (b) (6) was a 64-year-old female with relevant medical history of eczema, xerostomia, asthma, and intermittent anaphylaxis of unknown cause. Since 1974 the patient reported having intermittent allergic reactions where she would break out with itching and hives from an unknown cause. Nine months into the trial, the patient was camping and became very hot and then started itching. Within a few minutes the patient noticed that she had large (quarter-sized) hives. The patient took diphenhydramine orally. Within 5 to 10 minutes the patient began to have difficulty swallowing and breathing. The patient then called her husband to request that he call an ambulance. The ambulance transferred the patient to a hospital where she was treated with cetirizine, prednisone, and epinephrine. She recovered the same day.

- Saxenda – asthma: Patient (b) (6) was a 38-year-old female with a history of asthma. Sixteen months after starting the trial, the patient began to experience worsening shortness of breath and a productive cough with yellowish phlegm. Two days later, the patient presented to the emergency room and was hospitalized. Chest x-ray was negative. The patient was diagnosed with acute asthma exacerbation with bronchitis. The patient was treated with steroids, terbutaline, magnesium sulfate, and azithromycin and released the same day.

- Saxenda – circulatory collapse: Patient (b) (6) was a 65-year-old female with a medical history of obesity, hypothyroidism, osteoporosis, microlithiasis, and gallbladder surgery. Five months into the trial the patient experienced circulatory collapse at home after having diarrhea the day before. The patient hit her head and was hospitalized. Five days later, the patient recovered from the event and was discharged.

Reviewer comment: Although the PT 'circulatory collapse' is included in the allergic event SMQ, this event seems unlikely to have been the result of allergy, rather due to hypovolemia from GI losses.

- Placebo – angioedema: Patient (b) (6) was a 44-year-old female with no medical or family history of allergies or intolerances. After 1 year of treatment in the trial, the patient received a bee sting and developed angioedema (swelling of the face, tongue, and upper respiratory tract) approximately 10 minutes later. She was admitted to the hospital and recovered in 5 days.

Local Injection Site Reactions

A pre-defined MedDRA search based on the following terms was conducted to identify any potential injection site reactions:

Table 30. Injection Site Reaction Terms

Included terms	
HLT Administration site reactions NEC	HLT Lipodystrophies
HLT Application and instillation site reactions	HLT Injection site reactions
HLT Infusion site reactions	

Abbreviations: HLT: high level term.

Source: Trial 1839-3y CSR, Table 12-56

The proportion of patients with injections site reactions by MedDRA search was higher with Saxenda (14.8%) than with placebo (11.0%). This difference between treatment groups was primarily driven by PTs of injection site erythema, injection site reaction, injection site pruritus, injection site rash, and injection site urticaria (Table 31).

Table 31. Injection Site Reaction AEs

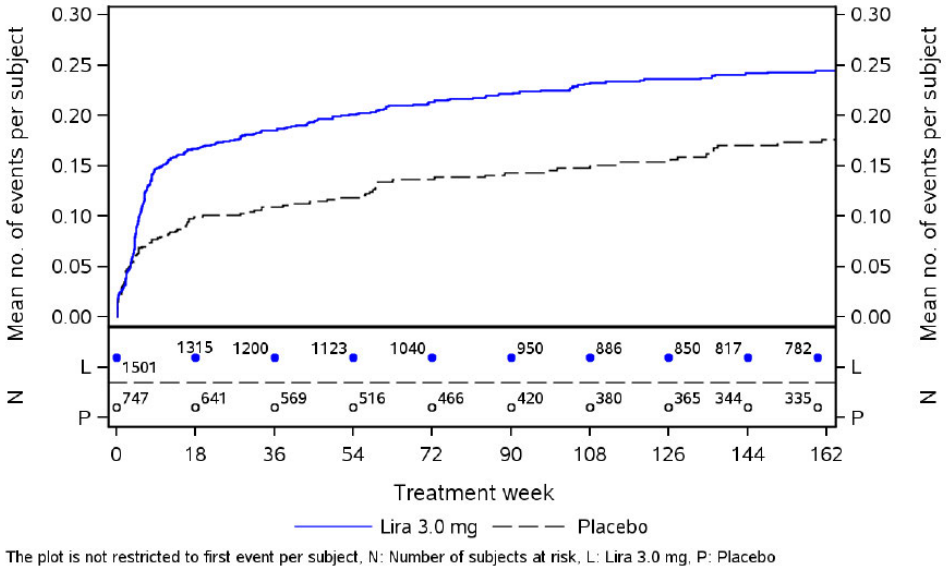
	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1501				747			
Years of observation time	3218.9				1470.2			
All events	222	(14.8)	325	10.1	82	(11.0)	107	7.3
General disorders and administration site conditions	221	(14.7)	324	10.1	82	(11.0)	107	7.3
Administration site reactions	221	(14.7)	324	10.1	82	(11.0)	107	7.3
Injection site haematoma	91	(6.1)	102	3.2	60	(8.0)	68	4.6
Injection site erythema	53	(3.5)	68	2.1	2	(0.3)	2	0.1
Injection site reaction	41	(2.7)	45	1.4	6	(0.8)	6	0.4
Injection site pain	22	(1.5)	26	0.8	14	(1.9)	14	1.0
Injection site pruritus	22	(1.5)	24	0.7	3	(0.4)	3	0.2
Injection site rash	13	(0.9)	13	0.4	2	(0.3)	2	0.1
Injection site urticaria	10	(0.7)	10	0.3	1	(0.1)	1	<0.1
Injection site nodule	6	(0.4)	8	0.2	0	(0.0)	0	0.0
Injection site haemorrhage	4	(0.3)	4	0.1	4	(0.5)	4	0.3
Injection site mass	4	(0.3)	4	0.1	1	(0.1)	1	<0.1
Injection site swelling	4	(0.3)	4	0.1	2	(0.3)	2	0.1
Vessel puncture site haematoma	4	(0.3)	4	0.1	0	(0.0)	0	0.0
Injection site hypersensitivity	2	(0.1)	2	<0.1	0	(0.0)	0	0.0
Injection site irritation	2	(0.1)	2	<0.1	0	(0.0)	0	0.0
Injection site paraesthesia	2	(0.1)	2	<0.1	0	(0.0)	0	0.0
Injection site hypertrophy	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Injection site induration	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Injection site inflammation	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Injection site papule	1	(<0.1)	1	<0.1	1	(0.1)	1	<0.1
Injection site scab	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Vessel puncture site swelling	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Injection site discomfort	0	(0.0)	0	0.0	1	(0.1)	2	0.1
Injection site dysaesthesia	0	(0.0)	0	0.0	1	(0.1)	1	<0.1
Skin and subcutaneous tissue disorders	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Skin and subcutaneous tissue disorders NEC	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Lipohypertrophy	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0

Source: Trial 1839-3y CSR, Table 12-58

None of the injection reaction AEs was serious. Two AEs (injection site pain) were severe, both in patients treated with Saxenda; both patients recovered without change in dose of trial drug. Six patients treated with Saxenda and 4 patients treated with placebo discontinued due to injection site reactions; all patients who discontinued early recovered from the events.

Figure 6 illustrates events of injection site reaction over time. Most events associated with Saxenda treatment were reported in the first 10-12 weeks.

Figure 6. Mean Cumulative Event Over Time Plot for Injection Site Reaction AEs



Source: Trial 1839-3y CSR, Figure 12-31

7.3.5 Submission Specific Primary Safety Concerns

Pancreatitis and Elevated Amylase/Lipase

In the pre-approval clinical trials for Saxenda, acute pancreatitis was confirmed by adjudication in 9 (0.3%) of 3291 Saxenda-treated patients and 1 (0.1%) of 1843 placebo-treated patients. In addition, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported post-marketing with liraglutide. Acute pancreatitis is included in the Warnings and Precautions section of the Saxenda label.

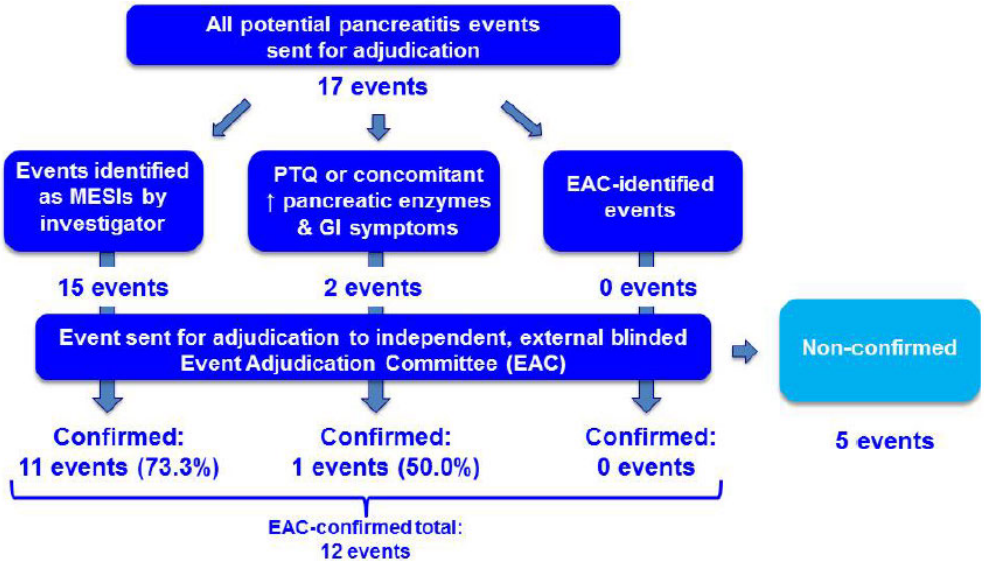
According to the 1839 protocol, the clinical diagnosis of acute pancreatitis was based on the presence of at least 2 of the following diagnostic criteria:
1. Amylase and/or lipase activity levels ≥ 3× the upper normal range (UNR)
2. Characteristic abdominal pain
3. Characteristic findings of acute pancreatitis by imaging (ultrasound, CT, MRI)

Pancreatitis and suspicion of pancreatitis (acute, severe, persistent abdominal pain) were to be reported as MESIs by the investigator and sent for adjudication by the external EAC. In addition, to identify potential cases of pancreatitis not reported as MESIs by the investigator, a sponsor-defined preferred term query (PTQ) search for pancreatitis [MedDRA SMQ Acute pancreatitis (narrow scope) and HLT Acute and chronic pancreatitis] and events of pancreatic enzyme elevations (e.g., amylase or lipase) that occurred within 30 days of pre-defined gastrointestinal symptoms (including abdominal distension / pain / tenderness / rigidity, ascites, gastrointestinal pain,

jaundice, nausea, vomiting), was conducted. All events identified by the searches were sent for pre-evaluation at an external independent company (ICON), which forwarded events relevant for adjudication together with source information to the EAC.

The figure below illustrates the flow of events that resulted in the positively adjudicated cases:

Figure 7. Adjudication of Potential Pancreatitis Events



Note: The percentages are calculated from the total number of events sent for adjudication within each subcategory.
Abbreviations: EAC = event adjudication committee; GI = gastrointestinal; MESI = medical event of special interest; PTQ = (Novo Nordisk defined) preferred term query.
Source: Trial 1839-3y CSR, Figure 12-15

All events except 1 that were reported by the investigator as 'pancreatitis acute' or 'pancreatitis' were confirmed by the EAC as acute pancreatitis. Events of pancreatic disorder or the more nonspecific term of abdominal pain (reported in isolation) were not confirmed. The single case with the PT 'pancreatitis' that was not confirmed by the EAC is as follows:

- Saxenda – pancreatitis: Patient (b) (6) was a 64-year-old female with a medical history of obesity, hysterectomy, operated diverticulosis, shigellosis, gastric ulcer, migraine, and elevated transaminases. After approximately 2 years on study drug, the patient presented with new soreness in her back, but without nausea, vomiting, fever or rapid pulse. No gallstones were present. The only reported abnormal laboratory result was lipase, at 67 (reference range 0 - 60). Amylase was 55 IU/L (reference range 20 - 112 IU/L). CT scan and MRI of pancreas showed mild edema in the anterior side of the pancreatic head and body. No free fluid and no signal

changes in tissue. Bile ducts were normal. The changes were reportedly consistent with mild irritation of pancreas (pancreatitis). The diagnosis was mild pancreatitis. The trial product was discontinued permanently due to withdrawal criteria 5, pancreatitis. The patient subsequently recovered.

Of the 12 EAC-confirmed events of acute pancreatitis, 10 events (0.7%) occurred in patients on Saxenda and 2 events (0.3%) occurred in patients on placebo. Two events in Saxenda-treated patients were non-TEAEs that occurred in patients who discontinued Saxenda during the first year; events were reported 74 and 125 days after the last dose of trial drug. One of the patients had a possible history of alcohol abuse and the other was withdrawn due to chronic cholelithiasis, which had not resolved at the onset of the pancreatitis event.

Eight of the 10 EAC-confirmed events of acute pancreatitis in the Saxenda group occurred within the first year of treatment, and 2 events within the second year. The 2 events in the placebo group occurred in year 1 and year 3.

In addition to the 12 EAC-confirmed pancreatitis cases, 1 additional pancreatitis event was identified after the 172-week trial completion in a patient previously treated with Saxenda (patient 503001); this case with onset 106 days after last dose of trial drug was later EAC-confirmed as acute pancreatitis.

Details of the EAC-confirmed pancreatitis events are listed below:

Table 32. Patients with EAC-Confirmed Acute Pancreatitis

Subject ID Age[a]/Sex/ BMI[a]	Preferred term	Onset (days)/ Duration (days) Period	Days on treatment[b]	Diagnostic criteria fulfilled acc. to EAC[c]	Withdrawal criterion	Serious (Y/N)/ Severity/ Outcome/ Causality	Elevated ALAT (Y/N)	Severity (revised Atlanta classification)[d]	Comments including relevant medical history
Liraglutide 3.0 mg									
(b) (6) 52/M/62.9	Pancreatitis acute	32/4 Treatment	N/A	Abdominal pain, enzymes	WC#5	Y/Severe/ R/Probable	Y ALAT 4×UNR	Mild	No relevant medical history
(b) (6) 51/M/32.7	Pancreatitis acute	30/5 Treatment	N/A	Abdominal pain, enzymes	WC#5	Y/Severe/ R/Probable	N	Mild	Hypercholesterolaemia at screening concomitant simvastatin use. Amylase and lipase ≥3×UNR at time of EAC-confirmed pancreatitis event
(b) (6) 58/M/34.7	Pancreatitis acute	44/2 Treatment	N/A	Abdominal pain, imaging	WC#5	N/Severe/ R/Possible	N	Mild	No relevant medical history
(b) (6) 64/M/38.1	Pancreatitis	110/5 Withdrawn	36 (74 days off liraglutide) Non-TEAE	Abdominal pain, enzymes	N/A	Y/Moderate/ R/Unlikely	Y ALAT 3×UNR	Mild	Possible alcohol abuse
(b) (6) 51/F/48.6	Lipase increased	278/15 Treatment	N/A	Abdominal pain, enzymes	AE (lipase increased)	N/Mild/ R/Possible	N	Mild	Smoker Lipase ≥3×UNR at time of EAC-confirmed pancreatitis event
(b) (6) 40/F/41.7	Pancreatitis	284/9 Treatment	N/A	Abdominal pain, enzymes, imaging	WC#5	Y/Severe/ R/Probable	Y ALAT 8×UNR	Moderately severe	Alcohol abuse, diagnosed with cholelithiasis at time of event
(b) (6) 41/F/42.9	Pancreatic pseudocyst	296/92 Withdrawn	171 (125 days off liraglutide) Non-TEAE	Abdominal pain, enzymes, imaging	N/A	Y/Severe/ R/Unlikely	Unknown (ASAT 24×UNR)	Moderately severe	Withdrawn due to a non-TEAE of cholecystitis chronic (microlithiasic according to the investigator) with onset on trial day 188; not yet recovered at time of the pancreatitis event.

Subject ID Age[a]/Sex/ BMI[a]	Preferred term	Onset (days)/ Duration (days) Period	Days on treatment[b]	Diagnostic criteria fulfilled acc. to EAC[c]	Withdrawal criterion	Serious (Y/N)/ Severity/ Outcome/ Causality	Elevated ALAT (Y/N)	Severity (revised Atlanta classification)[d]	Comments including relevant medical history
(b) (6) 40/M/34.0	Pancreatitis acute	331/92 Treatment	N/A	Abdominal pain, imaging	WC#5	Y/Moderate/ R/Possible	Y ALAT<1.5×UNR	Moderately severe	No relevant medical history
(b) (6) 62/F/38.7	Gastroenteritis	411/29 Treatment	N/A	Abdominal pain, enzymes	WC#5	Y/Moderate/ R/Probable	N	Mild	History of hyperlipidaemia, chronic gastritis, non-erosive reflux disease.
(b) (6) 48/F/45.1	Pancreatitis	626/9 Treatment	N/A	Abdominal pain, imaging	AE (pancreatitis)	Y/Moderate/ R/Possible	N	Mild	History of gastroesophageal reflux disease, hyperlipidaemia, hepatic steatosis.
(b) (6) 69/M/35.2	Pancreatitis acute	1224/5 After follow-up	1118 (106 days off liraglutide) Non-TEAE	Abdominal pain, enzymes, imaging	N/A	Y/Severe R with sequelae/ Unknown	Y ALAT 8×UNR	Moderately severe	History of cholecystectomy, acute cholecystitis and reflux oesophagitis.
Placebo									
(b) (6) 55/F/35.5	Pancreatitis	288/105 Treatment	N/A	Abdominal pain, imaging	AE (pancreatitis)	N/Mild/ R/Possible	Y ALAT 2.5×UNR	Mild	Diagnosed with cholelithiasis a few days prior to this event
(b) (6) 64/F/34.7	Pancreatitis acute	887/5 Treatment	N/A	Enzymes, imaging	WC#5	Y/Severe/ R/Possible	N	Moderately severe	Irritable bowel.

Note: Comments and information on elevated ALAT at onset of the pancreatitis events are based on information in the case narratives from the safety database and source documents.

Abbreviations: AE = adverse event; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; F = female; M = male; N = no; N/A = not applicable (for subjects who discontinued treatment permanently prior to the event); non-TEAE = non-treatment emergent adverse event; R = recovered; SAS = safety analysis set; UNR = upper limit of normal range; WC#5 = withdrawal criterion 5 (subjects who were diagnosed with acute pancreatitis had to be withdrawn from the trial); Y = yes.

[a] Baseline value. [b] Only applicable for subjects reporting non-TEAEs. [c] For diagnosis of pancreatitis, as a minimum 2 of 3 criteria (characteristic abdominal pain, amylase and/or lipase >3×UNR or characteristic findings on ultrasound/CT/MRI) had to be fulfilled. [d] According to Banks *et al*[70] (based on sponsor's review of case narratives).

Source: Trial 1839-3y CSR, Table 12-34

As noted in the table above, evidence of gallstones at the time of the pancreatitis event was observed for 3 patients (Saxenda 2, placebo 1), including 1 Saxenda patient who was withdrawn from the trial due to chronic cholecystitis prior to the pancreatitis event. All 3 events occurred >280 days post-baseline. In 3 additional cases without imaging evidence of gallstones, elevation of ALT > 3x ULN at the time of diagnosis of pancreatitis was reported (all in the Saxenda group). The sponsor has previously suggested that elevations in liver enzymes at the time of diagnosis of acute pancreatitis support a diagnosis of gallstone pancreatitis.[10]

All but 3 of the confirmed pancreatitis events were reported as SAEs by the investigator, and all patients with treatment emergent events were withdrawn from the trial due to the acute pancreatitis, either using the specific pancreatitis withdrawal criterion or the AE withdrawal criterion.

Amylase and Lipase

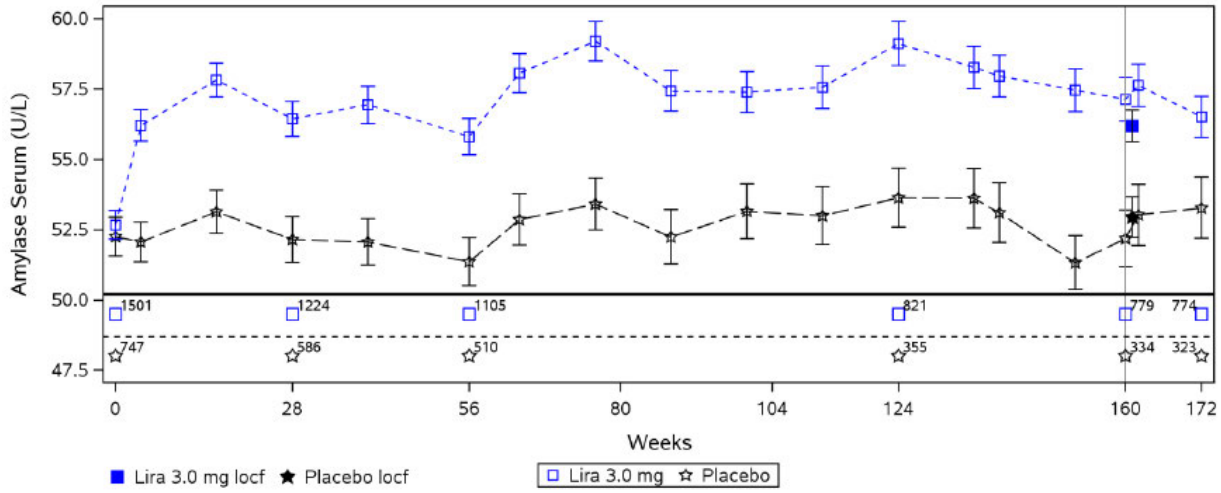
Liraglutide is associated with increases in serum amylase and lipase of unknown clinical significance.

Geometric mean plot of amylase and lipase values over time in the Saxenda and placebo treatment groups are shown below, demonstrating that mean amylase and lipase increased over the first few weeks to a greater extent with Saxenda treatment as

10 Novo Nordisk Advisory Committee Briefing Document, NDA 206321, referencing Tenner S, et al. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. Am J Gastroenterol 1994; 89(10):1863-6.

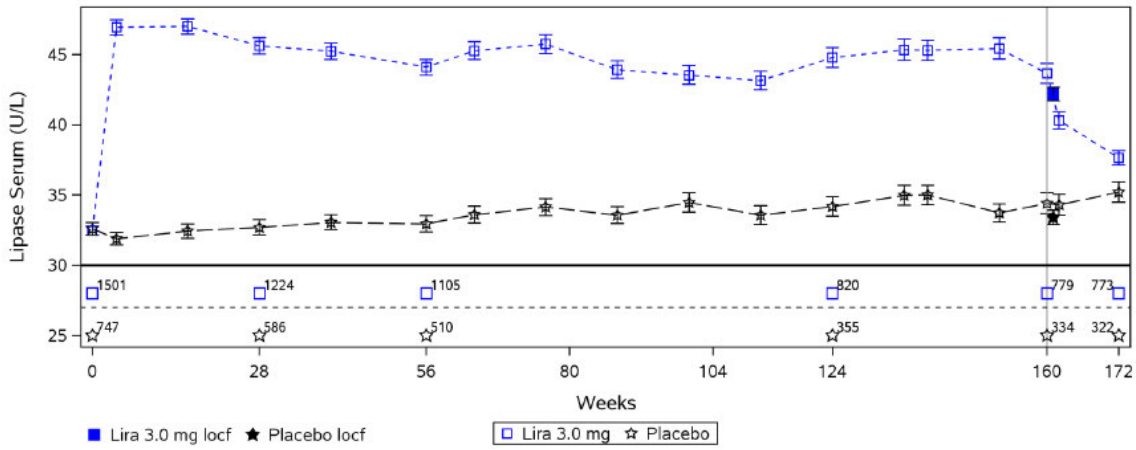
compared to placebo; however, mean values remained within the normal range (UNR 112 U/L and 60 U/L for amylase and lipase, respectively).

Figure 8. Mean Amylase Over Time



Source: Trial 1839-3y CSR, Figure 12-17

Figure 9. Mean Lipase Over Time



Source: Trial 1839-3y CSR, Figure 12-18

The proportions of patients with shifts to > UNR were greater in Saxenda-treated patients compared with placebo-treated patients (Table 33). Although only 2 patients treated with Saxenda (vs. no patients treated with placebo) with baseline value < UNR experienced more than 1 amylase elevation ≥ 3x ULN during the trial, 78 (5.2%) Saxenda-treated patients vs. 11 (1.5%) placebo-treated patients experienced more than 1 lipase elevation ≥ 3x UNR (Table 33). Amylase and lipase values ≥ 3x UNR were reported as MESI in this trial.

Table 33. Amylase and Lipase Category Shift from Baseline to Maximum Value During Treatment

Number of subjects	Max - Amylase/Lipase (U/L) until week 160				
Baseline (Week 0)	< UNR N (%)	UNR - <2xUNR N (%)	2xUNR - <3xUNR N (%)	>= 3xUNR N (%)	Missing N (%)
Amylase					
Lira 3.0 mg					
Safety analysis set	1501				
< UNR	1266 (84.3)	162 (10.8)	10 (0.7)	2 (0.1)	21 (1.4)
UNR - <2xUNR	5 (0.3)	29 (1.9)	3 (0.2)	1 (0.1)	1 (0.1)
2xUNR - <3xUNR	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
>= 3xUNR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Placebo					
Safety analysis set	747				
< UNR	683 (91.4)	37 (5.0)	2 (0.3)	0 (0.0)	13 (1.7)
UNR - <2xUNR	1 (0.1)	11 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
2xUNR - <3xUNR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>= 3xUNR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase					
Lira 3.0 mg					
Safety analysis set	1501				
< UNR	688 (45.8)	561 (37.4)	76 (5.1)	78 (5.2)	21 (1.4)
UNR - <2xUNR	3 (0.2)	26 (1.7)	21 (1.4)	17 (1.1)	1 (0.1)
2xUNR - <3xUNR	1 (0.1)	1 (0.1)	2 (0.1)	2 (0.1)	0 (0.0)
>= 3xUNR	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)
Placebo					
Safety analysis set	747				
< UNR	571 (76.4)	93 (12.4)	22 (2.9)	10 (1.3)	13 (1.7)
UNR - <2xUNR	6 (0.8)	23 (3.1)	4 (0.5)	3 (0.4)	0 (0.0)
2xUNR - <3xUNR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>= 3xUNR	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)

Lira: liraglutide, SAS: safety analysis set.
UNR: Upper limit of normal range for amylase is 112 U/L and for lipase is 60 U/L.
Numbers highlighted in grey indicate upward shifts in amylase or lipase activity level category.
Measurements from planned visits, unscheduled visits and retest are included.

Source: Trial 1839-3y CSR, Table 12-35

A MedDRA search was conducted to evaluate AEs of increased amylase and lipase. The proportion of patients with AEs of increased amylase and lipase were higher with Saxenda than with placebo (amylase increased: Saxenda 2.2%, placebo 0.3%; lipase increased: Saxenda 9.7%, placebo 3.1%). Two events of lipase increased with Saxenda were considered serious; neither patient (141026 and 173020) had EAC-confirmed pancreatitis or was hospitalized (however, one non-serious event of lipase increased was positively adjudicated as pancreatitis; see Table 32).

In addition, 8 AEs with the PT hyperamylasemia were reported by 6 patients, all treated with Saxenda, and 3 AEs of hyperlipasemia were reported by 2 patients, both treated with Saxenda.

Acute Gallstone Disease

Acute gallstone disease was a novel safety finding in the Saxenda phase 3 program as it had not been previously described with Victoza; (b) (4) The recent publication of the LEADER cardiovascular outcomes trial indicated that acute gallstone disease was reported more frequently with Victoza than placebo (3.1% vs. 1.9%).[11]

A pre-defined MedDRA search to identify events potentially related to acute gallstone disease was performed based on the SMQs listed below:

Table 34. Terms Included in the MedDRA Search for Acute Gallstone Disease

Included terms	
SMQ Bile duct related disorders	SMQ Infectious biliary disorders
SMQ Biliary system related disorders and investigations, signs and symptoms	SMQ Site unspecified biliary disorders
SMQ Gallstone related disorders	SMQ Gallbladder related disorders

Abbreviations: SMQ = standardised MedDRA query.
Source: Trial 1839-3y CSR, Table 12-38

The search identified 93 acute gallstone disease AEs in 74 (4.9%) patients treated with Saxenda and 18 events in 13 (1.7%) patients treated with placebo (Table 35). In the Saxenda group, 2.3% of patients had events that were serious and 1.2% severe compared with 0.8% and 0.3%, respectively, for placebo. None of the events were fatal. Events that led to withdrawal occurred in 0.3% of patients treated with Saxenda vs. no patients treated with placebo.

Cholecystectomy was performed in 30 of 45 patients (66.7%) on Saxenda and 5 of 11 patients (45.5%) on placebo with AEs of cholelithiasis. One patient on Saxenda withdrew from the trial due to cholelithiasis. Two patients (1 Saxenda, 1 placebo) had gallstones and concomitant elevated liver enzymes at the time of an EAC-confirmed pancreatitis event (see pancreatitis section, above). Six patients (4 Saxenda, 2 placebo) also reported cholecystitis or acute cholecystitis events in association with cholelithiasis.

The majority of cholecystitis AEs (PTs: cholecystitis and cholecystitis acute) were serious in both treatment groups. Severe events were only reported with Saxenda. Cholecystectomy was performed in 15 of 16 (93.4%) patients with events in the Saxenda group and 1 of 3 patients (33.3%) in the placebo group. One patient on Saxenda discontinued from the trial due to acute cholecystitis.

11 Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;374:311-22.

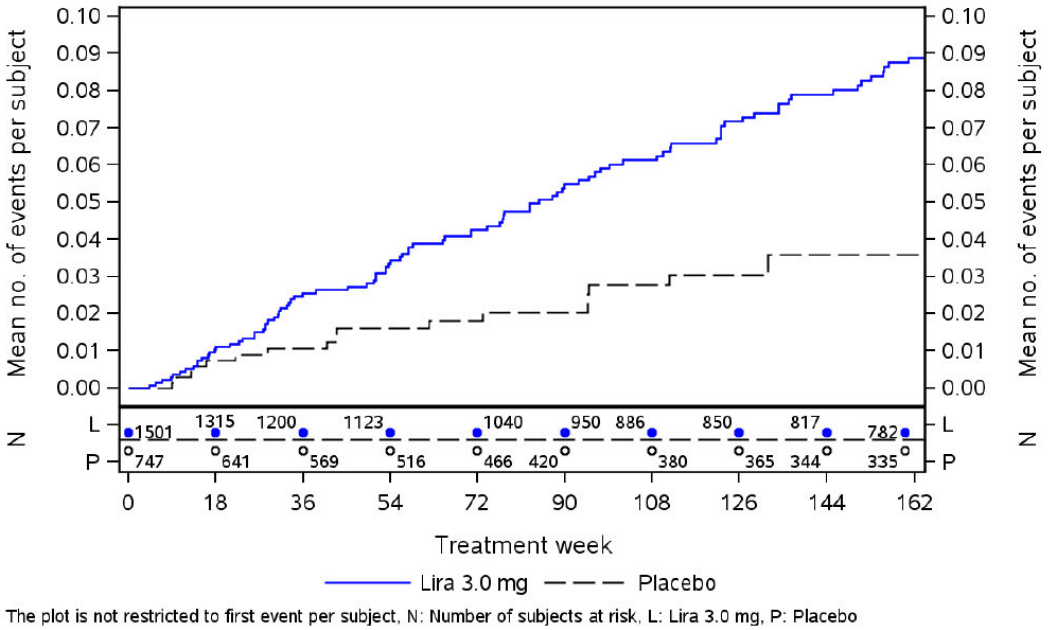
Table 35. Acute Gallstone Disease (Pre-Defined MedDRA Search) by SOC and PT

	Saxenda N=1501 n (%)	Placebo N=747 n (%)
Acute gallstone disease	74 (4.9)	13 (1.7)
Hepatobiliary disorders	69 (4.6)	13 (1.7)
Cholelithiasis	45 (3.0)	11 (1.5)
Cholecystitis acute	9 (0.6)	2 (0.3)
Cholecystitis	7 (0.5)	1 (0.1)
Biliary colic	5 (0.3)	1 (0.1)
Cholecystitis chronic	5 (0.3)	0
Bile duct stone	4 (0.3)	0
Gallbladder disorder	3 (0.2)	0
Hyperplastic cholecystopathy	1 (<0.1)	1 (0.1)
Hyperbilirubinemia	1 (<0.1)	0
Investigations	6 (0.4)	1 (0.1)
Blood alkaline phosphatase increased	5 (0.3)	1 (0.1)
Blood bilirubin increased	1 (<0.1)	0

Source: Trial 1839-3y CSR, Table 14.3.1.184

Time to onset of acute gallstone disease is shown in the figure below, indicating that patients reported acute gallstone disease during the trial at a relatively constant rate (and higher for Saxenda vs. placebo).

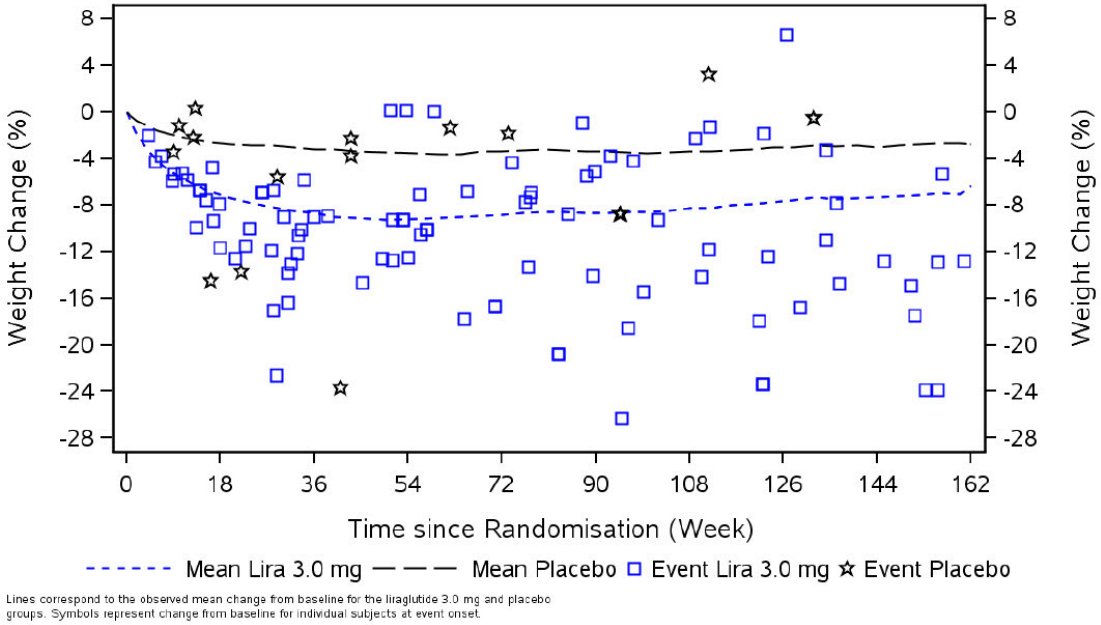
Figure 10. Mean Cumulative Event Over Time Plot of Acute Gallstone Disease



Source: Trial 1839-y CSR, Figure 12-20

As weight loss is associated with gallstone formation,[12] the sponsor analyzed the weight loss of patients with acute gallstone events. As shown in Figure 11, there was generally a greater weight loss among Saxenda-treated patients with gallstone AEs than in the overall Saxenda population; this pattern was not evident with placebo. Note that there is an ongoing post-marketing commitment (2802-9) to assess the effect of liraglutide on gallbladder motility, as an attempt to delineate any weight loss-independent effects of liraglutide on gallbladder safety.

Figure 11. Percent Weight Change from Baseline at the Onset of Acute Gallstone Disease AEs



Source: Trial 1839-3y CSR, Figure 12-21

Hypoglycemia

Although the glucose-lowering effect of liraglutide via insulin secretion is glucose-dependent, suggesting that hypoglycemia should be infrequent in patients not receiving concomitant insulin or insulin secretagogues, hypoglycemia remains an event of interest with liraglutide-containing products.

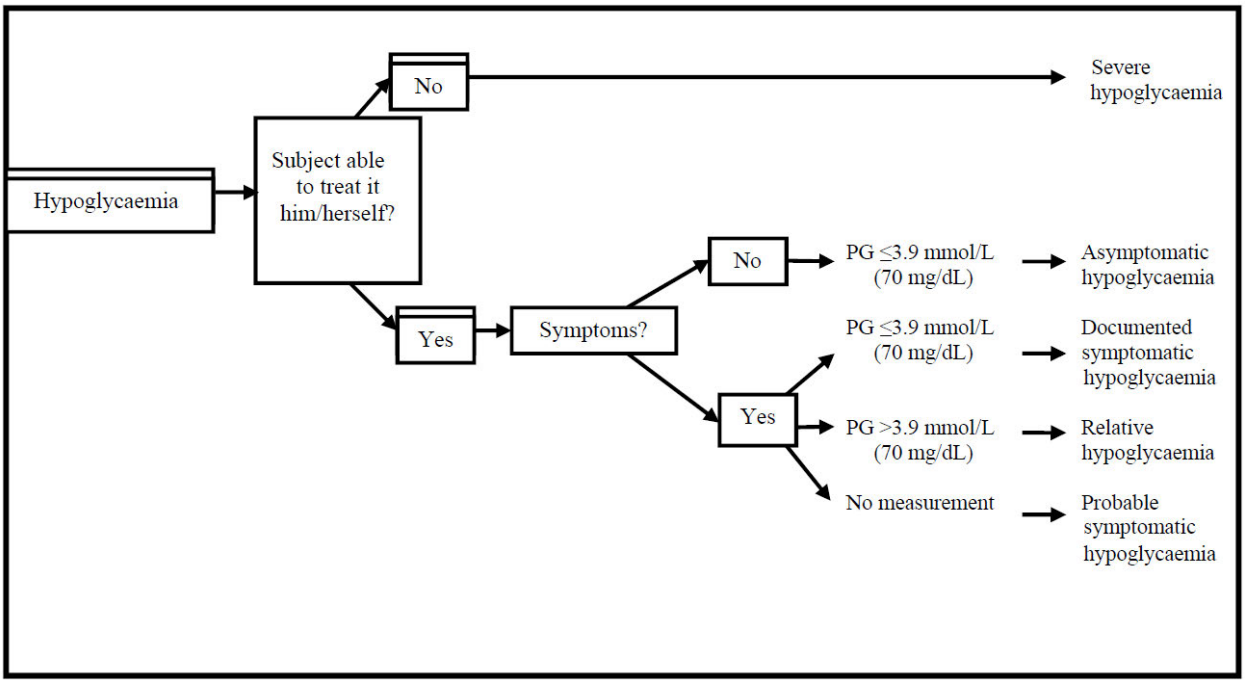
Hypoglycemic episodes (including all FPG values or PG values from OGTT visits measured by the central laboratory that met the definition of a hypoglycemic episode) during the trial were recorded on an AE page. If the hypoglycemic episode fulfilled the criteria for an SAE or an MESI (i.e., a severe hypoglycemic episode as defined below),

12 Weinsier RL and Ullmann DO. Gallstone formation and weight loss. Obes Res. 1993; 1: 51-6.

a hypoglycemic episode form, an AE form, and a safety information form (SIF) had to be completed.

Hypoglycemic episodes captured on a hypoglycemic episode form were classified according to the American Diabetes Association (ADA) definition:

Figure 12. Classification of Hypoglycemia



Source: Trial 1839-3y CSR, Figure 9-3

ADA hypoglycemia classification:

- *Severe hypoglycemia*: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
- *Documented symptomatic hypoglycemia:* An episode during which typical symptoms of hypoglycemia are accompanied by a measured PG concentration ≤ 70 mg/dL
- *Asymptomatic hypoglycemia:* An episode not accompanied by typical symptoms of hypoglycemia, but with a measured PG concentration ≤ 70 mg/dL
- *Probable symptomatic hypoglycemia:* An episode during which symptoms of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by a PG concentration ≤ 70 mg/dL)
- *Relative hypoglycemia:* An episode during which the person with diabetes reported any of the typical symptoms of hypoglycemia, and interpreted those as indicative of hypoglycemia, but with a measured PG concentration > 70 mg/dL

In addition, the sponsor had an additional definition of 'minor' hypoglycemia, where hypoglycemia symptoms occur at a blood glucose < 50 mg/dL (PG < 56 mg/dL) and which the patient handled himself/herself, or any asymptomatic blood glucose < 50 mg/dL (PG < 56 mg/dL).

During the trial, no severe hypoglycemic episodes by ADA criteria were reported.

Patients without T2DM
As shown below in Table 36, Saxenda was associated with more events of hypoglycemia reported spontaneously, at FPG visits, and at OGTT visits. In interpreting this finding, note that:

- The reporting of spontaneous hypoglycemia events was based on symptoms alone and not supported by biochemical measurements, as patients were not provided with a blood glucose meter unless they were diagnosed with T2DM.
- The investigators were instructed to report all FPG values ≤ 70 mg/dL as AEs of hypoglycemia.
- The mean FPG was reduced at end-of-treatment (week 160) with Saxenda and was slightly increased with placebo (see Section 6.1.6, Table 11). This suggests that Saxenda-treated patients were more likely to achieve the ≤ 70 mg/dL ADA threshold for hypoglycemia reporting as compared to placebo-treated patients.
- The AE form was used at the discretion of the investigator to report events of hypoglycemia during the OGTT.
- As symptoms were not systematically collected for the hypoglycemia events, it is not possible to differentiate between asymptomatic 'biochemical hypoglycemia' and symptomatic 'reactive hypoglycemia' during the OGTT.

