CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206321Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206321	Submission Date: 12/20/2013
Brand Name	Saxenda
Generic Name	Liraglutide
OCP Division	Clinical Pharmacology-2
OND Division	Metabolism and Endocrinology Products
Sponsor	Novo Nordisk
Submission Type, Code	NDA 505 (b) (1); Standard
Formulation; Strength(s)	Injection
Proposed Indication	For weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater or 27 kg/m^2 or greater in the presence of at least one weight related comorbidity
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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology (DCP-2 and DPM) has reviewed the clinical pharmacology data submitted on 12/2013 under NDA 206321 and recommend approval from a clinical pharmacology perspective. An optional Inter-Division Level OCP briefing was held on September 17, 2014 to discuss this submission. Labeling comments are on pages 38-39.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor analog with 97% amino acid sequence homology to human endogenous GLP-1. Liraglutide is approved to treat type 2 diabetes (T2DM) at doses up to 1.8 mg once a day (NDA 22-341). This current NDA application is proposing the use of liraglutide for weight management at doses of 3.0 mg once daily.

Refer to details of general clinical pharmacology information of liraglutide in clinical pharmacology review under NDA 22-341. This review will focus on the relevant clinical pharmacology information for the proposed indication.

According to the current proposed label, the proposed indication for liraglutide 3 mg is as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity such as dysglycemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidemia, or obstructive sleep apnea.

Similar to what is approved for T2DM population, to improve gastro-intestinal tolerability, for all patients, the starting dose is proposed to be 0.6 mg. The starting dose is then proposed to be increased to 3 mg with increments of 0.6 mg with at least one week intervals (i.e. 0.6, 1.2, 1.8, 2.4 and 3.0 mg). Treatment should be evaluated after a minimum of 12 weeks on the 3.0 mg dose to assess the treatment effect.

The clinical development program of liraglutide draws support from a clinical pharmacology study that evaluated the PK/PD of liraglutide in obese subjects, 1 Phase 2 dose ranging trial (1807) and two Phase 3 efficacy and safety trials (1839 and 1922).

Liraglutide pharmacokinetics (PK) and pharmacodynamics (PD) has been characterized following subcutaneous administration of 1.8 mg under the T2DM program and following 3.0 mg dose in obese subjects. Clinical pharmacology review of the information submitted under NDA 206321 revealed the following key findings:

Liraglutide PK:

The proposed drug product formulation of liraglutide (3.0 mg) used in the obesity development program is similar to the currently marketed formulation (1.8 mg). A population PK analysis was submitted under NDA 22-341 (Victoza) and for the current NDA for obesity (NDA 206321). The sponsor is referring to the data provided under the T2DM program to bridge clinical pharmacology and safety information (e.g., QT, and DDI).

Baseline body weight was the most significant covariate affecting the clearance (CL/F) of liraglutide as determined by the population PK analysis conducted for both programs.

The data indicates an increase in liraglutide clearance with increasing body weight. Hence, subjects with lower body weight are expected to have a higher liraglutide exposure (AUC) as compared to those with higher body weight. The PK parameter estimates (e.g., clearance, volume of distribution) obtained from the population PK analysis using data from the obesity program was consistent with those observed with the population PK analysis conducted in T2DM patients.

In the population PK analyses conducted using data from the obesity program, the effect of various covariates on the clearance (CL/F) of liraglutide was analyzed using data from the Phase 3 trials 1839 and 1922. The covariates analyzed in addition to baseline body weight were: age, gender, race, ethnicity, dose and glycemic status at baseline (normoglycemia, pre-diabetes, T2DM). Among these, gender was the other significant covariate with males having 24% lower liraglutide exposure than females (after accounting for body weight differences). About 72% of subjects included in the population PK analyses of obesity trials were females. When exposure following administration of 3.0 mg liraglutide was compared in obese subjects in Trial 1922 with different baseline glycemic status, there appears to be about 16% lower exposure in diabetic obese subjects as compared to obese subjects with normal glycemic or prediabetic status. None of the other covariates examined were found to have a significant effect on liraglutide PK. No dose adjustments are recommended based on gender or diabetic status.

Comparison of exposure (AUC and C_{max}) of liraglutide: 1.8 mg dose [T2DM (NDA 22-341)] versus 3.0 mg dose [obesity (NDA206321)]:

It should be noted that the doses are different in the two programs, with the dose in the obesity program being higher (3.0 mg) as compared to the T2DM program (1.8 mg).

AUC comparison: In order to relate the observed exposure of liraglutide in the obesity to that of T2DM population, it is important to understand the body weight distribution in the two programs as body weight was the important covariate affecting the clearance of liraglutide. The body weight range of the subjects in population PK analysis conducted for the T2DM and obesity program was 44 – 163 kg and 60 kg – 234 kg, respectively. Figure 1 shows the body weight distribution in the two programs. As shown, although there was substantial overlap in the subject's body weight in the two development programs, as expected, the proportion of subjects with higher body weight was greater in the obesity program as compared to that in T2DM program.

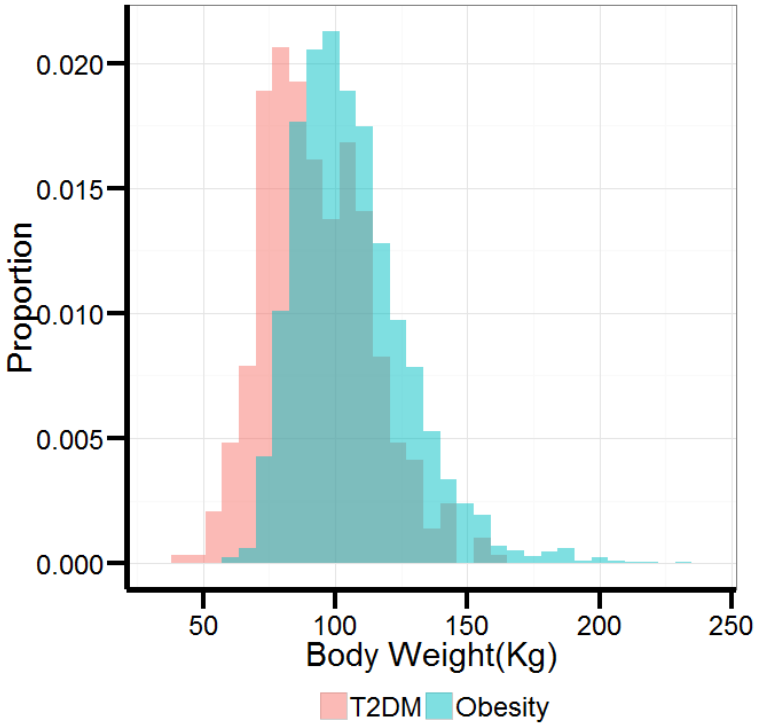


Figure 1: Body weight distribution in the T2DM and obesity programs

Figure 2 shows the correlation of body weight to the AUC for patients receiving 3.0 mg dose in the obesity trials and Figure 3 shows the distribution of AUC in the T2DM and obesity programs. There is considerable variability in the observed exposure of liraglutide (Figures 2 and 3). Although overlap in AUCs was observed in the two programs, the proportion of subjects in the obesity program having higher AUC at 3.0 mg dose appeared to be greater compared to T2DM patients receiving 1.8 mg dose (Figure 3). About 16% of subjects in the obesity trials receiving the 3.0 mg dose had higher exposure than the maximum exposure observed in the T2DM trial (>~4 mg.h/L) with 1.8 mg dose (Figures 2 and 3). This observation is consistent with the Figure 1, which shows a significant overlap of body weights between the two populations. Thus, subjects with similar body weight will likely have a higher exposure if the dose is increased from 1.8 to 3.0 mg.

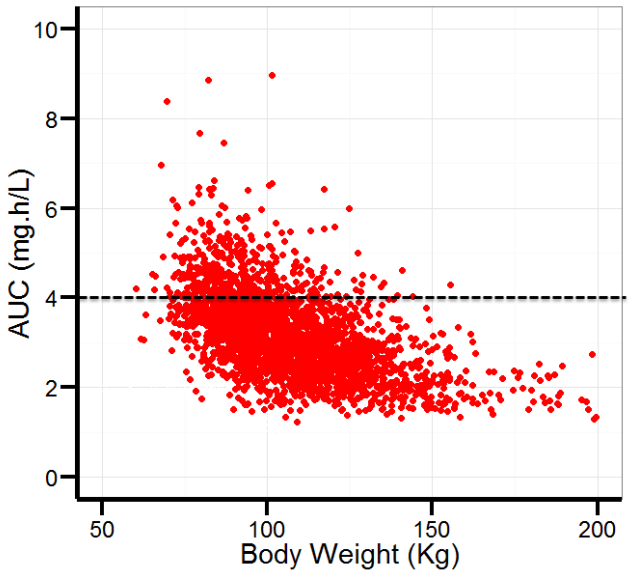


Figure 2: Correlation of liraglutide exposure to body weight in Obesity trials. Data for subjects receiving 3.0 mg dose is shown.

The horizontal line shows the maximum exposure level observed in the T2DM population receiving 1.8 mg dose.

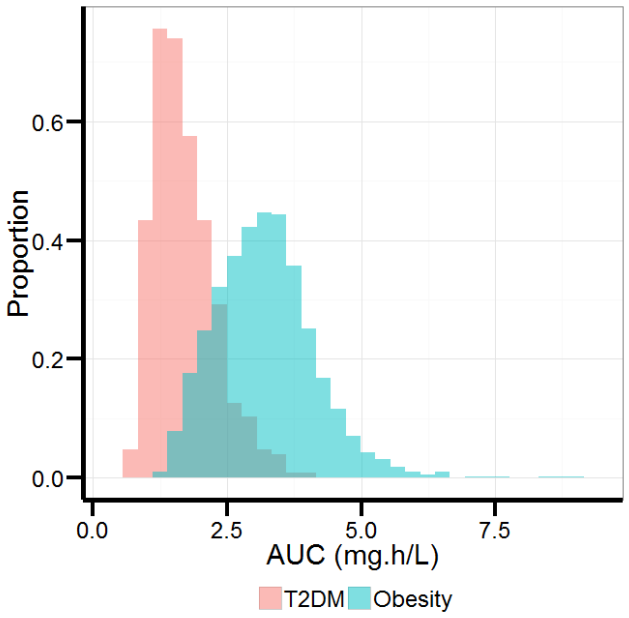


Figure 3: Distribution of liraglutide exposure obtained from population PK analysis following administration of 1.8 mg dose in T2DM program (Pink) and 3.0 mg dose in obesity program (Blue)

Note: The output from the T2DM and obesity population PK analyses was used for this purpose. All the patients in the T2DM population PK analysis were used. For patients on 1.8 mg dose, AUC was calculated using the formula, AUC= (1.8/CL). There were 235 patients at 1.2 mg in the T2DM population. For these

patients, the clearance (L/h) obtained from the population PK analysis was used to calculate the AUC following 1.8 mg dose (AUC=Dose/CL). In case of obesity trials, the AUC was calculated using individual clearance values for the patients receiving the 3.0 mg dose.

C_{max} comparison: The sponsor compared the observed liraglutide maximum concentrations (C_{max}) from various trials – cardiac electrophysiology (TQTc) trial (NN211-1644, conducted under T2DM NDA program), C_{max} sub study in 1839, 1807 and trial 3630 (Figure 4). There appears to be substantial overlap in the observed individual liraglutide concentrations in these studies conducted following administration of either 1.8 mg or 3.0 mg dose.

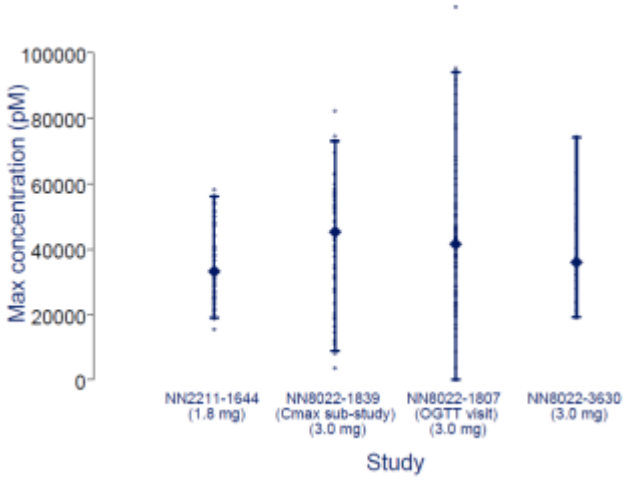


Figure 4: C_{max} values obtained from various trials. Data are individual C_{max} values with medians and 2.5-97.5% percentiles

Source: Sponsor report: Summary of Clinical pharmacology, page 45

Exposure/Dose-response relationship for effectiveness:

The dose-response is evident for the proposed 3 mg once daily liraglutide treatment based on efficacy data from the Phase 2 and 3 trials. Trial 1807 evaluated liraglutide 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg doses as compared to placebo and orlistat (active comparator), in obese subjects while trial 1922 evaluated 1.8 mg and 3.0 mg liraglutide doses as compared to placebo in T2DM subjects. Trials 1839 (subjects with or without pre-diabetes), 1923 (subjects with dyslipidemia and/or hypertension) and 3970 (subjects with obstructive sleep apnea) studied the effect of liraglutide 3.0 mg versus placebo. The 3.0 mg dose was selected based on the results of the dose-ranging trial (1807) where it showed superior weight loss as compared to the other lower liraglutide dose groups as well as orlistat. In Phase 3 trials, treatment with liraglutide 3.0 mg led to a mean weight loss (change from baseline in body weight) of 5.7−9.2% (6.0-8.8 kg) depending on the trial, while placebo treated subjects achieved a weight loss of 0.2−3.1% (0.2-3.0 kg). In the pooled analyses of all trials, the change from baseline in body weight was 7.5% (7.8 kg) with liraglutide 3.0 mg as compared to 2.3% (2.5 kg) with placebo *(Sponsor: Integrated summary of efficacy).*

The exposure-response relationship provides supportive evidence for the effectiveness of the liraglutide 3.0 mg dose. Consistent with the observed dose-response relationship, there was a clear relationship between liraglutide exposure (data from 1807, 1839 and 1922) and weight loss with increasing exposure leading to greater weight loss. There was considerable overlap between exposures achieved at 1.8 mg and 3.0 mg dose groups however there was incremental benefit with the 3.0 mg dose. The weight loss appeared to reach plateau at the highest exposure. Exposure-response relationship was similar among the three trials, 1807, 1839 and 1922. Further, categorical analysis shows that the proportion of subjects reaching at least 5% weight loss increased with increasing liraglutide exposure. The proportion of subjects achieving a weight loss of 5% or greater ranged from 46−78% across trials in the liraglutide 3.0 mg group as compared to 14−30% in the placebo group across trials.

Efficacy and safety analysis by baseline body weight:

As body weight is the significant predictor of liraglutide clearance, some obese subjects with lower body weight have an increased exposure with liraglutide 3.0 mg. The Agency therefore, requested the sponsor to conduct an exposure-response analyses for adverse events such as nausea (all grade and moderate-severe), vomiting (all grade and moderate-severe) and hypoglycemia. The Agency also requested sponsor to conduct efficacy and safety analysis based on baseline body weight. In addition, since patients lose body weight over time while on treatment with liraglutide, and clearance is related to body weight, there is a possibility that the drug exposure can increase over time based on the magnitude of weight loss. This increase in drug exposure with weight loss can potentially lead to higher adverse events in patients experiencing higher weight loss. Therefore, Agency recommended the sponsor to conduct an analysis of adverse events based on magnitude of weight loss and also evaluate if there is any time dependency of occurrence.

Sponsor's analysis of exposure-response analysis for safety data from the obesity trials did not reveal any significant relationship with observed adverse events such as nausea, vomiting, and hypoglycemia. The adverse events profile was also not different for different baseline body weight quartiles. There also appeared to be no trend in the efficacy when analyzed by baseline body weight. Evaluations of adverse event based on the weight loss categories also did not reveal any differences between the different groups. Further, adverse events over time in patients treated with liraglutide did not show an increase with treatment duration. Most of the events occurred within 0-3 months and did not increase in frequency over the duration of the trial.

Effect of liraglutide 3.0 mg on gastric emptying: The absorption of paracetamol (used as marked to assess gastric emptying) was similar following administration of liraglutide 1.8 mg and 3.0 mg dose. Therefore, sponsor's proposal to bridge drug interaction information from T2DM program is acceptable.

Bioanalytical Methodology: In the clinical pharmacology trials, liraglutide concentration in plasma was determined using a liraglutide specific enzyme-linked immunosorbent assay (ELISA) that measured both protein-bound and unbound

liraglutide. The assay method is acceptable and was adequately validated for recovery, accuracy, precision, sensitivity and specificity.

Overall:

- The proposed dose of 3.0 mg is acceptable from a clinical pharmacology perspective.
- There is no dosage adjustment needed based on any covariate (body weight, age, gender, race and glycemic status).
- The sponsor's proposal to bridge clinical pharmacology information [e.g., ADME, specific population PK (renal, hepatic impairment), TQT, and DDI] from T2DM program (Victoza) is acceptable.
- There is no need to change the dosing regimen if the patient experiences significant weight loss during treatment with liraglutide.

2 Question-Based Review (QBR)

2.1 General Attributes of the Drug and Drug Product

Liraglutide is a solution for subcutaneous injection. Liraglutide is proposed as an adjunct to diet and exercise for chronic weight management in adults. It is proposed to be administered as once daily 3 mg subcutaneous (SC) injection. The injection can be administered at any time of day independent of meals.

2.1.1 What pertinent background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Liraglutide is approved as Victoza (up to doses of 1.8 mg) to be used in patients with type 2 diabetes (T2DM). As stated in the package insert of Victoza, administration of liraglutide leads to insulin dependent insulin secretion, lowering of post-prandial glucose and lowering of glucagon secretion. In addition, in the clinical trials conducted in T2DM patients, body weight reduction was observed (Victoza Package Insert). This development program was conducted to systematically evaluate the effect of liraglutide in obese subjects.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The same formulation of liraglutide drug product was used in all the Phase 2 and 3 clinical trials. It is the same formulation as the approved formulation for the treatment of T2DM (under the trade name Victoza) and contains liraglutide (6.0 mg/mL), phosphate (b) (4) propylene glycol (b) (4) and phenol (b) (4)
Liraglutide 6.0 mg/ml is a clear, colorless or almost colorless solution dispensed in a 3

mL cartridge. Refer to reviews conducted under NDA 22-341 for details of the chemistry and formulation of the drug product.

2.1.3 What is the mechanism of action and therapeutic indication?

Liraglutide is a glucagon like peptide-1 (GLP-1) receptor analog. GLP-1 is a peptide hormone with several mechanisms of action including: lowering blood glucose, glucose-dependent increase in insulin secretion, glucose-dependent glucagonostatic effect and decreasing gastric emptying rate. GLP-1 is also proposed to be a physiological regulator of satiety, energy intake and body weight. This receptor is present in specific brain regions relevant for energy homeostasis.

The proposed indication for liraglutide 3 mg is "as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity such as dysglycemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidemia, or obstructive sleep apnea."

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical pharmacology information for liraglutide for the proposed indication was obtained from the following trials:

- Trial NN8022-3630 (clinical pharmacology trial)
- Trial NN8022-1807 (Phase 2 trial) for exposure-response analyses
- Trial NN8802-1839 (Phase 3 trial) for population pharmacokinetic analyses and exposure-response analyses
- Trial NN8802-1922 (Phase 3 trial) for population pharmacokinetic analyses and exposure-response analyses.

Trial 3630: This was a randomized, placebo-controlled, double-blind, incomplete crossover trial designed to evaluate the effects of liraglutide on gastric emptying, appetite, energy intake and energy expenditure, and to evaluate the pharmacokinetic properties of liraglutide in obese, but otherwise healthy subjects. Liraglutide doses of 1.8 mg and 3.0 mg was studied in this trial. Since it was an incomplete crossover design, no subject received all three treatments (placebo, 1.8 mg and 3.0 mg).

Trial 1807: This was a 20-week (with 84-week extension and interim analysis at 52 weeks), randomized, double-blind, placebo controlled, six armed parallel group, multi-center, multinational trial with an open label orlistat comparator group investigating the

effect of liraglutide 1.2, 1.8, 2.4 and 3.0 mg and placebo on body weight in obese subjects without diabetes. Samples for PK analysis were obtained at 20 weeks.

Trial 1839: This was a 56 weeks randomized, double-blind, placebo-controlled, parallel group, multi-center, multinational trial investigating the efficacy of 3.0 mg liraglutide versus placebo in inducing and maintaining weight loss in non-diabetic obese subjects and overweight subjects with comorbidities (dyslipidemia and/or hypertension). Blood samples for plasma liraglutide concentration measurements were drawn at 2, 12 and 28 weeks after first dosing for the population pharmacokinetic and exposure-response analyses.

