CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	206321
Drug Name:	Saxenda (liraglutide)
Indication(s):	An adjunct to a reduced caloric diet and physical exercise for chronic weight management in adult patients that are overweight with co-morbidities or obese.
Applicant:	Novo Nordisk
Date(s):	Stamp date: December 20, 2013 Primary review due date: September 12, 2014 PDUFA due date: October 20, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Bradley McEvoy, DrPH
Concurring Reviewers:	Mark Rothmann, PhD, Team Leader Thomas Permutt, PhD, Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Julie Golden, MD, Medical Officer Jim Smith, MD, Medical Team Leader Jean-Marc Guettier, MD, Medical Division Director (Acting)
Project Manager:	Patricia Madara

Keywords: Sensitivity and specificity

Introduction: This addendum to the statistical review for liraglutide signed into DARRTS 15 September 2014 investigates the potential association between changes in weight that were observed early in the trial and the subsequent weight change. At the 11 September 2014 advisory committee meeting several committee members made the point that the product insert should provide recommendation that patients not achieving a certain degree of weight loss within a few months of initiating treatment should discontinue treatment. This addendum discusses (1) statistical considerations for such a recommendation, and (2) findings from our investigation of early changes predicting later changes for the liraglutide group in Trials 1839 and 1922.

Early weight change predicting later weight change: The trials were not specifically designed to answer whether early changes could be predictive of later changes. Therefore, one has to appreciate that any recommendation for potential discontinuation of treatment derived from the completed trials are post hoc.

To explore the association between short-term and long-term weight loss, I cross-classified the extent of weight loss at week 16 with whether or not a reduction of at least 5% was achieved at week 56. The investigation is limited to subjects with an on-treatment measurement at both weeks 16 and 56. However, had we considered all subjects, it is likely that the probability of being a 5% responder at week 56 would be smaller for a given amount of weight loss at week 16 due to the observation that subjects tended to gain weight after going off-treatment. Data from the placebo group are not presented due the limitations of comparing post-randomization subgroups.

The greater weight loss at week 16 was predictive of achieving at least a 5% weight loss by week 56 (Table 1). This finding was consistent for both trials. In Trial 1839, among those with a reduction less than 2% by week 16, only 21% had a reduction of 5% at week 56, which is considerably lower than the 54% response rate for the group with 4% to 5% reduction at week 16. Although there was a considerable drop in the likelihood of being a 5% responder at week 56 for weight loss between 2% to 3% and 3% to 4% relative to the 4% to 5% group, they still had response levels that were in-line with the benchmark criteria of 35% in the experimental arm are 5% responders.

Table 1. Relationship between weight loss at week 16 and 5% weight loss at week 56 for liraglutide 3.0 mg

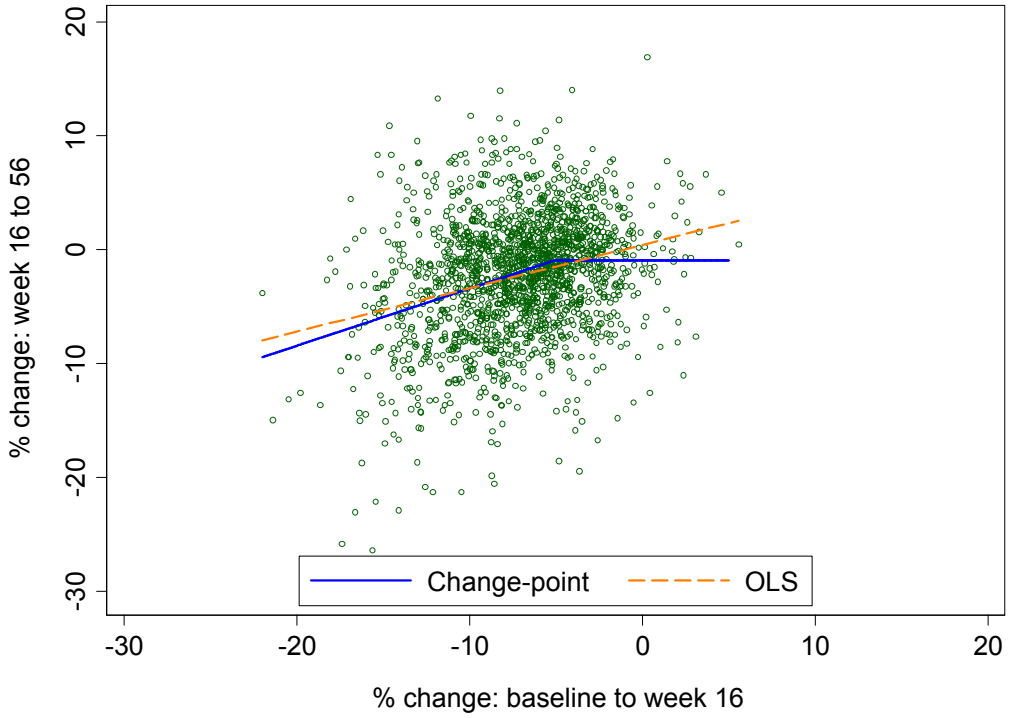
Trial	Weight loss at week 16	N	Weight loss at week 56 ≥ 5% n (%)
1839	< 2%	124	26 (21%)
	2% to 3%	103	32 (31%)
	3% to 4%	131	45 (34%)
	4% to 5%	177	96 (54%)
	5% to 6%	194	135 (70%)
	6% to 7%	206	172 (84%)
	≥ 7%	871	810 (93%)
1922	< 2%	47	7 (15%)
	2% to 3%	36	13 (36%)
	3% to 4%	22	12 (54%)
	4% to 5%	38	17 (45%)
	5% to 6%	36	19 (53%)
	6% to 7%	32	24 (75%)
	≥ 7%	106	94 (89%)

Note: Subjects without an on-treatment weight measurement at either week 16 or 56 were excluded from the analysis.

Given the limitation of the study designs, it is my opinion that the information in the table would be more informative for a physician to determine whether or not to discontinue liraglutide shortly after initiation. The table not only conveys the positive relationship between weight loss over the short-term and long-term, it also illustrates that patients who achieved modest short-term weight reductions could still benefit from liraglutide. It is, however, unclear what the best way to summarize this information in the label.

As an additional exploratory analysis, I investigated, for liraglutide 3.0 mg in Trial 1839, the relationship between the degree of weight change early in the trial (baseline to week 16) with the subsequent weight change (week 16 to week 56) (Figure 1). As evident from the least squares line (dashed orange line), subjects that lost weight early in the trial tended, on average, to experience additional weight loss. The estimated correlation between the early and the subsequent weight change was 0.27. As an additional exploratory analysis, I fit a change-point model to estimate the magnitude of weight change by week 16, where, for changes below this threshold, the degree of weight loss is assumed to be constant. The results from this analysis correspond to the blue solid line in the figure. The model estimated the threshold as -5.0% (95% CI = -6.3, -3.8), and for subjects below this change at week 16, we'd expect, on average, them to lose an additional 0.9% of their body weight.