Table 36. Hypoglycemic Episodes Reported as AEs by Visit Type and Plasma Glucose Value, Patients without T2DM

Visit Type	Nominal Time	Criteria	Saxenda			Placebo		
			N	%	E*	N	%	E*
Number of patients without T2DM			1470			700		
All events			293	19.9	634	33	4.7	49
Spontaneously reported			50	3.4	60	12	1.7	16
Reported at FPG visit			62	4.2	79	6	0.9	6
		FPG ≤ 70 mg/dL	60	4.1	77	6	0.9	6
		FPG < 56 mg/dL	3	0.2	3	0	0.0	0
Reported at OGTT visit			235	16.0	495	18	2.6	27
		FPG ≤ 70 mg/dL	37	2.5	52	2	0.3	3
		FPG < 56 mg/dL	2	0.1	2	1	0.1	1
		PG ≤ 70 mg/dL	212	14.4	465	16	2.3	24
		PG < 56 mg/dL	77	5.2	130	3	0.4	6
	10 min	PG ≤ 70 mg/dL	11	0.7	15	0	0.0	0
		PG < 56 mg/dL	2	0.1	2	0	0.0	0
	20 min	PG ≤ 70 mg/dL	2	0.1	3	0	0.0	0
		PG < 56 mg/dL	0	0.0	0	0	0.0	0
	30 min	PG ≤ 70 mg/dL	4	0.3	6	0	0.0	0
		PG < 56 mg/dL	0	0.0	0	0	0.0	0
	60 min	PG ≤ 70 mg/dL	35	2.4	55	1	0.1	1
		PG < 56 mg/dL	7	0.5	11	0	0.0	0
	90 min	PG ≤ 70 mg/dL	91	6.2	181	4	0.6	5
		PG < 56 mg/dL	18	1.2	32	1	0.1	2
	120 min	PG ≤ 70 mg/dL	190	12.9	388	15	2.1	23
		PG < 56 mg/dL	66	4.5	104	3	0.4	6

N: Number of patients experiencing at least one episode, %: percentage of patients experiencing at least one episode, E*: Number of hypoglycemic events or number of measurements leading to reporting of an hypoglycemic event, FPG: Fasting plasma glucose, OGTT: oral glucose tolerance test, PG: plasma glucose

Note: one hypoglycemic event can be based on multiple consecutive measurements of low PG values. PG values were sampled at nominal times 10, 20, 30, 60, 90 and 120 minutes.

Spontaneously reported events: events which are not reported on the same day as a (fasting) PG value.

Events that fulfill the < 56 mg/dL criterion also fulfill the ≤ 70 mg/dL criterion.

Source: Trial 1839-3y CSR, Table 12-69

None of these events were serious, were reported as a MESI by the investigator, or led to discontinuation of treatment. Five events in 4 patients (all in patients treated with Saxenda) were reported as 'severe' (by eCRF classification, *not* ADA criteria). For 1 of these subjects, the event was reported based on symptoms between trial visits and was

not confirmed by PG measurements. For 3 of these subjects, the severe hypoglycemia AEs were reported on the same day as an OGTT visit. All 4 patients recovered and continued without change to trial drug. See Table 37 for details (glucose values obtained from the patients' OGTTs are included in the table footnotes).

Table 37. Severe Hypoglycemia AEs (Investigator-Classified), Patients without T2DM

Subject ID Age[a]/Sex/ BMI[a]	Reported term	Event confirmed by PG measurement	Onset day/ Duration	SAE/WD/ Severity Outcome	Comments
Liraglutide 3.0 mg					
(b) (6) 38/F/36.3	Hypoglycemia (participant did not eat she said)	N	373/1	N/N/Severe Recovered	Spontaneously reported event with onset between trial visits. Recovered with no change to trial drug.
(b) (6) 58/F/38.2	Asyntomatic Hypoglicemia at 90' of OGTT	Y (reported at OGTT visit)	564/1	N/N/Severe Recovered	The subject also reported hypoglycaemia TEAEs (mild/moderate events) on 3 other OGTT visits dates (corresponding to nominal visits at week 28, 56 and 104). Recovered from all the hypoglycaemia events with no change to trial drug.
	Asyntomatic Hypoglicemia at 120' of OGTT	Y (reported at OGTT visit)	564/1	N/N/Severe Unknown	
(b) (6) 64/F/33.1	Asynthomatic hypoglicemia at 120' of OGTT	Y (reported at OGTT visit)	725/1	N/N/Severe Recovered	The subject also reported hypoglycaemia TEAEs (mild/moderate events) on 3 other OGTT visits dates (corresponding to nominal visits at week 28, 56 and 128). Recovered from all the hypoglycaemia events with no change to trial drug.
(b) (6) 43/F/41.1	Hypoglycemia	Y (reported at OGTT visit)	1065/1	N/N/Severe Recovered	The subject also reported 2 mild hypoglycaemia TEAEs: 1 on another other OGTT visits date (corresponding to nominal visit at week 128) and 1 with onset between trial visits (on day 290) without confirmation by PG measurement. Recovered from all the hypoglycaemia events with no change to trial drug.

Abbreviations: BMI = body mass index; F = female; N = no; OGTT = oral glucose tolerance test; PG = plasma glucoes; SAS = safety analysis set; TEAE = treatment-emergent adverse event; WD = withdrawn; Y = yes.

[a] Baseline value.

Glucose values from the OGTTs: Patient (b) (6): 45 and 43 mg/dL; Patient (b) (6): 50 mg/dL; Patient (b) (6): no reported OGTT glucose values on that date < 91 mg/dL (blood glucose on a subsequent visit reported as 69 mg/dL)
Source: Trial 1839-3y CSR, Table 12-70

The majority of hypoglycemia events occurred at a single visit; however, more Saxenda-treated patients reported hypoglycemia at multiple visits, particularly at OGTT visits:

Table 38. Number of Hypoglycemic Events, Patients without T2DM

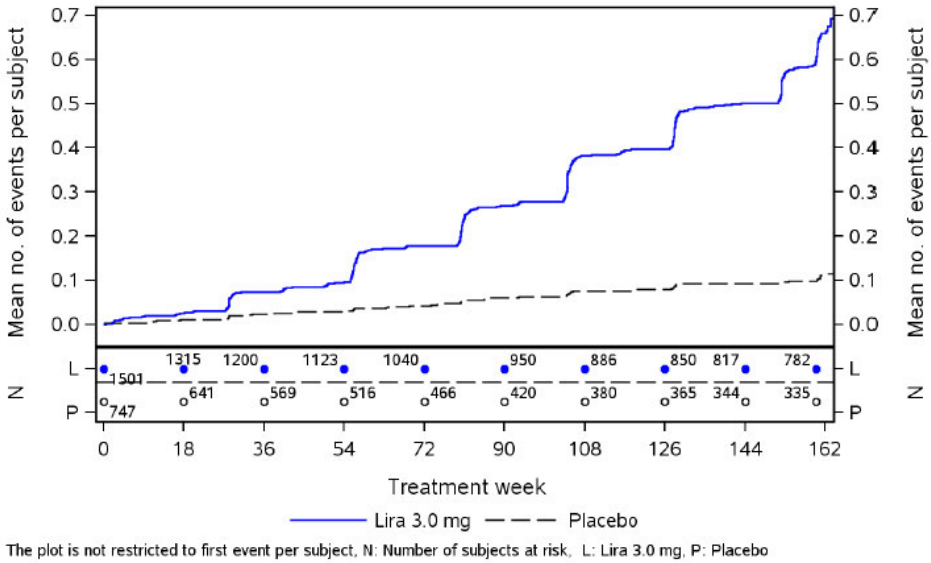
	Lira 3.0 mg	Placebo
Number of subjects without Type II Diabetes	1470	700
Number of subjects with at least one visits where a hypo AE is reported at the day of the visit	274	23
Number of subjects with AE's of hypo reported at 1 visit	143	17
Number of subjects with AE's of hypo reported at 1 FPG visit	31	5
Number of subjects with AE's of hypo reported at 1 OGTT visit	110	12
Number of subjects with AE's of hypo reported at 2 visits	55	4
Number of subjects with AE's of hypo reported at 2 FPG visits	4	0
Number of subjects with AE's of hypo reported at 2 OGTT visit	41	3
Number of subjects with AE's of hypo reported at 3 visits	36	1
Number of subjects with AE's of hypo reported at 3 FPG visits	2	0
Number of subjects with AE's of hypo reported at 3 OGTT visits	27	1
Number of subjects with AE's of hypo reported at 4 visits	19	0
Number of subjects with AE's of hypo reported at 4 FPG visits	0	0
Number of subjects with AE's of hypo reported at 4 OGTT visits	16	0
Number of subjects with AE's of hypo reported at 5 visits	6	1
Number of subjects with AE's of hypo reported at 5 FPG visits	0	0
Number of subjects with AE's of hypo reported at 5 OGTT visits	3	1
Number of subjects with AE's of hypo reported at 6 or more visits	15	0
Number of subjects with AE's of hypo reported at 6 or more FPG	0	0
Number of subjects with AE's of hypo reported at 6 or more OGTT visits	11	0

Please note that one hypoglycaemic event can be based upon multiple consecutive measurements of low PG values.
FPG: Fasting plasma glucose, OGTT: oral glucose tolerance test, PG: plasma glucose T2DM: type 2 diabetes mellitus
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.
A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment.
Output presents data for subjects with pre-diabetes at baseline and includes 6 subjects who did not have pre-diabetes at baseline, but participated in the extension period of the trial.

Source: Trial 1839-3y CSR, Table 14.3.1.387

Hypoglycemia AEs had an onset throughout the trial with both treatments; however, increases in the mean number of events were observed around the time points for OGTT and FPG visits, especially in the Saxenda group:

Figure 13. Mean Cumulative Hypoglycemia Events Over Time, Patients without T2DM



Source: Trial 1839-3y CSR, Figure 12-34

Patients with T2DM

Patients who developed T2DM during the trial were supplied with a glucose meter and a diabetes diary for recording hypoglycemia. Patients were encouraged to measure their FPG concentrations on a regular basis at the discretion of the investigator. In addition, patients were asked to measure PG upon symptoms of hypo- or hyperglycemia. The investigator could ask the subject to perform additional self-measurements if needed for safety reasons.

If self-measured FPG fell below 117 mg/dL, or increased above 270, 240, or 200 mg/dL depending on the week on 3 consecutive days/occasions, the subject was to contact the investigator. The outcome was to be recorded on an unscheduled visit form in the eCRF.

PG was always to be measured when there was a suspicion of a hypoglycemic episode. All PG values ≤ 70 mg/dL, as well as symptomatic values > 70 mg/dL were to be recorded by the patients in the diaries.

Hypoglycemic events were reported on the specific hypoglycemia form for patients with T2DM. As seen in Table 39, few subjects who were diagnosed with T2DM during the trial (up to 162 weeks) recorded hypoglycemic episodes on the hypoglycemia form. None of the hypoglycemia events reported in either treatment group were classified as severe or documented symptomatic according to the ADA classification.

Table 39. Hypoglycemic Episodes by Classification, Patients with T2DM

	Lira 3.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	26				46			
Years of observation time	26.9				59.0			
Novo Nordisk hypoglycaemia classification								
Minor	0	(0.0)	0	0.0	1	(2.2)	1	1.7
ADA hypoglycaemia classification	1	(3.8)	1	3.7	3	(6.5)	5	8.5
Severe	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Documented symptomatic	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Asymptomatic	1	(3.8)	1	3.7	3	(6.5)	5	8.5
Probable symptomatic	0	(0.0)	0	0.0	0	(0.0)	0	0.0
Relative	0	(0.0)	0	0.0	0	(0.0)	0	0.0
ADA unclassified	1	(3.8)	2	7.4	0	(0.0)	0	0.0

N: Number of subjects, %: Percentage of subjects, E: Number of events, R: Event rate per 100 years of observation time, T2DM: type 2 diabetes mellitus, ADA: American Diabetes Association, SAS: safety analysis set.
Minor hypoglycaemia: An episode with or without symptoms confirmed by plasma glucose < 3.1 mmol/L (56 mg/dL) or full blood glucose <2.8 mmol/L (50 mg/dL) and which is handled by the subject himself/herself.
Only subjects developing T2DM were given a blood glucose meter.
Table is based on the eCRF hypo form. The observation time is calculated from onset of T2DM.
A treatment-emergent hypoglycaemic episode is defined as an event that has onset date on or after the first randomised treatment and no later than 14 days after the last day of randomised.
Source: Trial 1839-3y CSR, Table 12-71

None of the hypoglycemia events reported as AEs in either treatment group were classified as serious or led to discontinuation. The single patient on Saxenda who had hypoglycemia events reported on the form (3 events: 1 asymptomatic and 2 ADA unclassifiable) was not on any concomitant antihyperglycemic medications, according to the concomitant medications dataset.

Spontaneous hypoglycemia and hypoglycemia during FPG and OGTT visits were also recorded in those patients who developed T2DM prior to their diagnosis. A total of 3 patients (9.7%) treated with Saxenda and no patients treated with placebo had hypoglycemia events reported. All events occurred during the OGTT.

Thyroid Disease and Elevated Calcitonin

Events of thyroid disease requiring thyroidectomy and thyroid neoplasms were sent for adjudication. Nine events of thyroid disease requiring thyroidectomy reported by 8 patients were sent for adjudication; of these, 5 events in 4 patients were confirmed thyroid events by the EAC [3 events in 3 patients were thyroid neoplasms (all in the Saxenda-treated group) and 2 events in 1 patient were thyroid non-neoplasm disorders (placebo-treated group)]. All events sent for adjudication and subsequent EAC diagnosis is reported in Table 40, below. Thyroid neoplasms are further discussed under Section 7.6.1, Human Carcinogenicity.

Table 40. Thyroid Disease Requiring Thyroidectomy Events Sent for Adjudication

Subject ID/ Treatment/ Country/ Age/Sex/BMI	AENO/ Ievt/ Cevt/ CbAE	MESI (Y/N)	EAC Category/ Confirmed (Y/N)	System Organ Class/ Preferred Term/ Reported Term	TE	Onset Date/ Study Day/ Exposure	Thyroid Neoplasm (Y/N)	Type of Thyroid Neoplasm	Neoplasm Malignancy Status/Stage	EAC Diagnosis
(b) (6) Placebo/ DE/ 68/F/42.5	7/ / /	Y	Thyroid/ Y	Endocrine disorders/ Goitre/ Struma multinodosa both sides	Y	(b) (6) 769/ 769	N			colloid nodules
	8/ / /	Y	Thyroid/ Y	Endocrine disorders/ Hyperthyroidism/ hyperthyriodism	Y	(b) (6) 960/ 960	N			colloid nodule
(b) (6) Placebo/ DE/ 69/M/52.1	12/ / /	Y	Thyroid/ N	Endocrine disorders/ Hyperthyroidism/ latente hyperthyreosis by struma nodosa	Y	(b) (6) 785/ 785	N			
(b) (6) Lira 3.0 mg/ AT/ 45/M/39.4	20/ / /	Y	Thyroid/ Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Thyroid cancer/ Thyroid papillary micro carcinoma	Y	(b) (6) 833/ 833	Y	PAPILLARY MICORCARCINOMA	MALIGNANT	papillary microcarcinoma
(b) (6) Placebo/ FR/ 64/F/36.9	5/ / /	Y	Thyroid/ N/A	Endocrine disorders/ Toxic nodular goitre/ toxic macronodular goiter	Y	(b) (6) 779/ 779	N			No tissue diagnosis provided for this thyroid mass

Subject ID/ Treatment/ Country/ Age/Sex/BMI	AENO/ Ievt/ Cevt/ CbAE	MESI (Y/N)	EAC Category/ Confirmed (Y/N)	System Organ Class/ Preferred Term/ Reported Term	TE	Onset Date/ Study Day/ Exposure	Thyroid Neoplasm (Y/N)	Type of Thyroid Neoplasm	Neoplasm Malignancy Status/Stage	EAC Diagnosis
(b) (6) Lira 3.0 mg/ FR/ 61/F/38.8	5/ / /	Y	Thyroid/ Y	Endocrine disorders/ Autoimmune thyroiditis/ lymphocitic thyroiditis	N	(b) (6) 378/ 142	Y	PAPILLARY MICROCARCINOMA	PRE-MALIGNANT/CARCINOMA IN SITU/BORDERLINE	papillary microcarcinoma
(b) (6) Lira 3.0 mg/ GB/ 49/M/33.9	11/ / /	Y	Thyroid/ N	Investigations/ Blood thyroid stimulating hormone increased/ Thyroid panel TSH-3 ultra high result	Y	(b) (6) 618/ 618	N			
(b) (6) Lira 3.0 mg/ GB/ 43/F/47.8	13/ / /	Y	Thyroid/ Y	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Thyroid cancer/ Incidental 3mm thyroid papillary microcarcinoma (pT1a pN0 TNM7)	Y	(b) (6) 552/ 552	Y	PAPILLARY MICROCARCINOMA	PRE-MALIGNANT/CARCINOMA IN SITU/BORDERLINE	papillary microcarcinoma
(b) (6) Lira 3.0 mg/ US/ 60/F/45.8	16/ / /	Y	Thyroid/ N	Endocrine disorders/ Goitre/ Worsening of Goiter	Y	(b) (6) 338/ 338	N			

AE: Adverse event, Age (years), BMI: Body mass index (kg/m^2), CbAE: Combined adverse event number, Cevt: Combined event (Y), EAC: Event adjudication committee (external), F: Female, Ievt: Index event (Y), M: Male, MESI: Medical event of special interest, N: No, N/A: Not applicable, Study day: Time from first drug date to AE onset, TE: treatment emergent, TIA: Transient ischemic attack, Y: Yes
A treatment emergent adverse event is defined as an event that has onset date on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment.Thyroid neoplasms identified through thyroidectomy are included in summaries of neoplasms sent for adjudication as well as in summaries of thyroid disease evaluated by the EAC. Thyroid neoplasms identified through thyroidectomy are included in summaries of neoplasms sent for adjudication as well as in summaries of thyroid disease evaluated by the EAC. Output presents data for subjects with pre-diabetes at baseline and includes 6 subjects who did not have pre-diabetes at baseline, but participated in the extension period of the trial.

Source: Trial 1839-3y CSR, Table 16.2.7.34

In addition to adjudicated thyroid events, a pre-defined MedDRA search for thyroid disease was conducted using the terms below:

Table 41. Terms Included in the MedDRA Search for Thyroid Disease

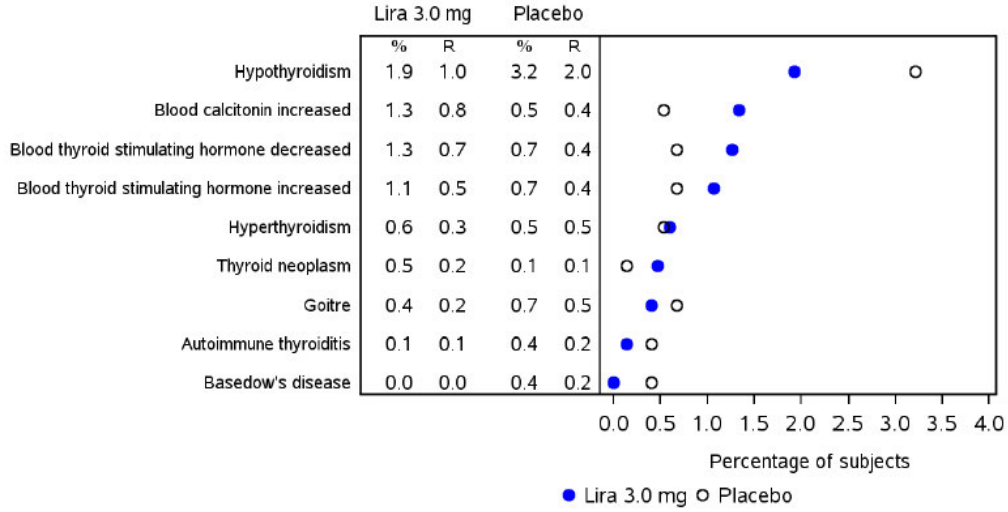
Included terms
SMQ Hyperthyroidism
SMQ Hypothyroidism
HLGT Thyroid gland disorders
PTs: Calcitonin secretion disorder, ectopic calcitonin production, hypercalcitoninaemia, blood calcitonin abnormal, blood calcitonin increased.

Abbreviations: HLGT =high level group term; PT = preferred term; SMQ = standardised MedDRA query.

Source: Trial 1839-3y CSR, Table 12-47

A similar proportion (6.7%) of patients treated with Saxenda (100 patients with 136 events) and placebo (50 patients with 72 events) reported AEs of thyroid disease according to the MedDRA search. The most frequently reported PTs were hypothyroidism, blood calcitonin increased, blood thyroid stimulating hormone decreased, and blood thyroid stimulating hormone increased (Figure 14).

Figure 14. Most Frequent Thyroid Disease AEs



Source: Trial 1839-3y CSR, Figure 12-27

Six thyroid disease AEs were considered serious: 2 SAEs in the Saxenda group of thyroid neoplasm and 4 SAEs in the placebo group of Basedow's disease,[13] goiter, hyperthyroidism, and toxic nodular goiter. One AE in the placebo group (hyperthyroidism) led to withdrawal.

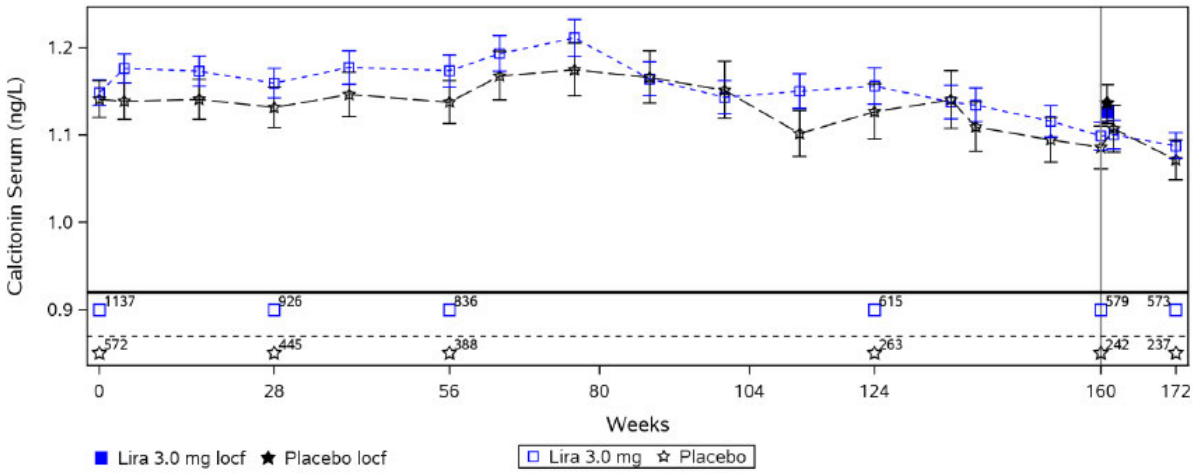
No AEs of the PT 'blood calcitonin increased' were serious, severe, or led to treatment discontinuation.

13 Another eponym for Grave's disease

Calcitonin

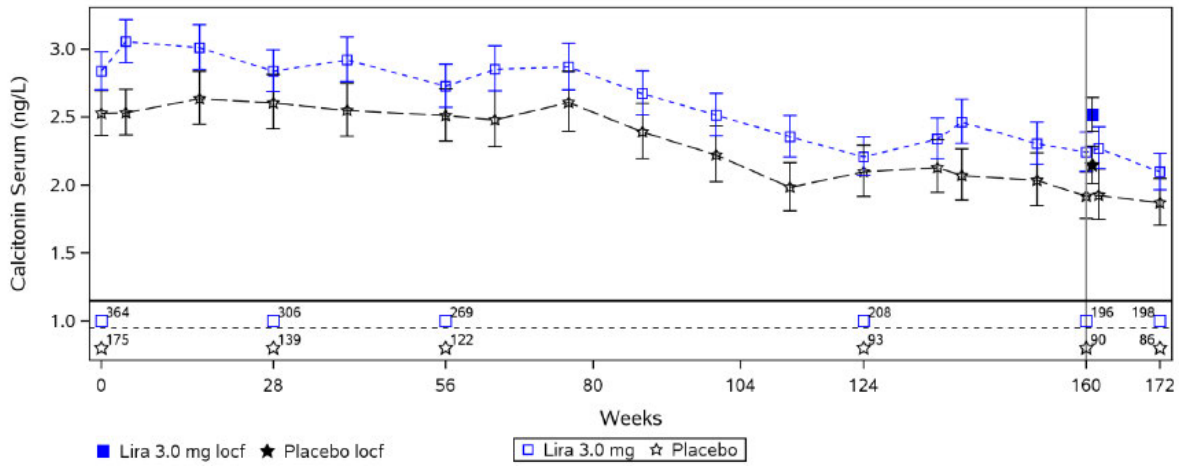
Elevated calcitonin, defined as any confirmed episode of calcitonin value ≥ 20 ng/L was to be reported by the investigator as a MESI. Calcitonin was monitored at regular intervals by an independent calcitonin monitoring committee of thyroid experts. Adjudication was not performed. The UNR for females is 5.0 ng/L and for males 8.4 ng/L. As seen in the figures below, mean serum calcitonin values at baseline were higher in the Saxenda vs. the placebo group in male patients, but this was not observed in female patients.

Figure 15. Calcitonin Over Time, Females



Source: Trial 1839-3y CSR, Figure 12-28

Figure 16. Calcitonin Over Time, Males



Source: Trial 1839-3y CSR, Figure 12-29

As shown in Table 42, by week 160 more female patients on placebo had calcitonin > UNR, whereas more male patients on Saxenda had calcitonin > UNR. One male patient had calcitonin > 50 ng/L during the trial (ID 214027, value 84 ng/L); his calcitonin levels were below UNR again at the retest performed 1 month later as well as at all subsequent measurements, and no symptoms were reported.

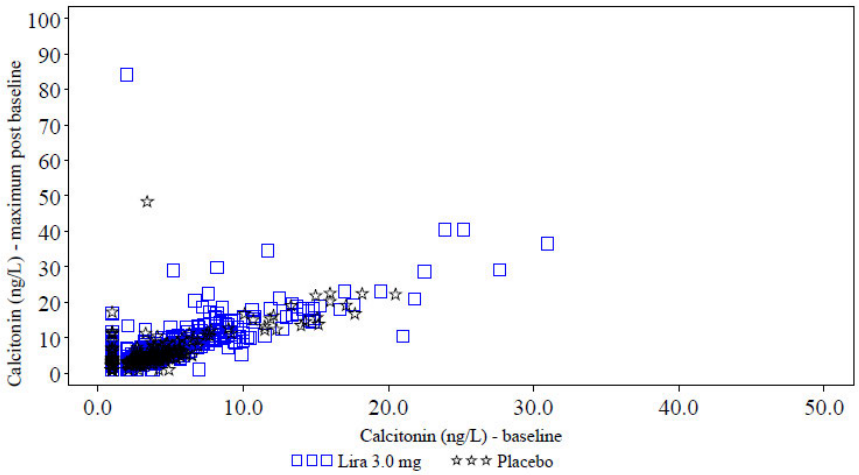
Table 42. Calcitonin Values Above Designated Cut-Points by Sex

	Female subjects						Male subjects					
	Lira 3.0 mg			Placebo			Lira 3.0 mg			Placebo		
	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
SAS	1137			572			364			175		
Calcitonin >= UNR												
Week -2	1132	39	(3.4)	571	21	(3.7)	363	81	(22.3)	175	24	(13.7)
Week 0	1137	30	(2.6)	572	13	(2.3)	364	52	(14.3)	175	15	(8.6)
Week 56	836	22	(2.6)	388	8	(2.1)	269	39	(14.5)	122	10	(8.2)
Week 112	631	20	(3.2)	268	4	(1.5)	218	23	(10.6)	94	9	(9.6)
Week 160	579	9	(1.6)	242	2	(0.8)	196	21	(10.7)	90	9	(10.0)
Week 160 LOCF	1119	20	(1.8)	561	12	(2.1)	361	46	(12.7)	172	16	(9.3)
Week 172	573	7	(1.2)	237	3	(1.3)	198	18	(9.1)	86	8	(9.3)
Calcitonin >= 1.5xUNR												
Week -2	1132	21	(1.9)	571	11	(1.9)	363	27	(7.4)	175	8	(4.6)
Week 0	1137	15	(1.3)	572	7	(1.2)	364	18	(4.9)	175	8	(4.6)
Week 56	836	11	(1.3)	388	5	(1.3)	269	11	(4.1)	122	5	(4.1)
Week 112	631	7	(1.1)	268	4	(1.5)	218	8	(3.7)	94	4	(4.3)
Week 160	579	2	(0.3)	242	2	(0.8)	196	4	(2.0)	90	1	(1.1)
Week 160 LOCF	1119	8	(0.7)	561	8	(1.4)	361	14	(3.9)	172	2	(1.2)
Week 172	573	4	(0.7)	237	2	(0.8)	198	5	(2.5)	86	3	(3.5)
Calcitonin >= 20 ng/L												
Week -2	1132	1	(0.1)	571	2	(0.4)	363	7	(1.9)	175	3	(1.7)
Week 0	1137	0	(0.0)	572	0	(0.0)	364	6	(1.6)	175	1	(0.6)
Week 56	836	0	(0.0)	388	0	(0.0)	269	2	(0.7)	122	0	(0.0)
Week 112	631	0	(0.0)	268	0	(0.0)	218	3	(1.4)	94	0	(0.0)
Week 160	579	0	(0.0)	242	0	(0.0)	196	1	(0.5)	90	0	(0.0)
Week 160 LOCF	1119	0	(0.0)	561	1	(0.2)	361	5	(1.4)	172	0	(0.0)
Week 172	573	0	(0.0)	237	0	(0.0)	198	2	(1.0)	86	0	(0.0)
Calcitonin >= 50 ng/L												
Week -2	1132	0	(0.0)	571	0	(0.0)	363	0	(0.0)	175	0	(0.0)
Week 0	1137	0	(0.0)	572	0	(0.0)	364	0	(0.0)	175	0	(0.0)
Week 56	836	0	(0.0)	388	0	(0.0)	269	0	(0.0)	122	0	(0.0)
Week 112	631	0	(0.0)	268	0	(0.0)	218	1	(0.5)	94	0	(0.0)
Week 160	579	0	(0.0)	242	0	(0.0)	196	0	(0.0)	90	0	(0.0)
Week 160 LOCF	1119	0	(0.0)	561	0	(0.0)	361	0	(0.0)	172	0	(0.0)
Week 172	573	0	(0.0)	237	0	(0.0)	198	0	(0.0)	86	0	(0.0)

N: Number of subjects, n: Number of subjects fulfilling criteria, %: Percentage of N, SAS: safety analysis set, UNR: Upper normal range (UNR for calcitonin is 5 ng/L for female subjects and 8.4 ng/L for male subjects).
Measurements from planned visits and retest are included (highest value used).

Source: Trial 1839-3y CSR, Table 12-48

Figure 17. Calcitonin Baseline vs. Maximum Post-Baseline



Source: Trial 1839-3y CSR, Figure 14.3.5.95

In general, more patients (primarily males) experienced incidental increases in calcitonin levels and at higher rates with Saxenda than with placebo.

Table 43. Incidental Increase in Calcitonin at Any Time During Treatment

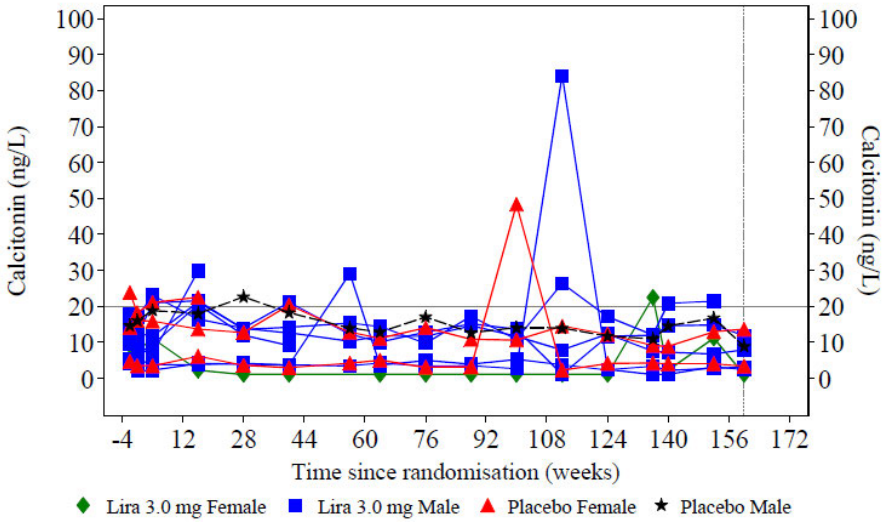
	Total				Females				Males			
	Lira		Placebo		Lira		Placebo		Lira		Placebo	
	N	R	N	R	N	R	N	R	N	R	N	R
Number of Subjects	1501		747		1137		572		364		175	
From < UNR to >= UNR	98	7.26	35	5.37	46	4.51	19	3.82	52	15.67	16	10.34
From < UNR to >= 1.5×UNR	30	2.22	6	0.92	19	1.86	6	1.21	11	3.32	0	0.00
From < UNR to >= 20 ng/L	4	0.30	1	0.15	0	0.00	1	0.20	4	1.21	0	0.00
From < UNR to >= 50 ng/L	1	0.07	0	0.00	0	0.00	0	0.00	1	0.30	0	0.00
From < 20 ng/L to >= 20 ng/L	8	0.59	4	0.61	1	0.10	3	0.60	7	2.11	1	0.65
From < 50 ng/L to >= 50 ng/L	1	0.07	0	0.00	0	0.00	0	0.00	1	0.30	0	0.00

Lira: Liraglutide 3.0 mg; N: Number of subjects, R: Rate per 100 exposure years, SAS: safety analysis set, UNR: Upper normal range.
UNR for Calcitonin is 5.0 ng/L for female subjects and 8.4 ng/L for male subjects.
Incidental increase: Baseline calcitonin value below upper limit and at least one scheduled post baseline calcitonin measurement above or equal to upper limit.

Source: Trial 1839-3y CSR, Table 12-49

The calcitonin profiles of individual patients with values ≥ 20 ng/L at any time during the trial are presented in Figure 18. No patient had a sustained calcitonin value ≥ 20 ng/L, although according to the figure below, 2 male patients on Saxenda had the last value recorded at ≥ 20 ng/L.

Figure 18. Individual Longitudinal Calcitonin Plots in Patients with Calcitonin ≥ 20 ng/L



Source: Trial 1839-3y CSR, Figure 14.3.5.107

No EAC-confirmed thyroid neoplasms were reported by patients with calcitonin values above 20 ng/L (see Section 7.6.1, Human Carcinogenicity, Table 71). The clinical significance of the observed calcitonin increases with liraglutide remains unclear.

Acute Renal Failure

The Warnings and Precautions section in the Saxenda label includes the following information regarding renal impairment:

In patients treated with GLP-1 receptor agonists, including Saxenda, there have been reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis. … Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea leading to volume depletion. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or volume status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Use caution when initiating or escalating doses of Saxenda in patients with renal impairment.

A pre-defined MedDRA search using the acute renal failure SMQ was performed to summarize AEs related to acute renal failure. A total of 26 events in 20 patients (1.3%) treated with Saxenda and 14 events in 11 patients (1.5%) treated with placebo were identified. The majority of preferred terms in the Saxenda group were of blood creatinine increased (Table 44). For approximately 62% of these events, the outcome

was recovered or recovering by the end of the trial in the Saxenda group (16 of 26 events), whereas all patients in the placebo group had recovered at the end of the trial (14 of 14 events). None led to permanent discontinuation of treatment in either treatment group.

Table 44. Acute Renal Failure SMQ by SOC, HLGT, and PT

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1501				747			
Years of observation time	3218.9				1470.2			
All events	20	(1.3)	26	0.8	11	(1.5)	14	1.0
Investigations	15	(1.0)	20	0.6	6	(0.8)	7	0.5
Renal and urinary tract investigations and urinalyses	15	(1.0)	20	0.6	6	(0.8)	7	0.5
Blood creatinine increased	13	(0.9)	15	0.5	4	(0.5)	4	0.3
Blood urea increased	2	(0.1)	3	0.1	1	(0.1)	1	<0.1
Glomerular filtration rate decreased	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Renal function test abnormal	1	(<0.1)	1	<0.1	1	(0.1)	1	<0.1
Protein urine present	0	(0.0)	0	0.0	1	(0.1)	1	<0.1
Renal and urinary disorders	5	(0.3)	6	0.2	7	(0.9)	7	0.5
Renal disorders (excl nephropathies)	4	(0.3)	5	0.2	4	(0.5)	4	0.3
Renal failure acute	2	(0.1)	2	<0.1	3	(0.4)	3	0.2
Renal impairment	2	(0.1)	2	<0.1	0	(0.0)	0	0.0
Renal failure	1	(<0.1)	1	<0.1	0	(0.0)	0	0.0
Oliguria	0	(0.0)	0	0.0	1	(0.1)	1	<0.1
Urinary tract signs and symptoms	1	(<0.1)	1	<0.1	3	(0.4)	3	0.2
Albuminuria	1	(<0.1)	1	<0.1	2	(0.3)	2	0.1
Proteinuria	0	(0.0)	0	0.0	1	(0.1)	1	<0.1

Source: Trial 1839-3y CSR, Table 12-51

SAEs captured within the search included 4 events reported by 3 patients with Saxenda (renal failure acute (2 events) and renal impairment (2 events)) and 3 events in 3 patients with placebo (renal failure acute (2 events) and oliguria (1 event)). One SAE of acute renal failure in the Saxenda group was co-reported with GI AEs (patient 510002, discussed in Table 45 below).

Details of the acute renal failure events within the HLGT ‘renal disorders’ are presented in Table 45.

Table 45. Acute Renal Failure SMQ Events within the Renal Disorders HLGT

Subject ID Age[a]/Sex/ BMI[a]	Preferred term	Onset day/ Exposure day/ Duration	SAE/WD/Severity Outcome	Comments including relevant medical history
Liraglutide 3.0 mg				
(b) (6) 64/F/47.1	Renal failure acute	49/49/6	Y/N/Severe Recovered	Medical history: chronic renal failure and hypertension. Creatinine ≥UNR at screening. The subject reported nausea, vomiting and diarrhoea on day 47. Trial drug temporarily withdrawn.
(b) (6) 43/M/38.3	Renal failure	283/283/-	N/N/Mild Not recovered	Medical history: hypertension. The subject reported a TEAE of atrioventricular block first degree on day 194 (not recovered at onset of renal failure event).
Subject ID Age[a]/Sex/ BMI[a]	**Preferred term**	**Onset day/ Exposure day/ Duration**	**SAE/WD/Severity Outcome**	**Comments including relevant medical history**
(b) (6) 57/M/40.9	Renal impairment	495/495/54	Y/N/Mild Recovering	Medical history: kidney stones and altered renal function (due to kidney stones). The subject also reported nephrolithiasis the day before the event (day 494).
(b) (6) 43/F/47.8	Renal failure acute	544/544/4	Y/N/Severe Recovered	Medical history: recurrent renal calculi and family history of hypertension. The subject reported nephrolithiasis on day 118 (lasted 493 days).
	Renal impairment	610/603/-	Y/N/Moderate Not recovered	
Placebo				
(b) (6) 68/M/50.7	Renal failure acute	308/308/31	N/N/Moderate Recovered	Medical history: chronic renal failure, hypertension, peripheral oedema. Creatinine ≥UNR at screening and at several visits during the trial. The subject also reported a TEAE of blood creatinine increased on day 28.
(b) (6) 60/M/37.5	Oliguria	391/391/2	Y/N/Moderate Recovered	Medical history: bladder dysfunction, chronic renal failure, hypertension. The subject also reported a TEAE of blood creatinine increased on day 617.
(b) (6) 46/M/40.2	Renal failure acute	1109/1108/3	Y/N/Moderate Recovered	Creatinine ≥UNR at screening.
(b) (6) 69/M/52.1	Renal failure acute	1129/1120/21	Y/N/Severe Recovered	Medical history: essential hypertension, renal insufficiency, peripheral oedema, renal cyst, Creatinine ≥UNR at screening and during the trial. The subject also reported non-TEAEs of renal failure and renal failure acute during the follow-up period (76 and 79 days after last dose of trial drug).

Abbreviations: BMI = body mass index; F = female; M = male; N = no; SAS = safety analysis set; TEAE = treatment-emergent adverse event; UNR = upper limit of normal range; WD = withdrawn; Y = yes.

[a] Baseline value.