Trail 1922: This was also a 56-week randomized, double-blind, placebo-controlled, three arm parallel group, trial with a 12-week follow up period investigating the effect of liraglutide on body weight in overweight or obese subjects with type 2 diabetes. Blood samples for plasma liraglutide concentration measurements were drawn at 2, 12 and 28 weeks after first dosing for the population pharmacokinetic and exposure-response analyses.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The Guidance for Industry "Developing products for weight management" has the following as efficacy endpoints:

a. Primary efficacy endpoint

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- Mean: The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group.
- Categorical: The proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group.

b. Secondary efficacy endpoints

Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic parameters:

- Blood pressure and pulse
- Lipoprotein lipids
- Fasting glucose and insulin
- HbA1c (in type 2 diabetics)
- Waist circumference

The efficacy benchmark as recommended in the guidance is as follows:
In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant
- The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

The primary endpoints of liraglutide clinical trials were related to body weight, and included both mean and categorical changes in body weight. The key efficacy endpoints in all the clinical trials conducted is summarized in Table 1 below:

Table 1: Key efficacy endpoints related to body weight by trial

Trial ID	1st Co-primary endpoint	2nd Co-primary endpoint	3rd Co-primary endpoint
1839 1922 (at 56 weeks)	Change in body weight from baseline (% and kg)	Proportion of subjects achieving ≥5% reduction of baseline body weight	Proportion of subjects achieving >10% reduction of baseline body weight
1923 (at 56 weeks)	Change in body weight from baseline (after LCD run-in period) (% and kg)	Proportion of subjects that maintained the ≥5% reduction in initial body weight achieved during the low calorie diet run-in period	Proportion of subjects achieving ≥5% reduction of baseline body weight
1807 (at 20 and 52 weeks)	Change in body weight from baseline (kg)	Proportion of subjects achieving >5% reduction of baseline body weight	–
Trial ID	**Key secondary endpoints related to body weight**		
3970 (at 32 weeks)	Change in body weight from baseline (% and kg)	Proportion of subjects achieving ≥5% reduction of baseline body weight	Proportion of subjects achieving >10% reduction of baseline body weight

Source: Sponsor summary of clinical efficacy; Table1-2, page 23

Body weight was measured with an empty bladder, without shoes and only wearing light clothing. The primary analyses were based exclusively on fasting measurements.

The sponsor also included the secondary endpoints as indicated in the guidance. Glycemic control parameters (including change from baseline in HbA1c, fasting plasma glucose, homeostasis model assessment (HOMA-B, HOMA-IR), parameters in OGTT), cardio-metabolic parameters (vital signs, fasting lipids, CV biomarkers), patient reported outcomes and concomitant medications (change from baseline) were also included as secondary endpoints. Refer to clinical review for the discussion of the secondary endpoints.

2.2.3 What are the ADME characteristics of liraglutide after SC administration?

The following is based on previous review of liraglutide in T2DM program (Victoza package insert) and is applicable to the current application.

Absorption: Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. After subcutaneous single dose

administrations, C_{max} and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg.

Distribution: The mean apparent volume of distribution after subcutaneous administration of Victoza 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of Victoza is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (>98%).

Metabolism and Excretion: During the initial 24 hours following administration of a single [^{3}H]-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. Following a [^{3}H]-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 1.2 L/h with an elimination half-life of approximately 13 hours.

2.2.4 What are the pharmacokinetic and pharmacodynamic characteristics of liraglutide in obese subjects?

Trial NN8022-3630 was conducted to assess the effect of liraglutide on gastric emptying, energy expenditure, appetite and evaluate the pharmacokinetics in non-diabetic obese subjects (BMI $\geq$30 kg/m^2 and <40 kg/m^2). Subjects were dose escalated to the maintenance dose in weekly increments of 0.6 mg (a starting dose of 0.6 mg which was then increased once to 1.2 mg, and then1.8 mg or further increased to 2.4 mg and finally to 3.0 mg). Subjects were on the final dose for at least 7 days (for 3.0 mg) before the PK/PD assessments at Visits 4 and 9 (21 days in the 1.8 mg dose).

PK: Liraglutide steady-state was reached with both 1.8 mg and 3.0 mg dose during the PK assessment time point (7-21 days). This is consistent with previous finding that steady state is attained after 3-5 days treatment. There appears to be a dose-dependent increase in the liraglutide trough values (12930-15275 pmol/L and 21220-22680 pmol/L for liraglutide 1.8 mg and 3.0 mg, respectively). The PK profile of the two liraglutide doses is shown in Figure 5. Liraglutide 3.0 mg resulted in a higher mean plasma concentration than liraglutide 1.8 mg. The T_{max}, terminal half-life, apparent plasma clearance, apparent volume of distribution were similar between the two dose groups (Table 2).

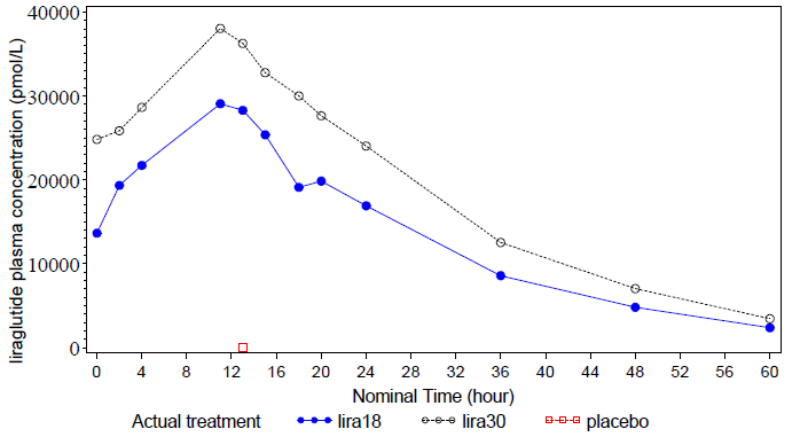


Figure 5: Mean liraglutide plasma concentrations following 1.8 mg and 3.0 mg dose in obese subjects

Source: Study 3630 study report, Figure 11-14, page 131.

Table 2: Liraglutide PK parameters following 1.8 mg and 3.0 mg dose in obese subjects

	Lira 1.8mg N	Lira 3.0mg N	Placebo N
Number of subjects			
N	30	32	32
AUC(0-24h) - h*pmol/L			
N	30	29	
Mean (SD)	546283 (315651)	742952 (271676)	
Median	461803	673423	
Geometric mean (CV)	485637 (57.8)	698540 (36.6)	
Min ; Max	217067 ;1689491	350349 ;1339077	
Cmax - pmol/L			
N	30	29	
Mean (SD)	30202 (20343)	39198 (14605)	
Median	23945	35940	
Geometric mean (CV)	26450 (67.4)	36796 (37.3)	
Min ; Max	11620 ;118900	18950 ;74290	
tmax - h			
N	30	29	
Mean (SD)	11.89 (3.3)	12.26 (2.0)	
Median	11.19	11.25	
Geometric mean (CV)	11.40 (27.7)	12.13 (16.2)	
Min ; Max	4.15 ;24.50	10.92;19.97	
t1/2 - h			
N	29	27	
Mean (SD)	12.96 (3.0)	12.85 (2.4)	
Median	12.58	12.90	
Geometric mean (CV)	12.67 (22.8)	12.64 (18.5)	
Min ; Max	8.34 ;22.98	8.33 ;18.62	
CL/F - L/h			
N	30	29	
Mean (SD)	1.09 (0.4)	1.22 (0.4)	
Median	1.04	1.19	
Geometric mean (CV)	0.99 (41.0)	1.14 (35.3)	
Min ; Max	0.28 ;2.21	0.60 ;2.28	
VZ/F - L			
N	30	28	
Mean (SD)	20.24 (10.7)	22.11 (8.2)	
Median	18.77	22.20	
Geometric mean (CV)	17.25 (53.0)	20.63 (37.3)	
Min ; Max	4.01 ;49.61	9.43 ;42.44	

Source: Study 3630 study report, Table 11-27, page 132.

Pharmacodynamics (PD):

Weight loss mechanism: In order to address the mechanism of action of weight loss by liraglutide, several exploratory PD characteristics were investigated. This included 24-hour energy expenditure and substrate oxidation rates in an open-circuit respiration chamber, measurement of appetite sensations (hunger, satiety, fullness, food

consumption) using visual analog scales (VAS) as well as urinary nitrogen (for assessment of protein oxidation), adrenaline and noradrenaline were measured. In addition, effect of liraglutide on various glycemic parameters was also assessed. The assessments were done at liraglutide PK steady-state. However, as liraglutide maintenance dose is reached by step-wise dose escalation, the mean treatment period in this study was 35 days during which some weight loss was observed in the liraglutide treatment groups. Therefore, the impact of weight loss on the exploratory PD endpoints cannot be ruled out and this could be a potential limitation for interpretation of the study results.

Subjective rating of appetite: Appetite sensations (hunger, satiety, fullness, and prospective food consumption) were assessed by VAS ratings during the meal test. The overall appetite score was the average of four scores for the different appetite sensations. Figure 6 depicts the mean profiles by treatment for overall appetite score (an increased rating denotes reduced appetite). As shown in the Figure 6, while liraglutide causes some changes in appetite sensations as compared to placebo, there appears to be no difference between the two dose groups.

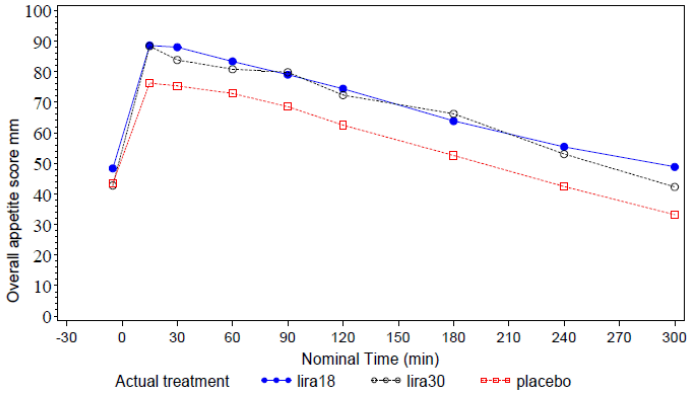


Figure 6: Mean visual analog scale (VAS) ratings for overall appetite score
Source: Study 3630 study report. Figure 11-6, page 102

Energy intake: Energy intake (measured as amount consumed in kJ) and duration of an ad libitum lunch was measured at liraglutide steady-state approximately 5 hours after the standardized breakfast meal. The subjects were instructed to eat until pleasantly satiated and the lunch meal was completed within 30 minutes. The estimated mean energy intake at the ad libitum lunch was reduced by 588 and 568 kJ with liraglutide 1.8 mg and 3.0 mg, respectively compared to placebo, corresponding to an approximate reduction in energy intake by 16% after liraglutide treatment.

Energy expenditure: 24-hour energy expenditure (expressed in kJ/h) and balance were measured in an open-circuit respiratory chamber at the end of treatment period. Subject's gas exchange was also calculated from measurements of oxygen and carbon dioxide concentrations. All treatment groups (1.8 mg, 3.0 mg and placebo) burned more energy than what they consumed during the 2-h stay in the chamber. Mean total energy expenditure was 3.0% and ~5% with 1.8 mg and 3.0 mg, respectively as compared to placebo. Protein oxidation rates were calculated from nitrogen excreted in the urine. Protein oxidation rates were reduced as compared to placebo. The reductions

corresponded to 90 kJ (3.77 kJ/h x 24) and 134 kJ (5.58 kJ/h x 24) per 24 hours for liraglutide 1.8 and 3.0 mg, respectively.

Other liraglutide PD characterization:

QT: Refer to the thorough QTc study conducted for the T2DM program. Sponsor is proposing to bridge the QT effect of 3.0 mg liraglutide to the study with the 1.8 mg dose conducted previously. QT-IRT concluded that sponsor's proposal is acceptable. As shown previously in Figure 4, the maximal concentrations observed in the TQT study is comparable to that seen in the studies conducted in the obesity development program. Sponsor's conclusions are acceptable.

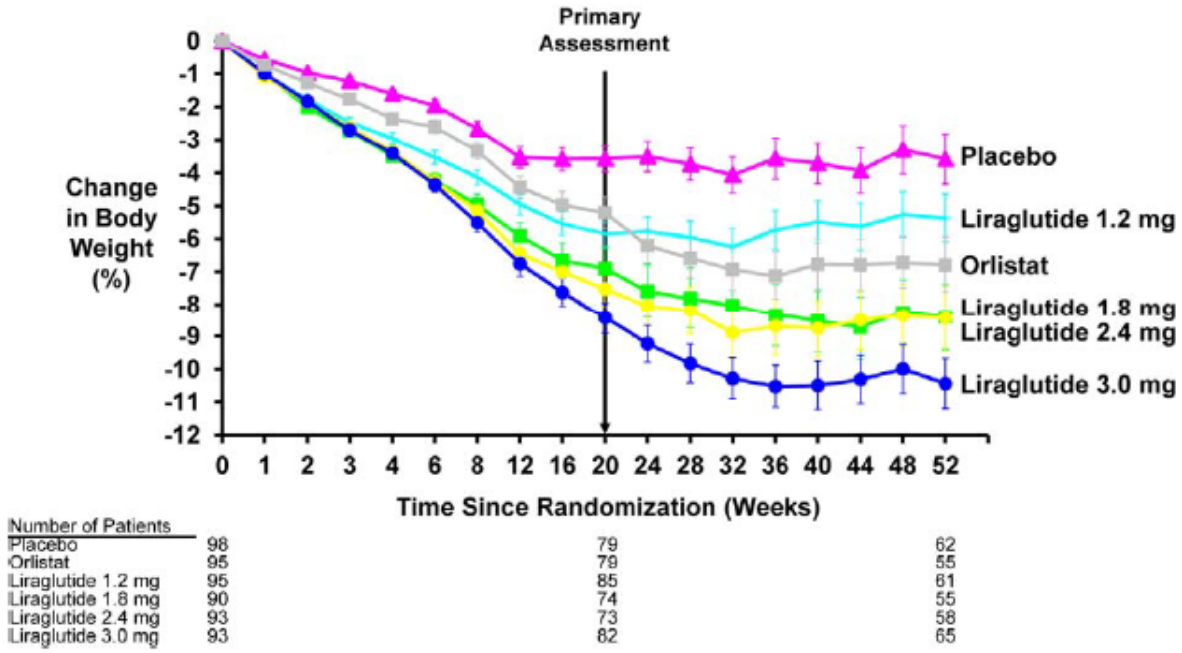
2.3 Exposure-Response

2.3.1 Does the dose-response or exposure-response data support the effectiveness of the proposed 3.0 mg daily dose for liraglutide?

Yes, the dose-response is evident for the proposed 3 mg once daily liraglutide treatment based on efficacy data from various trials.

Trial 1807 evaluated liraglutide 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg doses as compared to placebo and orlistat (active comparator), in obese subjects while trial 1922 evaluated 1.8 mg and 3.0 mg liraglutide doses as compared to placebo in T2DM subjects. Trials 1839 (subjects with or without pre-diabetes), 1923 (subjects with dyslipidemia and/or hypertension) and 3970 (subjects with obstructive sleep apnea) studied the effect of liraglutide 3.0 mg versus placebo. The sponsor's proposed dose of 3.0 mg is supported by both dose-response and exposure-response relationship.

According to the sponsor's report for the dose-ranging trial 1807, mean weight loss with liraglutide increased with increasing doses of liraglutide and all the liraglutide treatment groups led to a statistically significantly greater weight loss compared to placebo ($p<0.005$) (Figure 7). Treatment with liraglutide 2.4 and 3.0 mg also led to a statistically significantly greater mean weight loss compared to orlistat (active comparator) ($p<0.005$), Figure 7. The mean changes in body weight from baseline at 20 weeks for the liraglutide doses 1.2 mg, 1.8 mg, 2.4 mg, 3.0 mg, placebo and orlistat was -4.81 kg, -5.52 kg, -6.27 kg, -7.15 kg, -2.76 kg, and -4.12 kg, respectively.



Data are observed means with standard error bars for patients completing each scheduled visit.

Figure 7: Body weight change from baseline (%) by liraglutide dose: Trial 1807
Source: Sponsor AC briefing document, Figure 5-2, page 59.

As shown in above Figure 7, clear separation of liraglutide 3.0 mg was observed from placebo, active control and other low doses of liraglutide at the end of 20 weeks. A significantly higher subjects lost >5% of baseline weight with liraglutide (all doses) compared with placebo ($p<0.003$), and significantly more subjects in the liraglutide 3.0 mg group lost >5% of baseline weight compared with those in the orlistat group ($p<0.0001$). The proportion of subjects who lost > 5% of baseline weight increased with increasing doses of liraglutide with 52.1%, 53.3%, 60.9%, 76.1%, respectively with 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg doses of liraglutide. While the % subjects who lost > 5% baseline weight was 29.6% and 44.2%, respectively with placebo and active comparator, orlistat (*Source: Sponsor summary of clinical efficacy, Table 2-1. Page 43 of 138).*

In the extension phase of the trial 1807, at the end of 52 weeks (FAS with LOCF), similar to what was observed in 20 weeks, mean weight loss in subjects treated with liraglutide increased with increasing doses and was statistically significant as compared to placebo. Based on these dose-finding trial results, liraglutide 3.0 mg was chosen for the Phase trials.

Trial 1922 evaluated the efficacy and safety of liraglutide in T2DM subjects treated with either placebo, or liraglutide (1.2 mg or 3.0 mg). Both liraglutide doses showed statistically significant weight loss as compared to placebo (met all co-primary endpoints as well as significant difference in BMI, waist circumference). After 56 weeks, liraglutide 3.0 mg treatment produced a significantly greater reduction in body weight as compared to placebo (Figure 8).

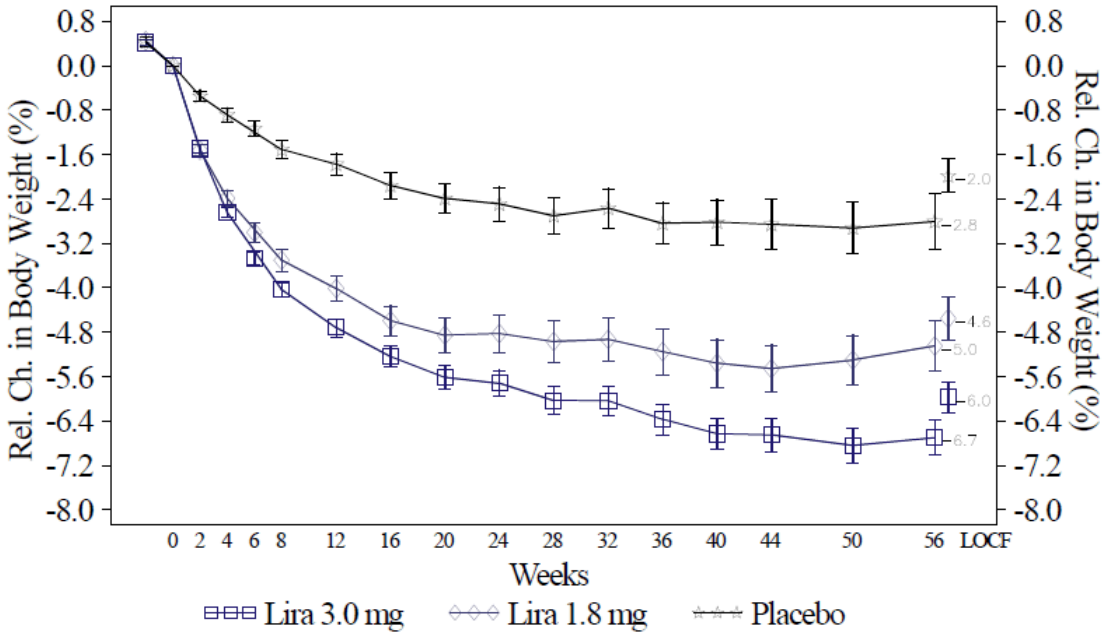
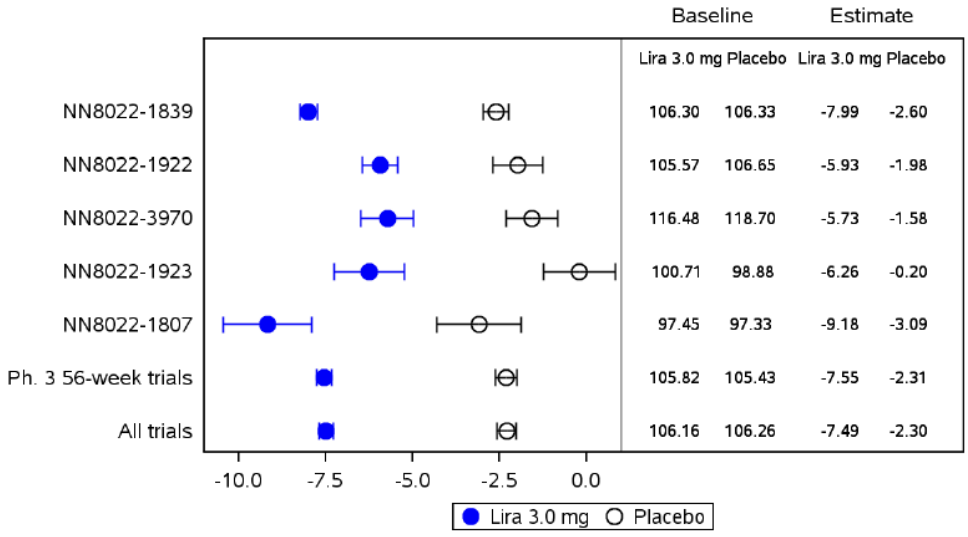


Figure 8: Body weight (%) change from baseline observed mean including LOCF at end of trial 1922- full analysis set.
Source: Sponsor Integrated summary of efficacy. Appendix 6.3, Figure 158; page 294 of 1254.