Figure 1. Relationship between % weight change from baseline and week 16 and from week 16 to week 56 for liraglutide 3.0 mg (Trial 1839)



Note: Subjects without week 16 and 56 on-treatment measurements were not included

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BRADLEY W MCEVOY
10/16/2014

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U.S. Department of Health and Human Services
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CLINICAL STUDIES

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Clinical Team:	Julie Golden, MD, Medical Officer Jim Smith, MD, Medical Team Leader Jean-Marc Guettier, MD, Medical Division Director (Acting)
Project Manager:	Patricia Madara

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Table of Contents

1 EXECUTIVE SUMMARY 5
1.1 CONCLUSIONS AND RECOMMENDATIONS 5
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES 5
1.3 STATISTICAL ISSUES AND FINDINGS 6
2 INTRODUCTION 8
2.1 OVERVIEW 8
2.1.1 Class and Indication 8
2.1.2 History of Drug Development 8
2.1.3 Specific Studies Reviewed 8
2.2 DATA SOURCES 9
3 STATISTICAL EVALUATION 9
3.1 DATA AND ANALYSIS QUALITY 9
3.2 EVALUATION OF EFFICACY 10
3.2.1 Study Design and Endpoints 11
3.2.2 Patient Disposition, Demographic and Baseline Characteristics 15
3.2.3 Statistical Methods 26
3.2.4 Results 31
3.3 EVALUATION OF SAFETY 39
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 39
5 SUMMARY AND CONCLUSIONS 41
5.1 SUMMARY AND CONCLUSIONS 41
5.2 RECOMMENDATIONS FOR LABELING 41
A. APPENDIX 43
A.1 SUPPORTIVE MATERIAL 43
A.2 ADDITIONAL TABLES AND FIGURES 46

Reference ID: 3627768

LIST OF TABLES

Table 1. Summary of trial findings at week 56 for the weight management trials 7
Table 2. Summary of Trial Designs 9
Table 3. Primary efficacy endpoints by trial 15
Table 4. Patient disposition by trial 17
Table 5. Select instances of withdrawal criteria related to inadequate weight loss (Trial 1839) 18
Table 6. Mean change from baseline (kg) by week 20 missing status and enrollment into the 84 week extension period (Trial 1807) 18
Table 7. Summary of missing data at week 56 (Trials 1839, 1922 and 1923) 20
Table 8. Comparison of fasting weight change (%) at LAO-OT and week 56 for subjects that discontinued and returned for a week 56 follow-up assessment 21
Table 9. Demographic and baseline characteristics by completer and retrieved dropout status (Trial 1839) 22
Table 10. Demographic and baseline characteristics by completer and retrieve dropout status (Trial 1922) 23
Table 11. Demographic and baseline characteristics by completer and retrieve dropout status (Trial 1923) 24
Table 12. Patient demographic and baseline characteristics by trial 25
Table 13. Analysis results for fasting weight change at week 20 in Trial 1807 (FAS, LOCF using LAO-OT) 32
Table 14. Analysis results for fasting weight change at week 52 in Trial 1807 (FAS, LOCF using LAO-OT) 32
Table 15. Primary analysis results for change in fasting body weight (%) in Trials 1839, 1922, and 1923 33
Table 16. Sensitivity analysis results for change in body weight (%) in Trials 1839, 1922, and 1923 33
Table 17. Primary analysis results for responder endpoints in Trials 1839, 1922, and 1923 34
Table 18. Sensitivity analysis results for responder endpoints in Trials 1839, 1922, and 1923 35
Table 19. Analysis of re-randomization period (Trial 1839) 37
Table 20. Analysis results for change in AHI (events/hour) and secondary weight endpoints in Trial 3970 (FAS, LOCF using LAO-OT) 39
Table 21. Results from subgroup analysis of fasting weight change (%, FAS with LOCF using LAO-OT) 40

Reference ID: 3627768

LIST OF FIGURES

Figure 1. Study design for Trial 1807 12
Figure 2. Study design for Trial 1839 13
Figure 3. Study design for Trial 1922 13
Figure 4. Study design for Trial 1923 14
Figure 5. Study design for Trial 3970 14
Figure 6. Mean profile of fasting bodyweight change (%) by last available on-treatment follow-up visit (FAS, Trial 1839) 18
Figure 7. Mean profile of fasting bodyweight change (%) by last available on-treatment follow-up visit (FAS, Trial 1922) 19
Figure 8. Relationship between mean proportion of having a retrieve dropout assessment and the number of discontinuations in a study site (Trial 1839) 20
Figure 9. Kernel density plot (smoothed histogram) comparing the actual week 56 fasting weight change (%) with the average imputed value from the sponsor' MI analysis for subjects that discontinued and returned for a week 56 follow-up assessment (Trial 1839) 29
Figure 10. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1839) 36
Figure 11. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1922) 36
Figure 12. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1923) 37
Figure 13. Analysis of secondary endpoints at week 56 (FAS, LOCF with LAO-OT) 38
Figure 14. Kaplan-Meier plot time-to-discontinuation—Adverse Event (Trial 1839) 46
Figure 15. Kaplan-Meier plot time-to-discontinuation—Adverse Event (Trial 1922) 46
Figure 16. Kaplan-Meier plot time-to-discontinuation—Adverse Event (Trial 1923) 47

Reference ID: 3627768

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Novo Nordisk proposes Saxenda (liraglutide) as an adjunct to a reduced caloric diet and physical exercise for chronic weight management in adult patients that are overweight with co-morbidities or obese. In three Phase 3 weight management trials designed to evaluate to change in body weight at liraglutide 56 weeks, the liraglutide 3.0 mg group had statistically significantly greater decreases in fasting body weight than placebo. This finding was consistent across both the sponsor's primary analysis and our preferred analysis (Table 1) that attempted to address shortcomings of the primary analysis. The shortcomings include the use of last observation carried forward and ignoring measurements taken off study drug. The magnitude of the treatment effect from our analysis comparing either the percent change in fasting body weight or the proportion of subjects with a weight loss that exceeds 5% were such that they were consistent with the efficacy benchmarks outlined in the 2007 Draft FDA Guidance for Industry: *Developing Products for Weight Management.* My review of the statistical evidence found that liraglutide is an effective therapy for weight management. The efficacy findings do support approval of the NDA for the proposed indication.

1.2 Brief Overview of Clinical Studies

Five trials were reviewed as part of this NDA submission. The trials were all randomized, multi-center, multi-national in obese (BMI $\geq$ 30 kg/m^2) or overweight (BMI $\geq$ 27 kg/m^2) subjects with or without type 2 diabetes mellitus (T2DM). In the four Phase 3 trials, they all had a liraglutide 3.0 mg arm, and one trial had a liraglutide 1.8 mg arm. The experimental drug was injected subcutaneously once daily. The primary endpoint in four trials was change in body weight from baseline to either week 20 (Phase 2 dose-finding trial) or week 56. The primary endpoint in the fifth trial was change in the apnea-hypopnea index (AHI) from baseline to week 32. The primary study hypotheses were to test for superiority of liraglutide to placebo. Key secondary hypotheses for secondary endpoints were not prespecified in any of the trials.

The four Phase 3 trials were all double-blind, placebo controlled but different in important ways. Trial 1839 was the largest trial and included over 3700 non-diabetic obese or overweight subjects; Trial 1922 was the only study in subjects with T2DM, and included the 1.8 mg dose; Trial 1923 randomized subjects who had lost 5% of their bodyweight during a 12 week low calorie diet (LCD); and Trial 3970 had a primary objective that was related to sleep apnea and not related to inducing or maintaining weight loss. In three trials subjects that prematurely discontinued were asked to attend a follow-up visit that took place 56 weeks after their randomization date.