Source: Trial 1839-3y CSR, Table 12-52

Psychiatric Disorders

As described in the original Saxenda review, the assessment of mood disorders and suicidality is a standard part of the safety review for any obesity drug with a centrally acting mechanism.[14,15,16,17] A warning for suicidal ideation and behavior is found in Section 5.8 of the Saxenda label.

The assessment of psychiatric disorders in the 1839 trial was based on AE reporting (SOC: psychiatric disorders) and the results of 2 mental health questionnaires (PHQ-9 and C-SSRS) conducted at baseline and during the trial to identify new-onset depression and/or suicidality.

Adverse Events
The proportions of patients with psychiatric AEs were similar between Saxenda-treated patients and placebo-treated patients, as were the proportions of patients with SAEs. No psychiatric events were fatal. The majority of events were captured within the HLGTs 'sleep disorders and disturbances', 'depressed mood disorders and disturbances', and 'anxiety disorders and symptoms'. Psychiatric SAEs reported for Saxenda were suicidal ideation, suicide attempt, and sleep apnea syndrome[18] (2 events), and for placebo, suicide attempt and depression. The patients with SAEs related to depression, suicidal ideation, or suicidal behavior recovered from the events. The sleep apnea SAEs were considered chronic conditions and the patients had not recovered at the end of the trial.[18]

A summary of AEs by PT from the SOC Psychiatric disorders[18] is provided below; the incidence was similar between groups. Most of the imbalance in individual PTs between groups not favoring Saxenda appears to be related to sleep disorders, such as insomnia, sleep disorder, and initial insomnia. Panic attack and suicidal ideation were also observed more frequently with Saxenda; AEs related to suicidality overall (i.e., not just in the Psychiatric disorders SOC) are discussed below.

14 Egan A. FDA Clinical Review of NDA [redacted] (b) (4) EMDAC 13 Jun 2007.
15 Golden J. FDA Clinical Review of NDA 22529 (lorcaserin), EMDAC 16 Sep 2010 and 10 May 2012.
16 Roberts M. FDA Clinical Review of NDA 22580 (phentermine/topiramate), EMDAC 15 July 2010 and 22 Dec 2012.
17 Craig E. FDA Clinical review of NDA 200063 (naltrexone/bupropion), EMDAC 7 Dec 2010.
18 The PT 'sleep apnea syndrome' is included in the Saxenda AE database with the SOC 'Respiratory, thoracic and mediastinal disorders', not 'Psychiatric disorders'. According to the MedDRA Browser version 19.1, 'Respiratory, thoracic and mediastinal disorders' is the primary SOC, with 'Psychiatric disorders' and 'Nervous system disorders' listed as secondary SOCs. In the reviewer summary tables that use the Saxenda datasets, 'sleep apnea syndrome' is not included.

Table 46. Psychiatric AEs, PTs with at Least 2 Patients on Saxenda Included

	Saxenda N=1501	Saxenda %	Placebo N=747	Placebo %
Psychiatric disorders SOC	233	15.5	117	15.7
Insomnia	68	4.5	25	3.3
Depression	56	3.7	31	4.1
Anxiety	49	3.3	27	3.6
Sleep disorder	16	1.1	4	0.5
Stress	12	0.8	10	1.3
Depressed mood	11	0.7	11	1.5
Panic attack	7	0.5	1	0.1
Initial insomnia	7	0.5	0	0.0
Suicidal ideation	7	0.5	0	0.0
Middle insomnia	6	0.4	2	0.3
Dysthymic disorder	5	0.3	1	0.1
Adjustment disorder	4	0.3	4	0.5
Major depression	4	0.3	3	0.4
Nervousness	3	0.2	2	0.3
Burnout syndrome	3	0.2	1	0.1
Panic disorder	3	0.2	1	0.1
Eating disorder	2	0.1	2	0.3
Libido decreased	2	0.1	2	0.3
Affective disorder	2	0.1	1	0.1
Agitation	2	0.1	1	0.1
Attention deficit/hyperactivity disorder	2	0.1	1	0.1
Restlessness	2	0.1	1	0.1
Terminal insomnia	2	0.1	1	0.1
Affect lability	2	0.1	0	0.0
Anxiety disorder	2	0.1	0	0.0
Decreased interest	2	0.1	0	0.0
Disorientation	2	0.1	0	0.0
Food aversion	2	0.1	0	0.0
Nightmare	2	0.1	0	0.0

Source: Reviewer created from trial 1839-3y datasets

Nine AEs in 7 patients (0.5%) treated with Saxenda and 2 AEs in 2 patients (0.3%) treated with placebo reported AEs related to suicidal ideation or self-injurious behavior using the MedDRA SMQ Suicide/self-injury. These events are described in Table 47. (The PTs for AEs that occurred in patients in the placebo group were 'suicide attempt' and 'depression suicidal'; neither was captured in Table 46, above.)

Table 47. AEs Related to Suicidality

Subject ID/ Age[a]/Sex/BMI[a]	Preferred term Onset/Duration	Other psychiatric AEs reported at onset	Comments and relevant medical history	SAE	WD due to event	PHQ-9 total score[b]		Q9 on PHQ-9		C-SSRS Ideation/behaviour	
						Screening/ Baseline	Max post-baseline	Screening/ Baseline	Max post-baseline	Lifetime	During treatment
Liraglutide 3.0 mg											
(b) (6) 42/F/43.9	Suicidal ideation 16/1	N	N	N	N	6/3	3	0/0	0	N/N	Y/N
(b) (6) 42/F/49.4	Suicide attempt 113/2 Suicidal ideation 113/29	Major depression, anxiety, depression	History of depression	Y N	N (WC#6) N	1/1	9	0/0	0	N/N	Y/N
(b) (6) 41/F/48.3	Suicidal ideation 327/1 Suicidal ideation 701/49	Depression, anxiety	History of depression. Ongoing personal stressors (child custody, employment, financial) associated with AEs.	N N	N N	0/0	12	0/0	1	Y/N	Y/N
(b) (6) 44/F/33.8	Suicidal ideation 416/34	N	History of depression, borderline personality disorder.	N	N	9/4	11	1/0	1	N/N	Y/N
(b) (6) 60/F/37.9	Suicidal ideation 616/1	N	Sister's cancer diagnosis was associated with AE	N	N	9/6	4	0/0	0	N/N	Y/N
(b) (6) 45/M/37.3	Suicidal ideation 689/1	Stress	History of depression and attention deficit hyperactivity disorder. Worsening of personal stressors (employment, financial) was preceding the event.	N	N	4/5	19	0/0	1	N/N	Y/N
(b) (6) 47/M/34.6	Suicidal ideation 697/48	Major depression, anxiety	Death of father associated with diagnosis of major depressive disorder related to the AE.	Y	N	0/2	23	0/0	3	N/N	Y/N

Subject ID/ Age[a]/Sex/BMI[a]	Preferred term Onset/Duration	Other psychiatric AEs reported at onset	Comments and relevant medical history	SAE	WD due to event	PHQ-9 total score[b]		Q9 on PHQ-9		C-SSRS Ideation/behaviour	
						Screening/ Baseline	Max post-baseline	Screening/ Baseline	Max post-baseline	Lifetime	During treatment
Placebo											
(b) (6) 33/M/37.8	Suicide attempt 728/1	N	N	Y	N	0/0	0	0/0	0	N/N	N/N
(b) (6) 60/M/37.5	Depression suicidal 742/15	Depression	Depression	N	Y	2/4	10	0/0	0	N/N	N/N

Note: Comments are based on information in case narratives from the safety database inSection 14.3.3.

Abbreviations: AE = adverse event; BMI = body mass index; C-SSRS = Columbia suicidality severity rating scale; F = female; M = male; N = no; PHQ-9 = patient health questionnaire-9; Q9 = question 9 on the PHQ-9 ("Thoughts that you would be better off dead or of hurting yourself in some way"); SAE = serious adverse event; Y = yes; WD = withdrawn; WC#6 = Psychiatric disorder withdrawal criterion.

[a] Baseline value.

[b] The total score of the 9 items ranges from 0 to 27; total scores of 1–4 represent no 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.

Source: Trial 1839-3y CSR, Table 12-61

A patient had to be referred to a mental health professional (MHP) if he/she had a PHQ-9 total score ≥ 10, any suicidal behavior, or any suicidal ideation of type 4 or 5 on the C-SSRS at any assessment (see additional information regarding these questionnaires below). If a patient's psychiatric disorder could not be adequately treated with psycho- and/or pharmacotherapy at the discretion of the investigator (in agreement with the MHP), the patient had to be withdrawn. Three patients (Saxenda: 1; placebo: 2) were withdrawn from the trial as they fulfilled the specific withdrawal criterion #6 of psychiatric disorder. Including the 3 patients who fulfilled withdrawal criterion #6, 10 (0.7%) patients treated with Saxenda and 9 (1.2%) treated with placebo discontinued the trial due to a psychiatric AE.

Patient Health Questionnaire 9 (PHQ-9)
The PHQ-9 is a 9-item depression subscale of the self-administered patient health questionnaire (mental disorder instrument for use in primary care).[19] It is a standard assessment in the development of any obesity drug with a centrally acting mechanism.

In the PHQ-9, 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 results of symptom criterion in Question 9, "thoughts that you would be better off dead or hurting yourself in some way," were also considered separately and counted if present at all, regardless of frequency.

Before making a final diagnosis, the clinician is expected to rule out physical causes of depression, normal bereavement, and history of a manic episode.[19]

Patients were excluded from the trial with a PHQ-9 score ≥ 15. At baseline, the mean PHQ-9 total scores for depression were comparable between Saxenda (mean total score: 2.9) and placebo (mean total score: 3.1). The proportion of patients who had a

19 Kroenke K, et al. The PHQ-9 – validity of a brief depression severity measure. J Gen Intern Med. 2001; 16: 606-13.

positive score for Question 9 at baseline was 0.5% for patients randomized to Saxenda and 0.8% for patients randomized to placebo.

Mean PHQ-9 scores at the end-of-treatment and total scores above designated cut-off during the trial were similar in the Saxenda and placebo groups (Table 48), as were the categorical shifts to maximum scores (Table 49).

Table 48. PHQ-9 Total Score Results

	Liraglutide 3.0 mg	Placebo
PHQ-9 mean scores		
Mean PHQ-9 total score at end-of-treatment (SD)	1.92 (2.85)	1.94 (2.89)
PHQ-9 total scores above designated cut-off	N (%)	N (%)
Safety analysis set	1501	747
≥10 at end-of-treatment (week 160 LOCF)	36 (2.4)	17 (2.3)
≥10 at any time during trial	160 (10.7)	87 (11.7)
≥15 at end-of-treatment (week 160 LOCF)	11 (0.7)	6 (0.8)
≥15 at any time during trial	40 (2.7)	25 (3.4)
≥20 at end-of-treatment (week 160 LOCF)	2 (0.1)	1 (0.1)
≥20 at any time during trial	11 (0.7)	7 (0.9)

Abbreviations: LOCF = last observation carried forward; N = number of subjects fulfilling criteria; PHQ-9: patient health questionnaire 9; SAS = safety analysis set; SD = standard deviation; % = percentage of subjects with valid assessment.

Source: Trial 1839-3y, Table 12-62

Table 49. Categorical Shifts to Maximum PHQ-9 Scores

	Lira 3.0 mg N (%)	Placebo N (%)
Safety analysis set	1501	747
Total number of subjects improving from baseline to best total score	121 (8.1)	61 (8.2)
Mild to None	84 (5.6)	40 (5.4)
Moderate to None	12 (0.8)	5 (0.7)
Moderate to Mild	25 (1.7)	14 (1.9)
Moderately Severe to Moderate	0 (0.0)	0 (0.0)
Moderately Severe to Mild	0 (0.0)	1 (0.1)
Moderately Severe to None	0 (0.0)	1 (0.1)
Severe to Moderately Severe	0 (0.0)	0 (0.0)
Severe to Moderate	0 (0.0)	0 (0.0)
Severe to Mild	0 (0.0)	0 (0.0)
Severe to None	0 (0.0)	0 (0.0)
Total number of subjects worsening from baseline to worst total score	421 (28.0)	201 (26.9)
None to Mild	279 (18.6)	127 (17.0)
None to Moderate	53 (3.5)	24 (3.2)
None to Moderately Severe	11 (0.7)	11 (1.5)
None to Severe	3 (0.2)	4 (0.5)
Mild to Moderate	51 (3.4)	25 (3.3)
Mild to Moderately Severe	14 (0.9)	4 (0.5)
Mild to Severe	5 (0.3)	2 (0.3)
Moderate to Moderately Severe	3 (0.2)	3 (0.4)
Moderate to Severe	2 (0.1)	1 (0.1)
Moderately Severe to Severe	0 (0.0)	0 (0.0)
No change	946 (63.0)	478 (64.0)
Missing	13 (0.9)	7 (0.9)

N: Number of subjects, PHQ-9: Patient health questionnaire 9 (depression module), %: Percentage of N based on safety analysis set, SAS: safety analysis set.
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, Moderately severe depression: PHQ-9 total score of 15-19, Severe depression: PHQ-9 total score of >=20

Source: Trial 1839-3y CSR, Table 12-63

The proportions of patients with a positive score for Question 9 at any time post-baseline were similar with Saxenda (3.2%) and placebo (4.0%). In both treatment groups, the vast majority of patients with positive scores on Question 9 post-baseline had a score of 1 (occurring 'several days a week'). Two patients, both on Saxenda, had a score of 3 ('nearly every day') on Question 9, and a PHQ-9 total score corresponding to severe depression at the same trial visit:

- Patient [redacted] (b) (6) had a history of depression and major depression and at screening the PHQ-9 total score was 10 (moderate depression)
- Patient [redacted] (b) (6) also co-reported AEs of suicidal ideation, major depression, and anxiety (see Table 47 for details)

Both patients improved on the PHQ-9 at the subsequent visits and continued in the trial.

The mean PHQ-9 total scores were similar after discontinuation of treatment with Saxenda and placebo (Weeks 160 to 172; see Table 50), suggesting that discontinuation of liraglutide treatment did not result in withdrawal or rebound effects as assessed by the PHQ-9.

Reviewer comment: This conclusion is limited by the fact that the PHQ-9 analysis off-treatment was only conducted in the approximately 50% of randomized patients who remained in the trial during this period.

Table 50. PHQ-9 Total Scores Weeks 160 to 172

	Saxenda	**Placebo**
Week 160 (End of treatment)		
N	795	338
Mean (SD)	1.56 (2.39)	1.50 (2.10)
Median	0.00	0.00
Min – Max	0.00 – 18.00	0.00 – 9.00
Week 162		
N	766	329
Mean (SD)	1.22 (2.01)	1.20 (1.79)
Median	0.00	0.00
Min – Max	0.00 – 12.00	0.00 – 10.00
Week 164		
N	749	315
Mean (SD)	1.25 (2.12)	1.08 (1.64)
Median	0.00	0.00
Min – Max	0.00 – 22.00	0.0 – 9.00
Week 168		
N	762	322
Mean (SD)	1.23 (1.99)	1.22 (1.87)
Median	0.00	0.00
Min – Max	0.00 – 15.00	0.00 – 9.00
Week 172		
N	782	326
Mean (SD)	1.33 (2.27)	1.21 (1.79)
Median	0.00	0.00
Min – Max	0.00 – 19.00	0.00 – 9.00

Source: Trial 1839-3y CSR, Table 14.3.6.40

Columbia Suicidality Severity Rating Scale (C-SSRS)
The C-SSRS is a standardized assessment to quantify the severity of suicidal ideation and behavior.[20] 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

In addition to the items listed above, the questionnaire also includes the following item under suicidal behavior: 'Suicidal behavior was present during the assessment period'. This item is not specified and mapped in the guidance, and is therefore included in the summary tables but presented separately.

Patients with suicidal ideation of type 4 or 5 on the C-SSRS at screening were to be excluded from the trial.

The lifetime C-SSRS assessment (performed at screening) identified a total of 44 (2.9%) patients with lifetime suicidal behavior and/or ideation who were randomized to Saxenda and 24 patients (3.2%) who were randomized to placebo. The vast majority of these patients had a history of suicidal ideation, and 3 patients (all randomized to Saxenda) had a history of suicidal behavior (1 reported a history of 'aborted suicide attempt' and 2 reported 'preparatory acts or behavior towards making a suicidal attempt'). One patient randomized to Saxenda reported suicidal ideation (type 1 and 2) at baseline.

20 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.

During the trial, no patients reported suicidal behavior on the C-SSRS; however, 2 suicide attempt AEs were reported without being captured on the C-SSRS (1 in each group, see Table 47).

During the trial, a total of 19 patients (1.3%) treated with Saxenda and 12 patients (1.6%) treated with placebo reported suicidal ideation. See Table 51 for an enumeration of C-SSRS responses by type.

Table 51. C-SSRS Responses Post-Baseline (Up to Week 172)

	Lira 3.0 mg N	Lira 3.0 mg n (%)	Placebo N	Placebo n (%)
Number of subjects	1501		747	
Subjects answering the C-SSRS post-baseline	1488		744	
Subjects with suicidal behaviour and/or ideation	1488	19 (1.28)	744	12 (1.61)
Subjects with suicidal ideation on the C-SSRS	1488	19 (1.28)	744	12 (1.61)
1. Wish to be dead	1488	18 (1.21)	744	11 (1.48)
2. Active suicidal ideation, non-specific thoughts	1488	8 (0.54)	744	4 (0.54)
3. Active suicidal ideation with any methods (no plan) without intent to act	1488	6 (0.40)	744	1 (0.13)
4. Active suicidal ideation with some intent to act, without specific plan	1488	1 (0.07)	744	0 (0.00)
5. Active suicidal ideation with specific plan and intent	1488	1 (0.07)	744	1 (0.13)
Subjects with suicidal behavior on the C-SSRS	1488	0 (0.00)	744	0 (0.00)
1. Completed suicide	1488	0 (0.00)	744	0 (0.00)
2. Actual suicide attempt	1488	0 (0.00)	744	0 (0.00)
3. Interrupted suicidal attempt	1488	0 (0.00)	744	0 (0.00)
4. Aborted suicide attempt	1488	0 (0.00)	744	0 (0.00)
5. Preparatory acts towards imminent suicidal behaviours	1488	0 (0.00)	744	0 (0.00)
Suicidal behaviour	1488	0 (0.00)	744	0 (0.00)
Non-suicidal self-injurious behaviour	1488	0 (0.00)	744	0 (0.00)

C-SSRS: Columbia-suicide severity rating scale, N: Number of subjects, n: Number of subjects answering yes, %: Percentage of N, SAS: safety analysis set.
The category 'Subjects with suicidal behaviour and/or ideation' does not include subjects with a positive response in the Suicidal behaviour item or Non-suicidal self-injurious behaviour.
The C-SSRS also includes the following item under suicidal behaviour: 'Suicidal behaviour was present during the assessment period' which is not specified and mapped in the FDA guidance. This item is therefore included in the summary tables but presented separately.

Source: Trial 1839-3y CSR, Table 12-64

In the Saxenda group, 1 patient reported both ‘active suicidal ideation with some intent to act, without specific plan’ (type 4) and ‘active suicidal ideation with specific plan and intent’ (type 5). In the placebo group, 1 patient reported type 5 suicidal ideation. Details of these 2 patients who reported type 4 or 5 suicidal ideation are provided below:

Table 52. Patients with Suicidal Ideation Type 4 or 5 on the C-SSRS

Subject ID/ Age[a]/Sex/BMI[a]	C-SSRS suicidal ideation		C-SSRS suicidal behaviour		Max PHQ-9 total score post-baseline[b]	PHQ-9 Q 9 positive answer[c]	Relevant medical history	Psychiatric disorder TEAE reported	Details
	Screening (lifetime)	Post-baseline	Screening (lifetime)	Post-baseline					
Liraglutide 3.0 mg									
(b) (6) 47/M/34.6	N	Type 4, Type 5	N	N	23	Y	None	Major depression, suicidal ideation, anxiety	The subject presented with suicidal ideation following the death of his father. He was sent to the emergency room for evaluation, but was not hospitalised. The subject found his father dead on the roof of the house, was very close to him, and felt a great amount of guilt. No action was taken to trial drug due to the event. The subject was also diagnosed with major depressive disorder, reported suicidal ideation (SAE) and initiated anti-depressive treatment and received psychotherapy. No change to dose of trial drug. Recovered.
Placebo									
(b) (6) 52/M/33.2	N	Type 5	N	N	15	Y	None	Depression, agression	During rehabilitation after 2 minor strokes, the subject was diagnosed with depression. During the rehabilitation stay at the hospital, the subject had suicidal thoughts (about jumping off a balcony), but never actively tried to commit suicide. The patient was referred to a mental health professional and initiated anti-depressant treatment. Withdrawn due to AE (depression). Recovering (from depression).

Note: Table presents subjects who reported 'active suicidal ideation with some intent to act, without specific plan' (type 4) and/or 'active suicidal ideation with specific plan and intent' (type 5) on the C-SSRS during the entire trial period. Details are based on information in case narratives from the safety database in Section 14.3.3.

Abbreviations: AE = adverse event; BMI = body mass index, C-SSRS = Columbia suicidality severity rating scale; M = male; PHQ-9 = patient health questionnaire-9; Q9 = question 9 on the PHQ-9 ('Thoughts that you would be better off dead or of hurting yourself in some way'); SAE = serious adverse event; SAS = safety analysis set.

[a] Baseline value

[b] The total score of the 9 items ranges from 0 to 27; total scores of 1–4 represent no 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.

[c] At same trial visit as the positive answer on the C-SSRS was recorded.

Source: Trial 1839-3y CSR, Table 12-65

Gastrointestinal Disorders

Gastrointestinal disorders are well-described side effects of liraglutide and are considered to be mediated via activation of the GLP-1 receptor. The Saxenda label (Section 6.1) currently states the following:

In the clinical trials, approximately 68% of Saxenda-treated patients and 39% of placebo-treated patients reported gastrointestinal disorders; the most frequently reported was nausea (39% and 14% of patients treated with Saxenda and placebo, respectively). The percentage of patients reporting nausea declined as treatment continued. Other common adverse reactions that occurred at a higher incidence among Saxenda-treated patients included diarrhea, constipation, vomiting, dyspepsia, abdominal pain, dry mouth, gastritis, gastroesophageal reflux disease, flatulence, eructation and abdominal distension. Most episodes of gastrointestinal events were mild or moderate and did not lead to discontinuation of therapy (6.2% with Saxenda versus 0.8% with placebo discontinued treatment as a result of gastrointestinal adverse reactions). There have been reports of gastrointestinal adverse reactions, such as nausea, vomiting, and diarrhea, associated with volume depletion and renal impairment.

Overall, the proportions of patients with AEs within the 'gastrointestinal disorders' SOC and the rates of events were higher with Saxenda (73.6%, 124.4 events per 100 PYO) than with placebo (50.2%, 62.4 events per 100 PYO). The most frequently reported

gastrointestinal AEs were nausea, diarrhea, constipation, vomiting, and dyspepsia (Table 53).

Gastrointestinal AEs were the most frequently reported event types leading to permanent treatment discontinuation (Saxenda 7.9% vs. placebo 1.5%). Nausea (3.5% vs. 0.7%), diarrhea (1.3% vs. 0.1%) and abdominal pain (0.9% vs. 0.1%) led to permanent treatment discontinuation by higher proportions and at higher rates with Saxenda than with placebo, respectively; vomiting only led to permanent treatment discontinuation with Saxenda (2.5% vs. 0).

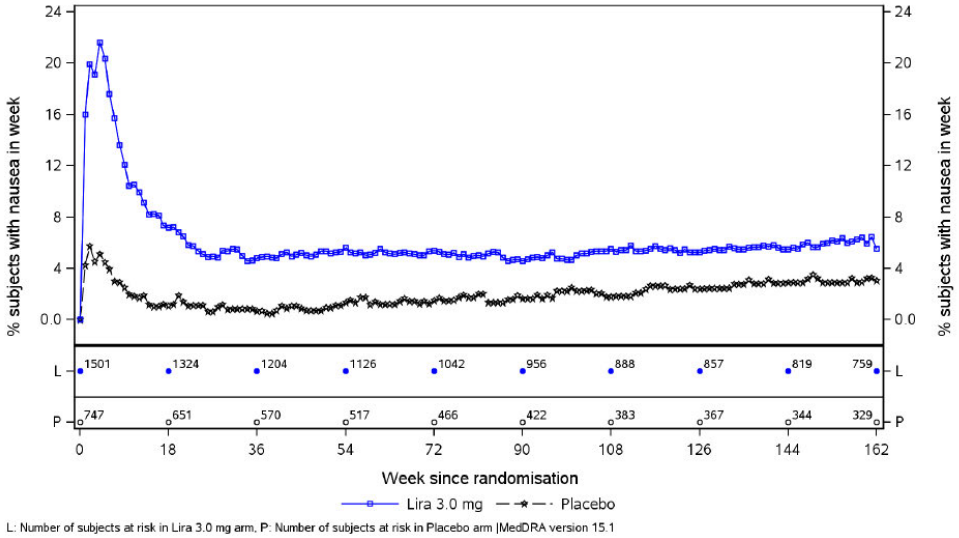
Table 53. Most Frequent (≥1%) AEs within the 'Gastrointestinal Disorders' SOC by PT

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1501				747			
Years of observation time	3218.9				1470.2			
Most frequent events (PT):								
Nausea	614	(40.9)	961	29.9	125	(16.7)	166	11.3
Diarrhoea	379	(25.2)	610	19.0	107	(14.3)	145	9.9
Constipation	331	(22.1)	419	13.0	85	(11.4)	100	6.8
Vomiting	295	(19.7)	472	14.7	40	(5.4)	53	3.6
Dyspepsia	154	(10.3)	192	6.0	35	(4.7)	40	2.7
Abdominal pain	114	(7.6)	152	4.7	38	(5.1)	50	3.4
Abdominal pain upper	112	(7.5)	139	4.3	39	(5.2)	47	3.2
Gastrooesophageal reflux disease	98	(6.5)	110	3.4	18	(2.4)	20	1.4
Eructation	85	(5.7)	95	3.0	4	(0.5)	4	0.3
Flatulence	81	(5.4)	94	2.9	20	(2.7)	23	1.6
Abdominal distension	67	(4.5)	83	2.6	32	(4.3)	41	2.8
Gastritis	55	(3.7)	71	2.2	25	(3.3)	27	1.8
Abdominal discomfort	41	(2.7)	45	1.4	18	(2.4)	20	1.4
Toothache	39	(2.6)	42	1.3	16	(2.1)	18	1.2
Dry mouth	38	(2.5)	42	1.3	12	(1.6)	12	0.8
Haemorrhoids	31	(2.1)	34	1.1	14	(1.9)	15	1.0
Food poisoning	23	(1.5)	31	1.0	4	(0.5)	4	0.3
Colitis	17	(1.1)	25	0.8	6	(0.8)	7	0.5
Hiatus hernia	17	(1.1)	18	0.6	4	(0.5)	4	0.3
Diverticulum	17	(1.1)	17	0.5	7	(0.9)	7	0.5
Abdominal pain lower	16	(1.1)	18	0.6	4	(0.5)	4	0.3

Source: Trial 1839-3y CSR, Table 12-18

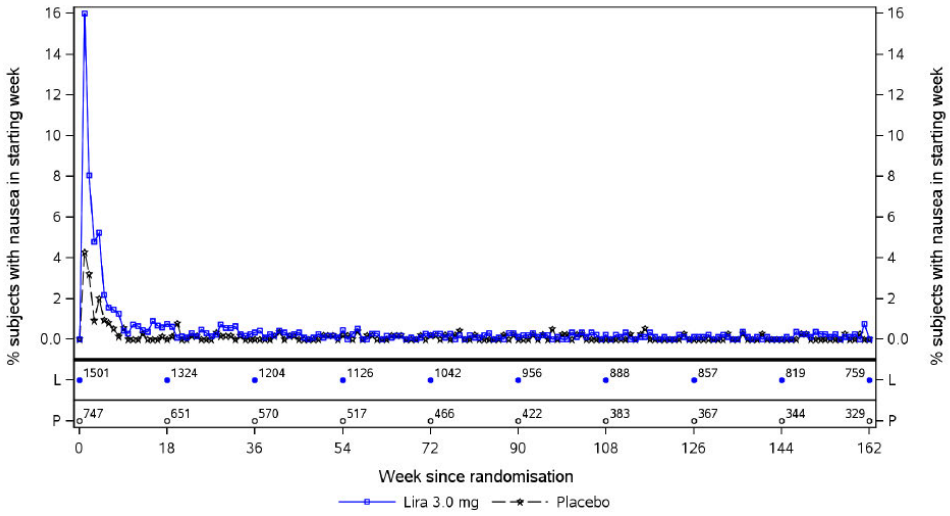
The proportion of patients with nausea AEs [including patients with ongoing (Figure 19) and new events (Figure 20)] peaked within the initial weeks of treatment with Saxenda and then gradually declined over the course of the trial. [Similar patterns were observed for vomiting AEs (not shown), although there was a lower frequency of events.]

Figure 19. Proportions of Patients with AEs of Nausea over Time



Source: Trial 1839-3y CSR, Figure 12-6

Figure 20. Proportions of Patients with New AEs of Nausea



Source: Trial 1839-3y CSR, Figure 12-7

Patients withdrawn due to gastrointestinal disorders during the initial weeks of treatment may have contributed to the observed decrease in proportion of patients with nausea events. However, of the patients treated with Saxenda, 41.0% reported nausea but, as above, only 3.5% of the patients discontinued treatment permanently due to nausea. This suggests that the decrease in incidence over time was not a result of patients discontinuing for nausea.

Cardiovascular Events and Increased Heart Rate

Increased heart rate is a known cardiovascular (CV) safety signal with liraglutide, and its potential impact on CV risk was discussed extensively prior to the approval of Saxenda. Saxenda is not a sympathomimetic, however, and blood pressure was shown to decrease with weight loss. Liraglutide administered as Victoza has been evaluated for CV risk in patients with type 2 diabetes in a dedicated CV outcomes trial (LEADER). The results of that trial – which appear favorable – have been published,[11] and are under review by the Division.

In trial 1839, the following CV events were to be reported by the investigator as a MESI, and certain events were subjected to external adjudication:

- Acute coronary syndrome (myocardial infarction (MI), hospitalization for unstable angina pectoris (UAP)) (*adjudicated*)
- Cerebrovascular event (stroke, transient ischemic attack (TIA)) (*adjudicated*)
- Heart failure (new episode or worsening of existing heart failure) (*adjudicated* if requiring hospitalization)
- Stent thrombosis (*adjudicated*)
- Revascularization procedure (*adjudicated* if coronary)
- Hospitalization for cardiac arrhythmia (*not adjudicated*)

In addition, the results of the central reading of ECGs that indicated new ischemia/infarction since last ECG reading were sent for adjudication.

CV events identified using pre-specified MedDRA searches (including a discussion of heart rate findings) and positively adjudicated CV AEs are each summarized in this section separately.

Cardiovascular Events Identified by MedDRA Search

Table 54. Terms Included in the MedDRA Search for All Potential Cardiovascular Events

Included SMQs		
SMQ Cerebrovascular disorders	SMQ Cardiac failure	SMQ Cardiomyopathy
SMQ Ischaemic heart disease	SMQ Embolic and thrombotic events	SMQ Torsade de pointes/QT prolongation
SMQ Cardiac arrhythmias	SMQ Shock	SMQ Vasculitis

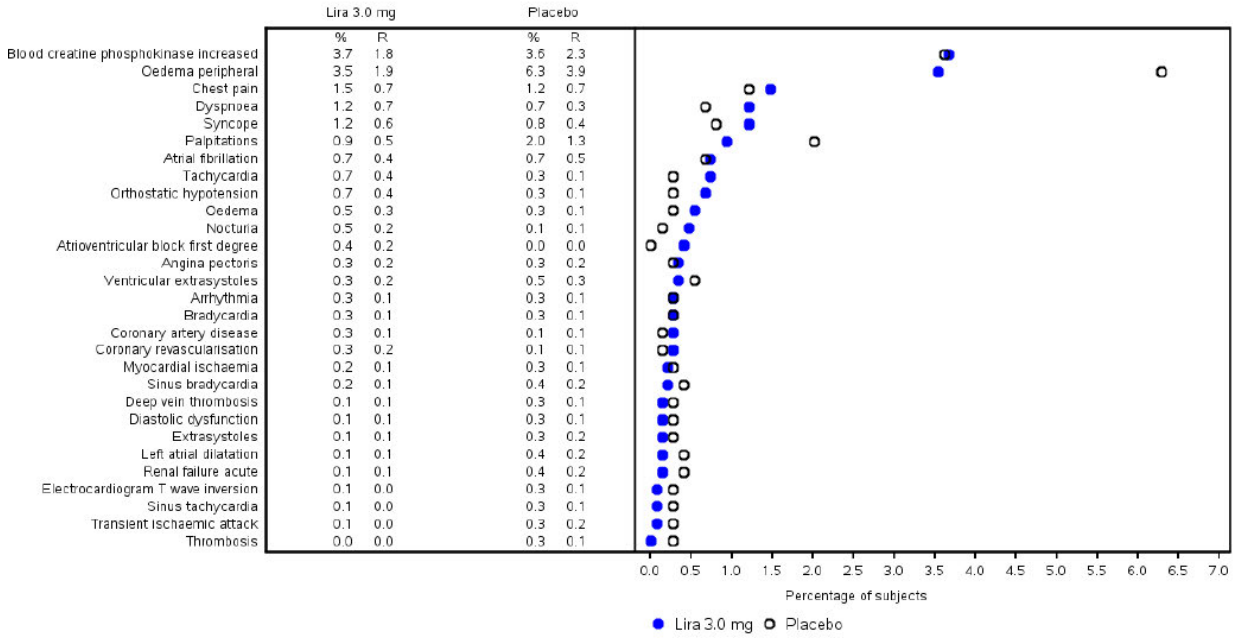
Abbreviation: SMQ = standardised MedDRA query.
Source: Trial 1839-3y CSR, Table 12-21

Utilizing the above search terms, the proportion of events in the Saxenda group was 16.1% (12.1 events per 100 PYO) and in the placebo group 19.0% (15.1 events per 100 PYO). The small imbalance in favor of Saxenda was primarily driven by an increased incidence of events of peripheral edema and palpitations in the placebo group (Figure

21). Events that were reported at a greater incidence in the Saxenda group include dyspnea, syncope, tachycardia, orthostatic hypotension, and first degree atrioventricular block. The most frequently reported event in Saxenda-treated patients – with a similar incidence in both groups – was blood creatine phosphokinase increased.

Reviewer comment: Events of increased CPK are non-specific and therefore might or might not have reflected true cardiovascular AEs. A number of additional terms are also included that are very non-specific: e.g., 'oedema peripheral', 'renal failure acute', etc.

Figure 21. Most Frequent CV AEs by MedDRA Search



%: Percentage of subjects experiencing at least one episode
R: Event rate per 100 years of observation time
MedDRA version 15.1

Source: Trial 1839-3y CSR, Figure 12-8

In addition to the previously described heart rate increase associated with liraglutide, the original Saxenda review identified an imbalance in cardiac conduction disorders; specifically first degree atrioventricular block, right bundle branch block, and left bundle branch block. The sponsor undertook a search specifically for cardiac arrhythmia in this 3-year trial.

Table 55. Terms Included in the MedDRA Search for Cardiac Arrhythmia

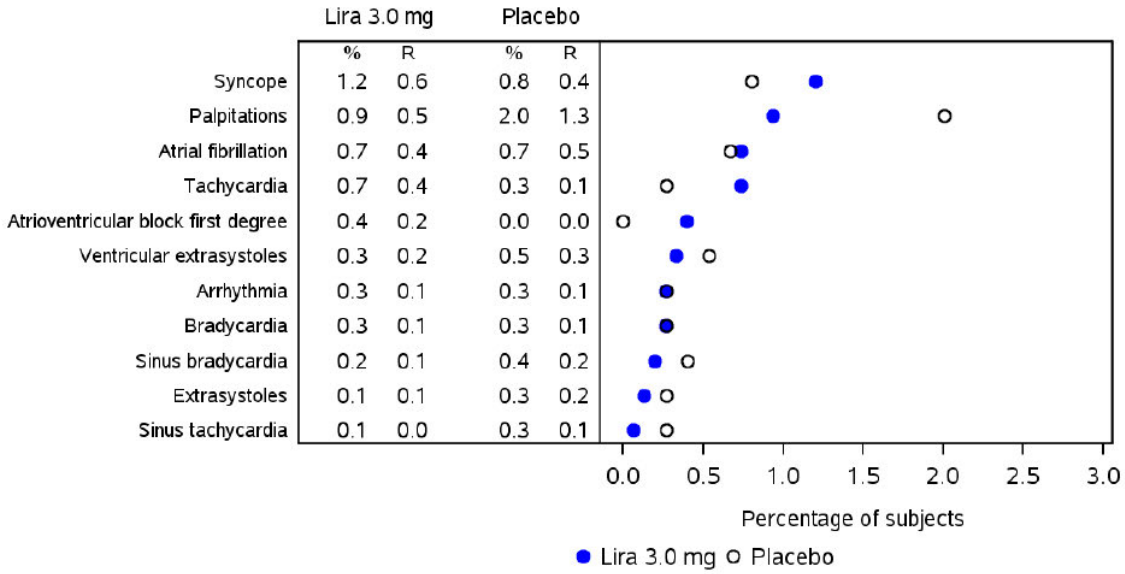
Included SMQs	
SMQ Arrhythmia related investigations, signs and symptoms	SMQ Cardiac arrhythmia terms, nonspecific
SMQ Bradyarrhythmia terms, nonspecific	SMQ Supraventricular tachyarrhythmias
SMQ Conduction defects	SMQ Tachyarrhythmia terms, nonspecific
SMQ Disorders of sinus node function	SMQ Ventricular tachyarrhythmias

Abbreviations: SMQ = standardised MedDRA query.

Source: Trial 1839-3y CSR, Table 12-23

Using the above search strategy, overall a similar proportion of patients in the Saxenda group (6.1%) and the placebo group (6.3%) had arrhythmia events. Individual PTs are plotted below:

Figure 22. Most Frequent Potential Cardiac Arrhythmia AEs by MedDRA Search



Source: Trial 1839-3y CSR, Figure 12-10

As noted in the figure above, syncope was reported more frequently in the Saxenda group. Three events in the Saxenda group and 1 in the placebo group were reported as SAEs. These events are described briefly below (a full narrative for patient 480003 is additionally presented with the discussion of events related to tachycardia):

Table 56. Patients with Syncope SAEs

Subject ID Age[a]/Sex/ BMI[a]	Onset day/ Duration	WD/Severity Outcome	Comments
Liraglutide 3.0 mg			
(b) (6) 68/F/30.8	946/1	N/Severe/ Recovered	The subject presented with a severe syncope event and was hospitalised due to dizziness. Potassium levels were noted to be low (2.4 mmol/L, reference 3.4-4.6 mmol/L). Hypotension was reported as alternative aetiology for the event. No change to trial drug due to the event.
(b) (6) 62/F/51.0	338/2	N/Severe/ Recovered	The subject presented with a severe syncope event and was admitted to the hospital. According to the investigator, the syncope could have been related to chemotherapy (due to breast cancer) or pituitary mass (unknown at the time of onset of the syncope event). No change to trial drug due to the event.
(b) (6) 61/M/45.2	907/1	N/Severe/ Recovered	The subject experienced dizziness (non-serious) and syncope and was hospitalised. Additional AEs reported on the same day included elevated CPK (value not provided; CPK was assessed at the clinic), unstable angina, paroxysmal ventricular tachycardia and hypovolemia. Trial drug was temporarily discontinued. The diagnosis of paroxysmal ventricular tachycardia was considered chronic; the subject recovered from the remaining events.
Placebo			
(b) (6) 40/F/37.1	747/2	N/Moderate/ Recovered	The subject was hospitalised due to a moderate syncope event. It was considered likely that the event was a vasovagal response related to gastroenteritis and dehydration. Trial drug was temporarily discontinued and the subject recovered.

Note: Comments are from case narratives in Section 14.3.3.

Abbreviations: AE = adverse events; BMI = body mass index; CPK = creatine phosphokinase; F = female; M = male; N = no; SAS = safety analysis set; TEAE = treatment-emergent adverse event; WD = withdrawn.

[a] Baseline value.

Source: Trial 1839-3y CSR, Table 12-25

In addition to the events of syncope, 4 AEs of loss of consciousness were reported in 3 patients on Saxenda. Of these, 1 patient had experienced 2 events of loss of consciousness and in 1 of the instances co-reported syncope. All 4 events were non-serious, mild or moderate in intensity, and the patients recovered.

Tachycardia was more frequently reported in the Saxenda group as compared with placebo; however, when expanding the search to related terms, incidence was similar between groups (Table 57).

Table 57. Tachycardia Terms

	Saxenda N=1501	Placebo N=747
Total tachycardia terms	14 (0.9%)	5 (0.7%)
Tachycardia	11 (0.7%)	2 (0.3%)
Sinus tachycardia	1 (0.1%)	2 (0.3%)
Supraventricular tachycardia	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0
Tachyarrhythmia	0	1 (0.1%)

Source: Reviewer created from trial 1839-3y datasets

The narrative for the Saxenda-treated patient with the AE of ventricular tachycardia is as follows (note that much of the narrative was taken verbatim from the clinical trial report):

- Patient (b) (6) was a 64-year-old male with a medical history of obesity, hypertension, hypercholesterolemia, gastroesophageal reflux disease, insomnia, low testosterone, muscle spasms, and seasonal allergies, who was randomized to Saxenda (b) (6). AEs reported for this patient included chronic paroxysmal ventricular tachycardia, unstable angina, syncope, and elevated creatine phosphokinase (CPK).