Trial 1839 was designed to demonstrate superior weight loss of liraglutide as compared to placebo over 56 weeks. After 56 weeks, liraglutide 3.0 mg treatment produced a significantly greater reduction in body weight than placebo treatment. Mean change from baseline in body weight for subjects achieving ≥5% weight loss at end of treatment was -11.7% for liraglutide 3.0-treated subjects (N=1536) versus -9.97% for placebo (N=331).

The change from baseline in body weight (%) for this trial along with the other trials that evaluated 3.0 mg dose is shown in Figure 9. Treatment with liraglutide 3.0 mg led to a mean weight loss of 5.7-9.2% (6.0-8.8 kg) depending on the trial, with the highest weight loss achieved in the 104- week trial (trial 1807) and the lowest in the 32-week trial (trial 3970). Placebo treated subjects achieved a weight loss of 0.2-3.1% (0.2-3.0 kg). In the pooled analyses of all trials, the change from baseline in body weight was 7.5% (7.8 kg) with liraglutide 3.0 mg as compared to 2.3% (2.5 kg) with placebo (Figure 9).



Data are LS means with 95% CI for the FAS with LOCF.

Figure 9: Body weight (%) mean change from baseline − individual trials and pooled

Source: Sponsor Summary of clinical efficacy. Figure 3-2, page 72 of 138.

Thus, as shown by the above trial results, liraglutide 3.0 mg demonstrated effectiveness in terms of achieving weight loss as compared to placebo and other lower liraglutide doses. Refer to statistical review for Agency's analysis of efficacy.

Exposure-Response for weight loss:

The exposure-response relationship provides supportive evidence for the effectiveness of the liraglutide 3.0 mg dose. Consistent with the observed dose-response relationship, there was a clear relationship between liraglutide exposure and weight loss in all three trials where increasing exposure lead to greater weight loss (Figure 10). There was overlap between exposures achieved at 1.8 mg and 3.0 mg dose, however there was incremental benefit with the 3.0 mg dose. The weight loss appeared to reach plateau at the highest exposure. Exposure-response relationship was similar among the three trials, 1807, 1839 and 1922.

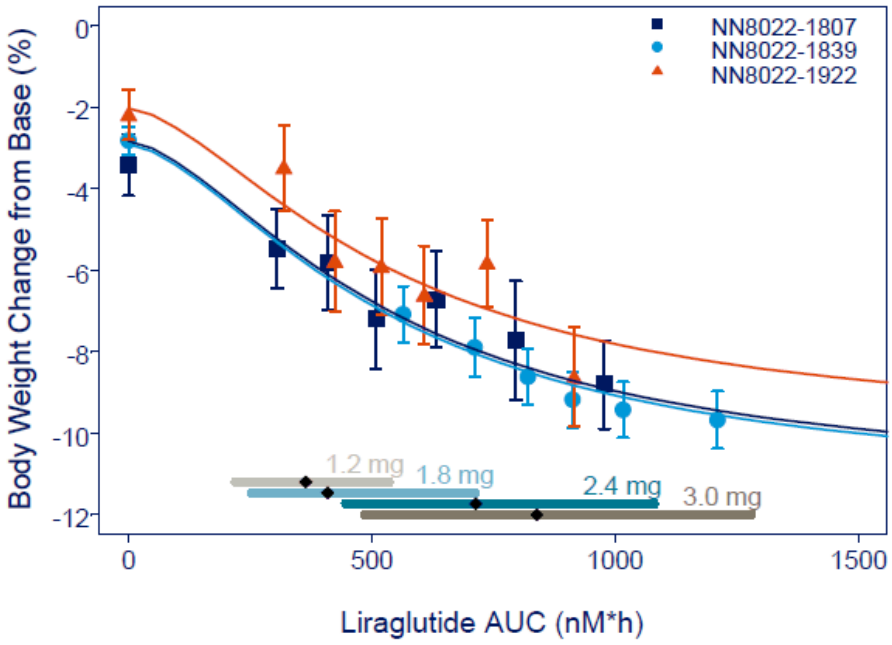


Figure 10: Body weight change from baseline versus exposure of liraglutide expressed as model-derived AUC at steady-state in trials 1807, 1839 and 1922.

Data are mean values with 95%CI versus exposure expressed as six quantiles of AUC values (plus placebo at AUC of 0 nM*h). Non-linear lines represent covariate-adjusted model-based estimates for each trial population. Horizontal lines with diamonds represent median and 90% exposure ranges from each dose level.

Source: Sponsor, modelling study report, page 43.

The body weight response versus liraglutide exposure was described by an E_{max} model with the assumption of identical EC_{50} values in the three trials. The common EC_{50} value for the three trials was estimated at 546±148 nM*h, corresponding to an average liraglutide concentration (C_{avg}) of approximately 24±6 nM. The C_{avg} obtained from population PK analysis (data from trials 1839 and 1922) following administration of liraglutide 3 mg was 35 nM, which is higher than the EC_{50} value, indicating that the average concentrations achieved are in the maximal response region of the exposure-response relationship. The model-derived value of E_{max} was 8.91% change from baseline in body weight for a reference subject (a normoglycemic female subject below 70 years with a baseline body weight of 100 kg).

The sponsor also analyzed the relationship between change in body weight and liraglutide exposure to determine the proportions of subjects reaching a weight loss of at least 5% change from baseline. Similar to the above exposure-response relationship, the proportion of subjects reaching at least 5% weight loss increased with increasing liraglutide exposure (Figure 11).

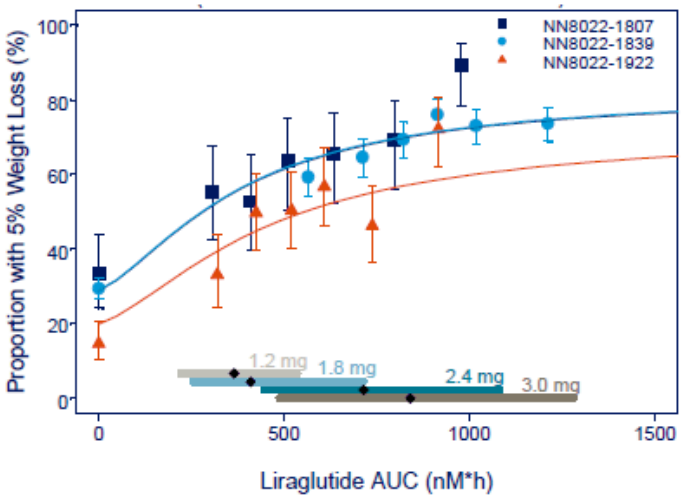


Figure 11: Observed and predicted proportions of subjects reaching at least 5 % weight loss versus liraglutide exposure in trials 1807, 1839 and 1922.

Data are mean proportions with 95%CI versus exposure expressed as quantiles of model-derived AUC values plus placebo (at AUC of 0 nM*h). Non-linear lines represent covariate-adjusted model-based estimates for each trial population. The vertical lines with diamonds along the abscissa represent medians and 90% exposure ranges from each dose level.

Source: Sponsor modelling report, page 45.

2.3.2 What is the dose/exposure-response relationship for HbA1c?

Liraglutide is approved for the treatment of T2DM at a maximum dose of 1.8 mg. Trial 1922 tested the effect of liraglutide 1.8 mg and 3.0 mg in overweight and obese subjects with T2DM. The time course for change in HbA1c from baseline is shown in Figure 12. As expected, liraglutide groups showed more reduction than placebo. The LS mean estimate for change in HbA1c from baseline was -1.32%, -1.13% and -0.38%, respectively for liraglutide 3.0 mg, 1.8 mg and placebo. The estimated treatment difference between liraglutide 3.0 mg and placebo was -0.9%.

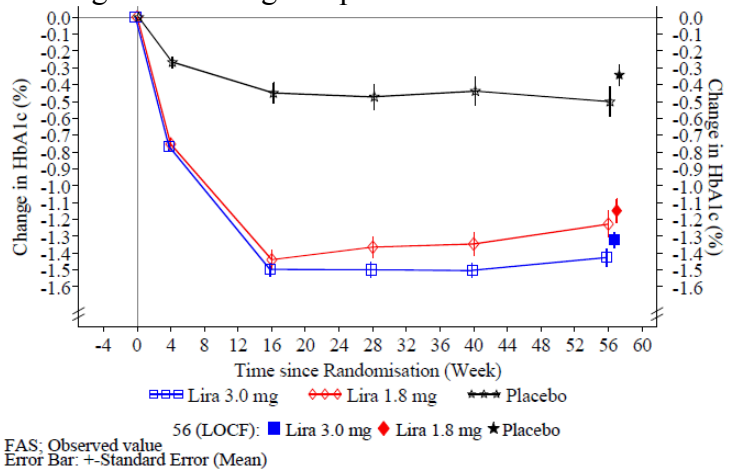


Figure 12: Change from baseline in HbA1c (%) by treatment.

Source: Sponsor study report study 1922, Figure 11-6, page 154

Exposure-response relationship for HbA1c is shown in Figure 13. As shown, there is overlap of concentrations from 1.8 mg and 3.0 mg, and there appears to be no incremental benefit beyond AUC of 500 nM*h. The observed relationship is similar to

that previously seen with T2DM program. When the exposure-response relationship was further stratified by baseline HbA1c, the patients with higher baseline HbA1c seem to have a higher response (Figure 13 (right panel)).

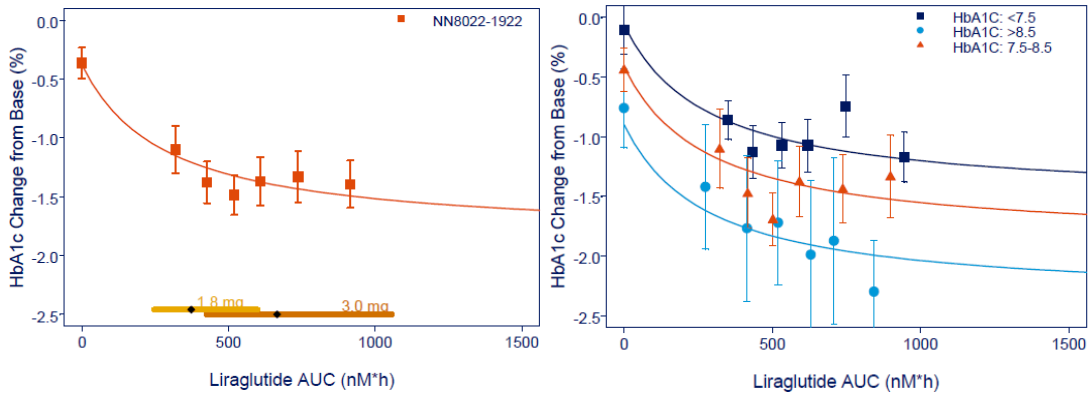


Figure 13: HbA1c change from baseline versus exposure of liraglutide expressed as model derived AUC at steady-state in obese subjects with type 2 diabetes (trial 1922) (Left panel) and stratified by baseline HbA1c (Right panel).

Data are mean values with 95%CI versus exposure expressed as six quantiles of AUC values (plus placebo at AUC of 0 nM*h). The line overlaying the data represents the covariate-adjusted model-based estimate for the trial population. Horizontal lines with diamonds represent median and 90% exposure ranges from each dose level (Left). The lines overlaying the data represent the covariate-adjusted model-based estimates for the three subgroups of baseline HbA1c (Right).

2.3.3 Is there a relationship between baseline body weight and efficacy that would warrant a dose-adjustment?

No, there was no correlation of efficacy with baseline body weight.

Body weight is a significant predictor of liraglutide clearance (see section 2.4.1). Therefore, some obese subjects with lower body weight may have an increased exposure with liraglutide 3.0 mg. In order to understand, whether increased liraglutide exposure due to differences in body weight correlates to efficacy, the Agency requested the sponsor to conduct efficacy analysis based on baseline body weight.

The effect of liraglutide 3.0 mg on the primary efficacy endpoints – percent change from baseline in body weight and proportion of patients achieving ≥ 5% weight loss after 1 year was consistent across baseline body weight quartiles for both men and women. Females in general had greater efficacy as compared to males (Table 3). To note is that the second weight quartile in men did not meet the criteria in terms of percent change from baseline (-6.05% in liraglutide arm vs. -3.35% in placebo) as well as for the categorical analysis (52.9% in liraglutide vs. 29.5% in placebo) (Table 4). However, this observation should be interpreted with caution as there may be other confounding factors and this analysis was not pre-specified.

The body weight quartiles used were as follows:
Males: Quartile 1 ≤102.1 Kg; Quartile 2 >102.1 to ≤ 114.4 Kg; Quartile 3 >114.4 to ≤ 130.8 Kg; and Quartile 4 >130.8 kg

Females: Quartile 1 ≤ 88.3 Kg; Quartile 2 >88.3 to ≤ 98.6 Kg; Quartile 3 >98.6 to ≤ 111.7 Kg; and Quartile 4 >111.7 Kg

Table 3: Fasting body weight (%) change from baseline until end of trial: Treatment effects stratified by gender and baseline body weight (pooled data set 1807, 1922 and 1839)

				Males				Females	
LS Means		FAS	N	Baseline BW(Kg)	Estimate	FAS	N	Baseline BW (Kg)	Estimate
1st Baseline Body Wt Quartile	Lira 3.0	202	202	93 28	-5 58	554	552	81 39	-9 02
	Placebo	85	85	93 66	-2 65	278	277	80 97	-2 4
	Trt Diff				-3 02				-6 63
2nd Baseline Body Wt Quartile	Lira 3.0	189	189	108 18	-6 05	521	519	93 67	-8 11
	Placebo	102	102	108 46	-3 35	311	308	93 41	-2 32
	Trt Diff				-2 76				-6 01
3rd Baseline Body Wt Quartile	Lira 3.0	188	188	122 42	-6 65	546	542	104 71	-8 21
	Placebo	100	98	121 86	-2 64	281	280	104 48	-2 24
	Trt Diff				-3 8				-5 9
4th Baseline Body Wt Quartile	Lira 3.0	183	183	150 82	-6 21	558	557	126 41	-7 89
	Placebo	103	103	150 25	-2 29	274	271	126 87	-3 09
	Trt Diff				-3 83				-4 78

Source: Table generated from sponsor's data provided in response to FDA request dated June 10, 2014

Table 4: Proportion of patients losing at least 5% baseline body weight stratified by gender and baseline body weight (pooled data set 1807, 1922 and 1839)

			Males				Females
LS Means		FAS	N	Estimate	FAS	N	Estimate
1st Baseline Body Wt Quartile	Lira 3.0	202	202	50.50%	554	552	69.40%
	Placebo	85	85	21.10%	278	277	24.50%
	Trt odds ratio			3.24			7.14
2nd Baseline Body Wt Quartile	Lira 3.0	189	189	55.30%	521	519	64.20%
	Placebo	102	102	29.50%	311	308	22.90%
	Trt odds ratio			3.15			6.43
3rd Baseline Body Wt Quartile	Lira 3.0	188	188	52.90%	546	542	67.60%
	Placebo	100	98	24.80%	281	280	22.10%
	Trt odds ratio			3.06			7.15
4th Baseline Body Wt Quartile	Lira 3.0	183	183	50.40%	558	557	61.20%
	Placebo	103	103	21.50%	274	271	29.00%
	Trt odds ratio			3.48			3.74

Source: Table generated from sponsor's data provided in response to FDA request dated June 10, 2014

Therefore, based on the observed efficacy results, there appears to be no need for a different dosing regimen for lower body weight patients.

2.3.4 Does the dose-response or exposure-response data support the safety of the proposed 3.0 mg daily dose for liraglutide?

Yes, both the dose-response and exposure response data support the 3 mg dose from a clinical pharmacology perspective.

From previous experience with Victoza and other GLP-1 agonists, certain adverse events were of special interest, for example, pancreatitis, gallbladder disorders, neoplasms, thyroid disease, acute renal failure, allergic reactions, injection site reactions, cardiovascular disorders, and psychiatric disorders. For detailed review on these safety issues, please see clinical review. This review will focus on whether there were any exposure-response relationships for some of these adverse events of interest.

At the request of the FDA, the sponsor conducted time to event and exposure-response analysis for gastrointestinal (GI) adverse events (such as nausea and vomiting) and hypoglycemia. The analysis was done using data from trials 1807, 1922 and 1839 individually and then pooled. The patients included for the exposure-response analyses were those with a concentration value during maintenance treatment. The multivariate analyses for nausea and vomiting included covariates: gender, baseline body weight, and the pre-diabetes status at screening. The pooled analyses also include trial as a covariate. In trial 1922 all patients had diabetes thus the inclusion of pre-diabetes status in the model had no impact.

Nausea and vomiting: The results showed that there was a relationship between plasma exposure and nausea (any grade, any time). However, there was no clear relationship for moderate-severe nausea events (Figures 14 and 15). Similarly, there was a relationship with vomiting at any time and any grade but not for moderate-severe events (Figures 16 and 17). Time to event analysis did not indicate any relationship between exposure and an increased risk of events over time. Most of the nausea and vomiting events were of mild category and occurred early, within the first three months of treatment.

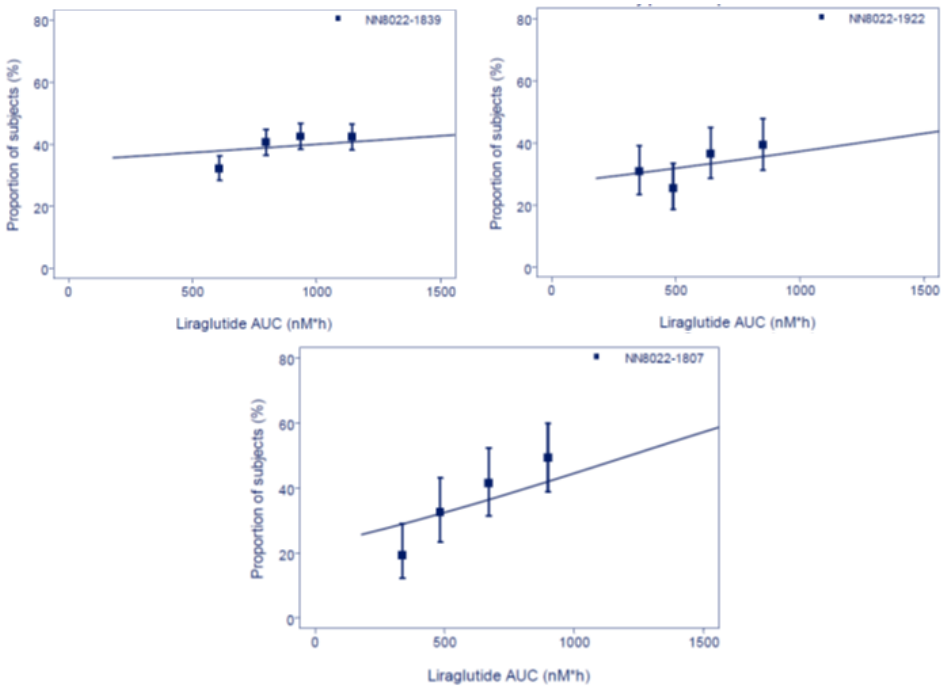


Figure 14: Observed proportion of subjects with nausea at any time at any grade versus liraglutide exposure in trials 1839, 1922 and 1807, respectively

Data are proportions with 95% CI versus exposure expressed as quantiles of model-derived AUC values. Line represents the multivariate regression line based on subject level data.

Source: Response to FDA request, Figure 1-3, page 14-16.