In Trial 1807 564 subjects were randomized 1:1:1:1:1:1 to one of four liraglutide doses (1.2, 1.8, 2.4, or 3.0 mg once daily), matching liraglutide placebo, or open-label orlistat (120 mg three times daily). The trial was 104 weeks, where after week 20 subjects had to reconsent for an optional 84 week extension period.

Reference ID: 3627768

Trial 1839 randomized 3731 subjects in a 2:1 ratio to liraglutide 3.0 mg or placebo, with the duration of treatment depending on the subject's pre-diabetes status..Subjects with pre-diabetes were randomized to 160 weeks of treatment in order determine whether treatment with liraglutide reduced the chances of developing T2DM. Subjects without pre-diabetes were randomized to 68 weeks of treatment, with the liraglutide group being re-randomized (1:1) at week 56 to liraglutide or placebo for an additional 12 weeks of follow-up.

In Trial 1922 846 subjects with T2DM were randomized in a 2:1:1 ratio to liraglutide 3.0 mg, liraglutide 1.8 mg or placebo for 56 weeks. In Trial 1923 422 subjects were randomized 1:1 to liraglutide 3.0 mg or placebo. Trial 3970 randomized 359 subjects in a 1:1 ratio to liraglutide 3.0 mg or placebo.

1.3 Statistical Issues and Findings

In the three Phase 3 weight management trials designed to evaluate efficacy of liraglutide at 56 weeks, the liraglutide 3.0 mg group had statistically significantly greater decreases in fasting body weight than placebo. This finding was consistent across both the sponsor's primary analysis and our preferred analysis (Table 1), which differed in important ways. The magnitude of the treatment effect comparing either the percent change in fasting body weight or the proportion of those with a weight loss exceeding 5% were such that they were consistent with the efficacy benchmarks outlined in the 2007 Draft FDA Guidance for Industry: *Developing Products for Weight Management* (See Section 3.2).

Based on our preferred analysis, the estimated average excess reduction in fasting weight was 4.8% in a non-diabetic population (Trial 1839) and 3.4% in the T2DM population (Trial 1922). After an initial weight loss using a LCD in Trial 1923, the estimated average excess reduction was 5.3%.

We have concern that the sponsor's primary analysis exaggerates the treatment effect at week 56. The shortcoming of their analysis is that they impute the response at the landmark visit using the last available observation while on-treatment and ignore weight measurements taken off study drug. Although the sponsor's endpoint imputation approach is consistent with the recommendations in the Draft FDA Guidance, it is at odds with the recommendations from the 2010 FDA commissioned report from the National Academy of Sciences on the prevention and handling of missing data in clinical trials. The concern with their analysis is reinforced by the trends that were observed in a non-random subset of subjects that had a fasting weight assessment while off-treatment at week 56. Across trials, the liraglutide group consistently gained weight after going off-treatment, while those in the placebo group consistently lost slightly more weight (Table 8).

The shortcoming of the sponsor's primary analysis is exacerbated by the inadequacies of their sensitivity analyses to estimate the treatment effect at week 56. This led us to fit our preferred analysis, which represents missing data at the landmark visit using information from subjects that prematurely discontinued but returned for their landmark assessment. This approach can be implemented only for Trials 1839, 1922 and 1923 because they retrieved dropouts.

Reference ID: 3627768

Table 1. Summary of trial findings at week 56 for the weight management trials

	Sponsor's primary analysis	FDA preferred analysis
	Lira 3.0 mg – Placebo	Lira 3.0 mg – Placebo
Trial	**95% CI**	**95% CI**
Change in bodyweight (%)		
1839	-5.4% (-5.8, -5.0)	-4.6% (-5.4, -3.9)
1922	-4.0% (-4.8, -3.1)	-3.4% (-4.5, -2.3)
1923	-6.1% (-7.5, -4.6)	-5.3% (-6.8, -3.8)
Reduction in bodyweight exceeds 5%*		
1839	36 (33, 39)	28 (24, 32)
1922	31 (22, 39)	36 (29, 43)
1923	29 (20, 38)	23 (14, 31)

*Risk difference per 100

The overall number of discontinuations was greater in the placebo group than in the liraglutide group. However, in the liraglutide group subjects were more than twice as likely to discontinue due to an adverse event (9.5% vs. 4.1%). This tended to occur early in the trial, and most of the events leading to discontinuation were related to a gastrointestinal disorder.

The extent of missing data varied across trials and treatment arms (Table 7). In the Phase 3 weight management trials the proportion of missing data at the landmark visit ranged from 17% to 20% for liraglutide 3.0 mg and from 19% to 26% for placebo. As it relates to the sponsor's primary analysis, the proportion subjects without an on-treatment assessment at the landmark visit ranged from 25% to 27% for liraglutide 3.0 mg and 31% to 45% for placebo.

Across the trials the average fasting weight reduction was fairly similar across the levels of subgroups defined by race (White, non-White), age (< 65 years, ≥ 65 years), region (US, non-US), BMI (< 30 kg/m^2, ≥ 30 kg/m^2), and baseline weight (below sample median, above sample median). There appears to be an interaction with sex, where females consistently experienced more favorable weight reductions than males.

Results from secondary endpoints support the efficacy of liraglutide compared to placebo. This review provides summaries for endpoints related to body composition (waist circumference, BMI), glucose control (HbA1c, fasting plasma glucose) and lipids (triglycerides, and total, LDL and HDL cholesterol). These endpoints were pre-specified in the individual study protocols but were not included in the individual study multiplicity testing framework.

Reference ID: 3627768

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Saxenda (liraglutide), an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist, is being investigated as an adjunct to a reduced caloric diet and physical exercise for chronic weight management in adult patients that are overweight with co-morbidities or are obese. Liraglutide is to be administered subcutaneously daily, with the starting dose being titrated to 3.0 mg in increments of 0.6 mg.

Liraglutide was approved January 2010 (NDA 22-341) for the treatment of T2DM, and is currently marked at doses up to 1.8 mg/day under the brandname, Victoza.

2.1.2 History of Drug Development

Novo Nordisk, the sponsor, submitted IND 73,306 for liraglutide for weight management on September 4, 2008.

The end-of-phase 2 (EOP2) meeting was held on March 10, 2008. At the meeting there were no questions from the sponsor or meeting discussion regarding statistical methods or handling of missing data. On February 20, 2013 the sponsor requested guidance on statistical methods for the integrated summary of efficacy (ISE). In the responses, shared May 6, 2013, FDA conveyed their reservations for the usefulness of the analysis of the individual and combined study datasets based on imputation using last observation carried forward (LOCF). FDA did not request the sponsor modify their primary analysis approach.

On September 11, 2014 there was an advisory committee meeting that discussed the safety and efficacy of the liraglutide weight management new drug application. The advisory committee voted 14-1 in favor of liraglutide having a favorable benefit-risk profile to support approval for the proposed indication.

2.1.3 Specific Studies Reviewed

Five trials were reviewed as part of this NDA submission. The trials were all randomized, multi-center, multi-national in obese (BMI $\geq$ 30 kg/m^2) or overweight (BMI $\geq$ 27 kg/m^2) subjects with or without T2DM. The proposed 3.0 mg dose was identified in the Phase 2 Trial 1807. The phase 3 trials were all double-blind, placebo controlled but different in important ways. In particular, Trial 1839 was the largest trial and included over 3700 non-diabetic obese or overweight subjects; Trial 1922 was the only study in subjects with T2DM, and included a liraglutide 1.8 mg arm; Trial 1923 studied subjects after having lost 5% of their bodyweight during a 12 week low calorie diet (LCD); and Trial 3970 was the only trial that did not follow-up subjects for at least 52 weeks and whose primary objective was not related to inducing or maintaining weight loss. Details of the trial design are available in the table below.