  On (b) (6), the patient experienced a dizzy spell for 20-30 seconds. Later, the patient experienced a feeling that the room was spinning, he fell, and he couldn't sit up. This lasted for 1 minute. The patient experienced the symptoms while performing yard work.

  On (b) (6), the patient developed syncope, elevated CPK (value not provided; CPK was performed in the clinic), unstable angina, paroxysmal ventricular tachycardia, and hypovolemia. The patient was prescribed dimenhydrinate 50 mg, every 4-6 hours, orally. He was admitted to the hospital due to the finding of paroxysmal ventricular tachycardia. He had a left heart catheterization performed the same day. The event of unstable angina was treated with beta blockers and nitroglycerin. The event of syncope was treated with cephalexin, metoprolol, magnesium oxide, and atorvastatin. According to the narrative, no treatment was provided for the hypovolemia. Electrocardiogram performed on (b) (6) showed first degree atrioventricular block with ventricular premature complex.

  On (b) (6), the patient had an electrophysiology study performed with an implantation of a Medtronic reveal loop recorder. The patient was discharged from the hospital on (b) (6) with a final diagnosis of paroxysmal ventricular tachycardia.

  The outcome of the event of syncope was reported recovered on (b) (6), hypovolemia was recovered on (b) (6) unstable angina was recovered on (b) (6)

[redacted] and elevated CPK was recovered [redacted]. The event of paroxysmal ventricular tachycardia was not recovered as it was considered chronic.

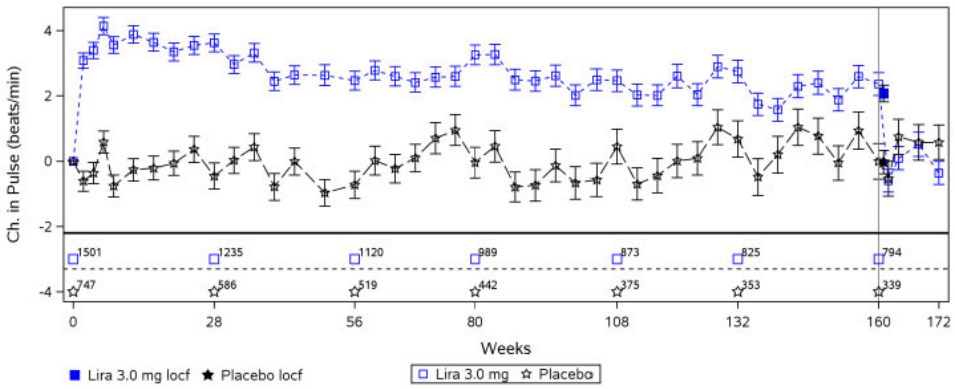
The trial product was temporarily discontinued [redacted] due to the events and was restarted on [redacted] at the same dosage. The events did not abate after discontinuation or reintroduction of the trial product.

First degree atrioventricular (AV) block was more frequently reported with Saxenda than with placebo (Figure 22). All events were mild and non-serious and all patients continued with no change to trial drug. Two events of second degree AV block were reported; 1 patient treated with Saxenda who also had an event of first degree AV block, and 1 patient treated with placebo.

Heart Rate

An increase in mean resting pulse was seen by week 2 with Saxenda vs. placebo and remained above baseline levels during the entire treatment period. At end-of-treatment (week 160 LOCF), the mean change in resting pulse was +2.07 beats per minute (BPM) with Saxenda and -0.02 BPM with placebo with a mean difference of +1.98 BPM (95%CI +1.22, +2.74), p < 0.0001. See Figure 23.

Figure 23. Change in Resting Pulse Over Time

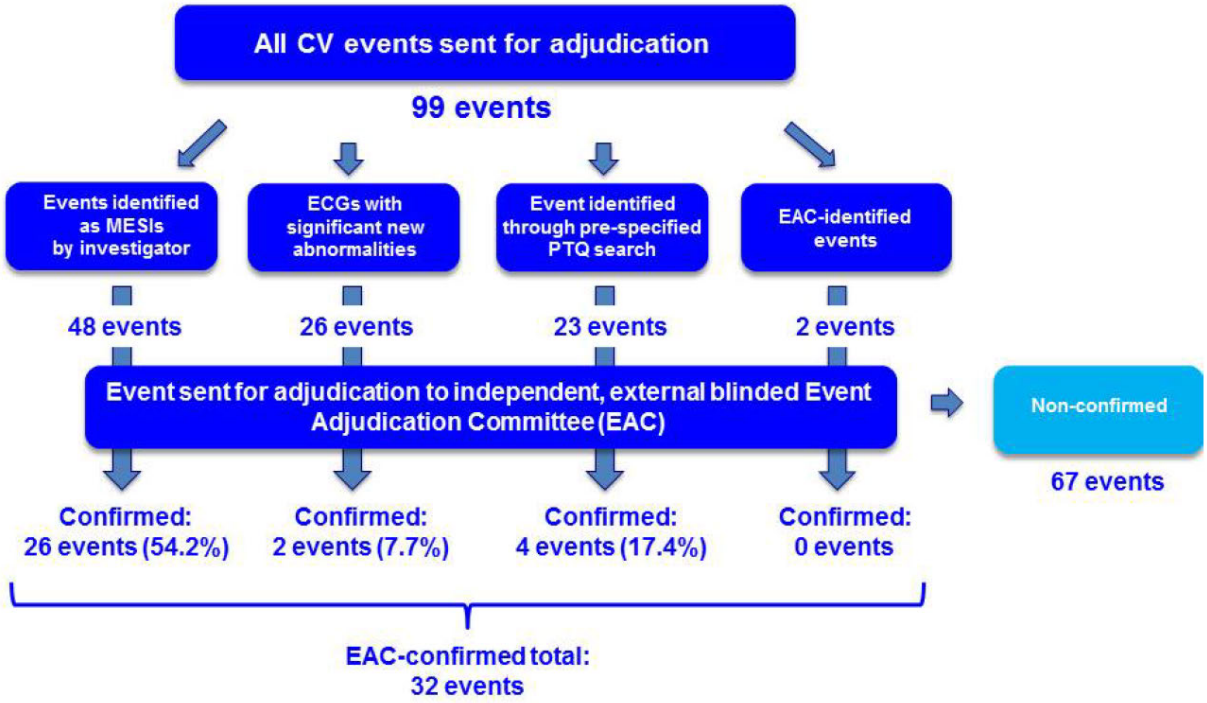


Source: Trial 1839-3y CSR, Figure 12-35

Adjudication of Cardiovascular Events

Of 99 CV events sent for adjudication, 32 events were EAC-confirmed. The breakdown of events by reporting method is shown in the following figure:

Figure 24. Adjudication of CV Events by Reporting Method



Note: The percentages are calculated from the total number of events sent for adjudication within each subcategory.
Abbreviations: CV= cardiovascular; EAC = event adjudication committee; ECG = electrocardiogram; PTQ = (Novo Nordisk defined) preferred term query; MESI = medical event of special interest.

Source: Trial 1839-3 CSR, Figure 12-12

Of the 99 events sent for adjudication, 89 were treatment-emergent (occurred during weeks 0-162). Of the 89 treatment-emergent events, 60 were reported with Saxenda (18 confirmed) and 29 with placebo (8 confirmed). Overall, the proportions of patients with EAC-confirmed CV events and rates of events were similar with Saxenda (0.80%, 0.56 events per 100 PYO) and placebo (0.80%, 0.54 events per 100 PYO), although the proportions of patients with adjudicated myocardial infarction, heart failure, and coronary revascularization were numerically higher with Saxenda vs. placebo (Table 58).

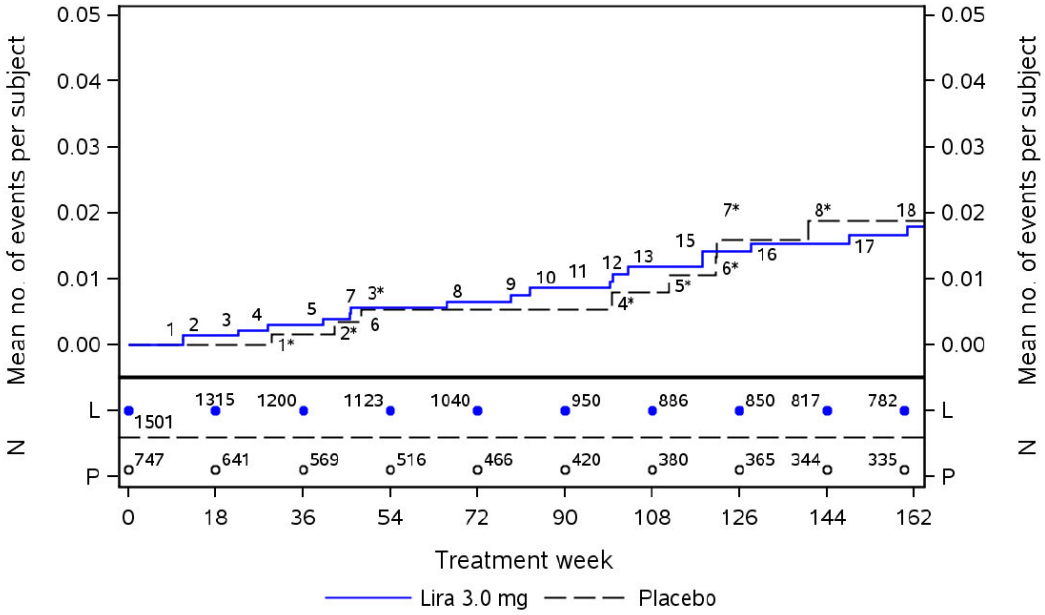
Table 58. Adjudicated Treatment-Emergent Cardiovascular Events by EAC Category

	Lira 3.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	1501				747			
Years of observation time	3218.9				1470.2			
All EAC confirmed CV events	12	(0.80)	18	0.56	6	(0.80)	8	0.54
Acute coronary syndrome	4	(0.27)	4	0.12	2	(0.27)	2	0.14
Unstable angina pectoris	1	(0.07)	1	0.03	1	(0.13)	1	0.07
Myocardial infarction	3	(0.20)	3	0.09	1	(0.13)	1	0.07
STEMI	1	(0.07)	1	0.03	1	(0.13)	1	0.07
NSTEMI	2	(0.13)	2	0.06	0	(0.00)	0	0.00
Cerebrovascular event	3	(0.20)	3	0.09	3	(0.40)	4	0.27
Stroke	2	(0.13)	2	0.06	2	(0.27)	2	0.14
Transient ischemic attack	1	(0.07)	1	0.03	2	(0.27)	2	0.14
Heart failure	3	(0.20)	3	0.09	1	(0.13)	1	0.07
Coronary revascularisation procedure	6	(0.40)	7	0.22	1	(0.13)	1	0.07
Cardiovascular death	1	(0.07)	1	0.03	0	(0.00)	0	0.00

CV: cardiovascular, EAC: (External) event adjudication committee, N: Number of subjects, TE: treatment-emergent, %: Percentage of subjects, E: Number of events, R: Event rate per 100 years of observation time, SAS: safety analysis set.
STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction
Heart Failure: All heart failures requiring hospitalisation defined as an admission that results in at least a 12 hour stay
A TE adverse event is defined as an event that has onset date on or after the first day of randomised treatment and no later than 14 days after the last day of randomised treatment.

Source: Trial 1839-3y, Table 12-29

Figure 25. Mean Cumulative Event over Time Plot for Treatment-Emergent EAC-Confirmed CV Events



The plot is not restricted to first event per subject, N: Number of subjects at risk, L: Lira 3.0 mg, P: Placebo, *:Placebo events

Source: Trial 1839-3y CSR, Figure 12-13

Of the 8 non-treatment-emergent CV events reported during the off-drug follow-up period (weeks 162-172) and sent for adjudication, 3 of 6 events in the Saxenda group (1 myocardial infarction, 1 heart failure, and 1 coronary revascularization) and 1 of 2 events in the placebo group (1 transient ischemic attack) were confirmed as CV events. Overall, the proportions of patients with non-treatment-emergent EAC-confirmed CV events and the rates of events were 0.38%, 1.95 events per 100 PYO with Saxenda, and 0.30%, 1.55 events per 100 PYO with placebo.

A total of 2 non-treatment-emergent CV events in patients who discontinued treatment were reported and sent for adjudication, both in the Saxenda group and both events were confirmed by the EAC as CV events: 1 cerebrovascular event (351 days after last dose of Saxenda) and 1 coronary revascularization procedure (395 days after last dose of Saxenda).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall, the proportion of patients reporting adverse events was higher with Saxenda (94.7%) than placebo (89.4%). The majority of the imbalance was driven by imbalances in the Gastrointestinal disorders, General disorders and administration site conditions, Metabolism and nutrition disorders, and Investigations SOCs. Individual PTs from these SOCs that were seen more commonly with Saxenda are:

- Gastrointestinal disorders: nausea, diarrhea, constipation, vomiting, dyspepsia, and abdominal pain
- General disorders and administration site conditions: fatigue and injection site erythema
- Metabolism and nutrition disorders: hypoglycemia and decreased appetite
- Investigations: amylase increased, lipase increased, blood glucose decreased, and blood calcitonin increased

Table 59 enumerates all AEs with Saxenda PT incidence at least 1% and greater than placebo. Specific AEs of interest are discussed further in Section 7.3.5, Submission Specific Primary Safety Concerns.

Table 59. Common AEs with Saxenda PT Incidence ≥ 1% and Greater than Placebo

	Saxenda N = 1501	Placebo N = 747
Total	1421 (94.7)	668 (89.4)
Gastrointestinal disorders	1104 (73.6)	375 (50.2)
Nausea	614 (40.9)	125 (16.7)
Diarrhea	379 (25.2)	107 (14.3)
Constipation	331 (22.1)	85 (11.4)
Vomiting	295 (19.7)	40 (5.4)
Dyspepsia	154 (10.3)	35 (4.7)
Abdominal pain	114 (7.6)	38 (5.1)
Abdominal pain upper	112 (7.5)	39 (5.2)
Gastroesophageal reflux disease	98 (6.5)	18 (2.4)
Eructation	85 (5.7)	4 (0.5)
Flatulence	81 (5.4)	20 (2.7)
Abdominal distension	67 (4.5)	32 (4.3)
Gastritis	55 (3.7)	25 (3.3)
Abdominal discomfort	41 (2.7)	18 (2.4)
Toothache	39 (2.6)	16 (2.1)
Dry mouth	38 (2.5)	12 (1.6)
Hemorrhoids	31 (2.1)	14 (1.9)
Food poisoning	23 (1.5)	4 (0.5)
Diverticulum	17 (1.1)	7 (0.9)
Colitis	17 (1.1)	6 (0.8)
Hiatus hernia	17 (1.1)	4 (0.5)
Abdominal pain lower	16 (1.1)	4 (0.5)
Hematochezia	15 (1.0)	2 (0.3)
Infections and infestations	974 (64.9)	473 (63.3)
Influenza	181 (12.1)	79 (10.6)
Gastroenteritis	140 (9.3)	46 (6.2)
Urinary tract infection	121 (8.1)	43 (5.8)
Gastroenteritis viral	66 (4.4)	23 (3.1)
Ear infection	40 (2.7)	19 (2.5)
Viral infection	38 (2.5)	14 (1.9)
Cystitis	35 (2.3)	8 (1.1)
Pneumonia	34 (2.3)	15 (2.0)
Rhinitis	34 (2.3)	12 (1.6)
Tooth abscess	32 (2.1)	14 (1.9)
Herpes zoster	26 (1.7)	11 (1.5)
Tonsillitis	23 (1.5)	8 (1.1)
Diverticulitis	21 (1.4)	3 (0.4)
Laryngitis	20 (1.3)	6 (0.8)
Fungal infection	15 (1.0)	6 (0.8)
Musculoskeletal and connective tissue disorders	628 (41.8)	304 (40.7)
Musculoskeletal pain	73 (4.9)	21 (2.8)
Muscle spasms	53 (3.5)	21 (2.8)
Tendonitis	39 (2.6)	16 (2.1)
Neck pain	32 (2.1)	15 (2.0)

Intervertebral disc protrusion	27 (1.8)	5 (0.7)
Plantar fasciitis	26 (1.7)	10 (1.3)
Arthritis	21 (1.4)	6 (0.8)
Musculoskeletal stiffness	18 (1.2)	5 (0.7)
Joint swelling	16 (1.1)	6 (0.8)
Rotator cuff syndrome	15 (1.0)	7 (0.9)
General disorders and administration site conditions	546 (36.4)	233 (31.2)
Fatigue	152 (10.1)	57 (7.6)
Injection site erythema	53 (3.5)	2 (0.3)
Pyrexia	51 (3.4)	24 (3.2)
Influenza like illness	45 (3.0)	21 (2.8)
Asthenia	43 (2.9)	10 (1.3)
Injection site reaction	41 (2.7)	6 (0.8)
Early satiety	34 (2.3)	6 (0.8)
Chest pain	22 (1.5)	9 (1.2)
Injection site pruritus	22 (1.5)	3 (0.4)
Non-cardiac chest pain	21 (1.4)	4 (0.5)
Metabolism and Nutrition Disorders	527 (35.1)	155 (20.7)
Hypoglycemia	296 (19.7)	35 (4.7)
Decreased appetite	164 (10.9)	26 (3.5)
Vitamin D deficiency	26 (1.7)	11 (1.5)
Gout	15 (1.0)	5 (0.7)
Increased appetite	15 (1.0)	4 (0.5)
Nervous System Disorders	521 (34.7)	233 (31.2)
Headache	270 (18.0)	122 (16.3)
Dizziness	146 (9.7)	54 (7.2)
Sciatica	27 (1.8)	13 (1.7)
Dysgeusia	23 (1.5)	5 (0.7)
Syncope	18 (1.2)	6 (0.8)
Injury, poisoning and procedural complications	409 (27.2)	189 (25.3)
Procedural pain	52 (3.5)	24 (3.2)
Fall	46 (3.1)	20 (2.7)
Joint injury	19 (1.3)	5 (0.7)
Laceration	17 (1.1)	6 (0.8)
Tooth fracture	15 (1.0)	7 (0.9)
Investigations	398 (26.5)	155 (20.7)
Lipase increased	146 (9.7)	23 (3.1)
Blood creatine phosphokinase increased	55 (3.7)	27 (3.6)
Amylase increased	33 (2.2)	2 (0.3)
Blood glucose decreased	23 (1.5)	5 (0.7)
Blood calcitonin increased	20 (1.3)	4 (0.5)
Blood pressure increased	19 (1.3)	7 (0.9)
Blood thyroid stimulating hormone decreased	19 (1.3)	5 (0.7)
Blood thyroid stimulating hormone increased	16 (1.1)	5 (0.7)
Blood calcium increased	16 (1.1)	4 (0.5)
Respiratory, thoracic and mediastinal disorders	321 (21.4)	170 (22.8)
Sinus congestion	29 (1.9)	14 (1.9)
Dyspnea	18 (1.2)	5 (0.7)
Skin and subcutaneous tissue disorders	274 (18.3)	134 (17.9)

Pruritus	28 (1.9)	8 (1.1)
Alopecia	21 (1.4)	6 (0.8)
Urticaria	19 (1.3)	3 (0.4)
Erythema	16 (1.1)	5 (0.7)
Psychiatric disorders	233 (15.5)	117 (15.7)
Insomnia	68 (4.5)	25 (3.3)
Sleep disorder	16 (1.1)	4 (0.5)
Vascular disorders	175 (11.7)	85 (11.4)
Hypotension	24 (1.6)	4 (0.5)
Hot flush	23 (1.5)	10 (1.3)
Reproductive system and breast disorders	140 (9.3)	66 (8.8)
Eye disorders	119 (7.9)	66 (8.8)
Renal and urinary disorders	101 (6.7)	55 (7.4)
Nephrolithiasis	21 (1.4)	7 (0.9)
Pollakiuria	15 (1.0)	5 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	97 (6.5)	50 (6.7)
Cardiac disorders	87 (5.8)	52 (7.0)
Hepatobiliary disorders	85 (5.7)	27 (3.6)
Cholelithiasis	45 (3.0)	11 (1.5)
Ear and labyrinth disorders	70 (4.7)	37 (5.0)
Vertigo	33 (2.2)	13 (1.7)
Ear pain	15 (1.0)	5 (0.7)
Blood and lymphatic system disorders	64 (4.3)	38 (5.1)
Immune system disorders	64 (4.3)	33 (4.4)
Seasonal allergy	33 (2.2)	14 (1.9)
Endocrine disorders	52 (3.5)	38 (5.1)

Source: Trial 1839-3y CSR, Table 14.3.1.9, and reviewer created from datasets

7.4.2 Laboratory Findings

See Section 7.3.5, Submission Specific Primary Safety Concerns for discussion of amylase, lipase, calcitonin, and low plasma glucose laboratory values.

Biochemistry

As shown in Table 60 below, there is a slight imbalance in patients with ALT, AST, creatine kinase, potassium (favoring placebo), and creatinine (favoring Saxenda) outside of certain designated cut-offs during treatment (weeks 0-160).

Table 60. Patients with Biochemistry Laboratory Values Above or Below Designated Cut-Offs, Weeks 0-160

	Lira 3.0 mg N (%)	Placebo N (%)	Total N (%)
Safety analysis set	1501	747	2248
ALAT			
3xUNR	32 (2.1)	13 (1.7)	45 (2.0)
5xUNR	9 (0.6)	2 (0.3)	11 (0.5)
10xUNR	3 (0.2)	0 (0.0)	3 (0.1)
20xUNR	0 (0.0)	0 (0.0)	0 (0.0)
ASAT			
3xUNR	15 (1.0)	4 (0.5)	19 (0.8)
5xUNR	6 (0.4)	1 (0.1)	7 (0.3)
10xUNR	0 (0.0)	1 (0.1)	1 (0.0)
20xUNR	0 (0.0)	0 (0.0)	0 (0.0)
Alkaline phosphate			
2.5xUNR	2 (0.1)	2 (0.3)	4 (0.2)
5xUNR	0 (0.0)	0 (0.0)	0 (0.0)
20xUNR	0 (0.0)	0 (0.0)	0 (0.0)
Bilirubin, total			
1.5xUNR	15 (1.0)	5 (0.7)	20 (0.9)
3xUNR	1 (0.1)	0 (0.0)	1 (0.0)
10xUNR	0 (0.0)	0 (0.0)	0 (0.0)
Creatine kinase			
5xUNR	45 (3.0)	12 (1.6)	57 (2.5)
10xUNR	17 (1.1)	4 (0.5)	21 (0.9)
Creatinine			
1.5xUNR	27 (1.8)	20 (2.7)	47 (2.1)
3xUNR	1 (0.1)	1 (0.1)	2 (0.1)
6xUNR	0 (0.0)	0 (0.0)	0 (0.0)
Calcium, total			
> 11.5mg/dL	8 (0.5)	2 (0.3)	10 (0.4)
> 12.5mg/dL	0 (0.0)	0 (0.0)	0 (0.0)
> 13.5mg/dL	0 (0.0)	0 (0.0)	0 (0.0)
< 6mg/dL	3 (0.2)	2 (0.3)	5 (0.2)
< 7mg/dL	7 (0.5)	4 (0.5)	11 (0.5)
Potassium			
> 6mmol/L	32 (2.1)	9 (1.2)	41 (1.8)
> 7mmol/L	0 (0.0)	0 (0.0)	0 (0.0)
< 3mmol/L	4 (0.3)	0 (0.0)	4 (0.2)
< 2.5mmol/L	0 (0.0)	0 (0.0)	0 (0.0)
Sodium			
> 150mmol/L	459 (30.6)	197 (26.4)	656 (29.2)
> 160mmol/L	10 (0.7)	5 (0.7)	15 (0.7)
< 130mmol/L	4 (0.3)	1 (0.1)	5 (0.2)
< 120mmol/L	0 (0.0)	0 (0.0)	0 (0.0)
Albumin			
< 3g/dL	2 (0.1)	1 (0.1)	3 (0.1)
< 2g/dL	0 (0.0)	0 (0.0)	0 (0.0)
ALAT or AST >= 3UNR and bilirubin, total >= 2UNR at same visit	0 (0.0)	0 (0.0)	0 (0.0)

N: Number of subjects, %: Percentages are based on N, SAS: safety analysis set, UNR: Upper normal range.
Measurements from planned visits, unscheduled visits and retest are included.

ALAT=ALT; ASAT=AST
Source: Trial 1839-3y CSR, Table 12-73

No subject fulfilled the criteria for Hy's law (ALT/AST ≥ 3x UNR and total bilirubin ≥ 2x UNR at the same visit). Brief narratives for patients with ALT or AST ≥ 5x UNR during the trial and follow-up (weeks 0-172) are presented in Table 61.

Reviewer comment: Laboratory data that were captured at outside laboratories are not included in the patient listing of ALT/AST ≥ 5x UNR. For example, see the narrative of patient (b) (6) ***with 'hepatitis' in Section 7.3.2, Nonfatal Serious Adverse Events; this patient is not included in Table 61.***

Table 61. Narratives for Patients with ALT and/or AST ≥ 5x UNR, Weeks 0-172

Subject ID Age[a]/Sex/BMI[a]	Relvant medical history	Relevant concomitant medication	Case narrative	Reason for narrative
Liraglutide 3.0 mg				
(b) (6) 55/F/32.9	Hypertension, headache	Aspirin, codeine, enalapril	ALAT was borderline normal at screening. On day 113, AEs of elevated ALAT and ASAT were reported (ALAT 464 U/L, ref: 6-37; ASAT 145 U/L, ref: 10-36). At the next visit (day 196), these laboratory values had normalised and essentially remained so throughout the duration of the trial, albeit incidental elevations in ALAT were observed at some trial visits (values were up to~2×UNR). Other hepatic laboratory parameters were normal throughout the trial. No change to trial drug due to the AEs and outcome of the AEs were reported as recovered. Subject completed the trial.	ALAT ≥10×UNR
(b) (6) 50/F/39.0	Hepatomegaly, gastritis, irritable bowel syndrome, uterine polyp, uterine leiomyoma	Oral contraceptives, omeprazole, cromolyn sodium	On day 30, an AE of elevated hepatic enzymes was reported (ALAT 377 U/L (ref: 6-37), ASAT 152 U/L (ref: 10-36)). Other hepatic laboratory parameters were normal. Repeat assessments on days 58 and 118 demonstrated slight elevations (ALAT 85-87 U/L; ASAT 40 U/L). From day 205 onwards, all hepatic laboratory parameters were normal. Abdominal ultrasound was reportedly normal. No change to trial drug due to the AEs and outcome of the AE was reported as recovered. Subject completed the trial.	ALAT ≥10×UNR
(b) (6) 48/F/31.4	Dyslipidaemia, hypertension, polycystic ovaries, brain neoplasm, abdominal pain upper	Enalapril, simvastatin, hydrochlorothiazide	Four (4) days prior to the start of treatment, the subject presented with an SAE of biliary colic. At baseline, elevations in ALAT (436 U/L, ref: 6-37), ASAT (145 U/L, ref: 10-36) and alkaline phosphatase (204 U/L, ref: 40-100) were observed. All subsequent hepatic laboratory results were normal. The subject had an elective cholecystectomy on day 52 and discontinued trial drug temporarily in relation to the procedure. Outcome of the AE was recovered. Subject discontinued treatment permanently (withdrew consent) on day 555.	ALAT ≥10×UNR
(b) (6) 35/F/36.7	None, except obesity	Ethinyl estradiol, chlormadinone	On day 160, an SAE of severe acute cholecystitis was reported. On day 165, body weight was noted to be down 13.6 kg from baseline. ALAT was elevated at baseline (88 U/L) and all subsequent measurements during the treatment period. On day 162, ALAT was 314 U/L and associated with elevations in ASAT (284 U/L, ref: 10-36), alkaline phosphatase (162 U/L, ref: 40-100) and total bilirubin (38 umol/L, ref: 3-21). On day 171, ALAT had decreased to 69 U/L and all other hepatic laboratory parameters had normalised. The subject had a cholecystectomy on day 188. Trial drug was permanently discontinued due to the AE (outcome: recovered).	ALAT ≥5×UNR, ASAT ≥5×UNR

Subject ID Age[a]/Sex/BMI[a]	Relvant medical history	Relevant concomitant medication	Case narrative	Reason for narrative
(b) (6) 53/F/37.7	Hypothyroidism, uterine leiomyoma, hysterectomy, osteoarthritis, headache, insomnia	Levothyroxine	ALAT and ASAT were borderline normal at screening. On day 29, subject had elevations in ALAT (235 U/L, ref: 6-37), ASAT (197 U/L, ref: 10-36), and alkaline phosphatase (108 U/L, ref: 40-100). Accompanying AEs of ALAT and ASAT increased were reported; outcome of these AEs were reported as recovered. On day 57, both parameters had decreased to baseline levels. On day 37, an AE of vomiting was reported and the subject discontinued trial drug permanently due to this AE approximately 5 weeks after.	ALAT ≥5×UNR, ASAT ≥5×UNR
(b) (6) 38/M/36.9	Hepatic steatosis, gastritis, duodenitis, coronary artery disease (coronary artery stenosis,myocardial ischaemia, coronary angioplasty), cardiac failure, hypertension, multiple valve regurgitation (mitral valve incompetence,tricuspid valve incompetence, aortic valve incompetence)	Clopidogrel, amlodipine, enalapril, metoprolol, ursodeoxycholic acid	ALAT was elevated at screening (267 U/L, ref: 6-48) and baseline (242 U/L). For the duration of trial, ALAT was elevated (range: 99-166 U/L). ASAT was also elevated at screening (90 U/L, ref: 10-45) and baseline (83 U/L). For the duration of trial, ASAT ranged 38-75 U/L. Other hepatic laboratory parameters were normal throughout the trial. No related AEs reported. Subject discontinued treatment permanently (withdrew consent) on day 1043.	ALAT ≥5×UNR
(b) (6) 44/F/41.8	Hepatic steatosis, hypercholesterolaemia	None noted	ALAT was elevated at baseline (77 U/L, ref: 6-37). For the duration of treatment with trial drug, ALAT ranged 19-72 U/L. During the off-drug follow-up period, ALAT increased to 155 U/L (day 1136) and 196 U/L (day 1207), and ASAT values were also elevated (73 and 94 U/L, respectively, ref: 10-36). Other hepatic laboratory parameters were essentially normal throughout the trial. No AEs reported. Subject completed the trial.	ALAT ≥5×UNR
(b) (6) 63/F/38.0	Hyperlipidemia, postmenopause, anxiety, depression, asthma, migraine, hypothyroidism, osteoarthritis	Levothyroxine, liothyronine, montelukast, sumatriptan, salbutamol, sertraline	SAEs of cholelithiasis were reported on days 354 and 375, and a severe SAE of cholodocholithiasis was reported on day 411. On day 407, increases were noted for ALAT (261 U/L, ref: 6-37), ASAT (95 U/L, ref: 10-36) and alkaline phosphatase (294 U/L, ref: 40-100). ASAT and ALAT were essentially normal at all other visits. Total bilirubin was normal throughout the trial. The subject had a cholecystectomy on day 411. Trial drug was temporarily withdrawn due to the SAEs (outcome: recovered). Subject discontinued treatment permanently (withdrew consent) on day 605.	ALAT ≥5×UNR

Subject ID Age[a]/Sex/BMI[a]	Relvant medical history	Relevant concomitant medication	Case narrative	Reason for narrative
(b) (6) 22/F/31.7	Bipolar disorder, depression, suicide attempt, multiple allergies (seasonal allergy, hypersensitivity, drug hypersensitivity), migraine	Oral contraceptives, sumatriptan	On day 46, AEs of nausea, vomiting and abdominal discomfort were reported and on day 48, an AE of elevated liver enzymes was reported (ALAT 328 U/L, ref: 6-37; ASAT 108 U/L, ref: 10-36). Trial drug was temporarily withdrawn due to the AEs. On day 56, ALAT had decreased to 83 U/L, and normalised thereafter; ASAT had normalised (20 U/L) and remained so thereafter. Other hepatic laboratory parameters were essentially normal throughout the trial. Outcome of these AEs were reported as recovered. Subject discontinued treatment permanently (due to pregnancy) on day 510.	ALAT ≥5×UNR
(b) (6) 52/F/43.1	Hyperlipidaemia, hypertension, goitre, hypothyroidism, skin candida, postmenopause, anxiety	Rosuvastatin, lisinopril, hydrochlorothiazide, levothyroxine, lotrisone, clobetasol propionate	On day 641, treatment with diclofenac (for 84 days) was initiated due to an ongoing AE of exostosis. On days 703 and 711, ALAT was elevated (191 and 201 U/L, ref: 6-37) as was ASAT (85 and 76 U/L, ref: 10-36). On day 792, the values had decreased (ALAT to 71 U/L and ASAT to 37 U/L); thereafter they normalised. Alkaline phosphatase was borderline normal at baseline and at the majority of visits during the trial (range: 93-129 U/L). No relevant AEs were reported in relation to the increased hepatic laboratory parameters. Subject completed the trial.	ALAT ≥5×UNR
(b) (6) 58/F/35.5	Cholecystectomy, hysterectomy	None	On day 389, elevations in ASAT (251 U/L, ref: 10-36) ALAT (81 U/L, ref: 6-37) and creatine kinase (11371 U/L, ref: 24-170) were observed and an AE of increased creatine phosphokinase was reported. On day 442, all these parameters had normalised and essentially remained so for the duration of the trial except for an elevated creatine kinase on day 872 (418 U/L). Other hepatic laboratory parameters were normal throughout the trial. No change to trial drug was made due to the AE and outcome was reported as recovered. Subject completed the trial.	ASAT ≥5×UNR
(b) (6) 38/F/36.1	Depression	None	Subject entered the trial with slightly elevated levels of creatinine phosphokinase (278 U/L at baseline, ref: 24-170) and this elevation persisted for the duration of the trial. On day 990, the subject had an incidental increases in ASAT to 223 U/L (ref: 10-36), ALAT to 70 U/L (ref: 6-37) and creatine kinase increased further to 9893 U/L and an AE of increased creatinine phospokinase was reported. On day 996, a re-test showed that values had decreased (ASAT 49 U/L, ALAT 50 U/L, creatine kinase 1113 U/L). On day 1007, ASAT and ALAT had normalised and creatine kinase had returned to baseline level. Other hepatic laboratory parameters were essentially normal throughout the trial except an elevation of ASAT ~2xUNR on day 1136 (off-drug). No change to trial drug was made due to the AE and outcome was reported as recovered. Subject completed the trial.	ASAT ≥5×UNR

Subject ID Age[a]/Sex/BMI[a]	Relvant medical history	Relevant concomitant medication	Case narrative	Reason for narrative
(b) (6) 61/M/45.2	Hyper-cholesterolaemia, insomnia, hypertension, gastro-oesophageal reflux disease, blood testosterone decreased	Lisonopril, simvastatin, testosterone, vicodin	Subject had elevated levels of creatinine phosphokinase (756 U/L, ref: 24-195) at baseline and for the duration of the trial (range: 200-1964 U/L) as well as elevated ASAT (62 U/L, ref: 10-45) up to ~2xUNR during the first 2 years. On day 871, elevations were observed for ASAT (121 U/L) and ALAT (80 U/L, ref: 6-48) and AEs of increased aspartate and alanine aminotransferase were reported (outcome: recovered). On day 907, SAEs of unstable angina, ventricular tachycardia, syncope and increased creatine phosphokinase were reported. On day 984, ASAT increased to >5×UNR (225 U/L), and elevations in ALAT (109 U/L) and creatine kinase (386 U/L) were also observed and new AEs of increased aspartate and alanine aminotransferase were also reported (trial drug was temporarily withdrawn due to the AEs and outcomes were reported as not recovered). ASAT and ALAT remained elevated for the remainder of the trial (ASAT ranged 165-318 U/L and ALAT ranged 121-199 U/L). Alkaline phosphatase and total bilirubin were normal throughout the trial. On day 974, the subject was diagnosed with T2DM. Subject completed the trial.	ASAT ≥5×UNR
(b) (6) 39/F/42.9	Cholelithiasis, cholecystectomy, migraine, insomnia, back pain	Paracetamol	Subject had elevated ASAT >5×UNR (194 U/L, ref: 6-36) and elevated ALAT (156 U/L, ref: 10-37) at baseline. At next visit (day 108), both values had decreased, ASAT to 59 U/L and ALAT to 63 U/L and both parameters remained around this level until the last measurement (day 393). Other hepatic laboratory parameters were normal throughout the trial. On day 393, an AE of increased hepatic enzymes was reported (outcome: not recovered). No change to trial drug due to the AE was reported. Subject was lost to follow-up.	ASAT ≥5×UNR

Subject ID Age[a]/Sex/BMI[a]	Relvant medical history	Relevant concomitant medication	Case narrative	Reason for narrative
Placebo				
(b) (6) 55/F/37.0	Cholecystectomy, gastrolithiasis, dyslipidaemia	Methotrexate, paracetamol	Subject had slightly elevated amylase (131 U/L, ref: 20-112) at baseline, that remained elevated during the treatment period. On day 28, elevations in ALAT (65 U/L, ref: 6-37) and ASAT (41 U/L, ref 10-36) were observed and an AE of increased transaminases was reported. On day 37, an AE of nausea was reported (duration: 1 day, recovered). On day 84, ALAT and ASAT were further increased to 330 U/L and 120U/L respectively. Other hepatic laboratory parameters were normal throughout the trial. On day 133, the subject was withdrawn due to the increased transaminases AE (outcome was reported as recovered). No further measurements of ALAT and ASAT were available.	ALAT ≥5×UNR
(b) (6) 23/F/52.5	Cholelithiasis, cholecystectomy, depression	None	Subject had elevated ALAT (93 U/L, ref: 6-37) and ASAT (63 U/L, ref: 10-36) at baseline. Both parameters stayed increased over the next months and after 112 days ALAT and ASAT reached 185 U/L and 101 U/L respectively and AEs of increased alanine and aspartate aminotransferase were reported (outcome: not recovered). A re-test on day 153, confirmed the elevated levels. Subject was withdrawn after 196 days due to the increased aminotransferase AEs with levels of ALAT and ASAT of 149 U/L and 77 U/L. No further laboratory measurements are available. Other hepatic laboratory values were essentially normal throughout the trial.	ALAT ≥5×UNR
(b) (6) 59/M/29.7	Headache, pulmonary embolism	Paracetamol, warfarin	On day 200, subject had an incidental increases in ASAT (504 U/L, ref: 10-36), ALAT (135 U/L, ref: 6-48) and creatine kinase (11354 U/L, ref: 24-195) and AEs of increased aspartate aminotransferase and creatinine phosphokinase were reported. On day 284, all parameters had normalised and remained essentially normal for the rest of the trial. Other hepatic laboratory parameters were normal throughout the trial. No change to trial drug due to the AEs and outcomes of were reported as recovered. Subject completed the trial.	ASAT ≥5×UNR

Abbreviations: AE = adverse event; ALAT = alanine amino transferase; ASAT = aspartate amino transferase; BMI = body mass index; PCOS = polycystic ovary syndrome; SAS = safety analysis set; T2DM = type 2 diabetes mellitus; UNR = upper limit of normal range.

UNR: ALAT: 37 U/L for females (18-91 years) and 48 U/L for males (18-91 years); ASAT: 36 U/L for females (18-91 years) and 45 U/L for males (18-91 years); alkaline phosphatase: 100 U/L for females and 145 U/L for males.

[a] Baseline value.

Source: Trial 1839-3y CSR, Table 12-74

As noted above, creatine kinase elevations ≥ 5 and 10× UNR during the treatment period were observed in a higher proportion of patients treated with Saxenda than with placebo. All cases of creatine kinase elevations ≥ 10× UNR observed in patients on Saxenda appeared to be incidental and the value had normalized at the subsequent measurements (either at re-test or following trial visit, when a subsequent value was available). Creatine kinase elevations ≥ 10× UNR on Saxenda did not appear to lead to treatment discontinuation; see a summary of cases in Appendix 9.2.

7.4.3 Vital Signs

See Section 7.3.5, under the cardiovascular events subsection for a discussion of heart rate. SBP and DBP were defined as secondary efficacy endpoints and are described in Section 6.1.6.

7.4.4 Electrocardiograms (ECGs)

ECGs were conducted at screening, every 6 months of the 160 week treatment period, and at the week 172 follow-up. ECGs were assessed by investigators and were also assessed centrally by cardiologists from ICON Medical Imaging for evidence of myocardial ischemia, silent MI, arrhythmia, or other abnormalities. All ECGs with findings suggestive of MI were sent for adjudication. Table 62 below presents the findings from the centrally read ECGs.