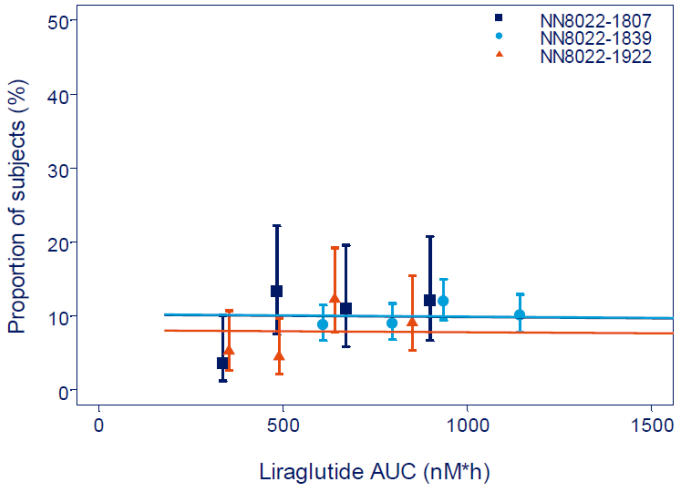


Figure 15: Observed proportion of subjects with moderate to severe nausea at any time versus liraglutide exposure in trials 1839, 1922, and 1807

Data are observed proportions with 95%CI versus exposure expressed as quantiles of model-derived AUC values. Lines represent the multivariate regression lines based on subject level data for the pooled analysis, colored for each trial population.

Source: Response to FDA request, Figure 8, page 21.

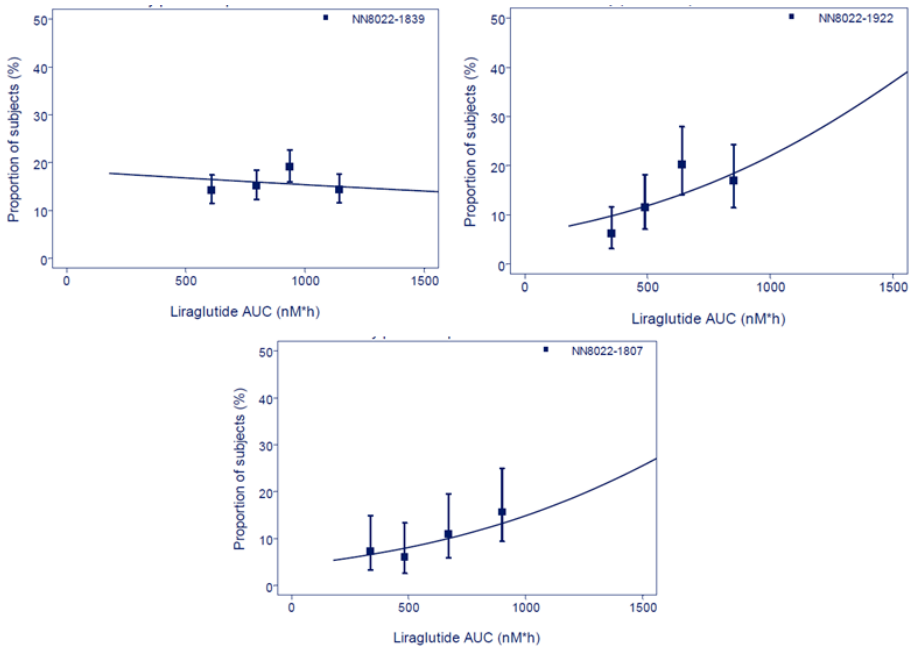


Figure 16: Observed proportion of subjects with vomiting at any time at any grade versus liraglutide exposure in trials 1839, 1922, and 1807

Data are proportions with 95%CI versus exposure expressed as quantiles of model-derived AUC values. Line represents the multivariate regression line based on subject level data.

Source: Response to FDA request, Figure 9-11, page 22-24.

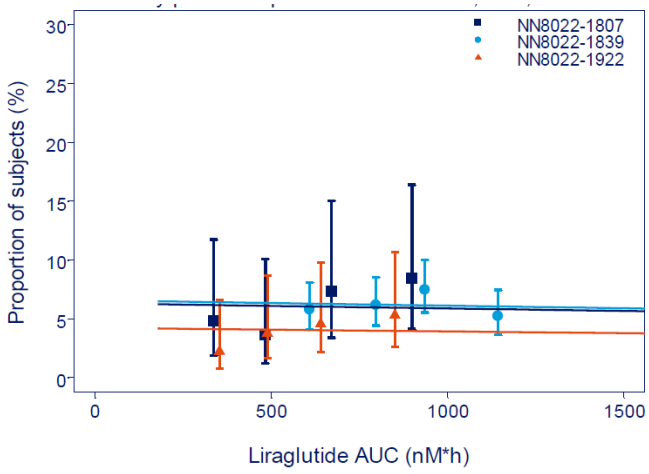


Figure 17: Observed proportion of subjects with moderate to severe vomiting at any time versus liraglutide exposure in trials 1839, 1922, and 1807

Data are observed proportions with 95%CI versus exposure expressed as quantiles of model-derived AUC values. Lines represent the multivariate regression lines based on subject level data for the pooled analysis, colored for each trial population.

Source: Response to FDA request, Figure 16, page 29.

Hypoglycemia: Exposure-response for hypoglycemia was conducted for trial 1922 (obese patients with T2DM). Sponsor conducted analysis using hypoglycemia defined using ADA classification as well as their own definition. The multivariate analysis for

hypoglycemia included gender, baseline body weight and the use of sulfonylureas. There was a flat exposure-response relationship with no specific trends for the proportion of subjects with hypoglycemia and exposure. Patients who were on sulfonylureas had more events as can be expected with these agents (Figure 18). There were five patients with severe hypoglycemia and all these patients were on sulfonylureas. There was no trend based on the liraglutide exposure in these patients with exposures being similar to those who didn't experience hypoglycemia (Table 5).

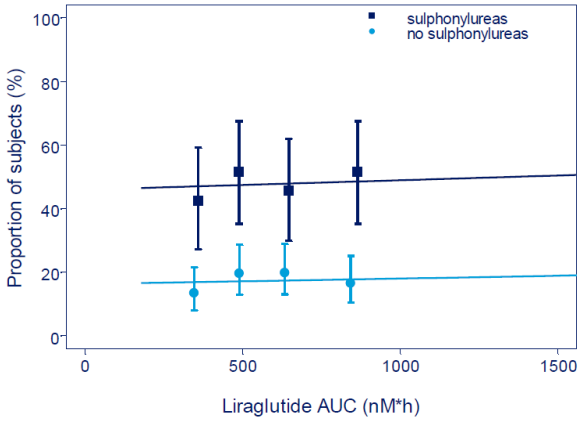


Figure 18: Observed proportion of subjects with a documented symptomatic hypoglycemia event (ADA classification) at any time versus liraglutide exposure in trial 1922

Data are observed proportions with 95%CI versus exposure expressed as quantiles of model-derived AUC values. Line represents the multivariate regression line based on subject level data.

Source: Figure 18, page31

Table 5: Exposure data for subjects with severe hypoglycemia

ID	***Trial***	***Dose***	***AUC (nM.h)***
702008	*1922*	*3.0*	*935.84*
705006	*1922*	*3.0*	*961.40*
920003	*1922*	*1.8*	*303.69*
931011	*1922*	*1.8*	*476.05*
933002			*No exposure data*
941001	*1922*	*3.0*	*438.85*

Calcitonin and other selected adverse events: Calcitonin levels from the three trials did not demonstrate any trend in elevation with liraglutide treatment. Figure 19 shows the calcitonin change from baseline for liraglutide and placebo. The change from baseline in calcitonin levels were close to zero and did not change with increase in exposure.

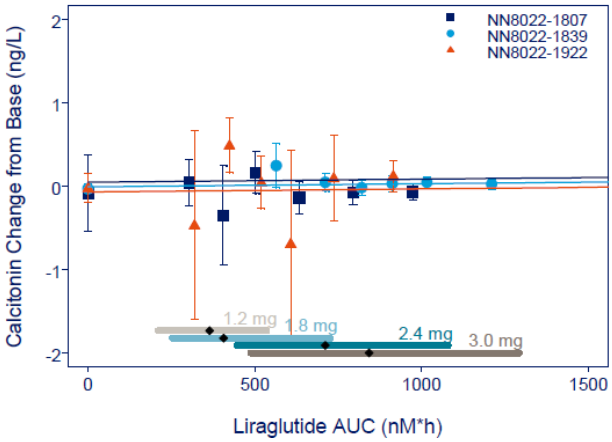


Figure 19: Calcitonin change from baseline versus exposure of liraglutide expressed as model derived AUC at steady-state in trials 1807, 1839 and 1922.

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

Source: Sponsor modelling report, page 55

Further, the relationship of liraglutide exposure and occurrence of adverse events such as pancreatitis and hepatobiliary disorders was investigated and did not reveal any correlation with liraglutide exposure.

2.3.4 Is there a relationship between body weight and safety that would warrant a dose-adjustment?

No. There does not appear to be any differences in the adverse event profile in the different body weight quartiles in both men and women treated with liraglutide 3.0 mg dose. Therefore, no dose adjustment based on body weight is warranted.

Body weight is the significant predictor of liraglutide clearance (see section 2.4.1). Therefore, some obese subjects with lower body weight may have an increased exposure with liraglutide 3.0 mg. In order to understand, whether increased liraglutide exposure due to differences in body weight of patients translates to greater number of adverse events, the Agency requested the sponsor to conduct safety analysis based on baseline body weight.

As expected, administration of liraglutide increased the gastrointestinal adverse events as compared to placebo. However, the proportion of patients experiencing the adverse events (focusing on GI events like nausea, vomiting) was similar across different body weight quartiles (Table 6). In general, adverse events were more in females as compared to males regardless of treatment group (liraglutide or placebo) (Tables 6 and 7). In the trial 1922, there was no pattern across baseline body weight quartiles for hypoglycemia.

Table 6: Proportion of patients (%) experiencing adverse events following administration of liraglutide 3.0 mg stratified by body weight quartiles and gender (pooled data set 1807, 1922 and 1839)

	Body weight Q1		**Body Weight Q2**		**Body Weight Q3**		**Body Weight Q4**	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number of subjects	206	567	190	527	191	564	186	565
Nausea (%)	29.6	40	35.8	47.1	23.6	44.9	23.1	41.8
Nausea (moderate-severe) (%)	8.3	12.2	8.9	13.5	5.2	13.1	4.8	13.1
Vomiting (%)	11.7	15	11.1	18.8	12	17.4	14.5	18.6
Vomiting (moderate-severe) (%)	5.8	6.3	4.7	8	6.3	9	4.8	7.1

The body weight quartiles used were as follows:
Males: Quartile 1 ≤102.1 Kg; Quartile 2 >102.1 to ≤ 114.4 Kg; Quartile 3 >114.4 to ≤ 130.8 Kg; and Quartile 4 >130.8 kg
Females: Quartile 1 ≤ 88.3 Kg; Quartile 2 >88.3 to ≤ 98.6 Kg; Quartile 3 >98.6 to ≤ 111.7 Kg; and Quartile 4 >111.7 Kg

Source: Table generated from sponsor's data provided in response to FDA request dated June 10, 2014

Table 7: Proportion of patients (%) experiencing adverse events following administration of placebo stratified by body weight quartiles and gender (pooled data set 1807, 1922 and 1839)

	Body weight Q1		**Body Weight Q2**		**Body Weight Q3**		**Body Weight Q4**	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number of subjects	87	284	102	314	100	283	104	278
Nausea (%)	14.9	15.1	3.9	13.1	7	17	12.5	18
Nausea (moderate-severe) (%)	2.3	2.8	0	2.2	1	3.9	2.9	4.3
Vomiting (%)	3.4	6	2	4.8	2	3.5	3.8	4.3
Vomiting (moderate-severe) (%)	3.4	2.8	0	2.5	0	1.4	1	1.8

The body weight quartiles used were as follows:
Males: Quartile 1 ≤102.1 Kg; Quartile 2 >102.1 to ≤ 114.4 Kg; Quartile 3 >114.4 to ≤ 130.8 Kg; and Quartile 4 >130.8 kg

Females: Quartile 1 ≤ 88.3 Kg; Quartile 2 >88.3 to ≤ 98.6 Kg; Quartile 3 >98.6 to ≤ 111.7 Kg; and Quartile 4 >111.7 Kg

Source: Table generated from sponsor's data provided in response to FDA request dated June 10, 2014

Therefore, there is no need for a different dosing regimen for lower body weight patients based on the observed adverse events profile.

2.3.5 Is there any correlation of adverse events with the magnitude of weight loss experienced and is there a time-dependency for occurrence of these adverse events?

No. There is no correlation of adverse events with the magnitude of weight loss experienced. Further, the adverse events did not increase over time and therefore, there is no need to adjust dosing during treatment with liraglutide.

Body weight is the significant covariate affecting liraglutide clearance (see section 2.4.1). There is a potential concern that in patients experiencing significant weight loss, the liraglutide exposure may increase leading to an increase in adverse events. At the request of the Agency, sponsor conducted an analysis by dividing the patient's weight loss into four groups and comparing their adverse events profile. The most common adverse events occurring in ≥ 5% of the total population were analyzed by weight loss categories in individual trials and pooled (1807, 1839 and 1922). The adverse events were also evaluated over time, 0-3, 3-6, 6-9 and 9-12 months to see if there is any change in occurrence with increase in treatment duration.

Overall, the adverse events were similar across the different weight loss groups. Table 8 shows the % of patients experiencing any adverse events and adverse events of interest (GI related) for liraglutide 3.0 mg dose and placebo groups. As expected the GI adverse events were higher for the liraglutide group as compared to placebo, however there was no trend with respect to events among the different weight loss categories (Table 8).

Table 8: Percent of patients experiencing adverse events by weight loss groups for treatment groups- liraglutide 3.0 mg (Lira) and placebo (PL)

	Weight loss category 1		**Weight loss category 2**		**Weight loss category 3**		**Weight loss category 4**	
Treatment	**Lira**	**PL**	**Lira**	**PL**	**Lira**	**PL**	**Lira**	**PL**
Number of Subjects	735	384	735	383	735	383	735	383
Total AE (%)	77.7	69.3	80.1	63.4	77.3	59	72.8	60.6
GI Disorders (%)	61.2	34.6	61.5	33.2	59	24	57.8	27.2
GI signs & symptoms (%)	49.7	19.5	50.2	19.8	45	14.4	46.5	19.1
Nausea (%)	41.8	14.1	41	17.5	37.4	11.5	37.3	14.1
Vomiting (%)	14.4	4.2	19	6.0	15	2.3	16.2	4.4

Weight loss category (%): category 1: Weight loss (WL) <= -11.4, category 2: -11.4 < WL <= -6.8, category 3: -6.8 < WL <= -3.0, category 4: -3.0

When the adverse events occurrence over time was evaluated, the adverse events profiles for the four weight loss categories was similar among the time periods, 0-3, 3-6, 6-9 and 9-12 months of treatment (Figure 20). Further, the events in each weight loss category were highest initially (0-3 months) and decreased in 3-6 months and did not change further in the remaining treatment duration through one year (Figure 20).

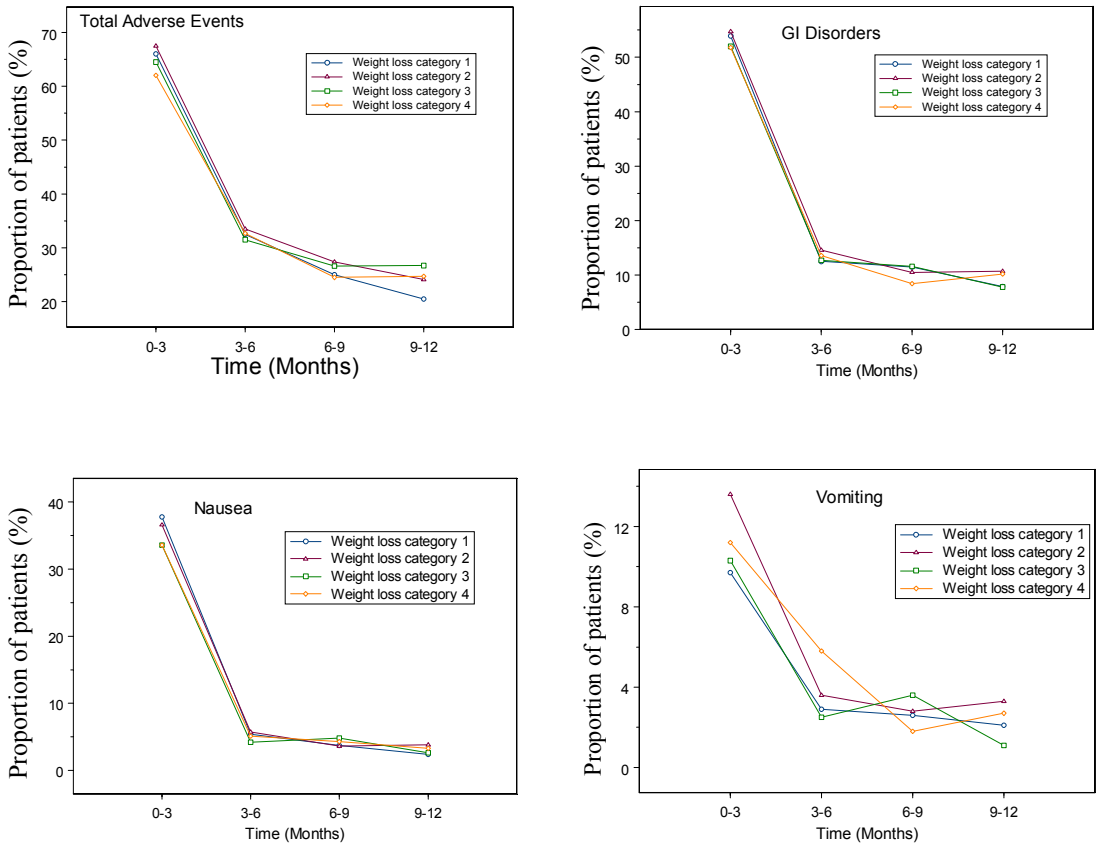


Figure 20: Percent of patients with adverse events over the treatment duration (0-3, 3-6, 6-9 and 9-12 months): Total adverse events (Top left); GI disorders (Top right); Nausea (Bottom left); and Vomiting (Bottom right)

Overall, it appears that there is no need to change the dosing regimen for patients who experience significant weight loss.

2.4 Intrinsic Factors

2.4.1 What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

A population PK analysis was conducted by the sponsor using data from trials 1839 and 1922. The effect of various covariates on liraglutide PK was determined.

Body weight: Among all the covariates that were evaluated, baseline body weight was the most significant covariate affecting the clearance of liraglutide. Liraglutide clearance increased with increasing body weight (Figure 21). The typical value for the apparent

clearance (CL/F) identified from the population PK analysis ranged from 0.86 L/h to 1.35L/h.

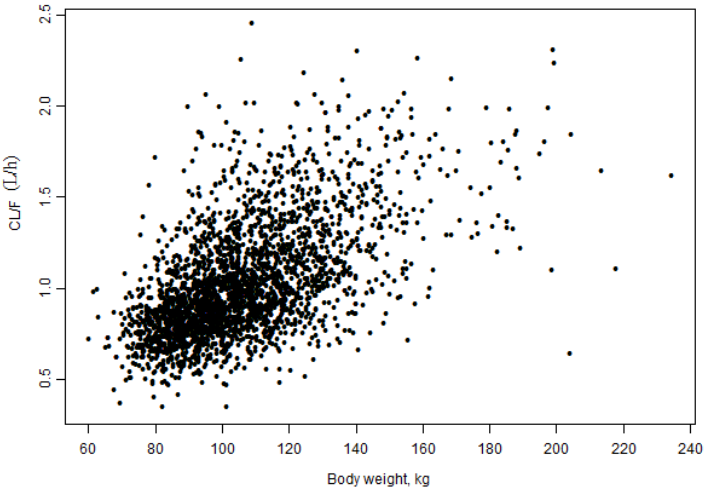


Figure 21: Correlation of liraglutide clearance (L/h) to body weight in Obesity trials.

Gender: The estimated exposure of liraglutide was 24% lower in males as compared to females due to higher liraglutide clearance in males. This effect of gender on exposure is observed after accounting for body weight differences. Males were in general heavier than females and both body weight and gender contribute towards the lower exposure in males than in females. However, no dose-adjustment is warranted based on gender.

Glycemic status: The effect of glycemic categories was evaluated in the population PK using categories- healthy, pre-diabetic and diabetic. Patients with diabetes were found to have 16% lower exposure than the other categories. All diabetes patients were from one trial, 1922 while normal and prediabetic status patients were from trial 1839. No dose adjustment is recommended based on glycemic status. The relationship between liraglutide exposure, body weight and glycemic status is shown in Figure 22.