Reference ID: 3627768

Table 2. Summary of Trial Designs

Trial	Study population	Design	Length of study (primary landmark visit)	Primary endpoints	Treatment arm (No. randomized)
1807 (Phase 2)	Obese subjects w/o T2DM	R, DB/OL*, PG, AC, PC	104 weeks (week 20)	1. Δ in bodyweight (kg) 2. 5% responder	Lira 1.2 mg –95 Lira 1.8 mg –90 Lira 2.4 mg –93 Lira 3.0 mg –93 Placebo – 98 Orlistat –95
1839 (Phase 3)	Non-diabetic subjects that are obese or overweight with co-morbidities	R, DB, PG, PC	160 weeks (week 56)	1. Δ in bodyweight (%) 2. 5% responder 3. 10% responder	Lira 3.0 mg –2487 Placebo –1244
1922 (Phase 3)	Obese or overweight subjects with T2DM	R, DB, PG, PC	56 weeks (week 56)	1. Δ in bodyweight (%) 2. 5% responder 3. 10% responder	Lira 1.8 mg –211 Lira 3.0 mg –423 Placebo –212
1923 (Phase 3)	Obese subjects without diabetes	R, DB, PG, PC	56 weeks (week 56)	1. Δ in bodyweight (%) 2. maintain run-in bodyweight 3. 5% responder	Lira 3.0 mg –212 Placebo –210
3970 (Phase 3)	Non-diabetic, obese subjects with moderate or severe sleep apnea	R, DB, PG, PC	32 weeks (week 32)	1. Δ in AHI	Lira 3.0 mg –180 Placebo –176

Source: FDA statistical reviewer
T2DM-Type 2 diabetes mellitus; R-Randomized; DB-Double-blind; PG-Parallel group; PC-placebo controlled; AC-active controlled; OL-open-label.
* DB/OL: the active control arm was open-label, and the liraglutide and placebo arms were double-blind.

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission, organized as an .enx file, was archived at the following link:

\\CDSESUB1\EVSPROD\NDA206321\206321.enx

All tables and figures in this review were created by this reviewer unless noted otherwise.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

I found the datasets for the five clinical trials difficult to work with and there was little documentation. On several occasions I requested that the sponsor provide their analysis program code. I was able to reproduce the results on the primary endpoints presented in the individual Clinical Study Reports.

Reference ID: 3627768

3.2 Evaluation of Efficacy

In 2007 FDA released the Draft Guidance for Industry: *Developing Products for Weight Management* that provides recommendations for the development of drugs for the indication of weight management. The content relevant to evaluating the effectiveness of liraglutide is described in the sections on efficacy benchmarks and statistical methods. Below excerpts from these sections are provided along with a discussion of statistical considerations.

Efficacy benchmarks:

Box-1. Efficacy Benchmarks (Section IV.B.3.c)
In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs: • The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant. • The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

It is useful to consider the benchmarks within the context of the goal of a product for weight management: long-term reduction in fat mass with a goal of reducing morbidity and mortality. It must therefore be recognized that the effectiveness is evaluated using a surrogate endpoint.

Analysis methods:

Box-2. Analysis Methods (Section VI.C)
The analysis of (percentage) weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model. The analysis should be applied to the last observation carried forward on treatment in the modified ITT population defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. The imputation strategy should always be prespecified and should consider the expected dropout patterns and the time-course of weight changes in the treatment groups. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. Repeated measures analyses can be used to analyze longitudinal weight measurements but should estimate the treatment effect at the final time point.

Since the publication of the Draft Guidance the Division's view and handling of missing data has evolved, which was communicated to the sponsor in a May 06, 2013 Advice letter. The letter

Reference ID: 3627768

stated while the Division was not requesting the primary analysis be modified, the Division has reconsidered the use of last observation carried forward (LOCF) following the publication in 2010 of the FDA commissioned report on missing data by the National Academy of Sciences (NAS), The "*Prevention and Treatment of Missing Data in Clinical Trials.*" For LOCF the report specifically recommends (page 110) "Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified." In this setting the assumption being made is your weight will not change after the last time it was assessed while on treatment. For a subset of subjects that prematurely discontinued but returned for an assessment at the landmark visit this assumption is found not to be supported.

The recommended LOCF imputation is different than the typically LOCF imputation since it uses the last available observation on-treatment (LAO-OT) even if a measurement at the landmark visit is available but occurs while the subject is off study drug. The recommend approach presents unique challenges interpreting the results overall and relative to the estimate of the intention-to-treat (ITT) effect. Some of the challenges associated with the recommended analysis are:

- Part of a therapy's effect is mediated through the ability to tolerate the therapy. Therefore, an analysis that excludes observations after discontinuing therapy likely inflates the treatment effect since subjects that go off-treatment tend to regain weight.
- The average endpoint may have limited utility for a patient making a treatment decision because it is not known (nor is it possible to know) how long they will tolerate treatment; this can only be known after starting a treatment.
- The endpoint may not be clinically relevant for subjects with limited treatment adherence (e.g., one or two months) given the long-term goals of weight management.
- The distribution of the timing of the last available on-treatment measurement can differ across treatment arms. When this occurs the comparison of on-treatment experiences across treatment arms can be time-confounded.

Based on these considerations our preferred analysis is one that estimates the ITT effect using data from all subjects at the landmark visit. Because none of the sponsor's sensitivity analyses were found to adequately estimate this quantity for reasons described in Section 3.3, we fit two different statistical models to estimate this quantity; details of these model are provided in Section 3.3.

3.2.1 Study Design and Endpoints

Study Designs

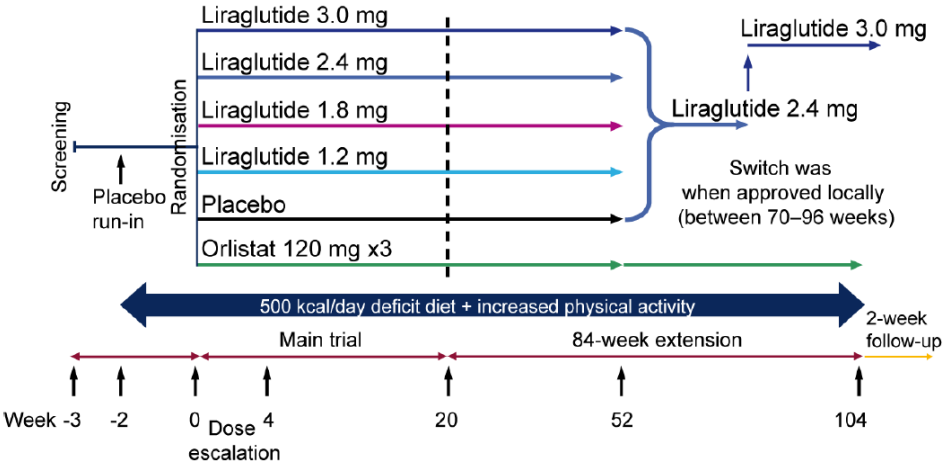
In the trials under review liraglutide (active or placebo) was administered once daily by subcutaneous injection. Treatment was titrated to dose based on a fixed dose strategy. Treatment started at 0.6 mg with a 0.6 mg dose level increment occurring every 7 days until target. For the 1.8 mg (Trial 1922) and 3.0 mg doses the target dose was to be reached 21 and 35 days after randomization, respectively. After reaching target dose the dose and dosing frequency was not to be changed. Subjects that could not tolerate the treatment dose were withdrawn from the trial.