Table 62. ECGs Evaluated by Central Assessment, Post-Baseline until End-of-Treatment

	Lira 3.0 mg N (%)	Placebo N (%)
Number of subjects	1501	747
Does ECG indicate the following	1389 (100.0)	653 (100.0)
New ischemia since prior ECG	4 (0.3)	2 (0.3)
New infarction since prior ECG	16 (1.2)	5 (0.8)
Anterior	5 (0.4)	3 (0.5)
Lateral	1 (0.1)	0 (0.0)
LBB and cannot assess location of infarction	0 (0.0)	0 (0.0)
Inferior	11 (0.8)	3 (0.5)
Posterior	0 (0.0)	0 (0.0)
New left bundle branch block since prior ECG	2 (0.1)	1 (0.2)
None of the above	1386 (99.8)	653 (100.0)
Other abnormalities	1389 (100.0)	653 (100.0)
Yes	34 (2.4)	23 (3.5)
New arrhythmia	12 (0.9)	8 (1.2)
New LVH	0 (0.0)	0 (0.0)
Other	23 (1.7)	16 (2.5)
No	1388 (99.9)	647 (99.1)
Overall conclusion	1389 (100.0)	653 (100.0)
Normal ECG or non significant changes	1385 (99.7)	648 (99.2)
New finding suggestive of MI	17 (1.2)	5 (0.8)
Other new significant abnormal ECG findings	27 (1.9)	20 (3.1)

ECG: Electrocardiogram, N: Number of subjects, LBB: Left bundle branch, LVH: Left ventricular hypertrophy, SAS: safety analysis set, %: Percentage of subjects.

Source: Trial 1839-3y CSR, Table 12-79

Of the 23 ECGs sent for adjudication [22 'new finding suggestive of MI' and 1 additional ECG in the Saxenda group with 'normal ECG or non-significant changes' (new left anterior fascicular block)], 1 in each treatment group was confirmed as MI by the EAC.

At week 172, 3 patients had new findings suggestive of MI during the off-drug follow-up period, 2 in the Saxenda group and 1 in the placebo group. All 3 cases were sent for adjudication, none was confirmed as MI.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Serum samples for anti-liraglutide antibodies were assessed at baseline and at the start of the off-drug follow-up period (week 162) or after premature discontinuation of trial product. Anti-liraglutide antibody positive samples were further characterized for cross reactivity towards native GLP-1 and for *in vitro* neutralization of liraglutide.

At baseline, 1 patient in the placebo group tested positive for anti-liraglutide antibodies.

Few patients treated with Saxenda (5, 0.4%) and placebo (1, 0.2%) tested positive for anti-liraglutide antibodies at any time post-baseline. One (0.1%) of the 5 liraglutide-treated patients had antibodies with cross reactivity towards native GLP-1 and an additional 3 (0.3%) of the 5 patients had antibodies with *in vitro* neutralizing effect to liraglutide (none of the patients had both antibodies with cross reactivity and *in vitro* neutralizing effect to liraglutide).

Of these 5 patients in the Saxenda group, 4 tested positive during the off-drug follow-up period and 1 tested positive after discontinuation of treatment. In the placebo group, 1 patient tested positive for anti-liraglutide antibodies post-treatment.

The antibody titers (%bound/total) in the Saxenda group ranged from 3.8 to 11.3.

Table 63 describes changes in efficacy endpoints (HbA1c and weight) in patients with positive antibodies. No apparent effect on efficacy was observed.

Table 63. Positive Anti-Liraglutide Antibodies and Effects on Efficacy Endpoints

Subject ID	With-drawn (Y/N)	Treatment	Age	Sex	BMI	Visit and week	Value (% B/T)	DF	Anti-lira glutide antibodies (Positive/ Negative)	Cross-reacting antibodies to native GLP-1 (Positive/ Negative)	Neutralizing effect (Positive/ Negative)	Ch - in HbA1c (%)	Ch - in Body-weight (%)
(b) (6)	N	Lira 3.0 mg	60	Female	31.6	Visit 44b (Week 162)	6.4		Positive	Positive	Negative	-0.8	-13.2
	N	Placebo	40	Male	44.9	Visit 44b (Week 162)	11.2		Positive	Positive	Positive	0.0	-8.4
	N	Lira 3.0 mg	50	Female	40.8	Visit 44b (Week 162)	3.8		Positive	Negative	Negative	-0.5	-8.7
	Y	Placebo	54	Female	40.6	Visit 3 (Week 0)	9.7		Positive	Negative	Negative	0.0	0.0
	Y	Lira 3.0 mg	55	Female	36.4	Visit 17 (Week 56)	11.3		Positive	Negative	Positive	-0.3	-10.7
	N	Lira 3.0 mg	43	Female	39.3	Visit 44b (Week 162)	9.2		Positive	Negative	Positive	-0.1	-8.0
	N	Lira 3.0 mg	58	Female	29.7	Visit 44b (Week 162)	5.5		Positive	Negative	Positive	-0.2	-2.8

Source: Trial 1839-3y CSR, Table 14.3.7.6

There was no obvious effect of antibodies on safety. Treatment-emergent adverse events that occurred in the 5 patients treated with Saxenda by SOC are listed below (patient (b) (6) experienced 4 events of asymptomatic hypoglycemia reported during OGTT visits):

Table 64. AEs in Saxenda-Treated Patients with Anti-Liraglutide Antibodies by System Organ Class

MedDRA System Organ Class	Number of Events
Patient (b) (6)	
Gastrointestinal disorders	7
Infections and infestations	6
Metabolism and nutrition disorders	6

Musculoskeletal and connective tissue disorders	3
Injury, poisoning and procedural complications	2
Eye disorders	1
General disorders and administration site conditions	1
Investigations	1
Nervous system disorders	1
Patient (b) (6)	
Vascular disorders	4
Musculoskeletal and connective tissue disorders	1
Nervous system disorders	1
Patient (b) (6)	
Investigations	2
Nervous system disorders	1
Patient (b) (6)	
Gastrointestinal disorders	3
Patient (b) (6)	
Injury, poisoning and procedural complications	2
General disorders and administration site conditions	1
Musculoskeletal and connective tissue disorders	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1
Respiratory, thoracic and mediastinal disorders	1

Source: Reviewer created from 1839-3y datasets

7.5.1 Dose Dependency for Adverse Events

Not applicable; Saxenda was only studied at the 3 mg dose.

7.5 Other Safety Explorations

7.5.2 Time Dependency for Adverse Events

Time dependency was explored for acute gallstone disease, hypoglycemia, gastrointestinal disorders, and adjudicated CV AEs in Section 7.3.5.

Overall, AEs by treatment period (year) are presented in the following table:

Table 65. Adverse Events by Period

	Lira 3.0 mg N	(%)	E	R	Placebo N	(%)	E	R
Safety analysis set	1501				747			
Total (excl. screening)	1426	(95.0)	16350	471.7	670	(89.7)	6581	417.5
TEAE (0 - 56 weeks)	1372	(91.4)	8503	622.2	637	(85.3)	3323	502.6
TEAE (57 - 108 weeks)	903	(83.1)	3990	404.2	398	(80.1)	1731	393.3
TEAE (109 - 162 weeks)	745	(84.1)	3266	377.6	307	(80.8)	1296	351.3
Non-TEAEs (observational follow-up, 162-172 weeks)	305	(38.8)	517	336.4	113	(33.6)	201	311.0
Non-TEAEs (0-172 weeks) in subjects withdrawn in treatment period	53		73		22		30	
Non-TEAEs (162-172 weeks) in subjects withdrawn during follow-up period*	2		2		0		0	

N: Number of subjects, E: Number of events, %: Percentage of subjects
R: Event rate per 100 years of observation time, TEAE: Treatment emergent adverse event
Table presents all adverse events (treatment emergent and non-treatment emergent) observed after first day of randomised treatment up to 172 weeks after randomisation. Non TEAEs in withdrawn subjects are also included.
A treatment emergent adverse event (TEAE) is defined as an event that has onset date on or after the first randomised treatment and no later than 14 days after the last day of randomised.
Non-treatment emergent AEs are events with onset more than 14 days after last treatment.
*Includes data from subjects who completed the treatment period but did not attend any visits in the follow-up period.
Output presents data for subjects with pre-diabetes at baseline and includes 6 subjects who did not have pre-diabetes at baseline, but participated in the extension period of the trial.

Source: Trial 1839-3y CSR, Table 14.3.1.8

7.5.3 Drug-Demographic Interactions

The following tables describe AEs by SOC in subgroups of the following demographic groups: age, sex, and race. No clear pattern emerged.

Table 66. AEs by SOC, by Age Subgroup

	18-<40 yrs		40-<65 yrs		65-<75 yrs		≥75 yrs	
	Sax N=393	Pbo N=202	Sax N=1003	Pbo N=492	Sax N=99	Pbo N=52	Sax N=6	Pbo N=1
Blood and lymphatic system disorders	16 (4.1)	21 (10.4)	42 (4.2)	13 (2.6)	5 (5.1)	4 (7.7)	1 (16.7)	0
Cardiac disorders	12 (3.1)	7 (3.5)	63 (6.3)	40 (8.1)	12 (12.1)	5 (9.6)	0	0
Congenital, familial and genetic disorders	0	0	5 (0.5)	1 (0.2)	1 (1.0)	0	0	0
Ear and labyrinth disorders	15 (3.8)	6 (3.0)	52 (5.2)	28 (5.7)	3 (3.0)	3 (5.8)	0	0
Endocrine disorders	15 (3.8)	11 (5.4)	36 (3.6)	23 (4.7)	1 (1.0)	4 (7.7)	0	0
Eye disorders	15 (3.8)	10 (5.0)	91 (9.1)	47 (9.6)	13 (13.1)	9 (17.3)	0	0
Gastrointestinal disorders	270 (68.7)	90 (44.6)	755 (75 3)	256 (52 0)	75 (75.8)	28 (53.8)	4 (66.7)	1 (100)
General disorders and administration site conditions	108 (27.5)	56 (27.7)	392 (39.1)	159 (32 3)	44 (44.4)	18 (34.6)	2 (33.3)	0
Hepatobiliary disorders	27 (6.9)	5 (2.5)	57 (5.7)	22 (4.5)	1 (1.0)	0	0	0
Immune system disorders	18 (4.6)	9 (4.5)	42 (4.2)	24 (4.9)	4 (4.0)	0	0	0
Infections and infestations	235 (59.8)	123 (60 9)	668 (66.6)	313 (63.6)	70 (70.7)	36 (69.2)	1 (16.7)	1 (100)
Injury, poisoning and procedural complications	85 (21.6)	38 (18.8)	285 (28.4)	135 (27.4)	39 (39.4)	16 (30.8)	0	0
Investigations	81 (20.6)	39 (19.3)	285 (28.4)	106 (21 5)	29 (29.3)	10 (19.2)	3 (50.0)	0
Metabolism and nutrition disorders	127 (32.3)	34 (16.8)	366 (36 5)	105 (21 3)	32 (32.3)	15 (28.8)	2 (33.3)	1 (100)
Musculoskeletal and connective tissue disorders	104 (26.5)	51 (25.2)	470 (46 9)	224 (45 5)	52 (52.5)	29 (55.8)	2 (33.3)	0

Neoplasms benign, malignant and unspecified	4 (1.0)	11 (5.4)	82 (8.2)	32 (6.5)	11 (11.1)	6 (11.5)	0	1 (100)
Nervous system disorders	115 (29.3)	50 (24.8)	372 (37.1)	168 (34.1)	33 (33.3)	15 (28.8)	1 (16.7)	0
Pregnancy, puerperium and perinatal conditions	3 (0.8)	3 (1.5)	3 (0.3)	0	0	0	0	0
Psychiatric disorders	53 (13.5)	34 (16.8)	169 (16 8)	77 (15.7)	11 (11.1)	6 (11.5)	0	0
Renal and urinary disorders	18 (4.6)	9 (4.5)	74 (7.4)	35 (7.1)	8 (8.1)	11 (21.2)	1 (16.7)	0
Reproductive system and breast disorders	34 (8.7)	27 (13.4)	98 (9.8)	36 (7.3)	8 (8.1)	3 (5.8)	0	0
Respiratory, thoracic and mediastinal disorders	63 (16.0)	32 (15.8)	233 (23 2)	124 (25 2)	25 (25.3)	14 (26.9)	0	0
Skin and subcutaneous tissue disorders	53 (13.5)	31 (15.3)	197 (19.6)	94 (19.1)	23 (23.2)	9 (17.3)	1 (16.7)	0
Social circumstances	2 (0.5)	0	7 (0.7)	5 (1.0)	1 (1.0)	0	0	0
Surgical and medical procedures	7 (1.8)	4 (2.0)	16 (1.6)	5 (1.0)	2 (2.0)	1 (1.9)	0	0
Vascular disorders	25 (6.4)	15 (7.4)	138 (13 8)	64 (13.0)	11 (11.1)	5 (9.6)	1 (16.7)	1 (100)

Source: Response to FDA Request – January 25, 2017, Appendix 1, Tables 1-4

Table 67. AEs by SOC, by Sex Subgroup

	Males		Females	
	Sax N=364	Pbo N=175	Sax N=1137	Pbo N=572
Blood and lymphatic system disorders	13 (3.6)	7 (4.0)	51 (4.5)	31 (5.4)
Cardiac disorders	32 (8.8)	18 (10.3)	55 (4.8)	34 (5.9)
Congenital, familial and genetic disorders	4 (1.1)	0	2 (0.2)	1 (0.2)
Ear and labyrinth disorders	10 (2.7)	10 (5.7)	60 (5.3)	27 (4.7)
Endocrine disorders	5 (1.4)	6 (3.4)	47 (4.1)	32 (5.6)
Eye disorders	28 (7.7)	13 (7.4)	91 (8.0)	53 (9.3)
Gastrointestinal disorders	247 (67.9)	75 (42.9)	857 (75.4)	300 (52.4)
General disorders and administration site conditions	113 (31.0)	46 (26.3)	433 (38.1)	187 (32.7)
Hepatobiliary disorders	22 (6.0)	9 (5.1)	63 (5.5)	18 (3.1)
Immune system disorders	8 (2.2)	5 (2.9)	56 (4.9)	28 (4.9)
Infections and infestations	226 (62.1)	107 (61.1)	748 (65.8)	366 (64.0)
Injury, poisoning and procedural complications	106 (29.1)	51 (29.1)	303 (26.6)	138 (24.1)
Investigations	129 (35.4)	45 (25.7)	269 (23.7)	110 (19.2)
Metabolism and nutrition disorders	132 (36.3)	37 (21.1)	395 (34.7)	118 (20.6)
Musculoskeletal and connective tissue disorders	160 (44.0)	70 (40.0)	468 (41.2)	234 (40.9)
Neoplasms benign, malignant and unspecified	26 (7.1)	13 (7.4)	71 (6.2)	37 (6.5)
Nervous system disorders	110 (30.2)	40 (22.9)	411 (36.1)	193 (33.7)
Pregnancy, puerperium and perinatal conditions	1 (0.3)	0	5 (0.4)	3 (0.5)
Psychiatric disorders	44 (12.1)	22 (12.6)	189 (16.6)	95 (16.6)
Renal and urinary disorders	24 (6.6)	17 (9.7)	77 (6.8)	38 (6.6)
Reproductive system and breast disorders	17 (4.7)	5 (2.9)	123 (10.8)	61 (10.7)
Respiratory, thoracic and mediastinal disorders	72 (19.8)	37 (21.1)	249 (21.9)	133 (23.3)
Skin and subcutaneous tissue disorders	68 (18.7)	26 (14.9)	206 (18.1)	108 (18.9)
Social circumstances	3 (0.8)	0	7 (0.6)	5 (0.9)
Surgical and medical procedures	11 (3.0)	2 (1.1)	14 (1.2)	15 (2.6)
Vascular disorders	43 (11.8)	23 (13.1)	132 (11.6)	62 (10.8)

Source: Response to FDA Request – January 25, 2017, Appendix 1, Tables 5 and 6

Table 68. AEs by SOC, by Race Subgroup

	White		Black		Asian	
	Sax N=1253	Pbo N=626	Sax N=145	Pbo N=71	Sax N=75	Pbo N=39
Blood and lymphatic system disorders	44 (3.5)	27 (4.3)	9 (6.2)	5 (7.0)	8 (10.7)	5 (12.8)
Cardiac disorders	75 (6.0)	44 (7.0)	4 (2.8)	5 (7.0)	5 (6.7)	3 (7.7)
Congenital, familial and genetic disorders	6 (0.5)	1 (0.2)	0	0	0	0
Ear and labyrinth disorders	61 (4.9)	33 (5.3)	7 (4.8)	1 (1.4)	2 (2.7)	3 (7.7)
Endocrine disorders	38 (3.0)	27 (4.3)	3 (2.1)	4 (5.6)	11 (14.7)	6 (15.4)

Eye disorders	96 (7.7)	57 (9.1)	11 (7.6)	5 (7.0)	7 (9.3)	2 (5.1)
Gastrointestinal disorders	933 (74.5)	324 (51.8)	100 (69.0)	33 (46.5)	48 (64.0)	14 (35.9)
General disorders and administration site conditions	450 (35.9)	201 (32.1)	54 (37.2)	13 (18.3)	30 (40.0)	13 (33.3)
Hepatobiliary disorders	82 (6.5)	24 (3.8)	0	2 (2.8)	2 (2.7)	1 (2.6)
Immune system disorders	47 (3.8)	27 (4.3)	12 (8.3)	5 (7.0)	1 (1.3)	0
Infections and infestations	831 (66.3)	411 (65.7)	88 (60.7)	37 (52.1)	38 (50.7)	19 (48.7)
Injury, poisoning and procedural complications	357 (28.5)	171 (27.3)	35 (24.1)	11 (15.5)	9 (12.0)	5 (12.8)
Investigations	318 (25.4)	124 (19.8)	42 (29.0)	16 (22.5)	32 (42.7)	14 (35.9)
Metabolism and nutrition disorders	442 (35.3)	130 (20.8)	52 (35.9)	14 (19.7)	25 (33.3)	8 (20.5)
Musculoskeletal and connective tissue disorders	532 (42.5)	267 (42.7)	62 (42.8)	23 (32.4)	20 (26.7)	8 (20.5)
Neoplasms benign, malignant and unspecified	83 (6.6)	45 (7.2)	8 (5.5)	3 (4.2)	5 (6.7)	2 (5.1)
Nervous system disorders	435 (34.7)	205 (32.7)	50 (34.5)	20 (28.2)	22 (29.3)	7 (17.9)
Pregnancy, puerperium and perinatal conditions	5 (0.4)	3 (0.5)	0	0	1 (1.3)	0
Psychiatric disorders	202 (16.1)	107 (17.1)	18 (12.4)	9 (12.7)	6 (8.0)	0
Renal and urinary disorders	85 (6.8)	48 (7.7)	10 (6.9)	5 (7.0)	5 (6.7)	1 (2.6)
Reproductive system and breast disorders	108 (8.6)	53 (8.5)	20 (13.8)	4 (5.6)	7 (9.3)	7 (17.9)
Respiratory, thoracic and mediastinal disorders	261 (20.8)	146 (23.3)	42 (29.0)	16 (22.5)	13 (17.3)	5 (12.8)
Skin and subcutaneous tissue disorders	222 (17.7)	120 (19.2)	27 (18.6)	5 (7.0)	17 (22.7)	6 (15.4)
Social circumstances	7 (0.6)	5 (0.8)	1 (0.7)	0	2 (2.7)	0
Surgical and medical procedures	23 (1.8)	15 (2.4)	0	2 (2.8)	1 (1.3)	0
Vascular disorders	157 (12.5)	76 (12.1)	11 (7.6)	5 (7.0)	4 (5.3)	4 (10.3)

Source: Response to FDA Request – January 25, 2017, Appendix 1, Tables 7-9

7.5.4 Drug-Disease Interactions

Drug-disease interactions with Saxenda were explored in the original NDA. Hypoglycemia by pre-diabetes/diabetes status is discussed in Section 7.3.5.

7.5.5 Drug-Drug Interactions

The Saxenda label notes that: *Saxenda causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, monitor for potential consequences of delayed absorption of oral medications concomitantly administered with Saxenda.*

As noted in Section 7.3.5 (Hypoglycemia), the single patient on Saxenda who developed T2DM and had hypoglycemia events reported on the hypoglycemia form was not on any concomitant antihyperglycemic medications according to the concomitant medications dataset. There were no ADA severe hypoglycemic episodes in patients with or without T2DM.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the 1839 trial, all neoplasms were to be reported by the investigator as a MESI and sent for EAC adjudication. The 1839 study report includes a MedDRA search for neoplasms (see Table 69), and a summary of the EAC-confirmed malignant neoplasms.

MedDRA Search

Table 69. Terms Included in the MedDRA Search for Neoplasms

Included terms	
SMQ Biliary neoplasms malignant and unspecified	SMQ Blood premalignant disorders
SMQ Biliary malignant tumours	SMQ Gastrointestinal premalignant disorders
SMQ Biliary tumours of unspecified malignancy	SMQ Premalignant disorders, general conditions and other site specific disorders
SMQ Breast neoplasms, malignant and unspecified	
SMQ Breast malignant tumours	SMQ Reproductive premalignant disorders
SMQ Breast tumours of unspecified malignancy	SMQ Skin premalignant disorders
SMQ Liver neoplasms, malignant and unspecified	SMQ Prostate neoplasms, malignant and unspecified
SMQ Liver malignant tumours	SMQ Prostate malignant tumours
SMQ Liver tumours of unspecified malignancy	SMQ Prostate tumours of unspecified malignancy
SMQ Malignant or unspecified tumours	SMQ Skin neoplasms, malignant and unspecified
SMQ Malignant tumours	SMQ Skin malignant tumours
SMQ Tumours of unspecified malignancy	SMQ Skin tumours of unspecified malignancy
SMQ Ovarian neoplasms, malignant and unspecified	SMQ Uterine and fallopian tube neoplasms, malignant and unspecified
SMQ Ovarian malignant tumours	SMQ Uterine and fallopian tube malignant tumours
SMQ Ovarian tumours of unspecified malignancy	SMQ Uterine and fallopian tube tumours of unspecified malignancy
SMQ Oropharyngeal neoplasms	SMQ Tumour markers
SMQ Premalignant disorders	SOC Neoplasm benign, malignant and unspecified (incl. cysts and polyps)

Abbreviations: SMQ = standardised MedDRA query; SOC = system organ class.

Source: Trial 1839-3y CSR, Table 12-40

In the entire trial period – including the 160 weeks on-treatment and 12 weeks follow-up, 276 neoplasm AEs (including benign, premalignant, malignant, unspecified neoplasms as well as polyps and cysts) in 179 patients treated with Saxenda (11.9%, 8.0 events per 100 PYO) and 139 events in 86 patients treated with placebo (11.5%, 8.8 events per 100 PYO) were identified using the MedDRA search. The majority of events were benign.

The proportions of patients with neoplasm SAEs captured within the MedDRA search and the corresponding event rates were higher with Saxenda (2.7%, 1.4 events per 100 PYO) than with placebo (1.2%, 0.6 events per 100 PYO).

- Nine SAEs were reported with Saxenda within the HLGT of 'breast neoplasms malignant', and breast cancer was the most frequently reported PT with Saxenda; no malignant breast neoplasms were reported with placebo. Breast neoplasms are covered in further detail in a dedicated section below (Breast Cancer PMR).

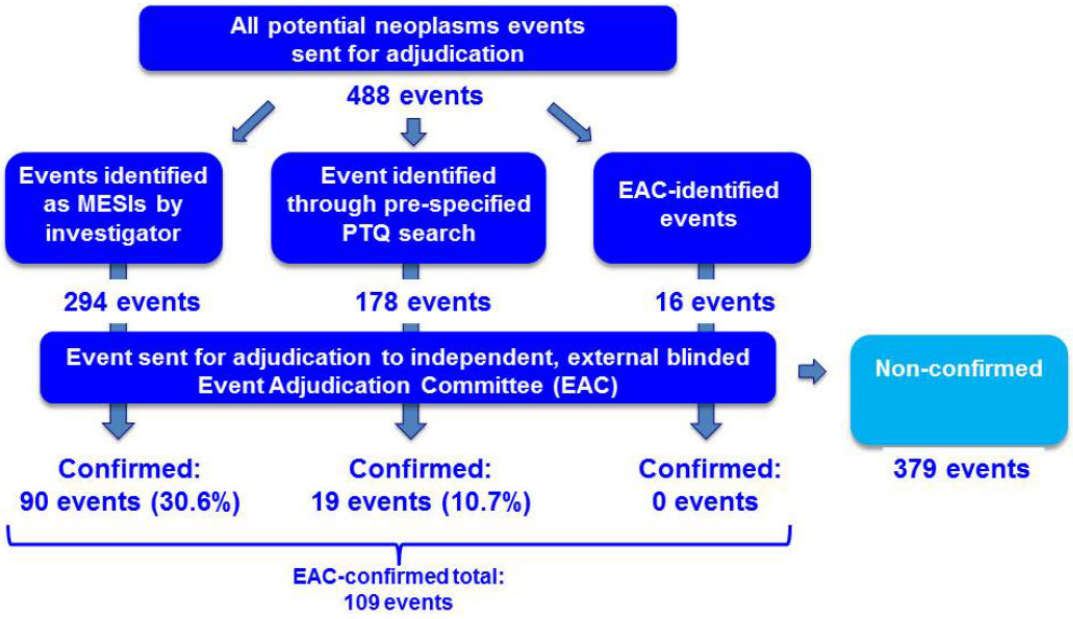
- SAEs within the gastrointestinal neoplasms malignant and unspecified HGLT were reported by 4 patients treated with Saxenda (colon cancer, colon cancer metastatic, colon cancer stage 0, rectal cancer) and 1 patient treated with placebo (pancreatic carcinoma metastatic).

Adjudication

Potential neoplasm events sent for adjudication were:
- identified as MESIs by the investigator or
- identified by a pre-defined company search for neoplasms or
- identified by the EAC during source data review

The results of this search are shown in the figure below:

Figure 26. Adjudication of Potential Neoplasms



Note: The percentages are calculated from the total number of events sent for adjudication within each subcategory.
Abbreviations: EAC = event adjudication committee; MESI = medical event of special interest; PTQ = (Novo Nordisk defined) preferred term query; SAS = safety analysis set.
Note: thyroid neoplasms adjudicated as thyroid disease requiring thyroidectomy are not included
Source: Trial 1839-3y CSR, Figure 12-23

The EAC confirmed a total of 75 neoplasm events in 66 patients treated with Saxenda and 37 neoplasm events in 28 patients treated with placebo. Overall, the proportions of patients with EAC-confirmed neoplasms and rates of events were 4.40% (2.16 events per 100 PYO) for Saxenda and 3.75% (2.35 events per 100 PYO) for placebo. For

malignant neoplasms, the proportions of patients with EAC-confirmed neoplasms and rates of events were 1.87% (0.92 events per 100 PYO) for Saxenda and 1.47% (0.89 events per 100 PYO) for placebo. Individual neoplasms are listed in the table below. Malignant breast neoplasms were reported more frequently in the Saxenda vs. placebo group.

Table 70. Adjudicated Neoplasms

	Lira 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	1501				747			
All EAC confirmed neoplasm events	66	(4.40)	75	2.16	28	(3.75)	37	2.35
Benign	33	(2.20)	35	1.01	15	(2.01)	17	1.08
Blood (Leukemias; Anemias; Myelomas)	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Breast	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Colorectal	13	(0.87)	13	0.38	7	(0.94)	7	0.44
Connective Tissue	3	(0.20)	4	0.12	1	(0.13)	1	0.06
Female Reproductive (Vaginal; Cervical; Ovarian)	8	(0.53)	8	0.23	3	(0.40)	4	0.25
Gastric/Intestinal	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Liver	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Renal/Adrenal	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Sarcoma	0	(0.00)	0	0.00	1	(0.13)	1	0.06
Skin	1	(0.07)	1	0.03	1	(0.13)	1	0.06
Soft Tissue	4	(0.27)	4	0.12	3	(0.40)	3	0.19
Malignant	28	(1.87)	32	0.92	11	(1.47)	14	0.89
Bladder	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Blood (Leukemias; Anemias; Myelomas)	2	(0.13)	2	0.06	0	(0.00)	0	0.00
Breast	6	(0.40)	7	0.20	0	(0.00)	0	0.00
Colorectal	3	(0.20)	4	0.12	1	(0.13)	1	0.06
Female Reproductive (Vaginal; Cervical; Ovarian)	0	(0.00)	0	0.00	1	(0.13)	2	0.13
Gall Bladder	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Laryngeal	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Lymphomas (Non Hodgkin; Hodgkin)	2	(0.13)	2	0.06	1	(0.13)	1	0.06
Male Reproductive (Penile; Prostate; Testicular)	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Pancreatic	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Skin	10	(0.67)	11	0.32	7	(0.94)	9	0.57
Thyroid	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Unknown Primary	0	(0.00)	0	0.00	1	(0.13)	1	0.06
Pre-Malignant/Carcinoma In Situ/Borderline	7	(0.47)	7	0.20	5	(0.67)	6	0.38
Breast	3	(0.20)	3	0.09	0	(0.00)	0	0.00
Colorectal	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Female Reproductive (Vaginal; Cervical; Ovarian)	0	(0.00)	0	0.00	1	(0.13)	1	0.06
Skin	1	(0.07)	1	0.03	4	(0.54)	5	0.32
Thyroid	2	(0.13)	2	0.06	0	(0.00)	0	0.00
Unclassified	1	(0.07)	1	0.03	0	(0.00)	0	0.00
Blood (Leukemias; Anemias; Myelomas)	1	(0.07)	1	0.03	0	(0.00)	0	0.00

EAC: (External) event adjudication committee, N: Number of subjects, %: Percentage of subjects, E: Number of events, non-TEAE: non-treatment emergent adverse event, R: Event rate per 100 years of observation time, SAS: safety analysis set, TEAE: treatment-emergent adverse event.
Adverse events (TEAEs and non-TEAEs) observed after first day of randomised treatment up to 172 weeks after randomisation are included.
A TEAE is defined as an event that has onset date on or after the first randomised treatment and no later than 14 days after the last day of randomised treatment. Non-TEAEs are events with onset more than 14 days after last treatment.

Source: Trial 1839-3y CSR, Table 12-41

Breast cancer is discussed fully below under the breast cancer PMR subsection (note that the breast PMR subsection includes patients without pre-diabetes enrolled in the 1-year main trial only; this explains the discrepancy in numbers of patients in Table 70 and Table 74).

Other neoplasms of interest from the original Saxenda NDA review included thyroid, pancreas, and colorectal cancers, and are discussed further below. (Thyroid disease and elevated calcitonin are discussed separately in Section 7.3.5, Submission Specific Primary Safety Concerns.)

Thyroid Neoplasms
Three patients (0.2%) on Saxenda and no patients on placebo had EAC-confirmed thyroid neoplasms. All 3 events were identified after thyroidectomies performed due to worsening of pre-existing thyroid disease or during evaluation for nodular goiter or hyperparathyroidism.

One case was considered malignant and 2 cases were pre-malignant. One of the events was a non-TEAE, reported 236 days after last day of Saxenda treatment. All events were papillary microcarcinomas and no cases of medullary thyroid cancer (MTC) or C-cell hyperplasia were identified during the trial. No elevations in calcitonin levels were observed prior to onset of the events. Details of the cases are provided below:

Table 71. EAC-Confirmed Thyroid Neoplasms

Subject ID/ Age*/Sex/ BMI*	Preferred term	EAC diagnosis	EAC malignancy status	Inv onset day/ EAC onset day/ Period	Relevant medical history	Details	TNM staging
Liraglutide 3.0 mg – Malignant							
(b) (6) 45/M/39.4	Thyroid cancer	Papillary microcarcinoma	Malignant Stage: N/A	788/833/ Treatment period	Hyperthyroidism, goitre, and 'foreign body sensation'	At trial entry, the subject reported foreign body sensation in relation to the thyroid gland according to the case narrative; this was not noted in the physical examination at screening. Thyroid ultrasound demonstrated thyroid nodules. Thyroidectomy planned due to worsening of hyperthyroidism. Histology showed papillary micro-carcinoma in a nodular goitre. No change to dose of trial drug. Recovered. Calcitonin levels were 5 ng/L at baseline and ≤5 ng/L at all visits (ULN: 8.4 ng/L)	pT1a
Liraglutide 3.0 mg - Pre-malignant							
(b) (6) 43/ F/47.8	Thyroid cancer	Papillary microcarcinoma	Pre-malignant/ Stage 0: *In situ*, Borderline	552/552/ Treatment period	Parathyroidectomy in 2011 (prior to trial entry)	Explorative surgery for persistent increased PTH levels revealed a suspicious nodule in left thyroid lobe leading to left hemi-thyroidectomy. Macroscopic details revealed a thyroid nodule measuring 15x12x10 mm, suggestive of a colloid nodule. Histology showed a small fibrotic area with incidental 3 mm thyroid papillary micro-carcinoma identified which was completely excised. Recovered. No change to dose of trial drug. Calcitonin levels 1 ng/L at all visits (ULN: 5.0 ng/L).	pT1a pN0 TNM7

Subject ID/ Age[a]/Sex/ BMI[a]	Preferred term	EAC diagnosis	EAC malignancy status	Inv onset day/ EAC onset day/ Period	Relevant medical history	Details	TNM staging
(b) (6) 61/F/38.8	Autoimmune thyroiditis	Micro papillary carcinoma	Pre-malignant/ Stage 0: *In situ*, Borderline	378/378/ Withdrawn (236 days after discontinuation of treatment) Non-TEAE	No relevant	Thyroidectomy for multi-nodular goiter 236 days after discontinuing treatment with trial drug. Diffuse appearance of thyroiditis with multiple nodules. Microscopy showed lymphocytic thyroiditis, marked, diffuse, with several partially oncocytic nodules. Incidental finding of a single micro-site (3 mm) of encapsulated papillary carcinoma, follicular variant, with excision margins in healthy tissue. The event was first confirmed as thyroid disease requiring thyroidectomy and indicated as not being a thyroid neoplasm. Upon re-adjudication due to availability of additional information (imaging and patient reports), it was then confirmed as a thyroid neoplasm (papillary carcinoma), premalignant/carcinoma *in situ*. Calcitonin was 1.0 ng/L prior to withdrawal (ULN: 5.0 ng/L). Recovered.	pT1a Nx Mx R0

Note: Details and TNM staging are based on information in the case narratives from the safety database as well as source documents.
Abbreviations: BMI = body mass index; EAC = event adjudication committee; EAC onset day = EAC assessment of onset day; F = female; M = male; inv onset day = investigator's assessment of event onset day; N/A = not applicable (thyroid neoplasm events evaluated as 'Thyroid disease requiring thyroidectomy' were not evaluated by the EAC with regards to stage of neoplasm); Non-TEAE = non-treatment-emergent adverse event; PTH = parathyroid hormone; SAS = safety analysis set; TEAE = treatment-emergent adverse event; ULN = upper limit of normal range (for calcitonin) (females: 5.0 ng/L; males: 8.4 ng/L); Unk = unknown.
[a] Baseline value.

Source: Trial 1839-3y CSR, Table 12-45

Pancreatic neoplasms

Only 1 pancreatic neoplasm was confirmed by the EAC in a Saxenda-treated patient, a 19-year-old female who was diagnosed with a pseudopapillary tumor of the pancreas. Pseudopapillary tumors of the pancreas are extremely rare epithelial tumors of low malignant potential that typically occur in young women during the second to fourth decade of life.[21] This was a non-TEAE reported during the off-drug follow-up period, 31 days after the last dose of Saxenda. Details are presented below:

Table 72. EAC-Confirmed Pancreatic Neoplasm

Subject ID Age[a]/Sex/ BMI[a]	Preferred term/ EAC diagnosis	EAC malignancy status	Inv onset day/ EAC onset day/ Period	Details including relevant medical history
Liraglutide 3.0 mg				
(b) (6) 19/F/35.7	Solid pseudopapillary tumour of the pancreas/ Pseudopapillary tumour of the pancreas	Malignant/ Stage 1: localised	1152/1152 Follow-up period (non-TEAE, 31 days off-drug)	Medical history: PCOS and alcohol consumption. Symptoms reported 5 days prior to diagnosis included headache, body ache, fever, abdominal pain, nausea, emesis and dehydration. Ultrasound scan and CT scan showed pseudopapillary tumour. Underwent CT-guided pancreatic mass biopsy and results were negative for malignancy. On day 1188, the subject still experienced discomfort and epigastric pain and was treated for pain. Underwent surgery for tumour removal. According to the case narrative, pathology results were negative for malignancy. Recovered.

Note: Details are based on information in the case narratives from the safety database as well as source documents.
Abbreviations: CT = computerised tomography; EAC = event adjudication committee; EAC onset day = EAC assessment of onset day; F = female; inv onset day = investigator's assessment of event onset day; Non-TEAE = non-treatment-emergent adverse event; PCOS = polycystic ovary syndrome; SAS = safety analysis set; TEAE = treatment-emergent adverse event.
[a] Baseline value.

Source: Trial 1839-3y CSR, Table 12-16

21 Yagci A, et al. Diagnosis and treatment of solid pseudopapillary tumor of the pancreas: experience of one single institution from Turkey. World J Surg Oncol (2103); 11:308.

It should be noted that an additional fatal case of pancreatic cancer was identified in a patient randomized to the placebo group (see Section 7.3.1); but for unclear reasons this event was not EAC-confirmed.

Colorectal neoplasms

Overall, a similar proportion of patients in the Saxenda and placebo groups had EAC-confirmed events of colorectal neoplasms (1.1%); although 4 events in 3 patients were malignant in Saxenda-treated patients (0.2%) vs. 1 event in 1 placebo-treated patient (0.1%). One pre-malignant case occurred in a Saxenda-treated patient. Details of the malignant and pre-malignant cases are in the table below. (It is noted that the sole case of colorectal cancer in the placebo group was potentially a recurrence from a tumor diagnosed prior to entering the trial.)

Table 73. EAC-Confirmed Malignant and Pre-Malignant Colorectal Neoplasms

Subject ID/ Age[a]/Sex/ BMI[a]	Preferred term	EAC diagnosis	EAC malignancy status	Inv onset day/ EAC onset day/ Period	Relevant medical history	Details	Size
Liraglutide 3.0 mg - Malignant							
(b) (6) 64/M/34.0	Colon cancer metastatic	Colon adenocarcinoma	Malignant/ Stage 4: metastatic	1058/722/ Treatment period	No relevant	The subject presented with anaemia with dyspnoea and vertigo. A CT scan demonstrated signs of multiple metastases of the liver. Diagnosed by colonoscopy followed by histology (adenocarcinoma without mucinous component). No change to dose of trial drug. Not recovered (metastatic disease).	Unk
(b) (6) 65/M/40.3	ectal cancer	Colon adenocarcinoma	Malignant/ Undetermined	856/856/ Treatment period	No relevant	Diagnosed during routine colonoscopy followed by histology (invasive well-differentiated adenocarcinoma). No change to dose of trial drug. Recovered.	Unk
	Rectal polyp	Adenoma	Benign	995/995/ Treatment period		Diagnosed by colonoscopy followed by histology (tubular adenoma). No change to dose of trial drug. Recovered.	Unk
(b) (6) 59/F/34.0	Colon cancer	Colon carcinoma	Malignant/ Stage 4: metastatic	1092/1092/ Treatment period	Medical history of ovarian cysts and complete hysterectomy	Colonoscopy performed due to rectal bleeding (diagnosis: colon carcinoma). Metastases to regional lymph nodes and liver (two hypermetabolic lesions, largest 2.3 cm diameter). Treated with chemotherapy. No change to dose of trial drug. Recovered with sequelae (colon cancer). Not recovered (metastatic disease).	Unk
	Metastases to liver	Metastatic colon cancer	Malignant/ Stage 4: metastatic	1147/1147/ Follow-up period			
Liraglutide 3.0 mg – Pre-malignant							
(b) (6) 64/M/30.6	Colon cancer stage 0	Colon adenocarcinoma *in situ*	Pre-malignant/ Stage 0: *In situ*	1057/1057/ Treatment period	No relevant	Diagnosed by routine colonoscopy followed by histology (carcinoma *in situ*). No change to dose of trial drug. Recovered.	Unk
Subject ID/ Age[a]/Sex/ BMI[a]	**Preferred term**	**EAC diagnosis**	**EAC malignancy status**	**Inv onset day/ EAC onset day/ Period**	**Relevant medical history**	**Details**	**Size**
Placebo – Malignant							
(b) (6) 51/M/31.1	Colonic polyp	Carcinoid tumor	Malignant: Undetermined	468/459/ Treatment period	Resection of colon polyp (2011, prior to trial entry), immuno-histological examination showed well differentiated endocrine tumour.	Colonoscopy performed due to medical history. Diagnosis confirmed by histology of a rectal polyp (malignant neuroendocrine tumour stage 1). Immunohistochemical examination revealed tumour formation with strong positive cytoplasmatic reactivity with the neuroendocrine markers synaptophysin and chromogranin. The proliferations fraction (marker Ki67) was under 2% - segment of a well differentiated endocrine tumour or a neuroendocrine tumour. It was suggested that the lesion diagnosed in 2011 may not have been completely removed. No change to dose of trial drug. Recovered.	Unk
	Neuroendocrine tumour	Neuroendocrine tumor[b]	Malignant/ Stage 1: localised	468/459/ Treatment period			

Source: Trial 1839-3y CSR, Table 12-44

Breast Cancer PMR

As noted above, during the Saxenda phase 3 development program, a numerical imbalance was observed in the proportion of women with positively adjudicated breast cancer [14 (0.6%) of 2379 Saxenda-treated women compared with 3 (0.2%) of 1300 placebo-treated women, including invasive cancer (11 Saxenda- and 2 placebo-treated women) and ductal carcinoma *in situ* (3 Saxenda-treated women and 1 placebo-treated woman)]. Therefore, as a post-marketing requirement (PMR), the sponsor was required to collect additional information on breast cancer cases reported in the (at the time) ongoing Saxenda phase 3 trial NN8022-1839 (the subject of the current supplement) and EX2211-3748 (LEADER), the phase 3 cardiovascular outcome trial for Victoza; PMRs 2802-8 and 2802-7, respectively. This section will review the data submitted from the 1839 trial; i.e., PMR 2802-8.