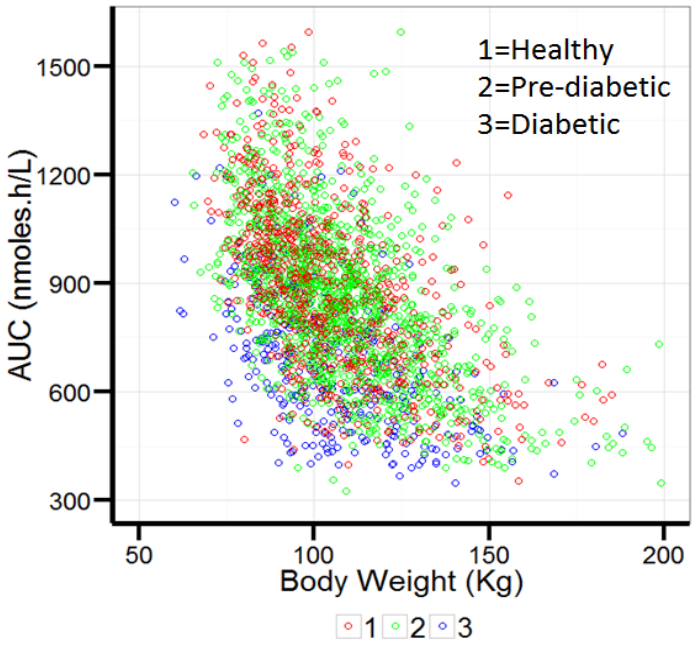
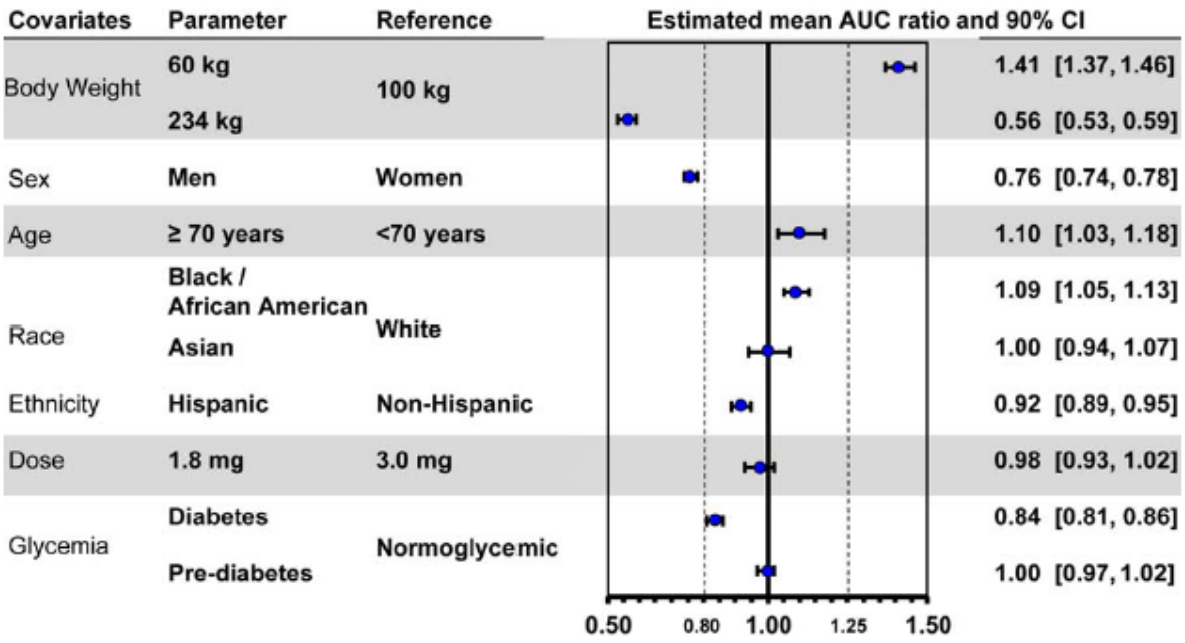


Figure 22: Estimated liraglutide exposure following administration of 3.0 mg dose versus body weight stratified by glycemic status

Age, race, and BMI: There was no effect of covariates such as age, race and BMI on liraglutide clearance.

The results of the covariate analysis were summarized as means and 90% confidence intervals for the steady-state of liraglutide $AUC_{0\text{-}24h}$ for each covariate relative to the reference subjects. The reference subject was selected to be a White, not Hispanic or Latino, female subject below 70 years of age and with a body weight of 100 Kg without diabetes or pre-diabetes dosed with liraglutide 3.0 mg (Figure 23). There was about 44% lower exposure for a subject weighing 234 kg (the maximum baseline body weight in the population PK analysis) relative to a subject with a reference body weight of 100 kg. Likewise, the exposure was 41% higher for a subject weighing 60 kg (the lowest baseline body weight) relative to a subject at the reference weight (Figure 23). Inclusion of the covariates for clearance (CL/F) in the population PK model resulted in a reduction of between subject variability for CL/F from 34.8% to 24.7% CV.



The values to the right (together with the symbols) show geometric mean exposures (AUC ratio) and 90% CI. Exposures are dose-normalized (AUC_{0-24h}/dose) and relative to the reference. Dotted lines indicate the bioequivalence limits (0.8–1.25). 60 kg and 234 kg are the lowest and highest observed body weights in trials 1839 and 1922. AUC: area under the curve. CI: confidence interval.

Figure 23: Covariate analysis expressed as steady-state dose-normalized exposure (AUC0-24h/dose) relative to reference from the Population PK

Source: Sponsor AC briefing document: Figure 4-3, Page 45

2.5 Extrinsic Factors

Drug-Drug Interactions

2.5.1 What is the effect of liraglutide on the pharmacokinetics of other co-administered drugs?

Effect on gastric emptying: Liraglutide doses of up to 1.8 mg have been demonstrated to cause some delays in the postprandial rates of gastric emptying in healthy and type 2 diabetic subjects. Gastric emptying was the primary endpoint in trial 3630 and was assessed by the paracetamol (acetaminophen) absorption method during a 5-hour standardized meal test (post prandial paracetamol area under the curve from time 0 to 300 min [$AUC_{0-300min}$] following intake of 1.5 g paracetamol. Paracetamol was administered at 13 h post-dose, in order to correspond with the T_{max} of liraglutide at steady-state.

At early time points (first 90 minutes), both liraglutide treatments resulted in slightly lower paracetamol concentration compared to placebo. The postprandial paracetamol plasma concentrations reached maximum levels at approximately 120 minutes in all groups with placebo group having the highest concentration and lowest in the 1.8 mg liraglutide group (Figure 24). However, at the end of the 5-hour period, all three

treatment groups had similar plasma paracetamol concentrations. Secondary endpoint such as $AUC_{0\text{-}60min}$ was reduced by 13% and 23% by liraglutide 1.8 mg and 3.0 mg doses, respectively compared to placebo. C_{max} was lower with liraglutide 1.8 mg as compared to placebo (Figure 24).

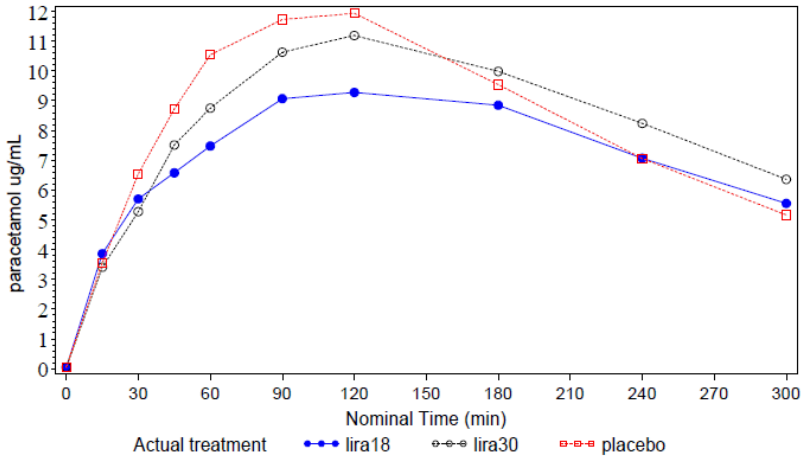


Figure 24: Mean postprandial paracetamol concentration time profiles following liraglutide (1.8 mg and 3.0 mg) and placebo

Source: Study report 3630, Figure 11-1, page 87.

The ratio of paracetamol $AUC_{0\text{-}300min}$ between liraglutide 1.8 and 3.0 mg was 1.03 and since the 90% confidence interval (CI) for the estimated ratio ([0.92 ; 1.15]) was fully contained within the pre-specified interval (0.80, 1.25), equivalence was demonstrated between the 2 groups. Therefore, it appears that the overall effect on gastric emptying is similar between the two dose groups. Equivalence was also observed between placebo and the two liraglutide doses.

To note is that the magnitude of interaction with paracetamol is lower in this study as compared to that conducted previously for the T2DM program. For example paracetamol C_{max} in study 3630 was 10% lower with 1.8 mg liraglutide as compared to 31% lower in the previous study. One potential reason could be that at the time of paracetamol administration, liraglutide concentrations were not at its C_{max}. Paracetamol was administered at 13 h post-liraglutide dose, while the median liraglutide T_{max} for 1.8 mg was 11.19 h and 11.25 h for 3.0 mg, respectively in this study. However, similar to the previous study overall AUC of paracetamol was not affected by liraglutide. The effect of 3.0 mg liraglutide was similar to that seen with 1.8 mg dose with respect to overall absorption of paracetamol.

Liraglutide is not expected to cause any drug-drug interactions related to inhibition or induction of cytochrome P450s as concluded in the review of Victoza NDA. The potential of drug interactions with liraglutide is via its effect on the gastric motility. Hence, sponsor's proposal to bridge the drug interaction information for the 3.0 mg dose with previously conducted studies using 1.8 mg dose is acceptable.

2.6 Analytical

Refer to the bioanalytical method of liraglutide in the review conducted for NDA 22-341. During the weight management development program, the bioanalysis of liraglutide from trials 3630, 1839 and 1922 was transferred to another laboratory ((b) (4) .) and the method validation by this new laboratory was submitted to the current NDA. Samples from the Phase 2 trial 1807, was analyzed using the method and validation process as described previously under NDA 22-341. The lower limit of quantitation (LLOQ) for this was 18 pM.

Liraglutide in plasma was analyzed using a liraglutide specific enzyme-linked immunosorbent assay (ELISA) that measured both protein-bound and unbound liraglutide. The ELISA was a sandwich immunoassay with two monoclonal antibodies directed against different epitopes on liraglutide. The capture antibody, coated on the microtitre plate, was directed against the N-terminal part of the amino acid chain. The detection antibody, labelled with biotin, was directed against the C-terminal part. Cross-reactivity with endogenous glucagon-like peptide-1 (GLP-1) was eliminated by degradation of endogenous GLP-1 by pre-incubation of the plasma sample for 4 hours at 37°C prior to analysis. Liraglutide was shown to remain intact at these conditions.

The assay was validated with two different curve ranges (30-4500 pM and 30-2000 pM). The ELISA was found to be as per the bioanalytical guidance regarding recovery, accuracy, precision, sensitivity and stability (Tables 9 and 10).

Table 9: ELISA assay validation parameters

Validation parameter	Summary of findings
Validated calibration range	10 pM to 4500 pM
Lower limit of quantification	30 pM
Upper limit of quantification	4500 pM
Intra-assay precision	2.1% to 11.5%
Intra-assay accuracy	-4.8% to 9.8%.
Inter-assay precision	5.3% to 16.7%
Inter-assay accuracy	2.4% to 17.5%
Mean recovery	94.6% (CV 10.7%)
Prozone	No hook effect observed up to 4500000 pM
Linearity of dilution	Up to 1 in 64000
Biological matrix stability	Up to 4 hours at room temperature (*ca* 22°C)
Freeze-thaw stability	Up to 5 freeze-thaw cycles
Long term stability	Up to 1 month at *ca* -20°C
Secondary std stability	Up to 3 months at *ca* -20°C
Sample acceptance criteria	± 20% variation from mean of 2 replicates
Standard curve acceptance criteria	The back-calculated value for each standard should be within ±20% of the theoretical concentration (± 25% at the limits of quantification). 75%, or a minimum of six concentration levels in the range 20.00 to 4500 pM, should meet these criteria. Standards not meeting these criteria can be excluded from the curve. No acceptance criteria for anchor points (10.00 pM)
Assay acceptance criteria	± 20% for precision and accuracy for 4 out of 6 QC samples

Source: Study report JLY0195, page 9

Table 10: ELISA assay validation parameters for second curve:

Validated standard curve range:	20.00 pM to 2000 pM - 20.00 pM anchoring point
Lower limit of quantification (LLOQ):	30 pM
Upper limit of quantification (ULOQ):	2000 pM
Inter-assay precision (CV):	8.2% - 9.4%
Inter-assay accuracy (RE):	-12.7% - -3.5 %
Inter-assay total error of measurement (TE):	12.9% - 21.0%
Intra-assay precision (CV):	0.9% – 12.9%
Intra-assay accuracy (RE):	-19.1% - 14.1%
Intra-assay total error of measurement (TE):	2.2% – 27.7%
Minimum required dilution (MRD)[a]:	Neat
Maximum validated dilution[a]:	1 in 64000
Acceptance criteria:	±20% for precision and accuracy for four out of six QC samples with at least one valid QC at each level ±20% accuracy (±25% at 30 pM and 2000 pM). No criteria on 20 pM anchor point. Up to 4 standard points (25%) in the range 30 pM to 2000 pM can be removed if outside criteria. (i.e. individual replicates)

[a] Validated in JLY0195

Source: Study report JLY0364, page 10.

3 Detailed labeling recommendation

- The language in the following sections is identical to that of the approved Victoza package insert and is acceptable.

  Highlights- Drug Interactions
  Highlights-Use in Specific Populations

  Section 7- Drug Interactions

  Section 8.6 – Renal Impairment
  Section 8.7 – Hepatic Impairment

  Section 12.3 – Renal Impairment, Hepatic Impairment, Pediatric, Drug Interactions

- Sponsor's proposed language is acceptable for the following sections

  Section 12.3 Pharmacokinetics

Distribution
Metabolism
Elimination
Specific Populations – Elderly, Gender, Race/Ethnicity

- For the following(Strikeout text should be removed from labeling and underlined text should be added to labeling)
-

Section 12.2 Pharmacodynamics

[redacted] (b) (4)

Cardiac Electrophysiology (QTc) in healthy volunteers
The effect of liraglutide on cardiac repolarization was tested in a QTc study. Liraglutide at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation. The maximum liraglutide [redacted] (b) (4) plasma concentration in [redacted] (b) (4) overweight and obese subjects treated with liraglutide 3.0 mg is comparable to the [redacted] (b) (4) maximum liraglutide plasma concentration- [redacted] (b) (4) 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 (AUCτ/24) reached approximately 116 ng/mL in obese (BMI 30-40 kg/m2) subjects following administration of Saxenda. Liraglutide exposure increased proportionally [redacted] (b) (4) in the dose range of 0.6 mg – 3.0 mg. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration. Liraglutide exposures were considered comparable among these three subcutaneous injection sites (upper arm, abdomen and thigh). Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Specific Populations
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 [redacted] (b) (4)

Appendix

1 RESULTS OF SPONSOR'S ANALYSIS

1.1 Population PK analysis

The population PK analysis of liraglutide was performed using data obtained from two Phase 3 trials (1922 and 1839). 1839 was a trial in obese subjects and overweight subjects with comorbidities, including a large subset of subjects with pre-diabetes. NN8022-1922 was a trial in overweight or obese subjects with type 2 diabetes. The primary objective of the population PK analysis was to:

- Characterize the PK and exposure-response properties of liraglutide in obese subjects.
- Identify covariates (age, gender, race, body weight etc.) that have a significant effect on PK.

1.1.1 Methods

In trials 1922 and 1839, PK sampling was done at 2, 12 and 28 weeks after dose. All subjects had to be at the target dose of 3.0 mg or placebo at the latest 35 days after randomization (NN8022-1839 and NN8082-1922, 3.0 mg cohort) or 1.8 mg or placebo at the latest 21 days after randomization (NN8022-1922, 1.8 mg cohort). Injections could be done at any time of day irrespective of meals. However, it was preferable that liraglutide be injected during the same overall time period on a day to day basis. Injections could be in the abdomen, thigh or upper arm and were not required to be kept consistent throughout the trial. Liraglutide concentration in plasma was determined using a validated ELISA with an LLOQ of 30 pmol/L in trials 1839 and 1922. For trial 1807, another laboratory was used for liraglutide assay and the LLOQ was 18 pmol/L.

The data file for exposure-response analysis comprised data from the two phase 3 trials trial 1922 and trial 1839 as well as from trial 1807, which was a phase 2 trial. The exposure data used for exposure-response analysis were individual model-derived AUC values of liraglutide dosed at steady-state. A total of 2923 subjects who received liraglutide were included in the PK analysis; 584 subjects were from trial 1922 and 2339 subjects from trial 1839.

A pre-specified approach was used for the population-PK analysis which comprised estimation of a base model without covariates and a full covariate model with all covariates included. A standard one-compartment models with first-order absorption and elimination was used to describe the liraglutide PK. The structural model was parameterized in terms of the following parameters: Ka (absorption rate constant for liraglutide), CL/F (apparent clearance of liraglutide), V/F (apprent volume of distribution of liraglutide). A proportional error model was used to describe the residual variability of liraglutide concentrations.

SPLUS, version 8.2 (TIBCO, Palo Alto, CA, USA) was used for data file processing, explorative data analysis and plotting. NONMEM version 7.1.2 (ICON Development Solutions, Ellicott City, MD, USA) was used for the population PK analysis and for simulation.

1.1.2 Final Model

The PK of liraglutide was successfully described by a one-compartment model with first-order absorption and first-order elimination. The full covariate model containing all the investigated covariates was used for obtaining point estimates and confidence intervals for all investigated covariate effects and for obtaining parameter estimates for quantifying covariate effects. The covariate analysis was restricted to effects on clearance (CL/F) due to the sparseness of data regarding the absorption rate constants (KA) and the volume of distribution (V/F). As a consequence, covariate effects on exposure are restricted to effects on AUC in this analysis.

The full covariate model was parameterized as:

$$CL/F_i = TVCL \cdot E_{weight} \cdot E_{dose} \cdot E_{gender} \cdot E_{age} \cdot E_{race} \cdot E_{ethnicity} \cdot E_{disease\_status} \cdot \exp(\eta_i)$$

$$E_{weight} = \left(\frac{weight}{100kg}\right)^{\theta_{wt}}$$

$$E_{dose} = \exp(\theta_{1.8mg})^{dose=1.8mg}$$

$$E_{gender} = \exp(\theta_{male})^{male}$$

$$E_{age} = \exp(\theta_{age\geq 70y})^{age\geq 70y}$$

$$E_{race} = \exp(\theta_{Black})^{Black} \cdot \exp(\theta_{Asian})^{Asian} \cdot \exp(\theta_{Other})^{Other}$$

$$E_{ethnicity} = \exp(\theta_{Hispanic})^{Hispanic}$$

$$E_{diaease\_status} = \exp(\theta_{Diabetes})^{Diabetes} \cdot \exp(\theta_{Pre-diabetes})^{Pre-diabetes}$$

where, TVCL was the typical liraglutide apparent clearance for an obese (100 kg), female, less than 70 years, White, not Hispanic or Latino subject without diabetes or pre-diabetes administering 3.0 mg liraglutide once daily.

The final model indicated that the exposure decreased with increasing body weight and was lower in males than in females. Further, a lower exposure was observed in subjects with diabetes as compared to subjects with normoglycemia or pre-diabetes. The remaining covariates (age, race and ethnicity) appeared to be without consistent effects on liraglutide exposure. The parameter estimated for the full covariate model is shown in Table.

Table 1: Parameter estimates from the full PK model with covariate effects included

Fixed-effects parameters	Description	Unit	Estimate	% RSE	95% CI
$K_{A,Lira}$	Absorption rate constant (fixed)	1/h	0.0806	NA	[NA;NA]
CL/F_{Lira}	Apparent clearance	L/h	0.863	2.12	[0.827;0.899]
V/F_{Lira}	Apparent volume of distribution	L	24.6	8.81	[20.3;28.8]
θ_{Weight}	Exponent for effect of body weight	NA	0.678	5.37	[0.607;0.75]
$\Theta_{1.8mg}$	Coefficient for effect of dose	NA	0.0244	119	[-0.0324;0.0812]
Θ_{Male}	Coefficient for effect of gender	NA	0.27	6.1	[0.237;0.302]
Θ_{Age_70y}	Coefficient for effect of age	NA	-0.0976	44.6	[-0.183;-0.0123]
Θ_{Other}	Coefficient for effect of race	NA	-0.0783	57	[-0.166;0.00914]
Θ_{Asian}	Coefficient for effect of race	NA	-0.00475	913	[-0.0897;0.0802]
Θ_{Black}	Coefficient for effect of race	NA	-0.0877	26.1	[-0.133;-0.0427]
$\theta_{Hispanic}$	Coefficient for effect of ethnicity	NA	0.0808	26.1	[0.0395;0.122]
$\Theta_{Pre\text{-}diabetes}$	Coefficient for effect of glycaemic status	NA	0.003	904	[-0.0501;0.056]
$\Theta_{Diabetes}$	Coefficient for effect of glycaemic status	NA	0.18	14	[0.131;0.23]
Random-effects parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**	
IIV – CL/F_{Lira}	Between-subject variability in CL/F	% CV	24.7	23.9	
IIV – V/F_{Lira}	Between-subject variability in V/F	% CV	34.7	83.2	
Residual error parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**	
Sigma	Residual error (proportional)	% CV	15.4	9.37	

Source: Modelling report, page 85

1.1.3 Liraglutide covariate effects

The reference subject was selected to be a white, not Hispanic or Latino, female subject below 70 years of age, of 100 kg body weight and without diabetes or prediabetes dosed by 3.0 mg liraglutide. The apparent clearance for a subject with the typical characteristics was found to be 0.86 and 1.03 L/h respectively, for normoglycemic and diabetic females, and 1.13 and 1.35 L/h, respectively for normoglycemic and diabetic males. In summary, the typical value for the apparent clearance (CL/F) identified from the population PK analysis ranged from 0.86 L/h to 1.35L/h.