Reference ID: 3627768

In addition to randomized therapy all subjects received dietary and physical activity counseling.

Trial 1807: Trial 1807 was a randomized, partially blinded, parallel group, placebo and active controlled dose-finding trial in non-diabetic, obese subjects. A total of 564 subjects in 19 sites in 8 European countries were randomized 1:1:1:1:1:1 to one of four liraglutide doses (1.2, 1.8, 2.4, or 3.0 mg once daily), matching liraglutide placebo, or open-label orlistat (120 mg three times daily). Randomization was stratified by gender. The treatment duration was planned for 20 weeks with an optional 84 week extension period. A total of 398 randomized subjects consented to and continued study treatment in the extension phase. After the 52 week visit subjects treated with liraglutide or placebo were initially treated with the open-label 2.4 mg dose. Subjects were subsequently switched to the 3.0 mg dose following discussion from the planned week 52 analysis. Additional study design elements are shown below.

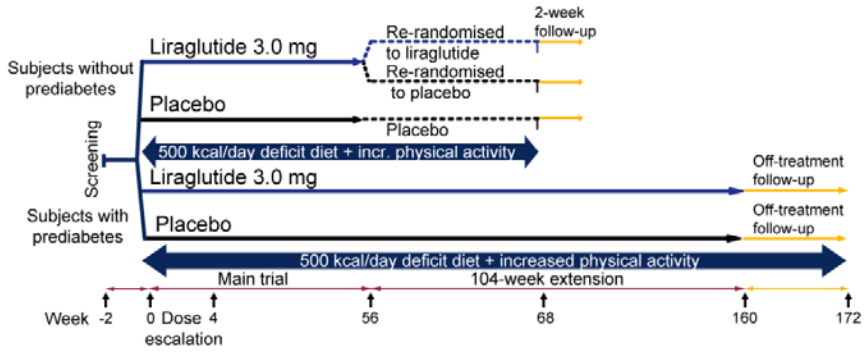
Figure 1. Study design for Trial 1807



Trial 1839: Trial 1839 was a randomized, double-blind, placebo controlled, parallel group trial in non-diabetic obese or overweight subjects with co-morbidities. A total of 3731 subjects in 191 sites including 69 in the US were randomized 2:1 to liraglutide 3.0 mg or placebo. All subjects received diet counseling in addition to randomized therapy. Randomization was stratified by pre-diabetes status (with, or without) and BMI ($\geq$ 30 kg/m^2, or < 30 kg/m^2). Subjects in the pre-diabetes stratum were randomized to 160 weeks of treatment; data post 56 weeks was not included in the submission. Subjects in the not having pre-diabetes stratum were randomized to 56 weeks of treatment followed by a 12 week re-randomization treatment period. Subjects randomized to liraglutide were re-randomized 1:1 to liraglutide or placebo. Subjects that prematurely discontinued were asked to attend a follow-up visit that took place 56 weeks after their randomization date. Additional study design elements are shown below.

Reference ID: 3627768

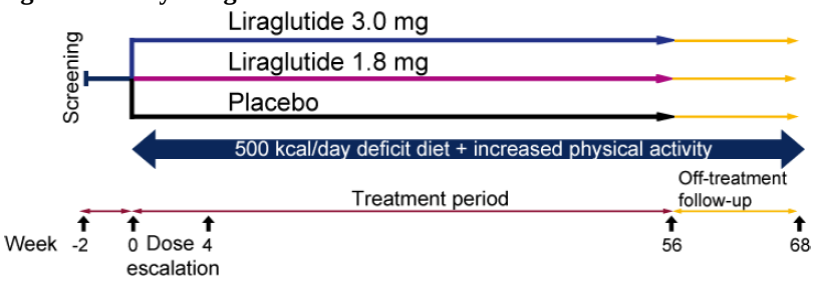
Figure 2. Study design for Trial 1839



Trial 1922: Trial 1922 was a 56 week randomized, double-blind, placebo controlled, three-arm parallel group trial in obese or overweight subjects with T2DM. A total of 846 subjects in 126 sites including 67 in the US were randomized 2:1:1 to liraglutide 3.0 mg, liraglutide 1.8 mg or placebo as an add-on to their background diabetes treatment. All subjects received diet counseling in addition to randomized therapy. Randomization was stratified by HbA1c (≥ 8.5%, or < 8.5%) and background treatment (diet and exercise or single compound oral antidiabetic treatment, or combination oral antidiabetic treatment). Oral antidiabetic treatment included [metformin, sulphonylurea or glitazone. Subjects that prematurely discontinued were asked to attend a follow-up visit that took place 56 weeks after their randomization date.

Subjects treated with sulphonylureas (SU) were asked to reduce the dose by 50% to prevent SU-induced hypoglycemia. If fasting plasma glucose exceeded pre-specified limits, the Investigator could provide glycemic rescue by increasing the dose of background oral antidiabetic medication or adding an additional background medication. Additional study design elements are shown below.

Figure 3. Study design for Trial 1922

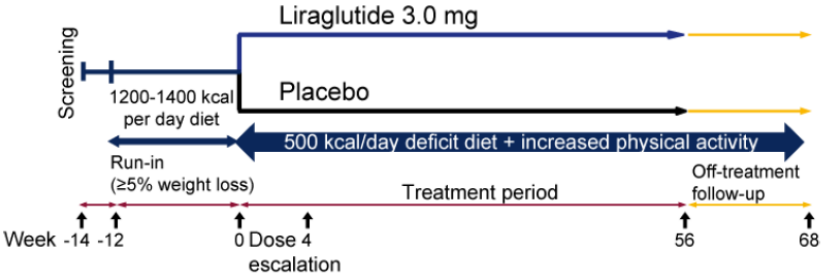


Trial 1923: Trial 1923 was a 56 week randomized, double-blind, placebo controlled parallel group trial in non-diabetic obese or overweight subjects with dyslipidaemia and/or hypertension. Subjects were randomized if they lost at least 5% of their bodyweight during a 12 week low calorie diet (1200-1400 kcal/day) run-in period. A total of 422 subjects in 36 sites in the US (26) and Canada (10) were randomized 1:1 to liraglutide 3.0 mg or placebo. All subjects received diet and physical activity counseling in addition to randomized therapy. Randomization was stratified by co-morbidity status (presence or absence of treated or untreated hypertension or dyslipidaemia). Subjects that prematurely discontinued were asked to attend a follow-up visit

Reference ID: 3627768

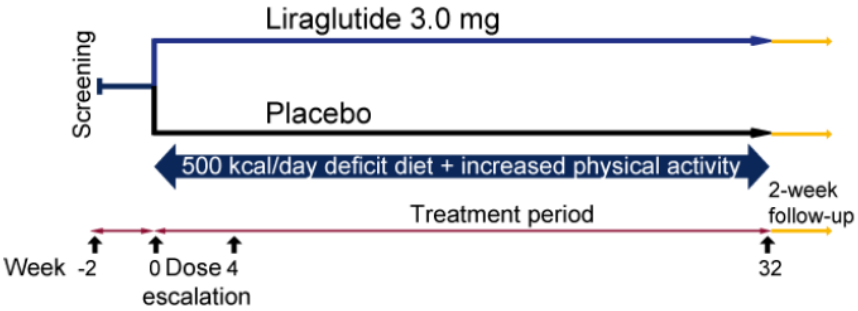
that took place 56 weeks after their randomization date. Additional study design elements are shown below.