PMR 2802-8 was as follows: To assess the risk of breast cancer associated with liraglutide in Trial 1839, collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in the trial, 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.

Data were collected as follows:

- Information about baseline risk and potential confounders in patients with positively adjudicated events of malignant breast neoplasm was collected by questionnaire. The questionnaire was adapted from a commonly used questionnaire in collaboration with an external breast cancer expert from the University of Toronto, Canada (Dr. Pamela Goodwin). Investigators (and delegate, if applicable) participated in a standardized, interactive teleconference training session on how to complete the questionnaire. Interviews could take place by phone or in-person. Both the interviewer and the patient were blinded to the patient's exposure status. Responses were based on information provided by the patient or relevant physician if in agreement with the patient. No additional testing was carried out, and no additional source documentation was required unless deemed necessary by the investigator. Up to 5 phone calls (at varying times) and 2 written contacts were required in an attempt to contact the patient to conduct the questionnaire. [If the sponsor was informed that 1 of the patients had died, the investigator was to contact a proxy (such as a close family member) to complete the questionnaire. However, as stated in the report, no patients with a positively adjudicated malignant breast neoplasm in NN8022-1839 had died.]

- Information about breast cancer grade, stage, and receptor status of the individual cases was provided by Dr. Goodwin, based on information in source documentation.

Limitations:

- Risk factor data were collected after breast cancer diagnosis (at times years after diagnosis), which could lead to the potential for recall, reporting and other biases.

- The absence of uniform ascertainment of breast cancer prior to study entry or during the trial (i.e., no requirement that breast cancer be absent at study entry based on history, physical exam and mammography, no systematic follow-up on patients discontinuing treatment after 56 weeks, inclusion of spontaneous reports after trial completion) may have led to differential reporting and to inclusion of cases that were present prior to study entry.

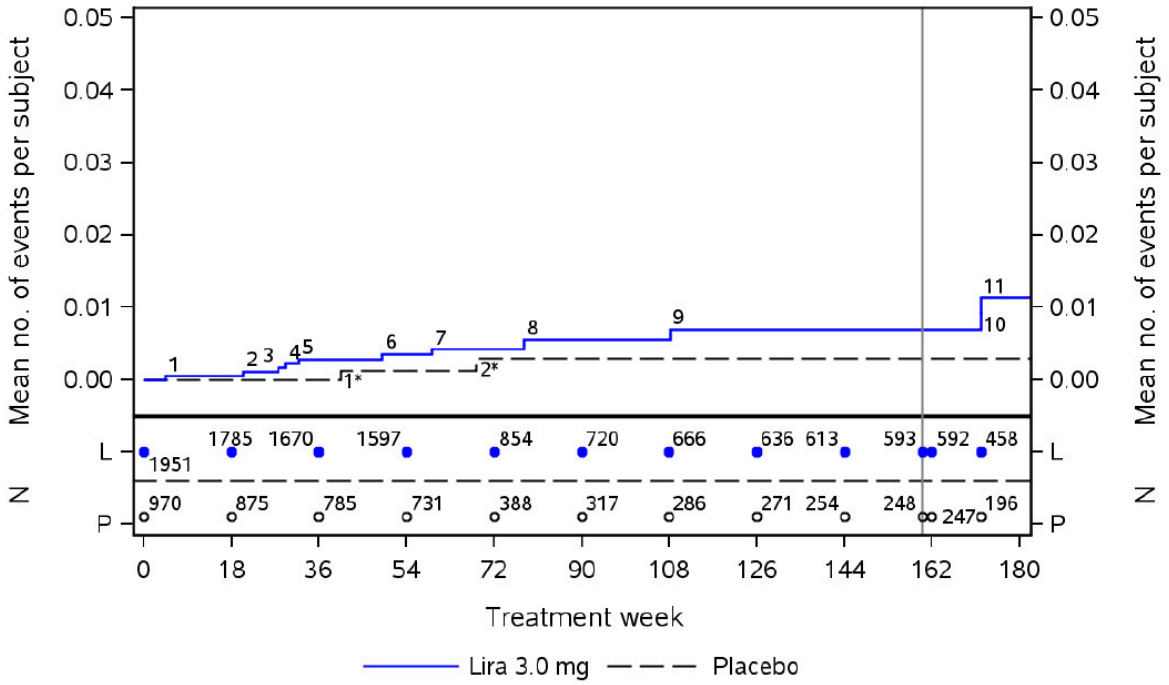
- There were low number of events in the placebo group (n=2) (see further discussion below).

- As questionnaire information per protocol was only collected from women with breast cancer, it is not possible to determine if the affected women differed from the entire population with respect to presence of risk factors.

Results

Event Rates
A total of 11 events of breast cancer (8 women with 9 events on Saxenda, 2 women with 2 events on placebo) were reported with the original approval. Two new events of breast cancer were reported since approval; both women had been treated with Saxenda and both had onset after 160-week study completion. Therefore, 10 out of 1951 women with 11 events on Saxenda (0.51%, 0.31 events/100 PYO) and 2 out of 970 women with 2 events on placebo (0.21%, 0.12 events/100 PYO) results in an odds ratio (95% CI) of 2.49 (0.53; 23.44).

Figure 27. Mean Cumulative Events of EAC-Confirmed Breast Cancer in Women Over Time in Trial 1839



N: Number of subjects at risk, L: Liraglutide 3.0 mg, P: Placebo
The events for patient 193010 (#10) and patient 476017 (#11) occurred after the 172-week study period, 1216 and 1354 days, respectively. These events are displayed at week 172.
Observation time is defined as the time between first drug date and last contact; non-treatment emergent events are included. Numbers in plot represent cumulative breast cancers at that time point.
Source: PMR 2802-8 Study Report, Figure 2

The sponsor compared the observed breast cancer cases in each treatment arm to the estimated expected number of breast cancer cases using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database.[22] SEER provided age-specific rates of invasive female breast cancer for the years 2008 through 2012. Exposure-specific standardized incidence ratios (SIRs) and 95% confidence intervals were calculated. SIRs summarize observed versus expected event counts using age-standardization, that is, expected clinical trial event counts that would be observed in a sample of the U.S. population with the identical age-distribution and cumulative follow-up time of trial NN8022-1839.

Based on SEER estimates, the observed number of breast cancer cases in the Saxenda group is numerically (although not statistically significantly) higher than what would be expected [11 versus 6.8, SIR (95% CI): 1.61 (0.85; 2.81)] and the observed

22 National Cancer Institute. Surveillance, Epidemiology, and End Results, Fast Stats interactive tool. http://seer.cancer.gov/faststats/.

number of cases on placebo is numerically (although not statistically significantly) lower than expected [2 versus 3.1, SIR (95% CI): 0.65 (0.11; 2.14)].

Disposition
Of the 12 patients with positively adjudicated events of malignant breast neoplasms, 11 (91.7%) agreed to be interviewed and no patients were lost to follow-up. One patient in the Saxenda arm was not willing to complete the questionnaire (Patient (b) (6)). The reason for non-participation was documented in the questionnaire and a signed memo was also obtained from the investigator.

Table 74. Patient Disposition in Patients with Positively Adjudicated Events of Malignant Breast Neoplasms

	Liraglutide 3.0 mg N (%)	Placebo N (%)	Total N (%)
Total safety analysis set	2481	1242	3723
Total safety analysis set female [1]	1951 (78.6)	970 (78.1)	2921 (78.5)
Patients with positively adjudicated events of malignant breast neoplasms [2]	10 (0.5)	2 (0.2)	12 (0.4)
Interviewed patients [3]	9 (90.0)	2 (100.0)	11 (91.7)
Lost to follow-up [3]	0 (0.0)	0 (0.0)	0 (0.0)
Patients not willing to participate [3]	1 (10.0)	0 (0.0)	1 (8.3)

N: Number of patients
[1] % is based on total safety analysis set
[2] % is based on total safety analysis set (female only)
[3] % is based on patients with positively adjudicated events of malignant breast neoplasms
Source: PMR 2802-8 Study Report, Table 1

One Saxenda-treated patient (b) (6) was not willing to provide source documentation to allow for grading and staging. Adjudication for this patient was based on available information.

The median time on treatment in patients with positively adjudicated breast cancer was 508.5 days in the Saxenda group and 400.0 days in the placebo group. Median time to breast cancer diagnosis was similar among groups: 342.0 days Saxenda and 379.5 days placebo (Table 75).

Table 75. Time on Treatment and Time to Diagnosis, Female Patients and Patients with Positively Adjudicated Malignant Breast Neoplasms

	Liraglutide 3.0 mg		Placebo	
	All female patients	Patients with positively adjudicated malignant breast neoplasms	All female patients	Patients with positively adjudicated malignant breast neoplasms
Number of patients	1951	10	970	2
Number of days on treatment (days)				
Mean (SD)	605.9 (388.6)	611.5 (418.5)	554.5 (385.2)	400.0 (114.6)
Median	478.0	508.5	476.0	400.0
Min; max	1.0; 1197.0	53.0; 1145.0	1.0; 1180.0	319.0; 481.0
Time to breast cancer diagnosis from first dose (days)				
Mean (SD)		492.4 (441.6)		379.5 (137.9)
Median		342.0		379.5
Min; max		30.0; 1354.0		282.0; 477.0

SD: Standard Deviation
Source: PMR 2802-8 Study Report, Table 2

Demographics and Baseline Characteristics
Demographics and baseline characteristics are shown in Table 76. Women with breast cancer events in both treatment groups were older than the overall study population. Given that there were only 2 women with breast cancer in the placebo group, no conclusions can be drawn about differences between Saxenda and placebo groups among women with breast cancer.

Table 76. Characteristics of All Female Patients and Patients with Positively Adjudicated Malignant Breast Neoplasms

	Liraglutide 3.0 mg		Placebo	
	All female patients	Patients with positively adjudicated malignant breast neoplasms	All female patients	Patients with positively adjudicated malignant breast neoplasms
Number of patients	1951	10	970	2
Age at randomization (years)				
Mean (SD)	44.8 (11.9)	56.4 (6.2)	44.9 (11.8)	51.0 (15.6)
Median	45.0	57.5	45.0	51.0
Min; max	18.0; 78.0	43.0; 63.0	18.0; 77.0	40.0; 62.0
Age at diagnosis (years)				
Mean (SD)		58.2 (6.7)		52.5 (16.3)
Median		60.0		52.5
Min; max		44.0; 67.0		41.0; 64.0
Height at randomization (m)				
Mean (SD)	1.63 (0.07)	1.64 (0.07)	1.63 (0.07)	1.69 (0.06)
Median	1.63	1.64	1.63	1.69
Min; max	1.07; 1.86	1.50; 1.72	1.41; 1.89	1.65; 1.73
Fasting body weight at randomization (kg)				
Mean (SD)	102.3 (18.6)	103.7 (19.9)	101.6 (18.7)	105.3 (3.7)
Median	99.6	100.5	98.6	105.3
Min; max	65.2; 217.8	78.1; 140.6	62.5; 244.0	102.6; 107.9
Body mass index at randomization (kg/m^2)				
Mean (SD)	38.3 (6.3)	38.7 (7.6)	38.1 (6.1)	36.9 (3.8)
Median	37.2	36.8	37.1	36.9
Min; max	27.1; 77.2	29.6; 53.2	27.4; 73.6	34.3; 39.6
Pre-diabetes status at screening				
Without pre-diabetes	799 (41.0)	2 (20.0)	390 (40.2)	2 (100.0)
With pre-diabetes	1152 (59.0)	8 (80.0)	580 (59.8)	
Race				
White	1631 (83.6)	10 (100.0)	812 (83.7)	2 (100.0)
Black or African American	215 (11.0)		105 (10.8)	
Asian	62 (3.2)		34 (3.5)	
American Indian or Alaska Native	4 (0.2)		4 (0.4)	
Native Hawaiian or Other Pacific Islander	2 (0.1)		2 (0.2)	
Other	37 (1.9)		13 (1.3)	
Ethnicity				
Hispanic or Latino	216 (11.1)	1 (10.0)	110 (11.3)	
Not Hispanic or Latino	1735 (88.9)	9 (90.0)	860 (88.7)	2 (100.0)

SD: Standard Deviation, Patients from France did not report race.

Source: PMR 2802-8 Study Report, Table 3

The change in weight (% and kg) in all female patients and patients who developed breast cancer is shown in Table 77. At the end of trial, patients who developed breast cancer generally had lost more weight than those who did not develop breast cancer.

Table 77. Change in Weight in All Female Patients and Patients with Malignant Breast Neoplasms

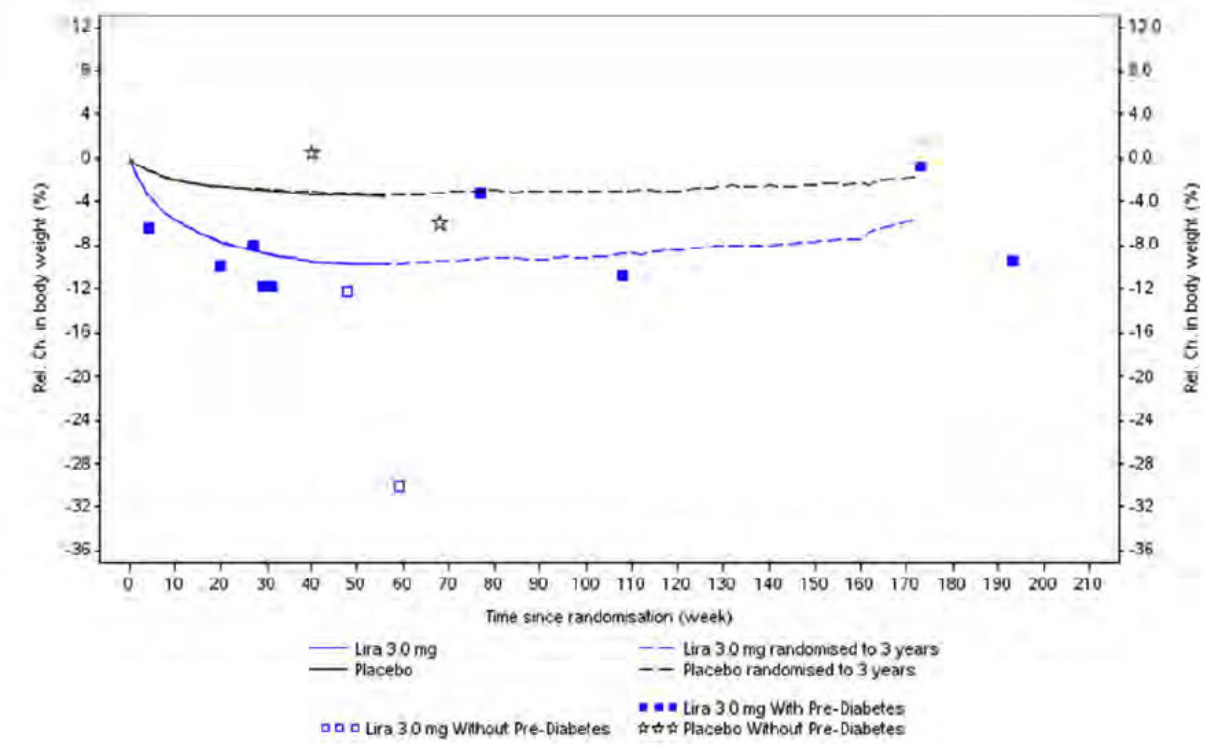
	Liraglutide 3.0 mg		Placebo	
	All female patients	Patients with positively adjudicated malignant breast neoplasms	All female patients	Patients with positively adjudicated malignant breast neoplasms
Number of patients	1951	10	970	2
At end of study (kg)				
Mean (SD)	-6.0 (7.5)	-11.0 (7.6)	-1.9 (7.1)	-3.0 (3.7)
Median	-5.0	-9.4	-0.6	-3.0
Min; max	-55.1; 22.1	-28.1; -0.6	-56.5; 22.2	-5.6; -0.4
At end of study (%)				
Mean (SD)	-5.9 (7.1)	-10.8 (8.3)	-1.7 (6.5)	-2.8 (3.4)
Median	-4.9	-10.6	-0.7	-2.8
Min; max	-42.5; 18.9	-31.3; -0.7	-39.6; 20.0	-5.2; -0.4
At time of diagnosis (kg)				
Mean (SD)		-10.3 (6.8)		-3.0 (4.9)
Median		-9.0		-3.0
Min; max		-27.0; -0.6		-6.4; 0.5
At time of diagnosis (%)				
Mean (SD)		-10.4 (7.5)		-2.7 (4.5)
Median		-10.0		-2.7
Min; max		-30.0; -0.7		-5.9; 0.5

SD: Standard Deviation

Source: PMR 2802-8 Study Report, Table 4

Weight loss (%) at the time of onset of individual breast cancer events is shown in Figure 28. The individual data points are compared to the mean weight loss achieved in all female patients treated with Saxenda and placebo.

Figure 28. Weight Loss in All Female Patients and Patients with Malignant Breast Neoplasms



Source: PMR 2802-8 Study Report, Figure 3

Questionnaire
The questionnaire information is only available from women with breast cancer events, and therefore it is not possible to determine whether these women with events differed with respect to breast cancer risk factors compared to women without events. However, questionnaire data were used to compare lifetime risk scores at the time of diagnosis for each of the affected women with the corresponding population-based risk score. Risk estimates are also given for the affected women 10 years prior to diagnosis using the same risk factor information (assuming height and weight were the same at study entry), adjusting timing of menopause and HRT use as necessary. The preceding 10 years would correspond to the period where the cancer would have developed.

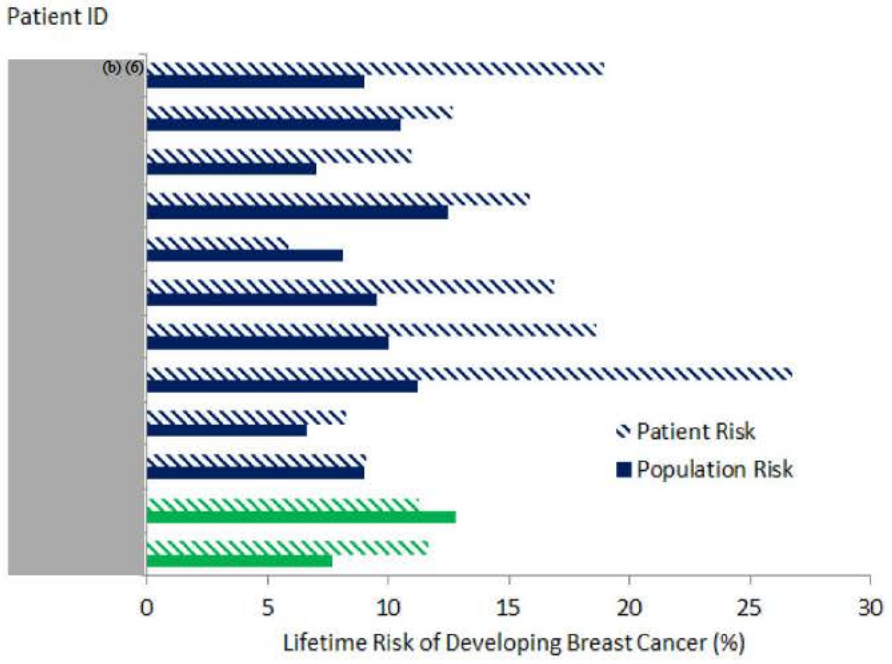
Individual and population-based absolute risks were estimated based on available information using the International Breast Intervention Study (IBIS) breast cancer risk evaluation tool.[23] The IBIS tool incorporates family history (which could reflect inherited risk due to BRCA1 or 2 or due to other predisposition genes) as well as personal factors: age, reproductive factors (age at menarche, first birth and menopause), prior

23 Tyrer J, Duffy SW, Cuzick JA. A breast cancer prediction model incorporating familial, genetic (BRCA1/2 mutations) and personal risk factors. Statist Med 2004;23:1111-30.

benign breast disease (including histology if available), use of hormone replacement therapy (HRT) (duration, recent use), height and weight. For each patient, it generates information on absolute risk of breast cancer from the current age to age 80. It also generates general population risks based on observed breast cancer rates (by age) in the United Kingdom national breast cancer incidence statistics. As opposed to the individual risk estimates, the model-based population norms are primarily based on age and not adjusted for the effect of obesity.

The majority of the affected women in the Saxenda group had a higher absolute risk than the reference population, both at the time of the event (Figure 29) and 10 years prior to breast cancer onset (data not shown in this review; results similar). Patients (b) (6) (Saxenda) and (b) (6) (Saxenda) had missing information on several risk factors; therefore their estimates are not reliable – the latter was the only Saxenda patient with breast cancer in whom individual risk was lower than population risk using age at diagnosis. By comparison, 1 of the 2 placebo patients with breast cancer had lower individual risk than population risk.

Figure 29. Lifetime Risk of Developing Breast Cancer, Patients with Breast Cancer versus Corresponding Population Risk (Using Age at Diagnosis)



* Information not available on age at menarche, age at first childbirth, menopause status, HRT use, or family history
** Information not available on age at menarche, menopause status or HRT use
Liraglutide-treated patients shown in blue, placebo-treated patients are shown in green

Source: PMR 2802-8 Study Report, Figure 4

Overall, these women reported a high number of mammograms and, on average, appear to be intensively screened compared to what is reported in the literature for obese women. However, some individuals with breast cancer (3 on Saxenda and 1 on placebo) do not appear to have been adequately screened prior to diagnosis.

Grade, Stage, and Receptor Status
Table 78 provides further information about the individual breast cancer cases, including what led to diagnosis, tumor grade and stage (TNM, AJCC)/EAC), and hormone receptor status. The events are ordered by time to diagnosis.

Table 78. Summary of Breast Cancer Cases

Patient ID	Study Day	Days on Treatment	Age at Randomization/ Age at Diagnosis	BMI	Screen Detected	Grade	Staging				ER/PgR/ HER 2 Status	Weight Loss, %
							T	N	M	AJCC/EAC		
Liraglutide 3.0 mg												
(b) (6)	30	53	51/51	53.2	Yes	2	pT2	pN1a	M0	IIB/Stage 3: advanced	+/+/-	-6.4
	142/203	274	60/60 and 61	29.6	No	2	pT1c	pN1	M0	IIA/Stage 1: localized	+/+/-	-10.0/-11.8
	193	175	43/44	37.0	No	3	cT3	pN1	M0	IIIA/Stage 3:advanced	-/-/-	-8.0
	222	1119	62/63	51.0	Yes	2	pT1c	pN1a		IIA/Stage 2: locally advanced	Unk	-11.8
	342	350	55/56	32.9	Yes	3	T1c	N0	M0	I/Stage 1: localized	-/-/-	-12.2
	413	465	57/58	36.3	Yes	2	pT1c	pN1a		IIA/Stage 3: advanced	+/+/-	-30.0
	545	552	53/54	36.6	Yes	1	pT1a	pN0	M0	I/Stage 1: localized	+/+/-	-3.2
	756	856	58/60	38.2	Yes	2	pT1c	N1		IIA/Stage 2: locally advanced	+/+/-	-11.1
	1216	1145	62/66	37.9	Yes	3	T1c	N1	M0	IIA/Stage 2: locally advanced	-/-/-	-0.7
	1354	1126	63/67	34.0	Yes	Unk	Tx	N0	M0	Unk/Stage 1: localized	+/+/-	-9.5
Placebo												
(b) (6)	282	319	40/41	34.3	Yes	2	T2	pN1	M0	IIB/Stage 3: advanced node positive	+/+/-	+0.5
	477	481	62/64	39.6	Unk	2	pT2	pN0	pMX	IIA/Stage 1:localized	+/+/-	-5.9

* Additional events reported since the original application. EAC: Event Adjudication Committee; ER/PgR/HER 2: estrogen/progesterone/human epidermal growth factor receptor 2; Body Mass Index (BMI) is at randomization; Unk: Unknown
Source: PMR 2802-8 Study Report, Table 5

The majority of events were screen detected. Six of the 11 events (in 10 women) on Saxenda were diagnosed within the first year, 5 were diagnosed within the following 2 years, including the 2 new events which were diagnosed and spontaneously reported several months after study completion. Breast cancer were mainly moderate to high grade, stage II, and 7/10 women with breast cancer had nodal involvement. The majority of cancers were estrogen (ER) and progesterone receptor (PgR) positive. Three cases (all Saxenda) were 'triple-negative' (ER, PgR, HER2 negative).

Summary
The numerical imbalance observed in breast cancer cases between Saxenda- and placebo-treated patients persists in this review of completed data from the 3-year 1839

trial: 2 new events on Saxenda were reported months after study completion, whereas none in patients on placebo had additional events.

- Based on SEER database estimates, the observed number in the Saxenda group is numerically (but not statistically significantly) higher than expected and the number in the placebo group is numerically (but not statistically significantly) lower than expected

- Based on the IBIS tool, women with events in the Saxenda group (except for 1) had greater absolute breast cancer risk compared to the general population; 1 patient on placebo had greater absolute risk and 1 had lesser absolute risk compared to the general population

- Women with events in the Saxenda group had greater than average weight loss; the sponsor postulates that greater weight loss could have led to increased detection in the Saxenda group

The sponsor concludes that “Although a true signal seems unlikely it cannot be excluded based on the available information”.

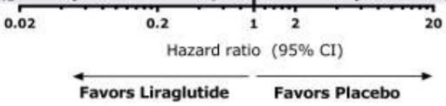
It should be noted that preliminary results from the cardiovascular outcomes LEADER trial (subject of PMR 2802-7), did not suggest a strong signal for breast cancer, although it cannot be ruled out; see below).

LEADER

In order to provide some context for the above neoplasms, the published neoplasm data from the liraglutide CVOT (LEADER) are presented below. The hazard ratio for malignant neoplasms overall was 1.06 (95% CI 0.90, 1.25), and for malignant breast (in women) 1.06 (0.57, 1.96), pancreatic 2.59 (0.92, 7.27), thyroid 1.66 (0.40, 6.95), and colorectal neoplasms 0.99 (0.59, 1.68).

Figure 30. Neoplasms, LEADER Trial

	Lira		Placebo		Hazard ratio (95% CI)
	N	%	N	%	
Total neoplasms	470	10.1	419	9.0	1.12 (0.98–1.28)
Malignant	296	6.3	279	6.0	1.06 (0.90–1.25)
Benign	168	3.6	145	3.1	1.16 (0.93–1.44)
Malignant neoplasms by tissue type					
Skin (non-melanoma)	78	1.7	62	1.3	1.25 (0.90–1.75)
Prostate	26	0.9	47	1.6	0.54 (0.34–0.88)
Breast	21	1.3	20	1.2	1.06 (0.57–1.96)
Lung/bronchus	28	0.6	33	0.7	0.85 (0.51–1.40)
Colorectal	28	0.6	28	0.6	0.99 (0.59–1.68)
Other	13	0.3	14	0.3	0.92 (0.43–1.97)
Urinary bladder	15	0.3	12	0.3	1.24 (0.58–2.66)
Kidney/renal pelvis	17	0.4	9	0.2	1.88 (0.84–4.22)
Hepatic/billiary	13	0.3	8	0.2	1.62 (0.67–3.90)
Leukemias	5	0.1	14	0.3	0.36 (0.13–0.99)
Pancreatic	13	0.3	5	0.1	2.59 (0.92–7.27)
Melanoma of the skin	13	0.3	5	0.1	2.59 (0.92–7.27)
Cervical/vaginal	6	0.4	2	0.1	3.03 (0.61–15.0)
Lymphoma	8	0.2	6	0.1	1.33 (0.46–3.82)
Oral cavity/pharynx	7	0.1	6	0.1	1.16 (0.39–3.46)
Uterine	2	0.1	3	0.2	0.68 (0.11–4.05)
Esophageal	4	0.1	6	0.1	0.66 (0.19–2.34)
Gastric	4	0.1	5	0.1	0.80 (0.21–2.97)
Thyroid	5	0.1	3	0.1	1.66 (0.40–6.95)
Bone/soft tissue	2	0.0	5	0.1	0.40 (0.08–2.05)
Ovarian	1	0.1	2	0.1	0.51 (0.05–5.58)



Note: Proportions are calculated based on number of female patients for breast, cervical/vaginal, uterine, and ovarian neoplasms, and based on number of male patients for prostate neoplasms.
Source: Supplementary Appendix to Marso et al.[11]

7.6.2 Human Reproduction and Pregnancy Data

Trial 1839 Data

During the trial, 39 female patients became pregnant, 27 (2.4%) in the Saxenda group and 12 (2.1%) in the placebo group.

All females who gave birth had healthy babies (Saxenda: 14; placebo: 6) and no congenital abnormalities were observed in any of the pregnancies that resulted in live births. For 3 pregnancies (Saxenda: 1; placebo: 2), the patients were lost to follow-up and the outcome of the pregnancies are unknown. Spontaneous abortions were reported by a higher proportion of the pregnant patients in the Saxenda group (8 of 27, 29.6%) than in the placebo group (1 of 12, 8.3%). All 8 spontaneous abortion cases in the Saxenda group occurred during the first trimester of pregnancy; 1 case was not substantiated, 1 event was reported as 'abortion' but unknown if it was spontaneous. Six patients had relevant medical histories, including previous miscarriages, thyroid disease, polycystic ovary syndrome, ectopic pregnancy, human papilloma virus, irregular menstrual cycles, and tuberculosis. One spontaneous abortion was reported in a patient in the placebo group and occurred in gestational week 26; relevant medical history included ectopic pregnancy and abortion.

Table 79. Summary of Pregnancies, 0-172 Weeks

	Liraglutide 3.0 mg		Placebo	
Pregnancies in female subjects				
All female subjects (N)	1137		572	
Pregnancies (N, % of female subjects)	27	(2.4)	12	(2.1)
Mean maternal age at baseline, years (min–max)	31.1	(18-43)	31.8	(20-40)
Mean BMI, kg/m2 (min–max)	39.1	(31.2-53.5)	39.6	(29.3-51.1)
Mean duration of exposure, days (min–max)[a]	391.8	(33-986)	379.1	(85-924)
Mean duration of exposure since conception, days (min–max)b	21.7	(7-40)	25.3	(5-57
Pregnancy outcomes[b]				
Healthy baby	14	(51.9)	6	(50.0)
Elective abortion	3	(11.1)	2	(16.7)
Spontaneous abortion[c]	8[d]	(29.6)	1	(8.3)
Ectopic pregnancy	1	(3.7)	1	(8.3)
Lost to follow-up	1	(3.7)	2	(16.7)
Contraception[b]				
Oral contraceptives	7	(25.9)	4	(33.3)
None	13	(48.1)	4	(33.3)
Other	7	(25.9)	4	(33.3)
Unknown	0	(0.0)	0	(0.0)
Partner pregnancies (N)	1		1	
Healthy baby (N)	0		1	
Elective abortion (N)	1		0	

Note: Details are based on information in the case narratives from the safety database as well as source documents.
Abbreviations: N = number of subjects, SAS = safety analysis set.

[a] The duration of exposure since conception was a conservative estimate based on available data in the safety database. For 2 subjects, the duration of treatment since conception was '<10 days' and '<26 days', in the calculations these number were changed to 9 and 25 days, respectively. For one subject duration of exposure since conception was unknown and this subject were excluded from the calculation. [b] Percentages are estimated from the total number of pregnancies in each treatment group. [c] 1 pregnancy (b) (6) could not be confirmed. [d] For 1 pregnancy, the outcome was reported as abortion. Unknown if it was spontaneous or induced.

Source: Trial 1839-3y CSR, Table 12-81

Table 80. Pregnancies by Patient, Weeks 0-172

Subject ID	Age/BMI[a]	Treatment duration (days)[b]	Treatment duration since conception (days)[b]	Pregnancy outcome[b]	Contraception[b]	Withdrawn	Comments and relevant medical history
Liraglutide 3.0 mg							
(b) (6)	25/37.6	124	13	Healthy child	None	WC#3	Epilepsy
	18/39.0	125	38	Healthy child	None	WC#3	PCOS, pre-eclampsia
	33/44.4	150	16	Healthy child	None	WC#3	Gestational diabetes. 2 previous live births
	38/37.0	280	19	Healthy child	None	WC#3	Endometriosis, PCOS, oligohydramnios in 2007, pregnancy-induced hypertension (2007), 7 previous pregnancies: 1 live birth and 6 miscarriages, gestational diabetes during the present pregnancy
	29/33.4	326	20	Healthy child	Oral contraceptives	WC#3	1 previous live birth
	30/47.1	345	15	Healthy child	Diaphragm	WC#3	PCOS, 1 previous live birth
	30/37.6	406	14	Healthy child	Oral contraceptives	WC#3	2 previous pregnancies: 1 live birth, 1 miscarriage
	22/31.7	478	16	Healthy child	Oral contraceptives	WC#3	1 previous live birth (child had dermoid cyst of left sinus cavity). Thyroid disease.
	36/33.6	505	12	Healthy child	None	WC#3	2 previous pregnancies: 1 live birth, 1 elective/induced abortion due to bleeding from an ectopic pregnancy. Thyroid disease.
	41/40.7	555	<26	Healthy child	Condoms	WC#3	5 previous pregnancies: 3 live births, 1 early foetal death, 1 late foetal death of unknown reason.
	21/47.3	615	36	Healthy child	None	WC#3	No relevant medical history
	22/46.3	784	28	Healthy child	Oral contraceptives	WC#3	1 previous live birth (baby born with myelomeningocele). Consaguity with father of the child, gestational diabetes and hypertention.

Subject ID	Age/BMI[a]	Treatment duration (days)[b]	Treatment duration since conception (days)[b]	Pregnancy outcome[b]	Contraception[b]	Withdrawn	Comments and relevant medical history
(b) (6)	35/31.8	914	30	Healthy child	None	WC#3	3 previous pregnancies: 2 live births and 1 spontaneous abortion and abnormal pap. Previous repair of torn cervix (from child birth).
	36/33.3	892	9	Healthy child	Oral contraceptives (failed for 5 non-consecutive days)	WC#3	2 previous live births
	31/40.4	33	13	Elective abortion	Condoms and spermicide	WC#3	6 previous pregnancies: 2 live births and 4 elective abortions for social reasons
	30/36.6	260	17	Elective abortion	None	WC#3	4 previous pregnancies: 2 live births and 2 elective abortions due to social circumstances. Oedema in lower legs.
	39/35.6	866	21	Elective abortion (due to Trisomy 21)	Vaginal ring	WC#3	3 previous pregnancies: 2 live births, 1 spontaneous abortion. Previous thyroid disease, uterine fibroids and myomectomy
	37/45.4	41	23	Spontaneous abortion	None	WC#3	Event reported as 'foetal death'. 1 previous live birth, thyroid disease
	29/48.4	88	40	Spontaneous abortion	None	WC#3	Irregular menstrual cycles
	43/31.9	109	40	Spontaneous abortion	None	Not withdrawn	Event reported as 'abortion missed'. 7 previous pregnancies: 2 live births, 5 miscarriages. The subject continued in the trial after the event.
	29/34.5	168	30	Spontaneous abortion	Condoms	WC#3	1 previous live birth, history of human papilloma virus
	42/35.9	354	24	Spontaneous abortion	None	WC#3	3 previous pregnancies: 2 live births, 1 ectopic pregnancy. Tuberculosis.
	34/35.6	355	Unknown	Spontaneous abortion	Tubal ligation	AE	Was withdrawn by the investigator due to an unsubstantiated event of pregnancy/miscarriage and later lost to follow-up. 3 previous live births

Subject ID	Age/BMI[a]	Treatment duration (days)[b]	Treatment duration since conception (days)[b]	Pregnancy outcome[b]	Contraception[b]	Withdrawn	Comments and relevant medical history
(b) (6)	27/40.4	647	8	Spontaneous abortion	Intrauterine device	WC#3	Event reported as 'abortion missed'. PCOS, enlarged thyroid, 1 previous live birth
	38/31.2	48	22	Abortion	Oral contraceptives	WC#3	Event reported as 'abortion'. It was unknown if the abortion was spontaneous or induced. No relevant medical or obstetric history
	24/45.9	986	7	Ectopic pregnancy	None	WC#3	1 previous live birth
	22/53.5	124	28	Lost to follow-up	Oral contraceptives	WC#3	No relevant medical history
	Partner	796	N/A	Elective abortion (due to absence of foetal heart beat)	N/A	Not withdrawn	N/A
Placebo							
(b) (6)	40/51.1	132	21	Healthy child	Oral contraceptives	WC#3	2 previous live births; thyroid disease.
	32/41.5	185	6	Healthy child	Barrier	WC#3	6 previous pregnancies: 1 live birth and 5 previous elective abortions due to social circumstances
	30/32.8	300	<10	Healthy child	Oral contraceptives	WC#3	PCOS, 1 previous live birth.
	33/50.0	379	57	Healthy child	None	WC#3	2 previous live births, irregular menstrual cycles, hypertension
	25/40.2	476	14	Healthy child	None	WC#3	2 previous pregnancies: 1 live birth and 1 elective/induced abortion due to social circumstances
	31/34.6	924	14	Healthy child	None	WC#3	11 previous pregnancies: 2 live births, 1 foetal death, 8 spontaneous abortions, hypertension in pregnancy
	33/35.5	85	24	Elective abortion	Condoms and spermicide (failure at time of conception)	WC#3	1 previous live birth, hypothyroidism

Subject ID	Age/BMI[a]	Treatment duration (days)[b]	Treatment duration since conception (days)[b]	Pregnancy outcome[b]	Contraception[b]	Withdrawn	Comments and relevant medical history
(b) (6)	34/38.0	139	51	Elective abortion	Condoms and double barrier	Not withdrawn	2 previous pregnancies, 1 live birth, 1 elective abortion due to social circumstances and gestational diabetes. The subject continued in the trial.
	39/45.1	258	31	Spontaneous abortion	Oral contraceptives	WC#3	Event reported as 'foetal death'. 3 previous pregnancies: 1 live birth, 1 ectopic pregnancy, 1 abortion.
	35/29.3	407	26	Ectopic pregnancy	Tubal ligation	Not withdrawn	4 previous live births. Hypertension. Previous pre-eclampsia. Trial drug (placebo) temporarily suspended for 14 days; subject continued in the trial.
	20/39.9	620	45	Lost to follow-up	Oral contraceptives	WC#3	Dysmenorrhea
	29/37.5	644	5	Lost to follow-up	None	WC#3	1 previous elective/induced abortion due to social circumstances.
	Partner	Unk	N/A	Healthy child	N/A	Not withdrawn	N/A

Note: Comments and relevant medical history are based on information in the subject narratives from the safety database in Section 14.3.3 as well as source documents

Abbreviations: AE = adverse event; BMI = body mass index; N/A = not applicable (for partner pregnancies); PCOS = polycystic ovary syndrome; SAS = safety analysis set; Unk = unknown; WC#3 = withdrawal criterion #3 (pregnancy or intention to become pregnant).

[a] Baseline values.

[b] Based on information in the subject narratives from the safety database in Section 14.3.3.

Source: Trial 1839-3y CSR, Table 12-82

PLLR Information

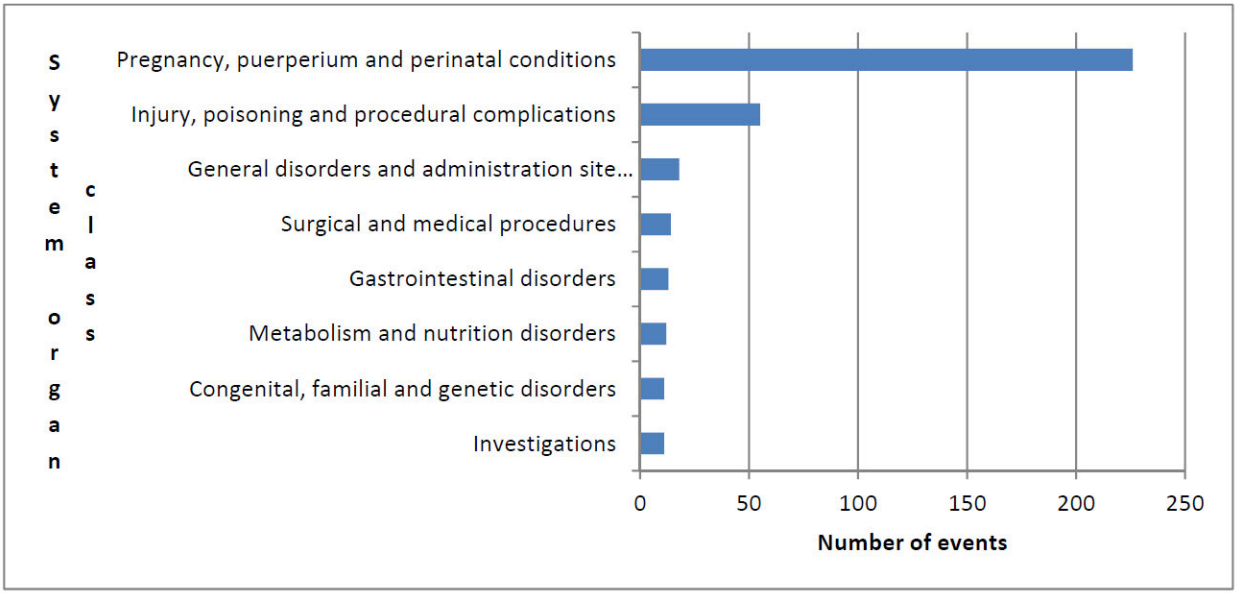
Pregnancy

The sponsor presented information required by FDA related to compliance with PLLR in a submission dated 03 Oct 2016, and with follow-up information provided upon request 07 Mar 2017.