The results of the covariate analysis for liraglutide are summarized as means and 90% confidence intervals for the steady-state liraglutide exposure ($AUC_{0\text{-}24\ h}$) for each covariate relative to the exposure for a reference subject. Population PK analysis (Figure) showed a 44% [90% CI: 41 – 47%] lower exposure (corresponding to 78% higher CL/F) for a subject weighing 234 kg (the maximum baseline body weight in the population PK analysis) relative to a subject with a reference body weight of 100 kg. Likewise, the exposure was 41% [90% CI: 37 – 46%] higher (corresponding to 29% lower CL/F) for a subject weighing 60 kg (the lowest baseline body weight) relative to a subject at the reference weight.

The estimated exposure of liraglutide was 24% [90%CI: 22-26%] lower in male than female subjects due to 32% higher CL/F in males compared to females (Figure). This corresponds to 32% higher exposure in females compared to males due to 24% lower CL/F in females than males and was in accordance with the graphical analysis showing overall lower concentrations of liraglutide in males than in females. Effects of glycemic

status were investigated using three categories: normoglycemia, pre-diabetes and type 2 diabetes. Subjects with type 2 diabetes were found to have 16% [90% CI: 14-19%] lower exposure than normoglycemic subjects (Figure). Inclusion of covariates for CL/F in the population PK model resulted in a reduction of the between subject variability for CL/F from 34.8 % to 24.7% CV.

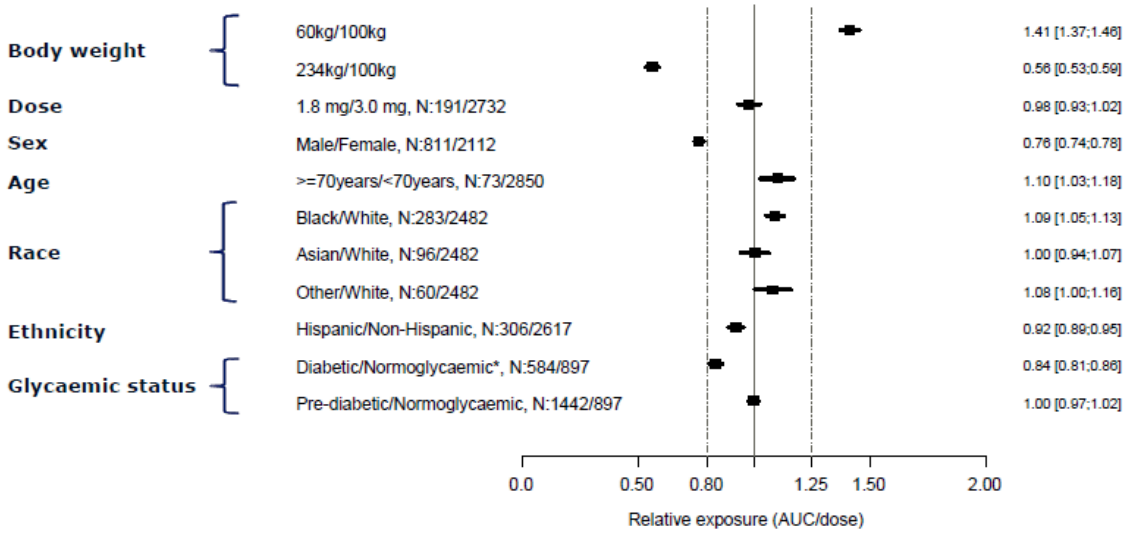


Figure 2: Forest plot of covariate analysis expressed as steady-state dose-normalized liraglutide exposure ($AUC_{0\text{-}24\ h}$/Dose) relative to a non-Hispanic or Latino, white, female subject below 70 years of age, of 100 kg body weight without diabetes or pre-diabetes dosed by 3.0 mg liraglutide.

Dotted lines indicate the interval used for bioequivalence testing, for comparison. The column to the right shows geometric mean relative exposures with 90% confidence intervals obtained by likelihood profiling.
*Diabetic/normoglycemic grouping was confounded with trial ID as all subjects with diabetes were from trial 1922.

Source: Modelling report, page 33

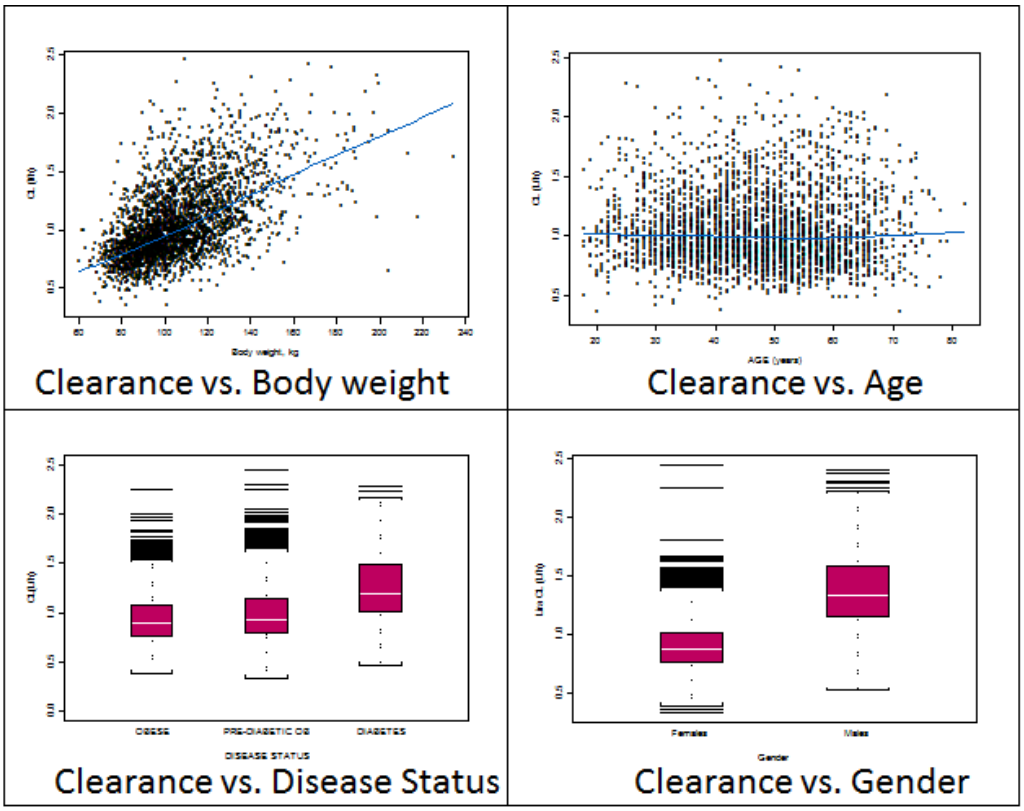


Figure 3: Effects of covariates of liraglutide clearance

2.2 Sponsor's conclusions

- Sex and body weight were the main covariates for liraglutide exposure: exposure decreased with increasing body weight and was 24% lower in males than in females. Age, race, ethnicity, glycemic status and dose were found not to be relevant covariates for dose-normalized exposure.
- Lower liraglutide exposures in trial 1922 than in trial 1839 suggest lower exposure in overweight/obese subjects with type 2 diabetes than in subjects without diabetes, although a trial effect cannot be excluded.

Reviewer's comment on sponsor's population PK analysis:

- *Sponsor's population PK analysis is generally adequate.*
- *The covariate analysis was restricted to effects on clearance (CL/F) due to the sparseness of data regarding the absorption rate constants (KA) and the volume of distribution (V/F). As a consequence, covariate effects on exposure are restricted to effects on AUC in this analysis.*
- *The body weight selected for the reference subject (100 kg) was a rounded value close to the median body weight of the studied population.*

- *Due to the high correlation between body weight and BMI, the latter was not included in the covariate analysis*
- *As sex and body weight are the most important covariates for liraglutide and account for a considerable fraction of the between-subject variability of CL/F, and hence exposure.*
- *Sponsor's conclusion that no dose adjustment based on age, gender, body weight, and race is supported by the population PK analysis and exposure-response results. Additionally, the efficacy and safety analysis by baseline body weight provided further support for not requiring dose adjustment based on body weight.*

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

/s/

JAYABHARATHI VAIDYANATHAN
09/19/2014

IMMO ZADEZENSKY
09/19/2014

NITIN MEHROTRA
09/19/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	August 13, 2014
Reviewers:	Debra L. Ryan, PharmD, MBA, Safety Evaluator Carolyn J. Tabak, MD, MPH, Medical Officer Division of Pharmacovigilance I
Team Leaders:	S. Christopher Jones, PharmD, MS, MPH Safety Evaluator Team Leader Allen Brinker, MD, MS Medical Officer Team Leader Division of Pharmacovigilance I
Acting Division Director:	Robert L. Levin, MD Division of Pharmacovigilance I
Product Name:	Victoza™ (liraglutide)
Subject:	Review of Select and Serious Events as Background Information for the September 2014 Advisory Committee for Saxenda™ (liraglutide)
Application Type/Number:	NDA: 206-321
Applicant/Sponsor:	Novo Nordisk, Inc.
OSE RCM #:	2014-634

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EXECUTIVE SUMMARY

Victoza™ (liraglutide) is indicated, at doses up to 1.8 mg, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). On December 20, 2013, the sponsor submitted an NDA (206-321), seeking approval of liraglutide, at a dose of 3 mg, for a new indication: as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults.

The Division of Metabolism and Endocrinology Products (DMEP) has requested an update of the postmarketing safety assessment for Victoza™ to further their understanding of the safety of liraglutide for this new indication and higher dose with specific interest in reports of gall-bladder related adverse events (AEs), breast cancer, hepatic injury, tachycardic /arrythmogenic AEs, and psychiatric AEs.

The majority of the spontaneous reports and post marketing safety reviews for liraglutide have focused on pancreatitis, acute renal failure, anaphylaxis and hypersensitivity reactions, and medication errors due to patients using the wrong injection technique. The prescribing information has been updated to reflect these safety concerns. Analysis of spontaneous reports for gallbladder and cardiovascular adverse events is problematic, because these events are relatively prevalent in the age group represented in these reports i.e., individuals over 50 years old, with or without a diagnosis of diabetes mellitus. Analysis of spontaneous report for cancers of interest (breast, thyroid, and pancreatic) is also problematic, because these are relatively common cancers in adults unless a rare subtype, like medullary thyroid carcinoma, is specifically stated in the report. A known limitation of spontaneous reporting is the inability to perform adequate causality assessments for events which are relatively common in the general population. Because of this high background rate, among other limitations, FDA must rely on adequately powered, randomized controlled trials or well-designed observational studies to determine if common events in the recipient population can be attributed to liraglutide exposure.

We note the continued accrual of a disproportionate number of liraglutide associated thyroid and pancreatic cancers relative to all other drugs in the FDA Adverse Event Reporting System (FAERS). However, the medical literature offers inconclusive data to determine the role that liraglutide may play in these malignancies. DPVI did not identify previously unknown safety signals for liraglutide in the FAERS database or the literature.

1 INTRODUCTION

1.1 BACKGROUND

This review provides an update to the safety profile for liraglutide (Victoza™) focusing on select and serious adverse events associated with the use of Victoza™ reported to the FDA Adverse Event Reporting System (FAERS) and reports from the published medical literature.

Victoza™ was approved on January 25, 2010 and is the second glucagon-like peptide-1 (GLP-1) agonist approved for marketing. Victoza™ is indicated, at doses up to 1.8 mg, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). On December 20, 2013 a new NDA (206-321) was submitted to the FDA seeking approval of liraglutide, at a dose of 3 mg, for a new indication: as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m2 or greater (obese) or 27 kg/m2 or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, dysglycemia (prediabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea.

The Division of Metabolism and Endocrinology Products (DMEP) has requested an update of the postmarketing safety assessment for Victoza™ to further their understanding of the safety of liraglutide for this new indication and higher dose with specific interest in reports of gall-bladder related adverse events (AEs), breast cancer, hepatic injury, tachycardic/arrythmogenic AEs, psychiatric AEs, and potential safety signals for liraglutide.

The objective of this review is threefold; 1) To provide a postmarketing overview of the safety profile of Victoza™ since approval including potential safety signals; 2) To review the regulatory actions that have been taken in response to postmarketing reports; and 3) To evaluate serious postmarketing reports and the published medical literature regarding the events of special interest cited in the above paragraph.

1.2 OVERVIEW OF GLP-1 AGONISTS

There are four GLP-1 agonists approved for marketing in the US, each indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Byetta™ (exenatide), the first in class, was approved for marketing in the US on April 28, 2005. Thereafter, three additional GLP-1 agonists have been approved for marketing in the US. Victoza™ (liraglutide), approved on January 25, 2010; Bydureon™ (exenatide extended release), approved on January 27, 2012; and Tanzeum™ (albiglutide), approved on April 15, 2014.

The GLP-1 agonists stimulate insulin release, slow gastric emptying, and inhibit post-prandial glucagon release; effects mediated by the GLP-1 receptor which is widely distributed throughout a variety of tissues. All FDA approved GLP-1 agonists share a mechanism of action and generally have a similar adverse event FAERS profile with the exception of the potential risk of medullary thyroid carcinoma (MTC) which appears to be associated with only long-acting GLP-1 agonists. Byetta is not considered to be a long-acting agent.

Victoza™ carries a **Boxed Warning** to notify prescribers that the drug causes thyroid C-cell tumors at clinically relevant exposures in rodents; however the human relevance of this observation could not be determined by clinical or nonclinical studies. The complete **Boxed Warning** is provided below:

WARNING: RISK OF THYROID C–CELL TUMORS

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Victoza® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors *[see Contraindications (4), Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.

Bydureon™ and Tanzeum™ carry a similar **Boxed Warning** to notify prescribers that thyroid C-cell tumors have been observed in rodent studies with GLP-1 agonists at clinically relevant exposures.

1.3 PREVIOUS OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE) REVIEWS

DPVI has reviewed reports associated with the use of Victoza™ reported to the FAERS database from approval on January 25, 2010 through June 30, 2012 in two separate reviews[1,2]. The following summarizes the safety issues identified in those reviews, other relevant OSE reviews, and the regulatory action taken:

Acute Renal Failure: An OSE safety review[3] (RCM#2010-2606) was completed on April 6, 2011 that determined that there was a temporal association between the initiation of Victoza™ and dehydration leading to acute renal failure. The Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections of the labeling for Victoza™ were updated on May 18, 2011 to include additional information about dehydration, including reports of altered renal function requiring dialysis.

Anaphylaxis and Hypersensitivity Reactions: An OSE safety review[4] (RCM#2011-4469) was completed on February 1, 2012 that determined that there was a temporal association between the initiation of Victoza™ and the onset of reported hypersensitivity reactions. The Contraindications and Warnings and Precautions sections of the labeling for Victoza™ were updated in April 2012 to include additional information about serious hypersensitivity reactions including anaphylaxis.

Pancreatitis (including Hemorrhagic Necrotizing Pancreatitis): On November 28, 2012 the sponsor submitted a supplement (S-018) to update the Warnings and Precautions and Adverse Reactions sections of the labeling to include additional information about pancreatitis. An OSE safety review[5] (RCM#2013-270) was completed on March 14, 2013 evaluating seventy-six cases of acute pancreatitis reported for Victoza™, including three fatalities and four cases of hemorrhagic/necrotizing pancreatitis supporting the sponsor's proposed labeling, with modifications. The supplement was approved on April 16, 2013.

Improper pen storage, wrong injection technique, and device malfunctions: A Post Marketing Medication Error Review[6] (RCM#2013-270) evaluating the Instructions for Use (IFU) regarding proper pen storage, injection technique, and device malfunction was completed on February 15, 2013. On May 2, 2013 the sponsor submitted a supplement (S-020) revising the IFU by providing additional language and visual representation on dose selection and correct injection technique. The supplement (S-020) was approved on June 13, 2013.

Drug-Induced Liver Injury: An OSE safety review[7] (RCM#2014-813) was completed on June 20, 2014 that identified six cases of liver injury possibly related to Victoza™ use. The FDA is currently considering whether these data warrant labeling changes for liraglutide.

2 SUMMARY ANALYSIS OF THE FAERS DATABASE

2.1 FAERS SEARCH STRATEGY

For this review we were interested in identifying postmarketing reports coded with Preferred Terms (PT) occurring with greater frequency, severity, or outcome than expected for liraglutide. In order to achieve this, we selected reports coded with a serious outcome that identified liraglutide as the primary suspect drug. Additionally, we limited our analysis of FAERS reports to those without the terms "Trial ID", "Study ID", "Attorney", "litigation", or "lawyer," thereby eliminating reports originating from clinical trials or litigation. To focus our review on the serious cases requiring hospitalization, we further filtered out reports coded with the outcome "Other Serious" that did not report hospitalization. The FAERS database was searched with the strategy described in Table 1.

Table 1. FAERS Quick Query Search Strategy (n=4585)	
Date of search	June 10, 2014
Time period of search	January 25, 2010 (date of US approval) – May 31, 2014
Product Terms	Liraglutide
Outcome	Serious
FAERS Export to Excel Filters (n=3110)	
Primary Suspect Column	Filter to include reports that identify liraglutide as the Primary Suspect (n=4168)
Narrative Column Search	Exclude clinical trial and litigation reports by searching narrative for the terms "Trial ID" & "Study ID" (n=395) and for the terms "litigation", "attorney", "legal" (n=73)
Case Type and Outcome Column	Filter to exclude "Other Serious" Non-direct reports that do not report Hospitalization as an Outcome (n=590)

2.2 RESULTS

2.2.1 Results: Case Characteristics

Table 2. Descriptive Characteristics for Serious Adverse Events Associated with the Use of Liraglutide from January 25, 2010 through May 31, 2014 (N=3,110)	
Category	**FAERS Cases**
Age	Range: 14 – 92 years Average: 58 years Median: 59 years Not Reported: 945
Gender	Female: 1449 Male: 1267 Not Reported: 394
Age Bands	<17 years: 3 17-20 year-old: 7 21-30 year-old: 34 31-40 year-old: 114 41-50 year-old: 371 51-60 year-old:675 61-70 year-old: 649 71-80 year-old: 258 81-92 year-old: 51 >90 years: 3
Outcome†: **(case may have more than one coded outcome)**	Death: 246 Hospitalization: 1,717 Life-Threatening: 230 Disability: 58 Congenital Anomaly: 5 Other: 1552
Year Report Received by FDA	2010: 511 2011: 888 2012: 709 2013: 664 2014: 338 (through May 31, 2014)
Country of Reporter	Domestic: 1,395 Foreign: 1,715
† Outcome as determined by the MedWatch reporter and categorized by 21 CFR 314.80	

Implementing the search strategy described in Section 2.1 DPVI identified 3,110 reports in the FAERS database for the time period January 25, 2010 through May 31, 2014. The 3,110 reports represent crude counts, and as such, duplicates have not been reconciled. In addition, reported outcomes are those submitted to the Agency; and the possibility of a causal role of liraglutide in these adverse events has not been fully analyzed for this evaluation.

Pediatric Use

Among the 3,110 reports were three patients under the age of 17 that received liraglutide for T2DM. The serious AE reported for each patient was Pancreatitis Acute (PT) n=1, Anaphylactic Reaction (PT) n=1, and Panniculitis (PT) n=1, respectively. All three patients were hospitalized and each recovered from the event.