Figure 4. Study design for Trial 1923



Trial 3970: Trial 3970 was a 32 week randomized, double-blind, placebo controlled parallel group trial in non-diabetic obese subjects with moderate or severe obstructive sleep apnea (OSA). The primary study objective was to evaluate whether liraglutide reduces the severity of OSA assessed by apnea-hypopnoea index (AHI). A total of 359 subjects in 40 sites in the US (35) and Canada (5) were randomized 1:1 to liraglutide 3.0 mg or placebo.

Figure 5. Study design for Trial 3970



Efficacy Endpoints

Primary Endpoints: The pre-specified primary efficacy endpoints for the individual trials are displayed in the table below. Note that for Trial 1839 the fourth primary endpoint is still being collected at the time of the NDA submission. Furthermore, it is noted that the primary endpoint definition from trial protocols (fixed time-point) is not consistent with the endpoint in the primary analysis that relies on LAO-OT. This lack of harmonization not only can lead to results being misinterpreted, it is also problematic for this submission because the treatment effect estimated from the primary analysis is found to over-state the estimated ITT treatment effect using our preferred approach.

The primary efficacy endpoints of percent change in fasting body weight from baseline and 5% responders is consistent with what is described in the Draft FDA Guidance. The 10% responder endpoint (Trials 1839 and 1922) is not described in the Guidance but is included due to different regulatory requirements for the European Medicines Agency.

In Trial 3970 AHI is captured during an overnight visit using polysomnography. An AHI event is characterized by either a transient reduction in, or cessation of breathing. The criteria for an

Reference ID: 3627768

event are included in the Appendix. Importantly, the ability to establish benefit by comparing the average change in AHI rate between treatment groups is limited because, as noted by the sponsor (protocol, page 82) "clinical relevant change in AHI has not been established."

Table 3. Primary efficacy endpoints by trial

Trial ID	1st primary	2nd primary	3rd primary	4th primary
1839, 1922 (at week 56)	Change in fasting body weight from baseline (%)	Proportion of subjects losing at least 5% of fasting baseline body weight (5% responders)	Proportion of subjects losing at least 10% of fasting baseline body weight (10% responders)	Onset of type 2 diabetes in subjects with pre-diabetes (at week 160)
1923 (at week 56)	Change in fasting body weight from baseline (%)	Proportion of subjects that maintained the ≥ 5% reduction in initial fasting body weight achieved during the low calorie diet run-in period	Proportion of subjects losing at least 5% of fasting baseline body weight (5% responders)	-
1807 (at week 20)	Change in fasting body weight from baseline (kg)	Proportion of subjects losing at least 5% of fasting baseline body weight (5% responders)	-	-
3970 (at week 32)	Change in AHI rate (events per hour)	-	-	-

Source: FDA statistical reviewer

Secondary Endpoints: Approximately 15 to 20 secondary endpoints were prespecified for investigation. For all trials no formal hypothesis tests were prespecified for any of the endpoints, including those related body composition for Trial 3970 or glycemic control in Trial 1922.

In this review change from baseline to landmark visit are presented for the following secondary endpoints: BMI, fasting body weight (kg), waist circumference, HbA1c, fasting plasma glucose, triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

3.2.2.1 Patient Disposition

Patient Disposition

Patient disposition is summarized for the individual trials in Table 4. A large proportion of subjects withdrew from the Phase 3 trials prior to the study specific landmark visit. In the placebo group the proportion of discontinuations was greater overall than in the liraglutide arms. Across the Phase 3 trials the key reasons for study discontinuation were as follows:

- *Adverse Events*: Adverse events accounted for 9.5% of early study discontinuations in the liraglutide arms compared to 4.1% in the placebo arms. In the liraglutide arm discontinuation tended to occur shortly after randomization (Figure 14 to Figure 16 in the Appendix).
- *Withdrawal Criteria:* In Trials 1839, 1922 and 1923 study discontinuations due to withdrawal criteria are non-specific and comprise several components including consent withdrawal, pregnancy, and target dose not tolerated. The majority of study

Reference ID: 3627768

discontinuations criteria were withdrawal of consent. Subjects in the placebo group were more likely to have a withdrawal related to withdrawal criteria than liraglutide.

- *Ineffective Therapy*: A small number of overall discontinuations were attributed to Ineffective Therapy (liraglutide 3.0 mg, 25 subjects; placebo, 42 subjects). From a sampling of subjects in Trial 1839 that discontinued for reasons other than this, several commented on the ineffectiveness of the therapy (Table 5). The extent to which this occurred in Trial 1839 and the other trials is not known.

In Trial 1922, the placebo group (24%) was over four times as likely to satisify the criteria for glycemic rescue than the liraglutide groups (3.0 mg: 5%; 1.8 mg: 5%). This occurred on average earlier in the trial for placebo (day 154) compared to either liraglutide 1.8 mg (day 194) or 3.0 mg (day 173).

In Trial 1807, 472 or 84% of the 564 randomized subjects completed the 20 week main treatment period, with 74 of them not enrolling into the 84 week extension period. The decision not to continue follow-up appears to be associated with degree of weight loss at week 20, with the subjects that enrolled in the extension having more favorable average weight reductions than those that did not (Table 6). This trend was consistent across study arms except for the 1.2 mg liraglutide dose.

A relationship was also observed between the timing of the last on-treatment assessment and the change in the primary endpoint for Trial 1839 (Figure 6) and Trial 1922 (Figure 7). In particular:

- Subjects that had a 56 week on-treatment assessment (thick lines) consistently had a more favorable mean response profile over the study duration than the subjects that did not have a week 56 assessment. This observation was consistent across treatment groups.
- There was a positive relationship between the timing of the last on-treatment assessment and weight loss, with the average reduction being more favorable for subjects that had their assessment later in the trial compared to earlier.
- The distribution of the timing of the last available on-treatment measurement was not the same across treatment arms.
- The plots do not describe the average response at week 56 for those that did not have an on-treatment assessment at week 56.