A cumulative total of 271 case reports describing exposure to liraglutide during pregnancy have been identified from all reporting sources in the Novo Nordisk safety database, up until 31 May 2016 [i.e., clinical trials, non-interventional and observational studies, patient support programs/market research programs (solicited cases), literature and spontaneously reported cases (unsolicited cases)]. These data were previously reviewed by the Division of Maternal and Pediatric Health (DMPH).

The most commonly involved SOCs were 'Pregnancy, puerperium and perinatal conditions', 'Injury, poisoning and procedural complications' and 'General disorders and administration site conditions' (Figure 31).

Figure 31. Distribution of Adverse Events by System Organ Class with More than Ten Reported Events



Source: Supporting Information for PLLR Labeling, Figure 2-1

The most commonly reported PTs in the most common SOCs were 'Pregnancy', 'Abortion spontaneous' 'Off-label use' and 'Fetal exposure during pregnancy'.

In the SOC 'Congenital, familial and genetic disorders', 11 events (in 10 cases) were reported. All these events were reported to be serious.

- Four events (3 cases) were received from clinical trials:
  - Patent ductus arteriosus
  - Atrial septal defect
  - Persistent fetal circulation
  - Trisomy 21
- Seven events were reported from spontaneous sources:
  - Congenital brain damage

- Congenital hydrocephalus
- Fetal malformation
- Osteogenesis imperfecta
- Univentricular heart
- Cytogenetic abnormality (2 events)

Of the 271 identified pregnancy cases, there were 16 mother-child link cases in the internal Novo Nordisk database. Therefore, 255 cases are considered to be the actual pregnancy cases. Of these 255 cases of liraglutide exposure during pregnancy, fetal outcome was available for 111 cases (the fetal outcome for the remaining cases is unknown or not reported at the data collection cutoff). Fetal outcomes were categorized as:

- Live birth without congenital anomalies (CA)
- Live birth with CA
- Fetal loss (includes spontaneous abortion, ectopic pregnancy and stillbirth)
- Termination

The table below describes the pregnancy cases with available fetal outcome[24]:

24 Note the discrepancies in total numbers of liraglutide pregnancies in Table 81 and Table 82 (59 vs. 60). In the period since the PLLR report was submitted, 1 pregnancy case was found to have been incorrectly assigned to liraglutide instead of placebo during the unblinding of the case. This case was related to subject (b) (6) who participated in trial NN8022-1839. The final clinical trial report for trial 1839 and the NDA documentation correctly attributed this case to placebo. The sponsor updated the table to reflect this correction in the response to a query by FDA.

Table 81. Pregnancies Associated with Liraglutide with Known Fetal Outcomes

Fetal outcome	Total N (%)	Source			
		Clinical trials N (%)	Other solicited N (%)	Spontaneous N (%)	Literature N (%)
Total	111 (100%)	60 (100%)	11 (100%)	39 (100%)	1 (100%)
Live birth without CA	51 (45.9 %)	30 (50.0%)	4 (36.4%)	16 (41.0%)	1 (100%)
Live birth with CA	2 (1.8%)	0 (0%)	0 (0%)	2 (5.0%)	0 (0%)
Fetal loss[a]	38 (34.2 %)	19 (31.7 %)	4 (36.4%)	15 (38.7%)	0 (0%)
Spontaneous abortion	*32 (28.8%)*	*16 (26.7%)*	*4 (36.4%)*	*12 (30.8%)*	*0 (0%)*
Ectopic pregnancy	*2 (1.8%)*	*2 (3.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*
Stillbirth	*2 (1.8%)*	*1 (1.6%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Stillbirth with fetal defects	*1 (0.9 %)*	*0 (0%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Stillbirth without fetal defects	*1 (0.9 %)*	*0 (0%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Termination	20 (18.0 %)	11 (18.3 %)	3 (27.3%)	6 (15.4 %)	0 (0%)
with fetal defects	*6 (5.4%)*	*1 (1.6%)*	*0 (0%)*	*5 (12.9 %)*	*0 (0%)*
without fetal defects	*2 (1.8%)*	*2 (3.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*
termination (without reasons)	*12 (10.8%)*	*8 (13.3 %)*	*3 (27.3%)*	*1 (2.6%)*	*0 (0%)*

Notes: [a] Fetal loss includes still birth, spontaneous abortion and ectopic pregnancy. **Abbreviations:** CA = congenital anomalies; N = number of cases.

Source: Supporting Information for PLLR Labeling, Table 2-1

As shown below, 59 cases of liraglutide exposure during pregnancy with known fetal outcome were identified from clinical trials.[24] In an additional 3 cases, the fetal outcome was unknown or not reported.

Table 82. Pregnancy Cases with Available Fetal Outcome, Clinical Trials[24]

Fetal outcome	Clinical trials Liraglutide N (%)	Liraglutide			Clinical trials Comparator[b] N (%)	Comparator[b]		
		Weight Management N (%)	Type 2 Diabetes N (%)	Type 1 Diabetes N (%)		Weight Management N (%)	Type 2 Diabetes N (%)	Type 1 Diabetes N (%)
Total	59 (100%)	41 (100%)	13 (100%)	5(100%)	25 (100%)	17 (100%)	6	2 (100%)
Live birth without CA	30 (50.8%)	22 (53.7%)	5 (38.5%)	3 (60%)	15 (60%)	10 (58.8%)	3 (50%)	2 (100%)
Live birth with CA								
Fetal loss[a]	18 (28.8 %)	13 (31.7 %)	3 (23.1%)	2 (40%)	4 (16%)	4 (23.5%)		
Spontaneous abortion	*15 (23.7%)*	*11 (26.8%)*	*3 (23.1%)*	*1 (20%)*	*1 (4%)*	*1 (5.9%)*		
Ectopic pregnancy	*2 (3.4%)*	*2 (4.9%)*			*2 (8%)*	*2 (11.8%)*		
Stillbirth	*1 (1.7%)*			*1 (20%)*	*1 (4%)*	*1 (5.9%)*		
Stillbirth with fetal defects								
Stillbirth without fetal defects								
Termination	11 (18.6 %)	6 (14.6 %)	5 (38.5%)		6 (24%)	3 (17.6%)	3 (50%)	
with fetal defects	*1 (1.7%)*	*1 (2.4%)*						
without fetal defects	*2 (3.4%)*	*1 (2.4%)*	*1 (7.7%)*					
termination (without reasons)	*8 (13.6 %)*	*4 (9.8 %)*	*4 (30.8%)*		*6 (24%)*	*3 (17.6%)*	*3 (37.5%)*	

Notes: [a] Fetal loss includes still birth, spontaneous abortion and ectopic pregnancy. **Abbreviations:** CA = congenital anomalies; N = number of cases. Weight management is identified by project id NN8022; type 1 diabetes is identified by project id NN9211; type 2 diabetes includes trials with a liraglutide arm and includes project ids NN2211, NN9068 and NN1250.
[b]Comparator is placebo in all cases but one case in type 2 diabetes which includes 1 live birth without CA where the treatment was insulin degludec.

Source: Response to FDA Request dated 06 Mar 2017, Table 1

- In trials evaluating liraglutide for type 1 diabetes (6 cases total):
  - 3 cases were reported with 'live birth without CA'
  - 1 case with 'stillbirth'
  - 1 case had an outcome of spontaneous abortion during the first trimester of pregnancy
  - 1 case the outcome was unknown
- In trials evaluating liraglutide for type 2 diabetes (14 cases total):
  - 5 cases were reported as 'live birth without CA'
  - 3 cases were reported with 'fetal loss' (all spontaneous abortion during first trimester of pregnancy)
  - 5 cases were reported as 'termination'
  - 1 case the outcome was unknown
- In trials evaluating liraglutide for weight management (42 cases total)
  - 22 were reported as 'live birth without CA'
  - 13 were reported as 'fetal loss' (2 with ectopic pregnancy and 11 spontaneous abortion in the first trimester of pregnancy)
  - 6 cases were reported as 'termination' (1 case without fetal defect, 1 with Down's syndrome, other 4 not described)
  - 1 case the outcome was unknown

From other solicited sources, 11 were reported with fetal outcome and 23 had no reported fetal outcome. Of the 34 total cases, 30 were with Victoza and 4 with Saxenda; all 11 cases with reported outcome were with Victoza:

- 4 as 'live birth without CA'
- 4 as 'spontaneous abortion'
- 3 as 'termination'

Cumulatively, 155 cases of liraglutide exposure during pregnancy have been received from spontaneous sources: 149 with Victoza and 6 with Saxenda. A total of 39 were identified with fetal outcome; all these cases were reported in patients treated with Victoza:

- 16 'live birth without CA'
- 2 'live birth with CA'
    - cytogenetic abnormality
    - univentricular heart
- 15 'fetal loss'
    - 12 spontaneous abortion
    - 1 'stillbirth with fetal defects': placental insufficiency, cardiac hypertrophy and microsomia
    - 1 'stillbirth'
    - 1 'stillbirth without fetal defects'
- 6 'termination'
    - 5 'termination with fetal defects'
        - osteogenesis imperfecta
        - fetal malformation
        - congenital brain damage
        - congenital hydrocephalus
        - fetal death

Two literature reports of liraglutide exposure (Victoza) during pregnancy in T2DM patients are available. Of the 2 reports, the fetal outcome was only reported for 1: 'live birth without CA'. Liraglutide was taken throughout the first trimester of pregnancy and was discontinued after the diagnosis of pregnancy. The patient gave birth to a normal healthy female baby at the 37th week of gestation with a cesarean delivery. The postpartum period was uneventful but the infant developed transient neonatal hypoglycemia and tube feedings was provided for 24 hours during hospitalization. No developmental abnormalities were found after 3 months of delivery.[25]

In the period from (b) (6), 7 pregnancy cases were received; all were post-marketing cases.

25 Greco D. Normal pregnancy outcome after first-trimester exposure to liraglutide in a woman with Type 2 diabetes. Diabet Med. 2015;32(10):e29-30.

- Four cases were reported with Saxenda: 1 spontaneous case and 3 from solicited sources
    - All unknown outcomes
- Three cases were reported with Victoza: 2 spontaneous cases and 1 from solicited sources
    - One with unknown outcome
    - One spontaneous abortion in the first trimester in a female patient with a medical history of obesity (BMI of 42), high blood pressure, and 2 previous miscarriages
    - One case concerned a fetus with cleft palate and cleft lip identified in a fetal scan in unknown week of the pregnancy in a mother with inadequate control of diabetes mellitus

Reviewer comment: The available clinical data for Saxenda did not provide any evidence of fetal malformations. Although in clinical trials, events of fetal loss were observed in the Saxenda-treated patients, given that events were also observed in the placebo group, a determination regarding a drug-associated risk for fetal loss cannot be made at this time. Current labeling language in another liraglutide-containing product regarding clinical data – specifically, **There are no available data with liraglutide in pregnant women to inform a drug associated risk for major birth defects and miscarriage –** ***is appropriate for the Saxenda label.***

Lactation
No cases of liraglutide exposure in lactating women have been identified in clinical trials conducted with liraglutide, data received from other solicited sources, or the literature, up until 31 May 2016.

Two spontaneous case reports concerning liraglutide exposure during lactation (PT: Exposure during breastfeeding) were identified in Novo Nordisk safety database. Both case reports were reported in women treated with Victoza. One of these case reports was also included in the review of pregnancy cases, as it was reported that the patient took Victoza during pregnancy and breastfeeding. No adverse events were reported in these case reports. Limited information was available for both case reports.

There were no cases reported concerning liraglutide use in lactating women from 01 Jun 2016 to 30 Jun 2016 from any source.

Fertility
A total of 21 events (in 20 cases) concerning fertility disorders [SMQ 'Fertility disorders' (narrow)] have been identified for liraglutide from all reporting sources cumulatively up until 31 May 2016:

- Three events in 3 cases were reported in clinical trials with Victoza for T2DM
    - PT: Hypogonadism
    - PT: Hematospermia

  - PT: Varicocele
- Eight events in 7 cases were reported in clinical trials with Saxenda
  - PT: Dysfunctional uterine bleeding [6 events]
  - PT: Polycystic ovaries [1 event]
  - One event associated with 'male fertility disorders' (not further described)
- One event in Victoza patent support program
  - PT Sperm concentration decreased
- Seven events in 7 cases were reported from spontaneous sources
  - PT: Polycystic ovaries (serious)
  - PT: Dysfunctional uterine bleeding
  - PT: Sperm concentration decreased
  - PT: Hypogonadism male
  - PT: Infertility male (serious)
  - PT: Semen volume decreased [2 events]
- One event in literature
  - PT: Spermatogenesis abnormal: This event was reported in a patient treated with Victoza who experienced interrupted sperm production, which was completely restored after 5 months of treatment interruption.[26]

There were no cases reported concerning liraglutide use related to fertility disorders from 01 Jun 2016 to 30 Jun 2016 from any source.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Eight AEs of overdose (including accidental overdose) were reported, all in patients treated with Saxenda. None was serious or severe (2 were of moderate severity):

- Patient (b) (6) administered 60 clicks (corresponding to 3.6 mg of liraglutide) for 28 days. The moderate overdose TEAE was associated with severe non-serious TEAEs of nausea and vomiting.
- Patient (b) (6) took a double dose of Saxenda to compensate for a missed dose the day before. The patient experienced nausea in association with the mild overdose TEAE.
- Patient (b) (6) took a double dose of Saxenda on one occasion unintentionally as she changed her working schedule. No associated TEAEs were reported.

26 Fontoura P, Cardosa M, Erthal-Martins M, Werneck C, Sartorio C, Ramos C. Reproductive biomedicine online. 2014;29(5):644-6.

- Patient [redacted] took a double dose of Saxenda on one occasion as she forgot that she had already done so. No associated TEAEs were reported.
- Patient [redacted] administered a double dose during one day. No associated TEAEs were reported.
- Patient [redacted] changed the dosing time from 7:00 to 17:00 during one day, and consequently took a double dose that particular day. The accidental overdose TEAE was classified as moderate in severity and was associated with nausea, vomiting, diarrhea, heartburn, and flatulence.
- For 2 patients [redacted] and [redacted]), no additional information on the nature of the mild overdose/accidental overdose TEAEs were available and no associated TEAEs were reported.

In addition to the AEs identified above, 4 cases of overdoses were registered as protocol deviations without any corresponding AE reported. Four patients ([redacted]) accidentally took the double dose of trial product on more than one occasion.

Abuse Potential

Not applicable. Liraglutide is not a scheduled drug.

Withdrawal or Rebound

Serious adverse events reported after drug discontinuation were evaluated. A total of 19 non-treatment emergent SAEs in 18 patients (2.5%) previously treated with Saxenda and 3 events in 3 patients (0.7%) previously treated with placebo were reported after treatment discontinuation. Many of the events in the Saxenda group were related to pregnancy conditions or complications. Note that females who became pregnant or intended to become pregnant were to be withdrawn from the trial; therefore, the pregnancy outcome fulfilling the criteria of an SAE would potentially occur after treatment discontinuation. Pregnancies and pregnancy outcomes are further discussed in Section 7.6.2, Human Reproduction and Pregnancy Data.

No patient reported non-TE SAEs after discontinuation during the off-drug follow-up period.

Table 83. Non-Treatment Emergent Serious AEs (0-172 Weeks) Occurring After Last Drug Date in Patients Withdrawn in Treatment Period

	Lira 3.0 mg			Placebo		
	N	(%)	E	N	(%)	E
Number of subjects	710			410		
Years of observation time	852.2			463.3		
Events	18	(2.5)	19	3	(0.7)	3
Congenital, familial and genetic disorders	1	(0.1)	1	0	(0.0)	0
Chromosomal abnormalities and abnormal gene carriers	1	(0.1)	1	0	(0.0)	0
Trisomy 21	1	(0.1)	1	0	(0.0)	0
Endocrine disorders	1	(0.1)	1	0	(0.0)	0
Thyroid gland disorders	1	(0.1)	1	0	(0.0)	0
Autoimmune thyroiditis	1	(0.1)	1	0	(0.0)	0
Gastrointestinal disorders	2	(0.3)	2	0	(0.0)	0
Exocrine pancreas conditions	2	(0.3)	2	0	(0.0)	0
Pancreatic pseudocyst	1	(0.1)	1	0	(0.0)	0
Pancreatitis	1	(0.1)	1	0	(0.0)	0
Hepatobiliary disorders	1	(0.1)	1	0	(0.0)	0
Bile duct disorders	1	(0.1)	1	0	(0.0)	0
Biliary colic	1	(0.1)	1	0	(0.0)	0
Immune system disorders	0	(0.0)	0	1	(0.2)	1
Immune disorders NEC	0	(0.0)	0	1	(0.2)	1
Heart transplant rejection	0	(0.0)	0	1	(0.2)	1
Infections and infestations	1	(0.1)	1	0	(0.0)	0
Infections - pathogen unspecified	1	(0.1)	1	0	(0.0)	0
Ovarian abscess	1	(0.1)	1	0	(0.0)	0
Musculoskeletal and connective tissue disorders	1	(0.1)	1	0	(0.0)	0
Joint disorders	1	(0.1)	1	0	(0.0)	0
Osteoarthritis	1	(0.1)	1	0	(0.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	(0.1)	1	0	(0.0)	0
Breast neoplasms malignant and unspecified (incl nipple)	1	(0.1)	1	0	(0.0)	0
Breast neoplasm	1	(0.1)	1	0	(0.0)	0
Nervous system disorders	1	(0.1)	1	0	(0.0)	0

	Lira 3.0 mg N	(%)	E	Placebo N	(%)	E
Central nervous system vascular disorders	1	(0.1)	1	0	(0.0)	0
Cerebrovascular accident	1	(0.1)	1	0	(0.0)	0
Pregnancy, puerperium and perinatal conditions	7	(1.0)	7	1	(0.2)	1
Abortions and stillbirth	5	(0.7)	5	1	(0.2)	1
Abortion spontaneous	2	(0.3)	2	0	(0.0)	0
Abortion	1	(0.1)	1	0	(0.0)	0
Abortion missed	1	(0.1)	1	0	(0.0)	0
Foetal death	1	(0.1)	1	1	(0.2)	1
Maternal complications of labour and delivery	1	(0.1)	1	0	(0.0)	0
Prolonged labour	1	(0.1)	1	0	(0.0)	0
Maternal complications of pregnancy	1	(0.1)	1	0	(0.0)	0
Pre-eclampsia	1	(0.1)	1	0	(0.0)	0
Respiratory, thoracic and mediastinal disorders	0	(0.0)	0	1	(0.2)	1
Respiratory disorders NEC	0	(0.0)	0	1	(0.2)	1
Sleep apnoea syndrome	0	(0.0)	0	1	(0.2)	1
Surgical and medical procedures	3	(0.4)	3	0	(0.0)	0
Obstetric and gynaecological therapeutic procedures	1	(0.1)	1	0	(0.0)	0
Abortion induced	1	(0.1)	1	0	(0.0)	0
Vascular therapeutic procedures	2	(0.3)	2	0	(0.0)	0
Carotid revascularisation	1	(0.1)	1	0	(0.0)	0
Coronary angioplasty	1	(0.1)	1	0	(0.0)	0

SOC: System organ class, HLGT: High level group term, PT: Preferred term
N: Number of subjects, %: Percentage of subjects, E: Number of events
MedDRA version 15.1
Non-treatment emergent AEs are events with onset more than 14 days after last treatment.
Output presents data for subjects with pre-diabetes at baseline and includes 6 subjects who did not have pre-diabetes at baseline, but participated in the extension period of the trial.

Source: Trial 1839-3y CSR, Table 14.3.1.43

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

Saxenda was recently reviewed as part of a FDAAA Section 915 non-NME postmarket safety review in conjunction with the Office of Surveillance and Epidemiology. Please refer to the review filed to DARRTS dated 09 Jan 2017. The 915 review did not suggest any new potential safety issue requiring additional safety review or regulatory action.

9 Appendices

9.1 Literature Review/References

Relevant literature is footnoted within this document.

9.2 Creatine Kinase Elevations

Patients with creatine kinase elevations ≥ 10× UNR in the trial are summarized in the table below.

Table 84. Patients with Creatine Kinase Greater than 10 Times Upper Limit of Normal (ULN)

(b) (6)

Treatment	Comment
Saxenda	CK slightly elevated at BL, normal-slightly high throughout the 3 year trial. Increased to 2677 U/L during the off-drug study period. No further results reported.
Placebo	CK 504 at BL, increased to 2541 on day 184, no further visits.
Saxenda	Patient in trial/on treatment for full 3 years; CK 11371 on day 389. All other CKs in trial and at follow-up WNL (range: 46-114) except increased to 418 on day 872.
Saxenda	Patient in trial/on treatment for ~1.5 years. CK elevated at baseline (319) and throughout trial (range: 234-346). Increased to 4840 on day 392; follow-up labs 570 then 470, then within baseline range for the remainder of the trial.
Saxenda	Patient in trial/on treatment for full 3 years. Screening CK 6224, otherwise ranged from 80-449 throughout trial.
Saxenda	Patient in trial/on treatment for full 3 years. CK at baseline elevated at 385, and elevated throughout trial. CK 5510 on day 112, but back to baseline on follow-up and throughout, except for 1 increase to 758 on day 562.
Saxenda	Patient in trial/on treatment for > 2.5 years; CK 2143 on day 622, otherwise WNL (except one value slightly elevated at 219 on day 971)
Saxenda	Patient in trial/on treatment for full 3 years. CK slightly elevated at baseline (247) and ranged throughout in 200s-300s range (high), except higher on day 624 (420 U/L), day 990 (9893 U/L), day 996 (1113 U/L), day 1136 during the off-drug follow-up (2699 U/L), and day 1199 (572 U/L).
Saxenda	Patient in trial/on treatment for 3 yrs. CK generally WNL throughout trial (occasional slight elevations), except 7334 U/L day 871 and 523 U/L day 1059. Returned to baseline by end of trial.
Saxenda	Patient in trial/on treatment for full 3 years. Normal baseline, increased to 3760 U/L on day 529 and then remained mildly elevated or WNL, except 1 value 438 U/L on day 1124.
Placebo	Patient in trial/on treatment for full 3 years. CK WNL or slightly elevated throughout, except for 1 value 11354 U/L on day 284.
Saxenda	Patient in trial/on treatment for full 3 years. CK 1304 on day 283, 1641 on day 982, and 1720 on day 1122; otherwise all values WNL.
Saxenda	Patient in trial/on treatment for full 3 years. CK WNL except for a few slight increases; 3120 U/L on day 987.

(b) (6)		
	Saxenda	Patient in trial/on treatment for > 2.5 years; CK WNL except 2130 U/L day 289 and 397 U/L day 782
	Placebo	Patient in trial/on treatment for ~2 years; day 1 CK 2604 U/L
	Saxenda	Patient in trial/on treatment for full 3 years; CK high throughout trial (305-1156 U/L); during off-drug follow-up CK 4021, no further results reported.
	Saxenda	Patient on in trial/on treatment ~ 7 mos; CK 388 on day 1 and 4015 U/L on day 29, otherwise WNL.
	Placebo	Patient in trial/on treatment for ~2 years; CK 3609 U/L on day 390, otherwise WNL
	Saxenda	Patient in trial/on treatment for full 3 years; CK elevated on day 1 (383 U/L) then ranged from 84 to 669 throughout the trial (447 U/L on off-drug follow-up). Increased to 1245 U/L on day 456 and 1810 U/L on day 697.
	Saxenda	Patient in trial/on treatment for > 2.5 years; CK slightly elevated (200s) throughout; increased to 5521 U/L on last visit day 952. Follow-up value 155 U/L ~ 4 wks later.
	Saxenda	Patient in trial/on treatment for > 2.5 years; CK 3388 U/L on day 537, all other values WNL.
	Saxenda	Patient in trial/on treatment for full 3 years; CK elevated throughout (756 U/L on day 1); CK 1964 U/L on day 623 and 1078 U/L on day 907. Returned to below baseline.
	Saxenda	Patient in trial/on treatment for full 3 years; CK elevated throughout (230-538). CK 3045 U/L on day 1065, then returned to baseline.
	Saxenda	Patient in trial/on treatment for full 3 years; CK WNL throughout (including on last day on treatment), except 248 U/L on day 951, 6106 U/L on day 981, 3101 U/L on day 983.

Source: Trial 1839-3y CSR Appendix 16.2.8, Tables 16.2.8.1.135 - 16.2.8.1.158

9.3 Labeling Recommendations

I recommend that the (b) (4) but that some descriptive data are included in Section 14 of the label regarding long-term weight changes.

9.3 Advisory Committee Meeting

Not applicable.

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/s/

JULIE K GOLDEN
04/19/2017

JAMES P SMITH
04/19/2017
See separate memo.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206321/S-004

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206321
Supporting document/s:	SD 267 / 06.27.16 / efficacy supplement S004
	SD 297 / 10.03.16 / draft labeling, includes changes for PLLR compliance
Product:	Saxenda (liraglutide injection)
Indication:	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 at least 30 kg/m^2 (obese) or at least 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition
Applicant:	Novo Nordisk Inc, PO Box 846, Plainsboro, NJ 08536
Review Division:	Metabolism and Endocrinology Products
Reviewer:	Anthony Parola, PhD
Supervisor/Team Leader:	Lee Elmore, PhD
Division Director:	Jean-Marc Guettier, MD
Project Manager:	Patricia Madara

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Liraglutide, a long-acting glucagon-like peptide 1 (GLP-1) receptor lipidated peptide agonist formulated as a solution for subcutaneous injection, is an active pharmaceutical ingredient in 3 approved products from Novo Nordisk. Liraglutide (6 mg/mL solution) was first approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) in January 2010 under NDA 22341 for Victoza at doses of 1.2 or 1.8 mg/day. A higher dose of 3 mg/day liraglutide using the same formulation of liraglutide was approved as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in obese adults (initial body mass index (BMI) $\geq$30 kg/m^2) or overweight adults (initial BMI $\geq$27 kg/m^2) with at least 1 weight-related comorbidity in December 2014 under NDA 206321 for Saxenda. Xultophy, a product combining 100 mg/mL insulin degludec with 3.6 mg/mL liraglutide, was recently approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in November 2016 under NDA 208583. Labels for Victoza and Saxenda are not compliant with the Pregnancy and Lactation Labeling Rule (PLLR) because these products were approved prior to PLLR's promulgation or implementation, but liraglutide information in the label for Xultophy is PLLR compliant.

Saxenda NDA efficacy supplement S004 received 24 June 2016 (supporting document 267) proposes to amend the label by adding information from the end of the 160 week treatment period and 12 week follow-up periods for subjects with pre-diabetes at randomization in phase 3 study NN8022-1839 titled "Effect of liraglutide on body weight in non-diabetic obese subjects or overweight subjects with comorbidities: A randomised, double-blind, placebo controlled, parallel group, multi-centre, multinational trial with stratification of subjects to either 56 or 160 weeks of treatment based on pre-diabetes status at randomization". In response to a 9 September 2016 information request from the Agency, the sponsor submit revised proposed labeling to comply with the PLLR and supporting information from published literature and pharmacovigilance databases on liraglutide use in pregnant and lactating women in supporting document 297 received on 3 October 2016. No new nonclinical information was submitted to support the changes to the Saxenda label intended to comply with the PLLR and none were required.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical studies were submitted to support the proposed changes to the Saxenda label to comply with the PLLR. Nonclinical information in sections "8.1 Pregnancy" and "8.2 Lactation" in the current Saxenda label are included in the proposed label intended to comply with PLLR (see Appendix 1).

1.3 Recommendations

1.3.1 Approvability

Saxenda was approved in December 2014. No new nonclinical information was submitted to support approval of Saxenda NDA efficacy supplement S004 or to support proposed modifications to the label required for PLLR compliance.

1.3.2 Additional Non Clinical Recommendations

Internal

Despite Saxenda being contraindicated in pregnancy, 42 liraglutide-exposed pregnancies with known outcomes occurred in clinical studies. Six of these pregnancies were terminated, and 1 of the terminated pregnancies reported a fetal abnormality of Down's syndrome. Of the 36 remaining Saxenda-exposed pregnancies, there were 14 cases of fetal loss, including 2 ectopic pregnancies and 12 spontaneous abortions during the first trimester. In Saxenda-exposed pregnancies, the apparent rate of birth defects was 1/42 (2.4%), within the range of 2% to 4% in the US general population, and the apparent rate of fetal loss was 14/36 (38.9%), above the rate of 15 – 20% in the US general population.,

An increased incidence of fetal loss in Saxenda-exposed pregnancies is consistent with the slightly increased incidence of of early embryonic deaths in maternal rats treated 2 weeks prior to mating through organogenesis with 1 mg/kg/day liraglutide, a dose that reduced body weight gain and food consuption of maternal rats and yeilded systemic exposures in maternal rats 11-times human exposure, based on AUC comparison. Consider including outcomes from Saxenda-exposed pregnancies in the label.

1.3.3 Labeling

Appendix 1 shows the sponsor's proposed label for Saxenda NDA 206321 efficacy supplements S004 that includes changes tracked from the current label intended to comply with PLLR by modifying sections "8.1 Pregnancy" and "8.2 Lactation". The reviewer recommended modifications to the sponsor's proposed label are shown in section "11 Integrated Summary and Safety Evaluation" (below). The following proposed verbiage in the Saxenda label is recommended to comply with the PLLR.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Risk Summary

(b) (4)

Data

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 0204656-20-2
Generic Name: liraglutide
Code Name: NNC 90-1170, NNC 0090-0000-1170, NN2211, glipacyl
Chemical Name: Arg^{34}Lys^{26}-(N-ε-(γ-Glu-(N-α-hexadecanoyl)))-GLP-1[7-37]
Molecular Formula/Molecular Weight: $C_{172}H_{265}N_{43}O_{51}$ / 3751.2 Daltons
Structure or Biochemical Description:

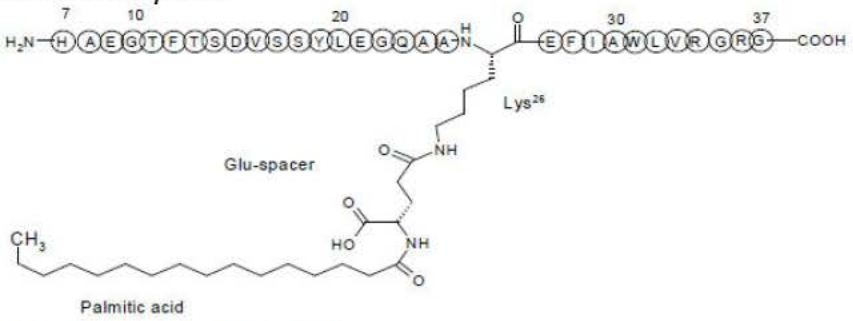

Figure 1 Molecular structure of liraglutide
One-letter amino acid codes are used in this figure.

[SD1 Module 2.6 Nonclinical Written and Tabulated Summaries Introduction P6]

Pharmacologic Class: glucagon-like peptide 1 (GLP-1) receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

Liraglutide NDAs from Novo Nordisk

NDA 22341: Victoza®, up to 1.8 mg/day liraglutide for the treatment of T2DM (approved January 2010)
NDA 206321: Saxenda®, up to 3 mg/day liraglutide for weight management in obese and overweight adults (approved December 2014)
NDA 208583: Xultophy® 100/3.6, up to 50 units insulin degludec / 1.8 mg liraglutide for the treatment of T2DM (approved November 2016)

Liraglutide INDs from Novo Nordisk
IND 61040: treatment of type 2 diabetes mellitus (T2DM) (opened October 2000)
IND 73206: treatment of obesity in adults (opened September 2008)
IND 77460: nasal delivery for diabetes (terminated October 2015)
IND 109121: liraglutide and insulin degludec for the treatment of T2DM (opened January 2011)
IND 115945: treatment of type 1 diabetes mellitus (T1DM) (opened April 2013)
IND 121763: NNC9204-0530 and liraglutide for the treatment of obesity (opened June 2014)
(b) (4)

2.3 Drug Formulation

Saxenda is a clear, colorless, aqueous solution of liraglutide in a glass cartridge provided in a pre-filled pen injector. The glass cartridge contains 3 mL of 6 mg/mL liraglutide and the inactive ingredients 1.42 mg/mL disodium phosphate dihydrate, 14 mg/mL propylene glycol, and 5.5 mg/mL phenol.

2.7 Regulatory Background

Liraglutide (6 mg/mL liraglutide injection) was investigated for the treatment of obesity under IND 73206 opened in September 2008 and approved as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in obese adults or overweight adults with at least 1 weight-related comorbidity under NDA 206321 for Saxenda in December 2014. Saxenda NDA efficacy supplement S004 received 24 June 2016 (supporting document 267) proposes to amend the label by adding information from phase 3 study NN8022-1839 titled "Effect of liraglutide on body weight in non-diabetic obese subjects or overweight subjects with comorbidities: A randomised, double-blind, placebo controlled, parallel group, multi-centre, multinational trial with stratification of subjects to either 56 or 160 weeks of treatment based on pre-diabetes status at randomization". Results from study NN8022-1839 up to week 56 were submitted in the original NDA and these results are included in the current label. Supplement S004 includes results from 160 weeks of treatment followed by a 12-week off-drug follow-up period for subjects with pre-diabetes at randomization in study NN8022-1839.

During review of S004, the Agency sent a request to the sponsor on 9 September 2016 to submit revised proposed labeling to comply with the PLLR and supporting information from published literature and pharmacovigilance databases on liraglutide use in pregnant and lactating women. A revised proposed label for Saxenda that includes changes proposed for S004 along with changes intended to comply with the PLLR and a document titled "NDA 206321: Supporting Information for Pregnancy Labeling and Lactation Rule" from the sponsor were received on 3 October 2016 (supporting document 297). Xultophy, a combination product containing liraglutide and insulin degludec, is currently the only approved drug product containing liraglutide as an active ingredient with an approved label that complies with the PLLR (see Appendix 2).

3 Studies Submitted

None.

3.1 Studies Reviewed

None.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Saxenda Nonclinical Reviews

15 September 2014 Nonclinical NDA review for approval

Xultophy Label

16 November 2016 PLLR compliant label information for liraglutide

11 Integrated Summary and Safety Evaluation

Liraglutide was approved for chronic weight management in obese adults or overweight adults with at least 1 weight-related comorbidity. The only approved dose and maximum recommended dose is 3 mg Saxenda subcutaneously injected into the abdomen, thigh, or upper arm once a day. To improve tolerability to gastrointestinal adverse effects, Saxenda treatment is initiated at a dose of 0.6 mg/day for 1 week with dose escalation at the rate of 0.6 mg/day/week to the maintenance dose of 3 mg/day. The sponsor submitted a efficacy supplement S004, and during review, the Agency sent a request to the sponsor to submit revised proposed labeling to comply with the PLLR

The sponsor's proposed changes to sections "8.1 Pregnancy" and "8.3 Nursing Mothers" of the Saxenda label to comply with PLLR are shown in Appendix 1. No new nonclinical studies were submitted or required to support changes to the label intended to comply with the PLLR and none were required.

Supporting Information for PLLR

Novo Nordisk submitted a document titled "NDA 206321: Supporting Information for Pregnancy Labeling and Lactation Rule" that summarized and reviewed reports concerning liragluitde exposure during pregnancy and lactation and effects on fertililty in adults from the Novo Nordisk pharmacovigilance database, including information from a previously submitted document for liraglutide containing information up to May 2016 to support PLLR labeling of Xultophy, new liraglutide information from Novo Nordisk's pharmacovigilance database from June 2016, and published literature.

Information submitted to support PLLR compliant labeling for liraglutide in Xultophy was reviewed by Dr. Carol Kasten, a Medical Officer in the Division of Pediatric and Maternal Health. Based on outcomes reported for 109 lirglutide-exposed pregnancies through 31 May 2016 from Novo Nordisk's pharmacovigilance database, there were 48.6% (53/109) live births, 29.4% (32/109) spontaneous aborations, 1.8% (2/109) ectopic pregnancies, 1.8% (2/109) stillbirths, and 18.3% (20/109) elective abortions. Nine total congenital abnormalities were reported in 3.8% (2/53) live births, 50% (1/2) of stillbirths, and 30% (6/20) of elective abortions. Case review of congential abnormalities concluded a relation to liraglutide exposure could not be exclueded for 6 of 9 cases (univentricular heart, stillbirth with placental insufficiency and poor maternal disease control, exencephaly, rare genetic brain damage disease, fetal death at 6 weeks, and hydrocephalus). The review concluded the incidence of birth defects in liraglutide-exposed pregnancies (5.5% (6/109)) was high compared to non-diabetic women (2% to 4% of the general population (draft Guidance for Industry titled "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products —Content and Format (December 2014))), but within the expected range of 6% to 10% in women with diabetes mellitus. The rate of spontaneous abortions in liraglutide-exposed pregnancies (29.4%) was higher than the the incidence expected in the U.S. general population (15% to 20%), but a higher risk of adverse pregnancy outcomes in women with diabetes was noted. Potential safety

signals of increased incidences of spontaneous abortion and birth defects in liraglutide-exposed pregnancies were attributed to maternal disease and not drug exposure.

Dr. Kasten's review noted liraglutide concentration in the milk of lactating rats was reported to be half the concentration in plasma, but animal data may not predict drug levels in human milk. Because of the increased risk of thyroid C-cell tumors in animals following prenatal exposure to liragultide, women treated with Xultophy should be advised not to breastfeed during treatment. The current label for Xultophy does not include the recommendation to discontinue breastfeeding while being treated with Xultophy. Dr. Kasten identified 1 published case report of adverse effects of liraglutide on male fertility in a 35 year old man with a history of primary infertility that developed decreased sperm count and non-motile sperm within 5 months of starting treatment with liraglutide with full recovery 5 months after discontinuing liraglutide treatment. This single report was not considered sufficient to warrant labeling with respect to effects of liraglutide in men.

The sponsor submitted a revised analysis of the effects of liraglutide on pregnancy, lactation, and fertility in humans to the Saxenda NDA in the document titled "NDA 206321: Supporting Information for Pregnancy Labeling and Lactation Rule" that included additional information from Novo Nordisk's pharmacovigilance database from June 2016 and an updated literature search. The sponsor reported 111 liraglutide exposed pregnancies with known outcomes (Table 2-1, below) up to May 2016. This information was previously reveiwed by Dr. Kasten. Of the 111 liraglutide exposed pregnancies with known outcomes up to the end of May 2016, 42 (37.8%) occurred in patients treated with Saxenda in clinical studies. Out of the 42 Saxenda-exposed pregnancies, 6 were terminated and 1 of the terminated pregnancies reported a fetal abnormality of Down's syndrome. Of the 36 remaining Saxenda-exposed pregnancies, there were 14 cases of fetal loss, including 2 ectopic pregnancies and 12 spontaneous abortions during the first trimester. In Saxenda-exposed pregnancies, the apparent rate of birth defects were 1/42 (2.4%), within the range of 2% to 4% in the US general population, and the apparent rate of fetal loss was 14/36 (38.9%), above the rate of 15 – 20% in the US general population. Four additional cases of Saxenda-exposed pregnancies with unknown outcomes were reported in June 2016; 1 spontaneous case and 3 from solicited sources. No additional cases concerning the use of liraglutide in lactating women or effects of liraglutide on fertility in men or women were identified in the sponsor's pharmacovigilance database from June 2016. The sponsor concludes reports on the use of liraglutide in pregnant and lactating women and information concerning effects of liraglutide on men and women are limited, and the sponsor will continue monitoring as part of routine pharmacovigilence. Please refer to Dr. Julie Golden's clinical review for a definitive assesment of Saxenda-exposed pregnancies.