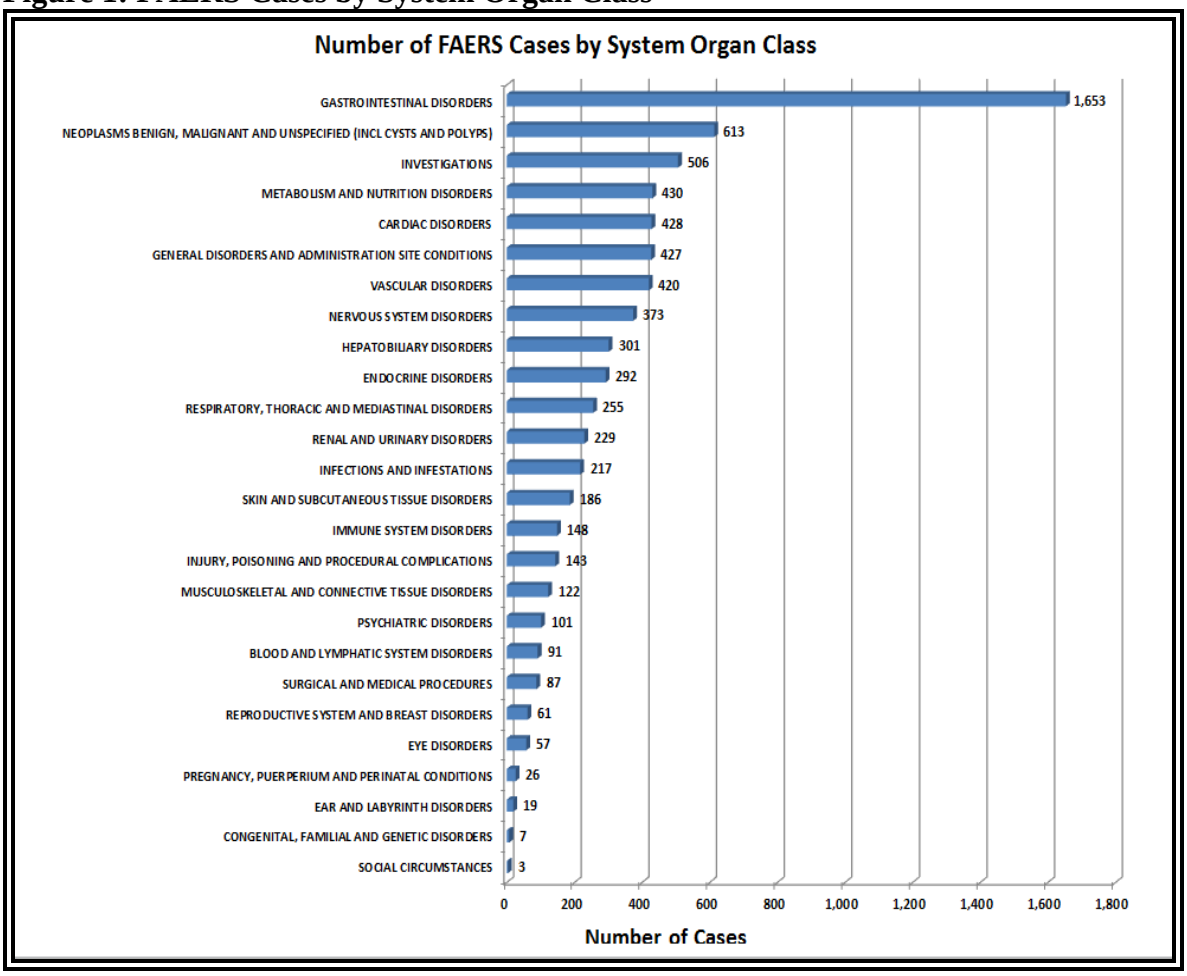
Deaths

The above search strategy identified 246 reported deaths associated with liraglutide use. Primary causes of death when reported were secondary to pancreatic carcinoma (n=88) or a cardiovascular event (n=57). For those cases reporting the age at death, the range was from 31 to 91 years-of-age. Nineteen reports were for individuals under the age of 50; myocardial infarction and morbid obesity were the most frequent reasons listed as a cause.

2.2.2 Results: FAERS Cases by SOC

The following figure represents the number of FAERS cases by System Organ Class (SOC). Note that the numbers do not sum to equal the number of cases identified by the search, because a case may be included in more than one SOC.

Figure 1: FAERS Cases by System Organ Class



The most frequently reported MedDRA PTs for serious adverse event reports associated with liraglutide are categorized under the following SOCs: *Gastrointestinal disorders; Neoplasms Benign, Malignant and Unspecified; Cardiac Disorders; Investigations; Metabolism and nutrition disorders; and General Disorders and Administration Site Conditions*. In general, the majority of the cases in these SOCs represent reports of pancreatitis, pancreatic cancer, cardiovascular events, thyroid neoplasms, acute renal failure, and those PTs that describe the symptoms, laboratory tests, and/or procedures associated with these diagnoses and/or with T2DM. In section 7.2 (Appendix B) of this document we further list the most frequently reported MedDRA preferred terms within select SOCs.

2.2.3 Results: Top PTs for Events of Special Interest

In section 7.3 (Appendix C) of this document we list the most frequently reported MedDRA preferred terms for liraglutide. The following tables are the most frequently reported PTs within each MedDRA High-Level Group Term (HLGT) or SOC for the events of special interest.

Gallbladder Disorders (HLGT) n=104*

Event-Preferred Terms(PTs)	Total Cases
CHOLELITHIASIS	83
CHOLECYSTITIS ACUTE	26
CHOLECYSTITIS	20
GALLBLADDER DISORDER	12
CHOLECYSTITIS CHRONIC	7
CHOLECYSTITIS INFECTIVE	2
GALLBLADDER PAIN	2
GALLBLADDER POLYP	2
BILIARY DYSKINESIA	1
CHOLELITHIASIS OBSTRUCTIVE	1
GALLBLADDER NECROSIS	1
GALLBLADDER NON-FUNCTIONING	1
GALLBLADDER PERFORATION	1

*Numbers may not sum; a case may include more than one PT

Breast Neoplasms Malignant and Unspecified (Incl Nipple) (HLGT) n=22*

Event-Preferred Terms(PTs)	Total Cases
BREAST CANCER	16
BREAST CANCER RECURRENT	3
INTRADUCTAL PROLIFERATIVE BREAST LESION	2
INVASIVE DUCTAL BREAST CARCINOMA	2
INVASIVE LOBULAR BREAST CARCINOMA	1
LOBULAR BREAST CARCINOMA IN SITU	1

*Numbers may not sum; a case may include more than one PT

Gastrointestinal Neoplasms Malignant and Unspecified (HLGT) n=240*

Event-Preferred Terms(PTs)	Total Cases
PANCREATIC CARCINOMA	204
PANCREATIC CARCINOMA METASTATIC	40
ADENOCARCINOMA PANCREAS	22
PANCREATIC NEOPLASM	16
PANCREATIC CARCINOMA STAGE IV	10

*Numbers may not sum; a case may include more than one PT

Cardiac Arrhythmias (HLGT) n=96*

Event-Preferred Terms(PTs)	Total Cases
ATRIAL FIBRILLATION	29
TACHYCARDIA	17
SUDDEN DEATH	16
CARDIAC ARREST	11
ARRHYTHMIA	8
CARDIO-RESPIRATORY ARREST	7
SUPRAVENTRICULAR TACHYCARDIA	6
VENTRICULAR TACHYCARDIA	5
VENTRICULAR EXTRASYSTOLES	3
VENTRICULAR FIBRILLATION	3

*Numbers may not sum; a case may include more than one PT

Psychiatric Disorders (SOC) n=101 *

DEPRESSION	16
SUICIDAL IDEATION	10
CONFUSIONAL STATE	8
SOMNOLENCE	6
ANXIETY	5
SUICIDE ATTEMPT	5
DYSPHONIA	4
INSOMNIA	4
INTENTIONAL OVERDOSE	4
LETHARGY	4
APHASIA	3
COMPLETED SUICIDE	3

*Numbers may not sum; a case may include more than one PT

Endocrine Neoplasms Malignant and Unspecified (HLGT) n=100*

Event-Preferred Terms(PTs)	Total Cases
THYROID CANCER	42
THYROID NEOPLASM	23
PAPILLARY THYROID CANCER	14
MEDULLARY THYROID CANCER	9
INSULINOMA	2
NEUROENDOCRINE CARCINOMA METASTATIC	2
PANCREATIC NEUROENDOCRINE TUMOUR	2
PARATHYROID TUMOUR	2
CARCINOID TUMOUR	1
GASTRINOMA	1
MALIGNANT PITUITARY TUMOUR	1
NEUROENDOCRINE TUMOUR	1
PARATHYROID TUMOUR MALIGNANT	1
PROLACTIN-PRODUCING PITUITARY TUMOUR	1
THYROID CANCER METASTATIC	1
THYROID CANCER STAGE IV	1

*Numbers may not sum; a case may include more than one PT

3 DISCUSSION

The most frequently reported MedDRA PTs for serious adverse event reports associated with liraglutide are categorized under the following SOCs: *Gastrointestinal disorders; Neoplasms Benign, Malignant and Unspecified; Cardiac Disorders; Investigations; Metabolism and nutrition disorders; and General Disorders and Administration Site Conditions*. In general, the majority of the cases in these SOCs represent reports of pancreatitis, pancreatic cancer, cardiovascular events, thyroid neoplasms, acute renal failure, and those PTs that describe the symptoms, laboratory tests, and/or procedures associated with these diagnoses and/or with T2DM.

Previous DPVI reviews of the safety profile for liraglutide have identified the following postmarketing safety concerns and led to strengthening of the label regarding pancreatitis[8], acute renal failure[9], and hypersensitivity events.[10] The resulting regulatory actions subsequent to these reviews have been summarized in Section 1.3.

Gallbladder Disorders

The most frequently reported preferred terms (PTs) for the 104 FAERS cases reporting gallbladder disorders are cholelithiasis and cholecystitis. However, three major risk factors for developing gallstones are present in the majority of the FAERS cases receiving liraglutide: 1) Age>40 years-old, 2) Obesity, and 3) History of Diabetes Mellitus. In addition, 59 of the FAERS cases reporting cholelithiasis and cholecystitis also report pancreatitis as an adverse event. Based on FAERS data alone, neither causality nor the contributory role of liraglutide in the presentation of cholelithiasis and cholecystitis can be clearly defined. DPVI recently authored a review of liraglutide-associated serious liver injury, and we determined that cases of hepatitis seemed to follow a cholestatic pattern of injury. In that same review, we were unable to determine the cause of liver injury. However, we speculate that if there are slight imbalances in hepatic safety findings from weight management trials, then these FAERS data may indicate a liraglutide-mediated effect on the biliary tract.

Drug-Induced Liver Injury

A literature report describing liraglutide-induced autoimmune hepatitis[11] prompted a recent review of postmarketing cases from the FAERS database, the published medical literature, and an assessment for disproportionality in reporting of liver adverse events using Empirica Signal to evaluate the risk of serious acute drug-induced liver injury (DILI) with liraglutide. This safety review,[12] completed on June 20, 2014 identified six cases of clinically serious liver injury associated with Victoza™. Using the WHO causality assessment scale, DPVI judged these cases to be possibly related to liraglutide therapy, meaning that the causal role of liraglutide could not be definitely established nor excluded in these cases. None of the six cases reported an outcome of death, liver transplant, or met criteria for Hy's law. The majority of the cases reported a cholestatic liver injury that resulted in hospitalization and drug discontinuation. The index literature case describing drug-induced autoimmune hepatitis was also reviewed by OSE hepatologist, Dr. Mark Avigan, who determined that a critical etiological question remains whether this was a case of idiopathic autoimmune hepatitis or autoimmune drug induced liver injury caused by liraglutide.

The true cause of liver injury in this patient remains in question, and despite our recent review that evaluated FAERS cases of suspected liraglutide induced liver injury, we could not definitively determine a cause.

Breast Cancer

The search strategy described in section 2.1 identified twenty-one reports of breast cancer in females between the ages of 51 to 72 years and one report for a 37 year-old female. Thirteen of the cases reported that they had been treated with liraglutide for less than a year when diagnosed with breast cancer, and five cases reported a recurrence of breast cancer, including one death. Breast cancer is the most common cancer in women, with an estimated 2014 annual incidence of 232,000 cases and approximately 2.9 million women in the United States living with the disease.[13] Approximately 95% of new cases are diagnosed in women 40 years of age and older.[14] FAERS spontaneous reports do not provide strong evidence of risk when an adverse event commonly occurs in the general population. Additionally, breast cancer is a disease that develops over an extended period of time, and FAERS is not a good tool to detect latent events attributed to a drug. Given these limitations, and based on FAERS data, we cannot infer a causal association between liraglutide exposure and the onset of breast cancer at this time. Controlled data are preferred and necessary to better evaluate this risk.

Major Cardiovascular Events (Including Cardiac Arrhythmias)

Although DPVI identified several reports coded with one or more MedDRA preferred terms associated with cardiovascular events, we are unable to attribute these events to liraglutide exposure. Cardiac dysrhythmias are prevalent among persons with type 2 diabetes. Spontaneous adverse events as reported to FAERS do not provide strong evidence of risk when the adverse event (i.e., cardiovascular events) frequently occurs in the general population. Spontaneous reporting systems are optimally used to detect rare and serious events. In addition, reports of cardiovascular safety concerns among diabetics are frequently confounded by the underlying disease being treated or other concurrent medical conditions. Controlled clinical studies assessing major adverse cardiac events (MACE) outcomes or studies that measure QTc changes are necessary to address this potential safety issue.

Psychiatric AEs

The FAERS search strategy described in section 2.1 identified 101 reports in the SOC Psychiatric Disorders, including three cases of Completed Suicide (PT). Two of the patients had previously attempted suicide; one patient had been recently diagnosed with pancreatic carcinoma, which was inferred as a potential reason for the suicide. Depression is the most frequently reported serious psychiatric event in these liraglutide cases, and it is a prevalent disease in the US (10% of the population). We are also unaware of a biological basis for liraglutide use to induce depression. Since diabetes and depression are well known comorbidities,[15] we find it more plausible that diabetes could increase the risk for depression, independent of a specific drug therapy used to treat T2DM.

Thyroid Neoplasms

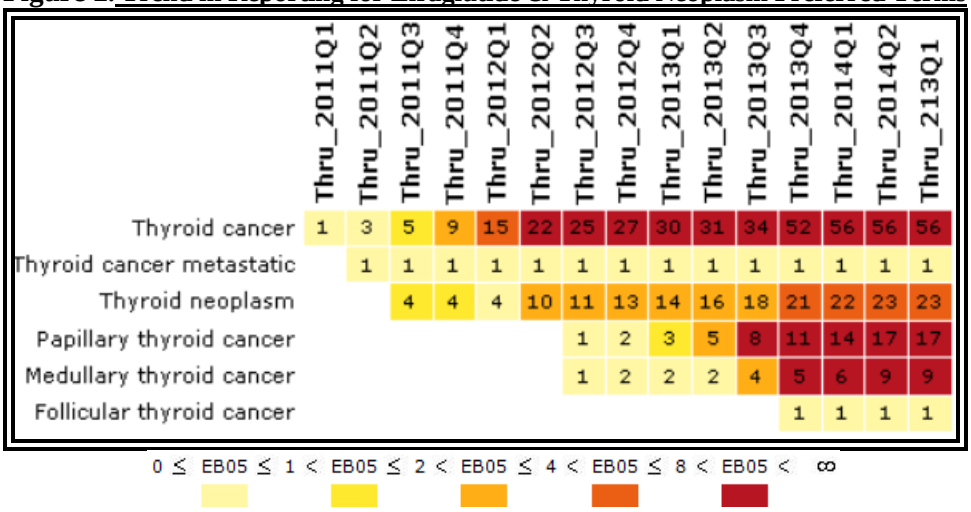
The FAERS search strategy described in section 2.1 identified 100 reports in the Endocrine Neoplasms Malignant and Unspecified (HLGT). DPVI reviewed the narratives of these 100 reports and found that the narratives reported 24 cases of unspecified thyroid cancer/neoplasm, 21 cases of papillary thyroid cancer, 8 cases of follicular thyroid cancer, and 9 cases of MTC. Sixteen cases were described as thyroid nodules. Pure papillary, mixed papillary-follicular, and follicular cancer represent over 90% of all thyroid carcinomas; they are characterized by the National Cancer Institute as common cancers, defined as occurring at a rate of greater than 35,000 new cases per year. A known limitation in analyzing spontaneous reporting is assessing causality for events which are relatively common in the general population.

However, MTC is a relatively rare cancer. Furthermore, liraglutide carcinogenicity studies in mice and rats demonstrated that liraglutide caused C-cell tumors in both species, in both genders, at clinically relevant exposures. Moreover, the occurrence of MTC in rodents was dose-related and treatment-duration-related. MTC is the human form of C-cell cancer. Current liraglutide labeling includes a **Boxed Warning** describing risk of thyroid C-cell tumors. At the time of approval, MTC had not been observed in humans exposed to liraglutide.

Our FAERS search yielded nine cases of MTC. DPVI forwarded these cases to the Division of Oncology Products 2 (DOP2) within FDA. We requested that they review these FAERS reports for clinical evidence confirming a diagnosis of MTC as well as to perform a causality assessment. Based on the clinical characteristics of the nine reports, DOP2 concluded that seven were consistent with the typical presentation of sporadic MTC and that six of these cases are possibly related to liraglutide.[16] Based on the DOP2 review of MTC cases, we cannot exclude the possibility that liraglutide is a casual determinant. These cases remain under internal review by FDA.

DPVI also notes the FAERS reporting trend of thyroid neoplasm as demonstrated in Figure 2.[17] We note increasing disproportionality of thyroid cancer, papillary thyroid cancer, and medullary thyroid cancer beginning in late 2011. We define disproportionate reporting as reporting for a drug-event combination in which the EB05 value is greater than two. Whether increasing disproportionality in reporting is attributable to a real increase in liraglutide-associated thyroid cancer, reporting bias related to litigation asserting that Victoza use may lead to thyroid cancer, detection bias in thyroid cancer screenings, or some other factor is unknown. We are limited in our ability to make causal inference from these reports for a potentially long latency event (e.g. cancer) using spontaneous data without a control group.

Figure 2. Trend in Reporting for Liraglutide & Thyroid Neoplasm Preferred Terms



Pancreatic Cancer

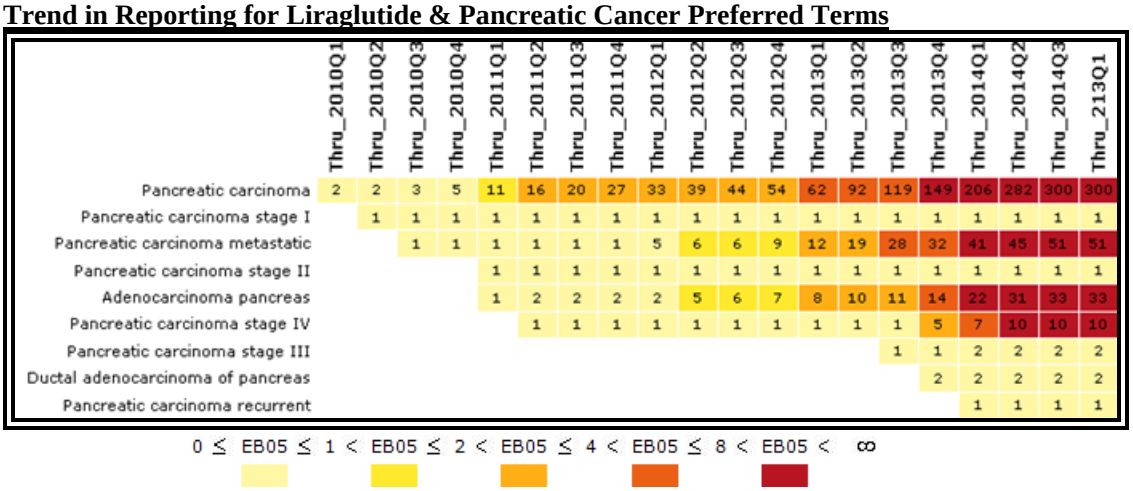
The FAERS search strategy described in section 2.1 identified 240 cases of pancreatic cancer associated with liraglutide use. A previous overview[18] of FAERS reports for pancreatic cancer did not provide new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza. The patient ages in the reports were generally consistent with the ages that are typical for patients with pancreatic cancer; no apparent gender imbalance and no rare subtype of pancreatic malignancy were identified. Pancreatic cancer has been hypothesized, although not proven, as a potential incretin mimetic-related adverse event in the literature.[19,20] To date, studies have been inconclusive in evaluating the risk of pancreatic cancer with incretin mimetic use.[18-22] Both FDA and the European Medicines Agency (EMA) have explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal, which to date, do not support pancreatic cancer as an incretin mimetic-mediated event.[21]

Pancreatic cancer is characterized by the National Cancer Institute as a common cancer, defined as occurring at a rate of greater than 35,000 new cases per year. Analysis of drug-related risk utilizing FAERS data does not provide strong evidence of risk when an event such as pancreatic cancer has a high prevalence (background rate) in the untreated population and has a long latency period. Because pancreatic cancer is relatively common, determining the risk compared to the background rate would require a well-designed, and adequately powered case-control or cohort study to better characterize this risk.[25] Therefore, using FAERS data alone is an inadequate approach to understanding the nature of the association. Currently, it is not possible using FAERS data to determine whether there is a causal association between exposure to liraglutide and pancreatic cancer.