Reference ID: 3627768

Table 4. Patient disposition by trial

	1807			1839		1922			1923		3970	
	Lira 3.0	**Orlistat**	**Placebo**	**Lira 3.0**	**Placebo**	**Lira 3.0**	**Lira 1.8**	**Placebo**	**Lira 3.0**	**Placebo**	**Lira 3.0**	**Placebo**
	N	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**
Randomized	93	95	98	2487	1244	423	211	212	212	210	180	179
Exposed	93	95	98	2481	1242	422	210	212	212	210	176	179
Completed treatment period*	82	79	79	1789	801	324	164	140	159	146	134	142
Withdrawn*	11	16	19	698	443	99	47	72	53	64	46	37
Adverse event	5	3	3	238	45	39	18	7	18	18	20	6
Ineffective therapy	0	1	2	23	36	0	0	3	0	2	2	1
Non-compliance with protocol	2	2	3	65	38	12	8	13	8	5	8	5
Other	4	10	11	79	63	16	7	12	10	15	14	25
Withdrawal criteria	0	0	0	293	261	32	14	37	17	24	2	0
Consented to 84 Week Extension	72	67	67	-	-	-	-	-	-	-	-	-
Interim Period (Weeks 20 – 52)												
Completed	65	55	62	-	-	-	-	-	-	-	-	-
Withdrawn	7	12	5	-	-	-	-	-	-	-	-	-
Adverse event	2	0	0	-	-	-	-	-	-	-	-	-
Ineffective therapy	0	0	2	-	-	-	-	-	-	-	-	-
Non-compliance with protocol	0	1	0	-	-	-	-	-	-	-	-	-
Other	5	11	3	-	-	-	-	-	-	-	-	-
Withdrew but attended 1yr visit	-	-	-	202	111	36	12	23	22	25	-	-
Entered re-randomization	-	-	-	701	304	-	-	-	-	-	-	-
Completed re-randomization	-	-	-	685	289	-	-	-	-	-	-	-
Full analysis set	92	95	98	2437	1225	412	204	211	207	206	180	179

*During 20 week main treatment period for Trial 1807;

Reference ID: 3627768

Table 5. Select instances of withdrawal criteria related to inadequate weight loss (Trial 1839)

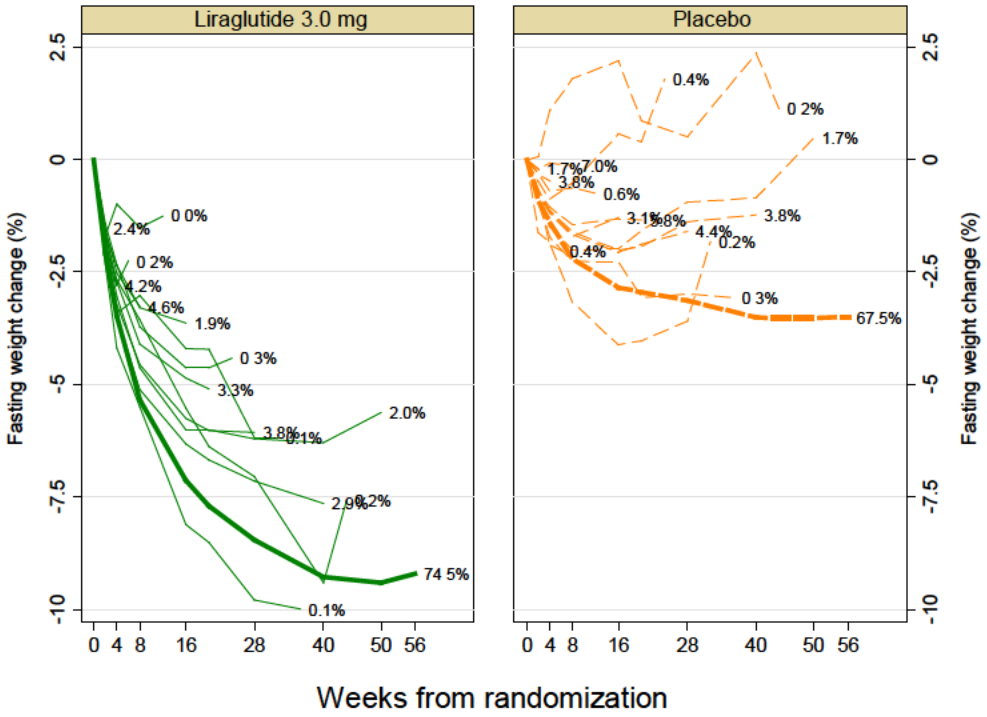
Subject ID	Reason noted in dataset
440012	Subject is tired of daily injections without weight loss over the year of participation
446016	Withdrew because subject was not losing weight
440026	Subject did not care to commit time and effort to study since she was not losing significant weight and did not want to continue daily injections.
445001	Weight loss stopped. Patient does not want to continue giving injections for no weight loss
446001	Withdrew consent because subject was not losing weight
446010	Withdrew consent because subject was not losing weight
446011	Withdrew consent because subject was not losing weight

Table 6. Mean change from baseline (kg) by week 20 missing status and enrollment into the 84 week extension period (Trial 1807).

Consented for 84 week extension	Yes		No		No	
Weight at week 20	**Available**		**Available**		**Missing**	
Treatment Group	**N**	**Mean Change**	**N**	**Mean Change**	**N**	**Mean Change***
Liraglutide 1.2 mg	68	-5.5	17	-5.7	9	-1.0
Liraglutide 1.8 mg	59	-7.1	15	-5.2	16	-2.2
Liraglutide 2.4 mg	65	-7.7	8	-4.6	19	-3.7
Liraglutide 3.0 mg	72	-8.4	10	-5.9	10	-3.4
Orlistat	67	-5.7	12	-0.3	16	-1.9
Placebo	67	-3.6	12	-2.6	19	-1.2

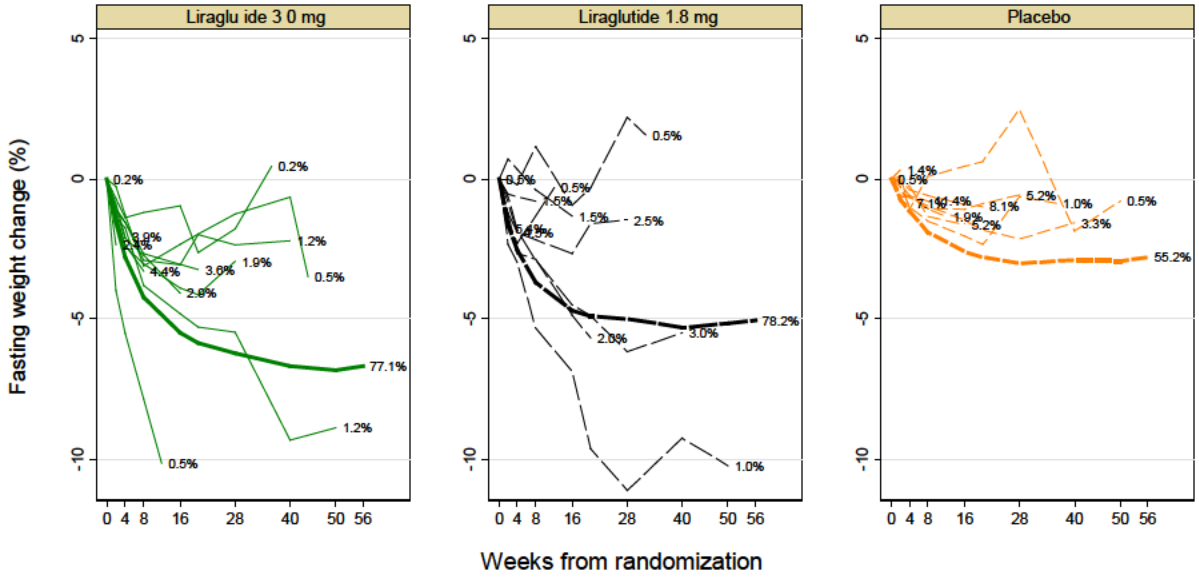
* Based on last available observation

Figure 6. Mean profile of fasting bodyweight change (%) by last available on-treatment follow-up visit (FAS, Trial 1839)



Reference ID: 3627768

Figure 7. Mean profile of fasting bodyweight change (%) by last available on-treatment follow-up visit (FAS, Trial 1922)



<u>Missing Data in Trials 1839, 1922, and 1923</u>: A sizable proportion of subjects did not have a have a 56 week weight assessment, with missing data occurring more frequently in the placebo group than in the liraglutide 3.0 mg group (Table 7). Across trials the proportion of missing data ranged from 17% to 20% for liraglutide 3.0 mg and from 19% to 26% for placebo. Importantly, these frequencies do not reflect the extent of missingness or treatment adherence as it relates to the primary analysis which was based on LAO-OT; the proportion of randomized subjects that did not have an on-treatment assessment at the week 56 visit ranged from 25% to 27% for liraglutide 3.0 mg and was more favorable than the 31% to 45% for placebo.