Table 2–1 Pregnancy cases with available fetal outcome

Fetal outcome	Total N (%)	Source			
		Clinical trials N (%)	Other solicited N (%)	Spontaneous N (%)	Literature N (%)
Total	111 (100%)	60 (100%)	11 (100%)	39 (100%)	1 (100%)
Live birth without CA	51 (45.9 %)	30 (50.0%)	4 (36.4%)	16 (41.0%)	1 (100%)
Live birth with CA	2 (1.8%)	0 (0%)	0 (0%)	2 (5.0%)	0 (0%)
Fetal loss[a]	38 (34.2 %)	19 (31.7 %)	4 (36.4%)	15 (38.7%)	0 (0%)
Spontaneous abortion	*32 (28.8%)*	*16 (26.7%)*	*4 (36.4%)*	*12 (30.8%)*	*0 (0%)*
Ectopic pregnancy	*2 (1.8%)*	*2 (3.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*
Stillbirth	*2 (1.8%)*	*1 (1.6%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Stillbirth with fetal defects	*1 (0.9 %)*	*0 (0%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Stillbirth without fetal defects	*1 (0.9 %)*	*0 (0%)*	*0 (0%)*	*1 (2.6%)*	*0 (0%)*
Termination	20 (18.0 %)	11 (18.3 %)	3 (27.3%)	6 (15.4 %)	0 (0%)
with fetal defects	*6 (5.4%)*	*1 (1.6%)*	*0 (0%)*	*5 (12.9 %)*	*0 (0%)*
without fetal defects	*2 (1.8%)*	*2 (3.3%)*	*0 (0%)*	*0 (0%)*	*0 (0%)*
termination (without reasons)	*12 (10.8%)*	*8 (13.3 %)*	*3 (27.3%)*	*1 (2.6%)*	*0 (0%)*

Notes: [a] Fetal loss includes still birth, spontaneous abortion and ectopic pregnancy. **Abbreviations:** CA = congenital anomalies; N = number of cases.

[SD297 Supporting Information for PLLR P10]

An increased incidence of fetal loss in Saxenda-exposed pregnancies is consistent with the slightly increased incidence of of early embryonic deaths in maternal rats treated 2 weeks prior to mating through organogenesis with 1 mg/kg/day liraglutide, a dose that reduced body weight gain and food consuption of maternal rats and yeilded sysstemic exposures in maternal rats 11-times human exposure, based on AUC comparison.

Recommended Modifications to Sponsor Proposed Saxenda Label for PLLR Compliance

Sponsor proposed modifications to the current Saxenda label for PLLR compliance are shown in Appendix 2 (blue text and comments). The reviewer proposed recommendations, shown below (red text and comments are mine, blue text and comments are the sponsors) were incorporated into the sponsor's modified label.

The sponsor proposed changes to section "8.1 Pregnancy" to comply to the PLLR are acceptable. The proposed summary of risk information based on animal data is consistent with the corresponding information for liraglutide in the Xultophy label. An increased incidence of fetal loss in Saxenda-exposed pregnancies is consistent with the slightly increased incidence of of early embryonic deaths in pregnant rats treated 2 weeks prior to mating through organogenesis with 1 mg/kg/day liraglutide, a dose that reduced body weight gain and food consuption of maternal rats and yeilded systemic exposures in maternal rats 11-times human exposure, based on AUC comparison. The sponsor should consider including outcomes from Saxenda-exposed human pregnancies in the label. Changes to section "8.2 Lactation" are recommended by the reviewer to be consistent with information about liraglutide in the correponding section of the approved Xultophy label.

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix 2: Sections "8.1 Pregnancy" and "8.2 Lactation" from the Approved PLLR Compliant Label for Xultophy Including Nonclinical Information for Liraglutide

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to liraglutide during pregnancy. XULTOPHY 100/3.6 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There are no available data with XULTOPHY 100/3.6, insulin degludec or liraglutide in pregnant women to inform a drug associated risk for major birth defects and miscarriage. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

For insulin degludec, rats and rabbits were exposed in animal reproduction studies at 5 times (rat) and 10 times (rabbit) the human exposure at a dose of 0.75 U/kg/day. No adverse outcomes were observed for pregnant animals and offspring *[see Data]*.

For liraglutide, animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day and early embryonic deaths at 11-fold clinical exposures at the MRHD. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD *[see Data]*.

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA_{1c} >7 and has been reported to be as high as 20–25% in women with a HbA_{1c} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically

recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Insulin degludec

Insulin degludec was investigated in studies covering fertility, embryo-fetal development and pre- and post-natal development in rats and during the period of embryofetal development in rabbits. Human insulin (NPH insulin) was included as comparator. In these studies insulin degludec was given subcutaneously at up to 21 U/kg/day in rats and 3.3 U/kg/day in rabbits, resulting in 5 times (rat) and 10 times (rabbit) the human exposure (AUC) at a human subcutaneous dose of 0.75 U/kg/day. Overall the effects of insulin degludec were similar to those observed with human insulin.

Liraglutide

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating, during mating and the period of organogenesis, through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were misshapen oropharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased maternal body weight gain during the dosing period. Liraglutide decreased fetal weight and dose dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), ≥ 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), ≥ 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebrae and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F2 generation rats descended from liraglutide-treated rats compared to F2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.2 Lactation

Risk Summary

There are no data on the presence of liraglutide or insulin degludec in human milk, the effects on the breastfed infant, or the effects on milk production. In lactating rats, insulin degludec and liraglutide, the two components of XULTOPHY 100/3.6, were present in milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XULTOPHY 100/3.6 and any potential adverse effects on the breastfed infant from XULTOPHY 100/3.6 or from the underlying maternal condition.

Data

Insulin degludec

In lactating rats, insulin degludec was present in milk at a concentration lower than that in plasma.

Liraglutide

In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

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

/s/

ANTHONY L PAROLA
02/17/2017

CALVIN L ELMORE
02/17/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206321/S-004

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#:	NDA 206321, S004
Drug Name:	Liraglutide/Saxenda
Indication(s):	An adjunct to a reduced calorie diet and increased physical activity for chronic weight management in obese patients, or overweight adult patients in the presence of at least one weight related comorbidity (hypertension, T2DM, or dyslipidemia)
Applicant:	Novo Nordisk
Date(s):	PDUFA: 04/24/2017; Primary Review Due Date: 3/20/2017 Submitted 06/24/2016
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Alexander Cambon
Concurring Reviewers:	Yun Wang, Acting Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Julie Golden/James P Smith
Project Manager:	Patricia Madara/Martin White

Keywords: censored observations, informative censoring, missing data, drop-outs, analysis of covariance, sensitivity analyses

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1 EXECUTIVE SUMMARY

Novo Nordisk is seeking additions to the product label for Saxenda (Liraglutide) for obese patients, or overweight adult patients in the presence of at least one weight related comorbidity: hypertension, Type 2 Diabetes Mellitus (T2DM), or dyslipidemia. The sponsor submitted this supplement (NDA) on June 24, 2016.

1.1 Brief Overview of Clinical Studies

This submission is a supplement and involves only the three-year part of Study 1839. Only subjects randomized at baseline to the pre-diabetes strata are included in the three-year study.

Trial 1839 is a 56/160+12 week parallel two-arm randomized double-blind study.

- Pre-diabetes is defined as: impaired fasting glucose - IFG (FPG ≥ 110 mg/dL / 6.1 mmol/L, and < 126 mg/dL / 7.0 mmol/L) or inmpaired glucose tolerance - IGT (2 hr post OGTT plasma glucose ≥ 140 mg/dL / 7.8 mmol/L, and < 200 mg/dL / 11.1 mmol/L).
- These subjects with pre-diabetes are randomized to 160 weeks of treatment, followed by a 12-week off drug/placebo observational follow-up period.
- Pre-diabetes subjects are randomized in a 2:1 fashion to Saxenda or placebo.
- Starting dose for Saxenda is 0.6 mg daily. It is titrated to 3 mg daily over a 4 week period.
- Novo Nordisk was un-blinded after 1 year (subjects and investigators were not unblinded at this time).
- The cut-off date for the study (database lock) was April 15, 2015. The last date of randomization for any subject was November 10, 2011.
- The 3-year primary endpoint is time to T2DM onset. Details of the primary endpoint and primary analysis are provided in Table 2 and Sections 3.2.1 and 3.2.2.

1.2 Conclusions and Recommendations

The primary efficacy endpoint for this supplement includes T2DM onset. (b) (6), (b) (4)

Descriptive statistics should be provided in the label for achievement of the secondary endpoint of ≥ 5% weight loss at 56 weeks and 160 weeks. Less than 50% of subjects continued treatment and had their three-year assessments.

1.3 Statistical Issues and Findings

This section addresses missing data and treatment dropouts. For further details, see Section 3.2.2.2.

- Subjects who discontinued treatment early were not followed up and were treated as censored for the primary analysis (T2DM onset). Therefore the censoring is likely informative, and it does not take into account differences between subjects who complete treatment and subjects who discontinue.
- The LOCF methodology used for the analysis of the secondary endpoint (≥5% Weight Loss) has a similar shortcoming.
- About 50% of subjects discontinued the study before the landmark visit and have missing data for both the primary and secondary endpoint. As well, a higher percentage of subjects discontinued treatment early in the study.
- 200 subjects on the Saxenda arm withdrew (before week 160) due to an adverse event.
- 46 subjects on the placebo arm withdrew due to an adverse event.
- 29 subjects on the Saxenda arm and 36 on the placebo arm withdrew due to “ineffective therapy”.
- Only one subject who discontinued treatment before week 100 had a weight endpoint measurement that was not an LOCF measurement (only one subject who discontinued before week 100 was followed up).

2 INTRODUCTION

2.1 Overview

This supplement includes the three-year part of one confirmatory safety and efficacy trial: study 1839. Only subjects randomized at baseline to the pre-diabetes strata are included in the three-year sub-study. The purpose of this supplement is to add information to the Saxenda product labeling that Novo Nordisk believes are supported by the 3-year part of study 1839.

Trial 1839 is a 56/160+12 week parallel two-arm randomized double-blind study with a 4-week titration period.

- This supplement is only for the 3-year (160 weeks) part of the study.
- Starting dose for Saxenda is 0.6 mg daily. It is titrated to 3 mg daily over a 4 week period.
- The (pre-diabetes) subjects are randomized to 160 weeks of treatment, followed by a 12-week off drug/placebo observational follow-up period.
- Pre-diabetes subjects are randomized in a 2:1 fashion to Saxenda or placebo.
- Figure 1 below gives further details of study design.

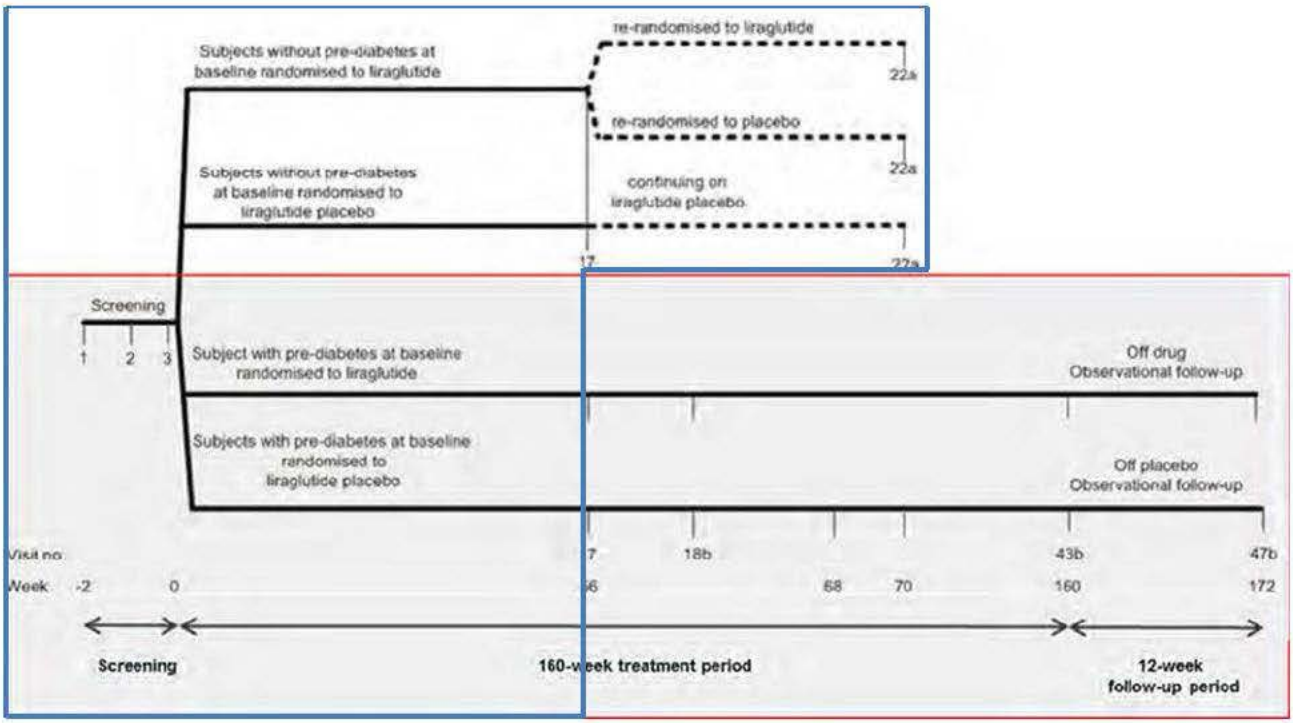

Figure 1: Design for Study 1839
(Taken from sponsor Summary of Clinical Efficacy for Study 1839, Figure 1-1, Page 9)

2.1.1 Class and Indication

Saxenda is in a class of drugs called incretin mimetics, which improve blood sugar control by mimicking the action of a hormone called glucagon-like peptide 1 (GLP-1). Incretin mimetics also suppress appetite.

Saxenda is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in obese patients, or overweight adult patients in the presence of at least one weight-related comorbidity (hypertension, T2DM, or dyslipidemia). In the draft label, there is no proposed change in this indication for this supplement.

2.1.2 Relevant Communication with Sponsor

From the original NDA 206321 Statistical Review:

> Novo Nordisk submitted IND 73,306 for liraglutide for weight management on September 4, 2008. The end-of-phase 2 (EOP2) meeting was held on March 10, 2008. At the meeting there were no questions from the sponsor or meeting discussion regarding statistical methods or handling of missing data. On February 20, 2013 the sponsor requested guidance on statistical methods for the integrated summary of efficacy (ISE). In the responses, shared May 6, 2013, FDA conveyed their reservations for the usefulness of the analysis of the individual and combined study datasets based on imputation using last observation carried forward (LOCF). FDA did not request the sponsor modify their primary analysis approach. On September 11, 2014 there was an advisory committee meeting that discussed the safety and efficacy of the liraglutide weight management new drug application. The advisory committee voted 14-1 in favor of liraglutide having a favorable benefit-risk profile to support approval for the proposed indication.

From General Advice Letter Sent to Sponsor on August 12, 2016 after the submission of the NDA supplement:

> 1. FDA has not discussed the primary endpoint of trial 1839 with you since the protocol was first submitted under IND 73206 (in 2008). At that time, (b) (4) ote that our current thinking on this issue is unchanged.
>
> 2. Your proposal to include a (b) (4) .
>
> 3. We also note that you have reported in the Clinical Overview that only 50% of patients were followed until the 160-week endpoint. This extent of missing data is likely to substantially undermine our confidence in the reliability of the results of this trial.

2.2 Data Sources

The data and final study report for this efficacy supplement to NDA 206321 (supporting Document Number 267) were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SDTM and ADaM data sets are located in the proper sections of the submission, and analysis reviewer guides are provided which defined variables and their locations.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Table 1 gives details of the treatment arms and study design for the three-year part of Study 1839. The primary endpoints for Study 1839 are shown in Table 2 below.

Table 1: Summary of Study 1839; 3-Year Part

Trial ID	Design*	Treatment/ Sample Size	Treatment Period	Follow-up Period	Study Population
NN8022-1839	MC, MN,R, DB, PG, PC trial (56/160** wks)	Saxenda/ 1505 Placebo/ 749	160 Weeks	12 Weeks	M/F ≥ 18 years, pre-diabetes, obese or overweight with comorbidities

* MC: multi-center, MN: multi-national, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled; Novo Nordisk was un-blinded after 1-year (subjects and investigators were not unblinded at this time); randomization ratio 2:1 (active to placebo);

**Subjects 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), and subjects 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). This supplement only includes results from 160 weeks of treatment and a 12-week off-drug follow-up period for subjects with pre-diabetes at randomization. Primary Endpoint: time to T2DM onset among subjects with pre-diabetes at baseline/Primary analysis-Weibull with censoring for early discontinuation; Pre-diabetes is defined as: impaired fasting glucose - IFG (FPG ≥ 110 mg/dL / 6.1 mmol/L, and < 126 mg/dL / 7.0 mmol/L) or inmpaired glucose tolerance - IGT (2 hr post OGTT plasma glucose ≥ 140 mg/dL / 7.8 mmol/L, and < 200 mg/dL / 11.1 mmol/L).

Table 2: Primary Endpoints for Study 1839

Study	Endpoint Type	Description
1839	Primary	Percent Weight Change from baseline (1-Year)
1839	Primary	Achievement of reduction in weight of at least 5% (1-Year)
1839	Primary	Achievement of reduction in weight of at least 10% (1-Year)
1839	Primary	Time to T2DM onset (3-year)

Abbreviations: T2DM –Type 2 Diabetes Miletus;* - (Saxenda 3mg vs Placebo). The 3- year weight-related endpoints are secondary endpoints and are not included in the testing hierarchy (see Section 3.2.1.1 below). Appendix 16.1.9 in the clinical trial report dated October 28, 2013, includes the statistical analysis plan for the one and three –year studies – including the hierarchical testing procedure. The same hierarchy is also included in Section 17 of the July 8, 2008 protocol (see below).

3.2.1.1 Multiple Testing Procedure

The multiple testing procedure is not specified in the NDA supplement, which is a sub-study of Study 1839. The hierarchical testing procedure for Study 1839, including the endpoint of T2DM onset at 3 years, is included in the original NDA submission. This endpoint is included in the hierarchical testing after the (one-year) endpoints of percent weight change, ≥5% weight change, and ≥10% weight change. This is the order shown in Table 2 above. The following is taken from the protocol dated July 8, 2008, Section 17.1:

> "…primary efficacy endpoints weight change, the proportion of subjects with a weight loss larger than 5%, the proportion of subjects with a weight loss larger than 10%, and onset of diabetes. The hypothesis of equality between liraglutide and liraglutide placebo with respect to the primary endpoints will be tested in a hierarchical manner in the order in which the endpoints are mentioned."

In Section 17.2.2 of the same protocol (Primary analysis of the co-primary endpoints) it specifies that these weight loss endpoints are for 56 weeks. The three-year (160 week) endpoints of ≥5% and ≥10% weight loss are secondary endpoints and are not included in the testing hierarchy.

3.2.2 Statistical Methodologies

3.2.2.1 Sponsor Statistical Methodology

Primary Analysis Population

The primary analysis population (as defined by the sponsor) is the Full Analysis Set (FAS), which is defined as:

> …all randomized subjects exposed to at least one dose of the trial product and with at least one post baseline assessment of any endpoint.

However we do not agree with this definition. All randomized subjects were included in our efficacy analyses.

Primary Analysis

For the three year part of Study 1839, the sponsor's defined primary analysis uses a Weibull survival model. The response variable is time to onset of T2DM. In turn, T2DM onset is defined as the first time point one of the following criteria is fulfilled and where the following non-missing measurement of the same type confirms the high value (from Section 9.5.2.1 of Report Body):

- HbA1c $\geq$ 6.5 % and/or
- Fasting Plasma Glucose (FPG) > 7.0 mmol/L (126 mg/dL) and/or
- 2-hour post-challenge plasma glucose $\geq$11.1 mmol/L (200 mg/dL) - OGTT (oral glucose tolerance test)

Page 94 of the protocol, Section 17.2.2 ("Primary analysis of the co-primary endpoints"), gives more detail about the measurement assessment method for T2DM onset:

> The time of onset of type 2 diabetes in subjects with pre-diabetes at baseline will be registered at specific visits. If presence of diabetes is observed at a visit, the onset must have occurred between this visit and the previous visit where diabetes was examined. Thus the observations can be considered as interval censored data. The time of onset will be set to be in between the first of the two required registrations of elevated FPG or OGTT 2 hr plasma glucose, and the diabetes assessment visit prior to the first registration.

Sex and BMI stratification status were fixed factors. Baseline FPG (fasting plasma glucose) was a covariate. Subjects leaving the study early are treated as censored.

Sensitivity Analysis

The sponsor also incorporated sensitivity analyses including:

- Cox proportional hazards.
- Logistic regression.
- ANCOVA.
- For weight change, an imputation model where missing post baseline values are imputed using last observed value +0.3 kg for each month.

Secondary Analysis

Secondary analysis (of secondary endpoints) include:

- ANCOVA for continuous measurements (percent weight change).
- Logistic regression for dichotomous endpoints (achievement of at least 5% and at least 10% weight loss).

Last observation carried forward (LOCF) was used to address missing data

3.2.2.2 Characterization of Missing Data

Missing Measurements

Table 3 shows censoring and event (T2DM onset) patterns by 4-month intervals for the primary endpoint. Figure 2, taken from the weight data set, shows treatment exposure by 4-month intervals. The pattern in Figure 2 is similar to that in Table 3 for the primary endpoint. Slightly more than 50% of subject in the placebo arm discontinued treatment and slightly less than 50% discontinued treatment on the Saxenda arm. As well Figure 2 shows a pattern of early treatment discontinuation similar to the censoring pattern in Table 3. Finally, as expected, the 3-year discontinuation rate shown in Figure 2 is consistent with the 3-year missing rate shown in Table 3 for achievement of 5% and 10% weight loss.

The rate of missing primary efficacy data (treated as censored) was around 50% (Table 4). The time to T2DM onset for a subject is treated as censored (with respect to the 3-year primary endpoint) if the subject leaves the study before the 3-year landmark visit without having the event (T2DM onset). The placebo group had 54% missing/censored data compared to 47% for the Saxenda arm.

In addition, a higher percentage of subjects discontinued treatment early (and were censored) in the trial. The placebo arm experienced somewhat higher early rates of discontinuation than the treatment arm:

- 170 (11%) of subjects on the Saxenda arm discontinued treatment in the first four months.
- 102 (14%) of subjects on the placebo arm discontinued in the same period.
- 349 (23%) of subjects on the Saxenda arm discontinued in the first year compared to 228 (30%) on the placebo arm.

Two hundred subjects on the Saxenda arm withdrew and were censored before week 160 due to an adverse event, compared to 46 subjects on the placebo arm; 29 subjects on the Saxenda arm and 36 on the placebo arm withdrew due to “ineffective therapy”. Only one subject who discontinued treatment before week 100 had a non-missing weight measurement at the landmark visit.

No Retrieved Dropouts

The sponsor stated that it was not able to bring withdrawn subjects in to the landmark visit at week 160. From page 16 of the sponsor's Summary of Clinical Efficacy for this supplement:

> In accordance with the trial protocol, LOCF was used as the primary method of imputing missing data addressing outcome improvement during treatment adherence. A panel of sensitivity analyses using other imputation methods were also pre-specified in the trial protocol for fasting body weight. However, recent discussions have challenged the use of LOCF for imputation of missing data in clinical trials, and multiple imputation using data from returning dropouts have now been suggested as a better method for handling of missing data in clinical trials.[58] The 3-year part of trial 1839 was, however, ongoing at the time of this discussion and it was not possible to bring in withdrawn subjects for a landmark visit at week 160. Accordingly, no data from returning dropouts were available in trial 1839 (3-year part).

Table 3: Censoring/Event Status (T2DM Onset) for 4-Month Intervals by Treatment Arm

Censor/Event Status- 4 Month Intervals	Saxenda 3.0 mg	Placebo
Subjects Randomized	1505	749
No post baseline assessment – N (%)	33 (2)	11 (1)
0-4 Months –Still on Study*	1472	738
Had onset** - N (%)	4 (0)	4 (1)
Censored - N (%)	170 (12)	102 (14)
4-8 Months–Still on Study	1298	632
Had onset - N (%)	0 (0)	5 (1)
Censored - N (%)	105 (8)	67 (11)
8-12 Months–Still on Study	1193	560
Had onset - N (%)	0 (0)	5 (1)
Censored - N (%)	74 (6)	51 (9)
12 -16 Months–Still on Study	1119	504
Had onset - N (%)	2 (0)	4 (1)
Censored - N (%)	82 (7)	50 (10)
16-20 Months- Still on Study	1035	450
Had onset - N (%)	4 (0)	6 (1)
Censored - N (%)	84 (8)	44 (10)
20-24 Months- Still on Study	947	400
Had onset - N (%)	2 (0)	7 (2)
Censored - N (%)	61 (6)	38 (10)
24-28 Months- Still on Study	884	355
Had onset - N (%)	5 (1)	0 (0)
Censored - N (%)	35 (4)	14 (4)
28-32 Months- Still on Study	844	341
Had onset - N (%)	4 (0)	8 (2)
Censored - N (%)	35 (4)	21 (6)
32-36 Months- Still on Study	805	312
Had onset - N (%)	5 (1)	7 (2)
Censored - N (%)	23 (3)	8 (3)
> 36 Months- Still on Study (but off-	777	297
Had onset - N (%)	5 (1)	1 (0)
Censored or left study after completion- N (%)	772 (99)	296 (100)

*Still on study just before the interval. Subjects that were censored in the interval left the study due to reasons such as inability to tolerate treatment or "withdrawal of consent.**Subjects that "had onset" had T2DM onset in the interval as defined by criteria listed in first paragraph above. 200 subjects on the Saxenda arm withdrew due to an adverse event; 6 subjects on the placebo arm withdrew due to an adverse event (Table, Page 2 of Synopsis). Each interval is: >= lower interval and < upper interval.

Table 4: Summary of T2DM Onset Event/Censoring Status Over All Intervals

Group	Total	Total Censored < 36 Months	Total Had Event (Onset Diabetes) Before 36 Months	Total Missing (Excluding censored)
Saxenda 3.0 mg	1505	702 (47%)	26*	0
Placebo	749	406 (54%)	46*	0

*Does not take into account the 50% of subjects that discontinued early and were not followed up to see if they had diabetes onset

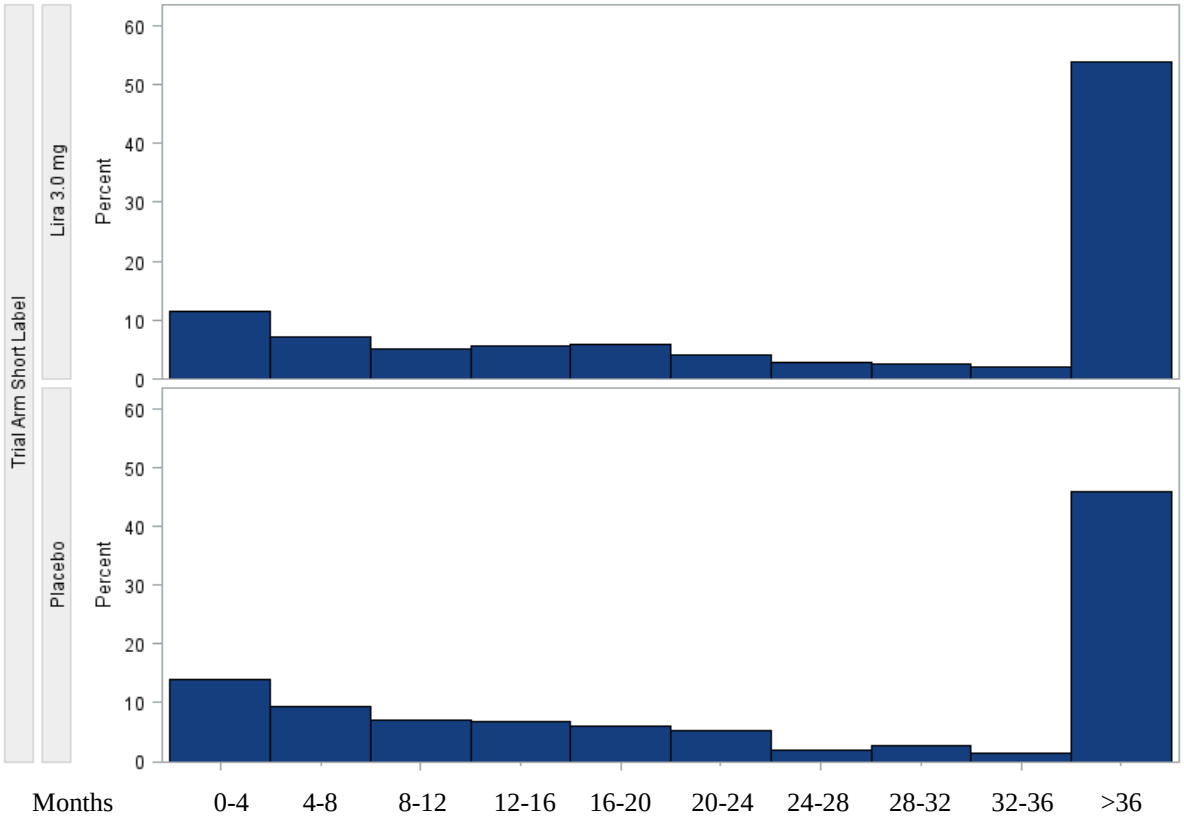

Figure 2: Subject Treatment Discontinuation by 4 –Month Intervals- Weight Assessment Data.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The distribution of baseline demographic characteristics for study 1839 is shown in Table 5 below. In general these characteristics seem evenly distributed between treatment arms for each of the two studies. In particular, baseline BMI and baseline fasting body weight values are similar between arms.

Table 5: Demographics and Baseline Characteristics by Treatment Arm-Study 1839 (3-Year Part)

Treatment Group	**Saxenda 3.0 mg**	**Placebo**
N per Group	**1505**	**749**
Sex		
Female (%)	1141 (76)	573 (77)
Male (%)	364 (24)	176 (23)
Age Group		
18-39 years (%)	395 (26)	202 (27)
40-64 years (%)	1005 (67)	493 (66)
65-74 years (%)	99 (7)	53 (7)
>= 75 years (%)	6 (0)	1 (0)
Age (years)		
Mean (95%CI)	47.5 (47.0 - 48.1)	47.3 (46.5 - 48.2)
Median (min - max)	48 (18 - 78)	48 (18 - 77)
Ethnicity		
Hispanic Or Latino (%)	143 (10)	70 (9)
Race		
Asian (%)	75 (5)	39 (5)
Black Or African	146 (10)	71 (9)
White (%)	1256 (83)	628 (84)
Other (%)	22 (1)	8 (1)
BMI at Baseline (kg/m)		
Mean (95%CI)	38.8 (38.4 - 39.1)	39.0 (38.5 - 39.4)
Median (min - max)	37.8 (27.0 - 77.2)	38.2 (27.3 - 60.0)
Baseline Fasting Wt (kg)		
Mean (95%CI)	108 (106 - 109)	108 (106 - 109)
Median (min - max)	105 (65 - 234)	104 (63 - 198)
Missing	6	4

Abbreviations: CI-confidence interval

3.2.4 Results and Conclusions

The results for the primary analysis using the sponsor's Weibull analysis demonstrated superiority of Saxenda 3 mg with respect to Placebo (Table 6 below). However the censoring mechanism does not differentiate between subjects who discontinued and had missing data and those who continued treatment. Because of the high number of censored observations (50% of subjects were censored and were not assessed at the three-year landmark visit), results obtained from sensitivity analysis attempting to address this large a proportion of missing data may be questionable.

Table 6: Description of Sponsor Primary and Secondary Analysis Results

Endpoint	Arms	Analysis* Method	Treatment Ratio/Difference	UCL	LCL	P-Value
Time-to-T2DM Onset	Ratio Saxenda vs. placebo	Weibull	2.68	1.86	3.87	<.0001
% Weight Loss	Saxenda – Placebo	ANCOVA	4.32 %	3.70	4.94	<.0001
5% Weight Loss	Saxenda – Placebo		25.9%			<.0001

* All analyses in table are sponsor analyses. Because of the high amount of missing/censored data (~50%), methods to address missing data may be questionable. I therefore did not perform alternative sensitivity analysis. Note that sponsor analysis is based on FAS- all randomized subjects exposed to at least one dose of the trial product and with at least one post baseline assessment of any endpoint. We do not agree with this analysis population. All our efficacy analyses are based on all randomized subjects. Table 7 below shows descriptive statistics for 5% weight loss for 1, 2, and 3years, including missing data.

Table 7 shows counts and percentages of subjects achieving, not achieving, and missing the 5% and 10% weight loss goal assessments. These descriptive statistics are shown by treatment arm after one, two, and three years on study. Note that even at year 2 (104 Weeks) the missing rate exceeds 40% on the Saxenda arm, and it is 50% on the placebo arm.

Table 7: Subjects Achieving at Least 5/10 Percent Weight Loss by Treatment Arm; One, Two and Three Years (All Subjects-in Three-Year Sub-Study)

Treatment Group	**Saxenda 3.0 mg**	**Placebo**
N Per Group	**1505***	**749***
≥5% Weight Loss		
56 Week –		
Yes (%)	817 (54)	182 (24)
No (%)	283 (19)	326 (44)
Missing (%)	405 (27)	241 (32)
104 Week –		
Yes (%)	594 (39)	136 (18)
No (%)	291 (19)	239 (32)
Missing (%)	620 (41)	374 (50)
160 Week –**		
Yes (%)	424 (28)	102 (14)
No (%)	323 (21)	220 (29)
Missing (%)	758 (50)	427 (57)
≥ 10% Weight Loss		
56 Week –		
Yes (%)	440 (29)	73 (10)
No (%)	660 (44)	435 (58)
Missing (%)	405 (27)	241 (32)
104 Week –		
Yes (%)	314 (21)	61 (8)
No (%)	571 (38)	314 (42)
Missing (%)	620 (41)	374 (50)
160 Week – **		
Yes (%)	234 (16)	49 (7)
No (%)	513 (34)	273 (36)
Missing (%)	758 (50)	427 (57)

* Includes all randomized subjects; - 6 subjects randomized to Saxenda arm and 4 subjects randomized to placebo arm had a missing baseline measurement. **P-values not given for 160-Week treatment difference due to high missing rate.

Table 8 shows descriptive statistics similar to those shown in Table 7, but only for subjects who achieved the respective 5% or 10% one-year weight loss goal. This table shows how well subjects who achieved the respective 1-year weight loss goal were able to maintain that weight loss in years 2 and 3. The missing rate at 160 weeks is lower than for Table 7: 29% and 34% for Saxenda and placebo arms respectively for achievement of ≥5% weight loss, and slightly lower on the two arms for ≥ 10% weight loss. This is because subjects who achieve the 1-year target are by definition not missing at this time point, so their missing rates at years 2 and 3 will tend to be lower. As well, since they achieved the 1-year target, they may be more likely to follow up for the two and three-year assessments than patients who did not achieve the 1-year target.

Table 8: Durability of Achievement of 1-Year Weight Loss of at Least 5 / 10 Percent

Treatment Group	Saxenda 3.0 mg	Placebo
56 Week (Year 1) - ≥5% Weight Loss		
N	1505**	749**
Yes (%)*	**817 (54)**	**182 (24)**
No (%)	283 (19)	326 (44)
Missing (%)	405 (27)	241 (32)
104 Week (Year 2) –		
N*	**817**	**182**
Yes (%)	550 (67)	107 (59)
No (%)	132 (16)	34 (19)
Missing (%)	135 (17)	41 (23)
160 Week (Year 3) –		
N*	**817**	**182**
Yes (%)	391 (48)	74 (41)
No (%)	193 (24)	47 (26)
Missing (%)	233 (29)	61 (34)
56 Week (Year 1) - ≥ 10% Weight loss		
N	1505	749
Yes (%)*	**440 (29)**	**73 (10)**
No (%)	660 (44)	435 (58)
Missing (%)	405 (27)	241 (32)
104 Week (Year 2) –		
N*	**440 (30)**	**73 (10)**
Yes (%)	358 (81)	54 (74)
No (%)	18 (4)	3 (4)
Missing (%)	64 (15)	16 (22)
160 Week (Year 3) –		
N*	**440 (30)**	**73 (10)**
Yes (%)	260 (59)	39 (53)
No (%)	60 (14)	13 (18)
Missing (%)	120 (27)	21 (29)

*Only the subjects who achieved 5/10% weight loss at 56 weeks are evaluated in years 2 and 3- to see if they maintained the 5/10% weight loss.** includes all randomized subjects – see Table 3 note on missing baseline data

Secondary Endpoints

The sponsor's analysis of the secondary endpoint of 5% weight loss at 160 weeks used last observation carried forward (LOCF) to address missing data. This method also does not differentiate between subjects who discontinue treatment and those who complete it. Due to the high missing rate, sensitivity analysis methods to address missing data may be questionable. I therefore did not perform alternative sensitivity analyses. As well, secondary endpoints are not included in the multiple testing hierarchy.

3.3 Evaluation of Safety

Please see the clinical review of Dr. Julie Golden for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Region

Table 9 gives descriptive statistics for achievement of $\geq$5% weight loss at 160 weeks by gender, race, ethnicity, age and geographic region. The subgroup of patients at least 65 years old had the highest response rate (40%) as well as the lowest missing rate on the treatment arm (39%); however the sample size for this subgroup is small. Not counting region subgroups, Black/Africans and Hispanics had the lowest response rates on the treatment arm (23% and 20% respectively) and the highest missing rates: 57% and 69% for Black/Africans on the treatment and placebo arms respectively, and 59% and 57% for Hispanics respectively on the two arms.

Table 9: Achievement of at Least 5% Weight Loss at 160 Weeks by Subgroup

Female		
Yes (%)	321 (28)	71 (12)
No (%)	234 (21)	163 (28)
Missing (%)	586 (51)	339 (59)
Male		
Yes (%)	103 (28)	31 (18)
No (%)	89 (24)	57 (32)
Missing (%)	172 (47)	88 (50)
Age ≥65		
Yes (%)	42 (40)	10 (19)
No (%)	22 (21)	16 (30)
Missing (%)	41 (39)	28 (52)
Age< 65		
Yes (%)	382 (27)	92 (13)
No (%)	301 (22)	204 (29)
Missing (%)	717 (51)	399 (57)
Black/African		
Yes (%)	33 (23)	7 (10)
No (%)	30 (21)	15 (21)
Missing (%)	83 (57)	49 (69)
White		
Yes (%)	362 (29)	85 (14)
No (%)	271 (22)	189 (30)
Missing (%)	623 (50)	354 (56)
Asian		
Yes (%)	23 (31)	9 (23)
No (%)	19 (25)	13 (33)
Missing (%)	33 (44)	17 (44)
Hispanic		
Yes (%)	29 (20)	10 (14)
No (%)	29 (20)	20 (29)
Missing (%)	85 (59)	40 (57)
US		
Yes (%)	145 (23)	35 (11)
No (%)	123 (20)	82 (26)
Missing (%)	358 (57)	198 (63)
Non-US		
Yes (%)	279 (32)	67 (15)
No (%)	200 (23)	138 (32)
Missing (%)	400 (46)	229 (53)

5 SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

The primary endpoint for study 1839 is T2DM onset evaluated at three years. I was able to verify the results of the primary analysis, which showed a significant result for Saxenda vs. Placebo. However the primary analysis does not adequately address missing data. As well, due to the high missing data rate of 50%, methods to address missing data may be questionable. As stated in the FDA Draft Guidance for Industry, Developing Products for Weight Management:

> "No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum."

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071612.pdf

5.2 Labeling Recommendations

Please see the clinical review of Dr. Julie Golden for labeling recommendations for the primary endpoint. The descriptive statistics shown in the text and table below should be provided in the label. The sponsor already has a labeling claim for one-year weight loss. Results at three years can further describe the effects of the drug on weight loss.

> The number and percentages of patients known to have lost ≥ 5% body weight at week 56 and/or week 160 in Study 1 (patients with abnormal glucose at baseline only) are summarized in Table 5.

Table 5: Changes in Weight at Week 56 and Week 160 from Baseline for Study 1 ((b) (4) Patients with Abnormal Glucose at Baseline)

	Saxenda N=1505	**Placebo N=749**
Baseline mean body weight (SD) (kg)	107.5 (21.6)	107.9 (21.8)
Number (%) of patients known to lose greater than or equal to 5% body weight at 56 weeks	817 (56%)	182 (25%)
Number (%) of patients known to lose greater than or equal to 5% body weight at 160 weeks	424 (28%)	102 (14%)
Number (%) of patients known to lose greater than or equal to 5% body weight at both 56 weeks and 160 weeks	391 (26%)	74 (10%)
Number (%) of patients with weight assessment missing at 160 weeks	(b) (4)	(b) (4)

SD = Standard Deviation; Includes all randomized subjects who had a baseline body weight measurement. All available body weight data at 56 and 160 weeks are included in the analysis.

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/s/

ALEXANDER CAMBON
03/31/2017

YUN WANG
03/31/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 206321/S-004

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **March 28, 2017**

To: Martin White, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 206321 / S-004 SAXENDA (liraglutide [rDNA origin] injection), solution for subcutaneous use

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On October 25, 2016 OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) for Saxenda. OPDP's comments on the proposed draft PI are based on the version sent by Martin White via email on March 24, 2017 and are provided directly on the marked version below.

Thank you for the opportunity to comment on this material. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

27 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANKUR S KALOLA
03/28/2017