DPVI also notes the FAERS reporting trend of pancreatic cancers as illustrated in Figure 3.[26] We note increasing disproportionality (EB05>2) of pancreatic cancers since approval of Victoza™. The volume of FAERS reports increased rapidly after the March 2013 FDA Drug Safety Communication [27] which discussed an association between pancreatitis and pre-cancerous findings of the pancreas with the use of incretin mimetics, though evidence of a reporting disproportionality existed prior to the March 2013 Drug Safety Communication.

Like the reporting trend for thyroid neoplasm, the drivers for this pancreatic cancer reporting trend have not been elucidated.

Figure 3.
Trend in Reporting for Liraglutide & Pancreatic Cancer Preferred Terms



4 LITERATURE REVIEW

In order to identify the most relevant articles for the literature review, three separate searches were conducted. The first search, conducted on May 14, 2014, used the terms “liraglutide AND (safety OR side effects OR adverse effects OR adverse events OR case reports)” and yielded 350 items. Titles were reviewed for relevance to safety issues, and of these, 24 were retrieved. These 24 articles were reviewed in depth; eleven contained relevant safety information.
Following the first search, two additional searches were conducted that targeted specific safety issues of interest. The second search contained terms directed at each potential adverse event that was requested in the consult (gallbladder disease, breast cancer, liver injury, arrhythmia, and psychiatric adverse events). The second search yielded eight articles, seven of which were retrieved, and were unique from those in the first search. One of these articles was written in Spanish, and translation was not readily available; another article was irrelevant. In total, six articles were reviewed in depth.

In previous reviews, other adverse events including thyroid neoplasms and pancreatic cancer were raised as potential concerns. Therefore, the third search added search terms that targeted these particular events. This search yielded 23 articles, of which three were duplicates identified in the second search (one of which was the Spanish article). Of the total yielded in the second and third search (27), three were not available from the library, one was written in Spanish, and through a careful reading of the abstracts, three were irrelevant.

The search strategy is shown in detail in Table 3. From the three searches combined, a total of 31 unique articles that contained relevant safety information were reviewed in depth.

Table 3. Literature Search Strategy	
Date of search	May 14, 2014, June 17, 2014, and July 15, 2014
Database	PubMed@FDA
Search Terms	liraglutide AND (safety OR side effects OR adverse effects OR adverse events OR case reports) liraglutide AND (gallbladder or cholestasis or cholelithiasis or breast cancer or liver injury or arrhythmia or psychiatric adverse events) liraglutide AND (gallbladder OR cholestasis OR cholelithiasis OR breast cancer OR liver injury OR hepatic injury OR tachycardia OR arrhythmia OR psychiatric adverse events OR thyroid neoplasms OR pancreatic cancer)
Years included in search	all through the date of each search
Limits	English

4.1 ADVERSE EVENTS OF INTEREST

4.1.1 Gallbladder related AE

None of the articles reviewed suggested that liraglutide, independent of its use in overweight or obese patients, is associated with gallbladder disease.

4.1.2 Breast Cancer

A meta-analysis, including 25 studies, indicated that liraglutide was not associated with an increased risk for cancer of any type.[28] The literature review did not identify a study specific to breast cancer risk alone.

4.1.3 Hepatic Injury

Liraglutide use, probably because of associated weight loss, resulted in reductions in ALT.[29] A case report recently published in June 2014 reported a case of autoimmune hepatitis in which history, laboratory test and liver biopsy results indicate a possible association with liraglutide use.[30] To date, no other reports of hepatic injury were identified in the literature search.

4.1.4 Tachycardic/arrythmogenic AE

Mundil et al[31] described a previous study that concluded that liraglutide did not cause a significant increase in QTc interval. A study using existing clinical data found liraglutide to have low rates (<1%) of MACE; these rates were similar to or lower than comparator drugs.[32] A meta-analysis had similar findings and suggested that GLP-1 receptor agonists do not pose an increased risk of cardiovascular adverse events.[33]

4.1.5 Psychiatric AE

One review article concluded, based on liraglutide clinical trials, that psychiatric disorders (insomnia, depressed mood, and nervousness) were reported with high-dose liraglutide (2.4 mg and 3.0 mg vs. placebo) and should be further investigated.[34] Because the dose of liraglutide indicated for obesity will be higher than that recommended for diabetes, special attention should be given to further reports of psychiatric adverse events associated with Saxenda.

4.1.6 Thyroid Neoplasms

GLP-1 agonists, such as liraglutide, have been shown to stimulate calcitonin secretion, C-cell proliferation, induction of C-cell hyperplasia, and development of C-cell adenomas and carcinomas in rodents.[35] At the time of approval, these events had not been observed in non-human primates or humans exposed to liraglutide. Serum calcitonin (CT) is a marker of C-cell proliferation, particularly in medullary thyroid carcinoma. Hegedus et al published a study in which CT concentrations were measured at 3-month intervals in subjects receiving liraglutide or control therapy for up to two years.[36] A review article also noted increased incidence of C-cell neoplasia in rodents exposed to liraglutide, however longitudinal data from clinical trials do not support any significant risk of activation or growth of C-cell cancer in humans.[37] Liraglutide was not associated with an increased risk of thyroid cancer in a meta-analysis of serious adverse events reported with GLP-1 agonists.[38] A commentary suggested that a careful history and physical exam pertaining to the thyroid be performed prior to initiating treatment with liraglutide or another GLP-1 receptor agonist.[39]

4.1.7 Pancreatic Carcinoma

Two immunohistochemistry studies of GLP-1R expression in human pancreatic cancer demonstrated that GLP-1R activation has an antitumor effect, and suggests that liraglutide and other GLP-1R based therapies may be beneficial in patients with pancreatic cancer.[40,41] A prospective study examined the risk of pancreatitis and pancreatic cancer with liraglutide and did not observe excess risk of either pancreatitis or pancreatic cancer compared to other antidiabetic drugs.[42] A literature search concluded that pancreatitis is a potential complication of liraglutide therapy, and this might result in imaging studies and early detection of pancreatic cancer.[43] Writing in 2010, Anderson et al[44] reported four cases of pancreatitis among liraglutide-treated subjects (4 cases pancreatitis/1916 subjects exposed) and one case among comparator-treated subjects (1 case of pancreatitis/956 comparator subjects exposed) from three phase 3 trials known as the LEAD studies.[45,46,47] We calculate a crude two-fold increase in the relative risk of pancreatitis among liraglutide users; however, this estimate is limited by a small number of events. Additionally, several case reports of pancreatitis that were possibly related to liraglutide have been reported.[48,49,50] Finally, a meta-analysis, including 25 studies, indicated that liraglutide was not associated with an increased risk of acute pancreatitis or pancreatic cancer.[51]

4.2 ALL EVENTS LITERATURE REVIEW

A letter to the editor of The Journal of Clinical Pharmacology reported that a chronic (seven month) 10-fold liraglutide overdose resulted in only minor adverse effects.[52] Another patient reportedly attempted suicide with liraglutide by injecting 80 times her daily dose (72 mg) and experienced gastrointestinal symptoms but not hypoglycemia.[53] This year, a case report of acute interstitial nephritis following liraglutide exposure was published.[54] The patient's kidney

function progressively improved after receiving steroids and transient dialysis, and liraglutide was discontinued. Another case report of presumably liraglutide-induced acute kidney injury was published in 2012.[55] Use of the Naranjo adverse drug reaction probability scale indicated a possible relationship between the patient's development of acute kidney injury and liraglutide. Several other review articles offered no new safety information.[56-63]

5 CONCLUSION

The majority of the spontaneous postmarketing reports that are the focus of this review have been previously assessed by OSE, and our reviews have identified several safety concerns: pancreatitis, acute renal failure, anaphylaxis and hypersensitivity reactions, and medication errors due to patients using the wrong injection technique. Accordingly, prescribing information has been updated to reflect these safety concerns. [64]

The majority (75%) of these serious adverse event reports are for individuals over the age of 50. This demographic, in addition to the indication for which liraglutide is used, make any analysis of risk using spontaneous reporting for gallbladder, cardiovascular adverse events, or the cancers of interest (breast, thyroid, and pancreatic) problematic, because these events are relatively prevalent in individuals over 50 years old, with or without a diagnosis of diabetes mellitus. A known limitation analyzing spontaneous reporting is the inability to perform adequate causality assessments for events which are relatively common in the untreated population. Because of this high background rate, FDA must rely on adequately powered, randomized controlled trials, or well-designed observational studies, to better assess the cause and to determine if any of these events are attributable to liraglutide exposure. Additionally, there are a number of postmarketing investigations that are either complete or underway for Victoza™, including disease registries, animal models, and meta-analysis of controlled data that should aid in FDA's understanding of these safety risks.[65] Unfortunately, evidence that we have reviewed from FAERS and the literature in this current document do not substantially advance our knowledge of these safety risks. Better methods are needed to quantify and characterize these risks, preferably through large randomized trials or observational studies with controls.

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7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.2 APPENDIX B. TOP PREFERRED TERMS FOR SELECT SOCS

Gastrointestinal disorders (SOC) n=1,653

Event-Preferred Terms(PTs)	Total Cases
PANCREATITIS	395
NAUSEA	257
PANCREATITIS ACUTE	227
PANCREATIC CARCINOMA	204
VOMITING	200
DIARRHOEA	160
ABDOMINAL PAIN	142
ABDOMINAL PAIN UPPER	64
CONSTIPATION	44
PANCREATIC CARCINOMA METASTATIC	40

Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) n=613

Event-Preferred Terms(PTs)	Total Cases
PANCREATIC CARCINOMA	204
THYROID CANCER	42
PANCREATIC CARCINOMA METASTATIC	40
THYROID NEOPLASM	23
ADENOCARCINOMA PANCREAS	22
BREAST CANCER	16
PANCREATIC NEOPLASM	16
PAPILLARY THYROID CANCER	14
NEOPLASM MALIGNANT	11
PANCREATIC CARCINOMA STAGE IV	10
MEDULLARY THYROID CANCER	9

Cardiac disorders (SOC) n=428

Event-Preferred Terms(PTs)	Total Cases
CHEST PAIN	46
DIZZINESS	44
DYSPNOEA	42
ATRIAL FIBRILLATION	29
PALPITATIONS	29
MYOCARDIAL INFARCTION	26
CARDIAC FAILURE	23
SYNCOPE	23
CARDIAC FAILURE CONGESTIVE	20
TACHYCARDIA	17
SUDDEN DEATH	16
CHEST DISCOMFORT	15
ACUTE MYOCARDIAL INFARCTION	13
ANGINA PECTORIS	13
ANGINA UNSTABLE	13
CARDIAC ARREST	11

Vascular disorders (SOC) n=420

Event-Preferred Terms(PTs)	Total Cases
DIZZINESS	44
MYOCARDIAL INFARCTION	26
HYPOTENSION	25
CEREBROVASCULAR ACCIDENT	23
SYNCOPE	23
HYPERTENSION	17
ACUTE MYOCARDIAL INFARCTION	13
ANGINA PECTORIS	13
ANGINA UNSTABLE	13
TRANSIENT ISCHAEMIC ATTACK	13
GASTROINTESTINAL HAEMORRHAGE	10
PULMONARY EMBOLISM	10

7.3 APPENDIX C. TOP 100 PREFERRED TERMS REPORTED FOR LIRAGLUTIDE IN FAERS

Preferred Term (PT)	Total Cases	Percent Of Total
Pancreatitis	395	12.70096463
Nausea	257	8.263665595
Pancreatitis Acute	227	7.29903537
Pancreatic Carcinoma	204	6.559485531
Vomiting	200	6.430868167
Diarrhoea	160	5.144694534
Weight Decreased	156	5.01607717
Abdominal Pain	142	4.565916399
Dehydration	108	3.47266881
Cholelithiasis	83	2.668810289
Decreased Appetite	77	2.475884244
Blood Glucose Increased	76	2.443729904
Renal Failure Acute	72	2.31511254
Abdominal Pain Upper	64	2.057877814
Lipase Increased	60	1.92926045
Headache	57	1.832797428
Chest Pain	46	1.479099678
Diabetic Ketoacidosis	46	1.479099678
Constipation	44	1.414790997
Dizziness	44	1.414790997
Dyspnoea	42	1.350482315
Malaise	42	1.350482315
Thyroid Cancer	42	1.350482315
Renal Failure	41	1.318327974
Pancreatic Carcinoma Metastatic	40	1.286173633
Asthenia	38	1.221864952
Death	36	1.15755627
Loss Of Consciousness	35	1.125401929
Amylase Increased	34	1.093247588
Fatigue	34	1.093247588
Hypoglycaemia	34	1.093247588
Atrial Fibrillation	29	0.932475884
Palpitations	29	0.932475884
Abdominal Discomfort	28	0.900321543
Diabetes Mellitus Inadequate Control	28	0.900321543
Urinary Tract Infection	28	0.900321543
Hepatitis	27	0.868167203
Blood Glucose Decreased	26	0.836012862
Cholecystitis Acute	26	0.836012862
Myocardial Infarction	26	0.836012862
Off Label Use	26	0.836012862

Preferred Term (PT)	Total Cases	Percent Of Total
Hypotension	25	0.803858521
Pneumonia	24	0.77170418
Cardiac Failure	23	0.739549839
Cerebrovascular Accident	23	0.739549839
Gastrooesophageal Reflux Disease	23	0.739549839
Syncope	23	0.739549839
Thyroid Neoplasm	23	0.739549839
Adenocarcinoma Pancreas	22	0.707395498
Condition Aggravated	22	0.707395498
Abdominal Distension	21	0.675241158
Heart Rate Increased	21	0.675241158
Cardiac Failure Congestive	20	0.643086817
Cholecystitis	20	0.643086817
Gastroenteritis	20	0.643086817
Hyperglycaemia	20	0.643086817
Pyrexia	20	0.643086817
Back Pain	19	0.610932476
Flatulence	19	0.610932476
Liver Function Test Abnormal	19	0.610932476
Fall	18	0.578778135
Hypersensitivity	18	0.578778135
Dyspepsia	17	0.546623794
Gastritis	17	0.546623794
Hypertension	17	0.546623794
Nephrolithiasis	17	0.546623794
Sepsis	17	0.546623794
Tachycardia	17	0.546623794
Breast Cancer	16	0.514469453
Depression	16	0.514469453
Pancreatic Neoplasm	16	0.514469453
Sudden Death	16	0.514469453
Chest Discomfort	15	0.482315113
Convulsion	15	0.482315113
Drug Interaction	15	0.482315113
Gastrointestinal Disorder	15	0.482315113
Hyperhidrosis	15	0.482315113
Pain	15	0.482315113
Tremor	15	0.482315113
Alanine Aminotransferase Increased	14	0.450160772
Blood Creatinine Increased	14	0.450160772
Exposure During Pregnancy	14	0.450160772
Hepatic Steatosis	14	0.450160772
Papillary Thyroid Cancer	14	0.450160772

Preferred Term (PT)	Total Cases	Percent Of Total
Acute Myocardial Infarction	13	0.418006431
Angina Pectoris	13	0.418006431
Angina Unstable	13	0.418006431
Blood Pressure Increased	13	0.418006431
Myalgia	13	0.418006431
Transient Ischaemic Attack	13	0.418006431
Urticaria	13	0.418006431
Anaemia	12	0.38585209
Coronary Revascularisation	12	0.38585209
Eructation	12	0.38585209
Gallbladder Disorder	12	0.38585209
Glycosylated Haemoglobin Increased	12	0.38585209
Jaundice	12	0.38585209
Liver Disorder	12	0.38585209
Vertigo	12	0.38585209

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/s/

DEBRA L RYAN
08/13/2014

CAROLYN J TABAK
08/13/2014

ALLEN D BRINKER
08/13/2014

STEVEN C JONES
08/13/2014
Signing on my behalf and for the acting director of DPVI Dr. Robert Levin.

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206321**	**Brand Name**	**Saxenda**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Liraglutide**
Medical Division	**DMEP**	**Drug Class**	**GLP-1 analog**
OCP Reviewer	**Jayabharathi Vaidyanathan**	**Indication(s)**	**Indicated for the treatment of weight loss and maintenance as an adjunct to diet and exercise for the treatment of overweight patients with BMI ≥ 27 kg/m2 with co-morbidities, or for the treatment of obese patients with a BMI ≥ 30 kg/m2**
OCP Team Leader	**Immo Zadezensky**	**Dosage Form**	**Injection**
Pharmacometrics Reviewer	**TBD**	**Dosing Regimen**	**Once daily**
Date of Submission	**12/20/2013**	**Route of Administration**	**Subcutaneous**
Estimated Due Date of OCP Review	**TBD**	**Sponsor**	**Novo Nordisk**
Medical Division Due Date	**TBD**	**Priority Classification**	**Standard**
PDUFA Due Date	**10/20/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**5**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**X**	**1**		
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**1**		**Exposure-response analysis**
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		**Population PK analysis**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**7**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The to-be-marketed formulation is identical to approved Victoza formulation.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			The applicant is referring to the studies conducted for Victoza program.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Submission in Brief:

Background:

Liraglutide was approved by the FDA in January 2010 (NDA 22-341) for the treatment of type 2 diabetes mellitus and is currently marketed at doses up to 1.8 mg/day under the brand name, Victoza® (NDA 22-341). Novo Nordisk is now submitting the NDA for liraglutide 3.0 mg for weight management. Liraglutide 3.0 mg is being planned to be available in the following presentations:

(b) (4)

Sponsor has stated that liraglutide 3.0 mg drug product is the same formulation as approved Victoza® and therefore will have the same shelf life (b) (4) months at 2º-8ºC). The clinical pharmacology program for liraglutide 3.0 mg in weight management builds upon the clinical pharmacology characteristics of liraglutide at doses up to 1.8 mg addressed comprehensively in Victoza® program. Novo Nordisk is cross referencing to the Victoza® NDA (NDA 22-341) for a substantial part of the weight management NDA in the quality (Module 3), nonclinical (Module 4), and clinical (Module 5) sections.

For the clinical pharmacology assessment of liraglutide 3.0 mg for weight management, the following trials have contributed with data:

- Trial 3630 (clinical pharmacology trial)
- Trial 1807 (phase 2 trial) for exposure-response analyses
- Trial 1839 (phase 3 trial) for population pharmacokinetic analyses and exposure-response analyses
- Trial 1922 (phase 3 trial) for population pharmacokinetic analyses and exposure-response analyses.

The clinical pharmacology trial (trial 3630) was conducted in obese subjects to assess the effect of liraglutide 3.0 mg on the rate of gastric emptying, explore the mechanism of the weight lowering effect of liraglutide and to characterize the pharmacokinetics of liraglutide 3.0 mg. The sponsor states that comparable overall pharmacokinetic characteristics of liraglutide 3.0 mg and liraglutide 1.8 mg together with the results of population pharmacokinetic analysis, in which no

new relevant covariates for exposure were identified, provide the justification for referring to the clinical pharmacology characteristics of liraglutide as provided in the Victoza® program.

Pharmacokinetic data from trials 1839 and 1922 were analyzed using population pharmacokinetic analysis. Exposure-response was analyzed on data from trials 1839, 1922 and 1807 by relating body weight loss and HbA1c to exposure. Different safety parameters such as pulse, calcitonin, and adverse events (pancreatitis and gall stone disease) were also evaluated in relation to exposure. Sponsor states that no relationship between liraglutide exposure and pulse, calcitonin or incidence of pancreatitis and gall stone disease was identified.

The potential effect of liraglutide 3.0 mg on the absorption of oral medicines were considered similar to that of liraglutide 1.8 mg based on the shown equivalence between the two liraglutide doses' effect on the rate of gastric emptying (trial 3630). This is the basis for the sponsor's justification the applicability of the drug-drug interaction program with liraglutide 1.8 mg (Victoza®) to the liraglutide 3.0 mg for weight management. The sponsor also refers to the Victoza® program for the TQT and *in vitro* metabolism, protein binding and drug-interaction displacement studies.

The sponsor concludes that the pharmacokinetic properties of liraglutide 3.0 mg in obese or overweight subjects were overall similar to that for liraglutide at doses up to 1.8 mg in healthy subjects and subjects with type 2 diabetes. Liraglutide 3.0 mg generally resulted in higher exposure than liraglutide 1.8 mg in obese and overweight subjects and the exposure increased in a dose-proportional manner.

Pediatric plan: Novo Nordisk intends to seek a waiver in children from birth to less than 6 years of age and a deferral to conduct studies in children ≥6 years to <18 years until safety and efficacy have been established in adults. In order to satisfy the PREA requirements, the sponsor has submitted a pediatric study plan in this application.

Comments:

- (b) (4)
- The application is fileable from clinical pharmacology.
- Review focus
    - What are the PK/PD characteristics of liraglutide 3.0 mg in obese subjects?
    - Does exposure-response for liraglutide support the proposed 3.0 mg dose?
    - Is the liraglutide bioanalytical assay/validation acceptable?

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/s/

JAYABHARATHI VAIDYANATHAN
02/26/2014

IMMO ZADEZENSKY
02/26/2014