Included in the counts of subjects with a week 56 assessment are subjects that prematurely discontinued the study but returned for an assessment 56 weeks after randomization ("retrieved dropout"). The majority of subjects that prematurely discontinued did not return for the 56 week assessment. The proportion of those returning did vary across treatment arms and trials. In the placebo group the proportion of subjects returning ranged from 25% to 39%, which was slightly worse that the 29% to 42% for liraglutide 3.0 mg.

In the sponsor's report on missing data they appropriately question whether subjects that did return are representative of those that did not return. It is also notable that study site also appears to impact the likelihood of returning for a follow-up assessment; sites that had a greater frequency of study discontinuations were less likely to have a follow-up assessment (Figure 8). A noteworthy example is the site that had none of the 23 subjects that discontinued returned for the 56 week assessment. How this additionally impacts the representativeness of subjects that did not return for a follow-up assessment is unclear, but it raises concern that site investigators did not uniformly adhere to the study protocol.

Reference ID: 3627768

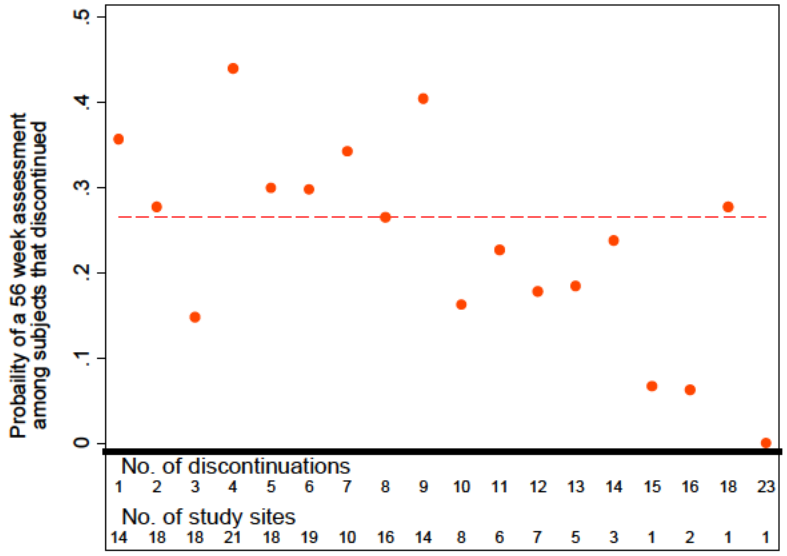
Table 7. Summary of missing data at week 56 (Trials 1839, 1922 and 1923)

	1839		1922			1923	
	Lira 3.0 mg N=2487	**Placebo N=1244**	**Lira 3.0 mg N=423**	**Lira 1.8 mg N=211**	**Placebo N=212**	**Lira 3.0 mg N=212**	**Placebo N=210**
Missing	492 (20%)	318 (26%)	67 (16%)	39 (18%)	56 (26%)	35 (17%)	39 (19%)
Available	1995 (80%)	926 (74%)	356 (84%)	172 (82%)	156 (74%)	177 (83%)	171 (81%)
On-treatment	1811 (73%)	818 (66%)	317 (75%)	158 (75%)	116 (55%)	156 (74%)	144 (69%)
Retrieve dropout	180 (7%)	103 (8%)	36 (9%)	11 (5%)	23 (11%)	21 (10%)	25 (12%)
Other‡	4 (0%)	5 (0%)	3 (1%)	3 (1%)	17 (8%)	0 (0%)	2 (1%)

Source: FDA statistical reviewer

‡ A subject that had a fasting weight measurement within the visit window for the primary landmark visit (56 weeks ± 3 days) but was neither retrieve dropout or on-treatment.

Figure 8. Relationship between mean proportion of having a retrieve dropout assessment and the number of discontinuations in a study site (Trial 1839)



<u>Comparison of LAO-OT and responses at week 56</u>: This section presents findings from an empirical comparison of responses at LAO-OT and at week 56 for subjects that discontinued but returned for a week 56 assessment. The importance of this comparison is it enables us to emperically evaluate whether the sponsor's imputation of the response at week 56 in the primary analysis can be accurately described by LAO-OT.

Notable differences between weight measured at both times were observed (Table 8), which include:

- For liraglutide the change from baseline at the LAO-OT over-estimates the change at week 56. The proportion of subjects that maintained their weight reduction from their LAO-OT to week 56 was low for the 3.0 mg dose, with only 29%, 30%, and 8% doing so in Trials 1839, 1922, and 1923, respectively.

Reference ID: 3627768

- For placebo the change from baseline at the LAO-OT consistently under-estimated the weight reduction at week 56.
- The responses at week 56 had greater variability than the responses at the LAO-OT. This finding was consistent across trials and treatment groups.

These finding provide empirical confirmation that the primary analysis cannot be used to describe the ITT effect.

Table 8. Comparison of fasting weight change (%) at LAO-OT and week 56 for subjects that discontinued and returned for a week 56 follow-up assessment

Treatment Group	N	Imputed (LAO-OT) Mean change from baseline (SE)	Actual Mean change from baseline(SE)	Mean Difference; Week 56 –LAO-OT
Trial 1839				
Liraglutide 3.0 mg	171	-4.9% (0.4)	-3.0% (0.6)	1.8%
Placebo	100	-0.4% (0.4)	-1.3% (0.7)	-0.9%
Trial 1922				
Liraglutide 3.0 mg	33	-4.4% (0.7)	-2.5% (0.8)	1.8%
Liraglutide 1.8 mg	8	-4.3% (1.3)	-2.4% (1.8)	1.9%
Placebo	23	-1.4% (0.4)	-1.7% (0.7)	-0.3%
Trial 1923				
Liraglutide 3.0 mg	12	-6.4% (1.0)	-1.1% (1.9)	5.3%
Placebo	18	-0.5% (1.0)	-1.1% (2.0)	-0.5%

Source: FDA statistical reviewer

For the 5% responder endpoint, differences were observed between the frequency of 5% responders based on the imputation using LAO-OT and their actual response at week 56. In Trial 1839 the proportion of 5% responders for placebo using LAO-OT under-estimated the response rate at week 56 (9% vs. 22%); for liraglutide the proportion of responses were fairly similar (LAO-OT: 34%; week 56: 32%). In Trial 1923, the proportion subjects that were able to maintain their baseline weight (i.e., the weight after a 5% reduction during the LCD run-in) was over-estimated at week 56 using LAO-OT for liraglutide (LAO-OT: 11/12; week 56: 7/12) and under-estimated using LAO-OT for placebo (LAO-OT: 7/18; week 56: 11/18).

Completers, retrieved dropouts and non-retrieved dropouts in Trials 1839, 1922, and 1923: This section summarizes patient characteristics and disposition for completers, retrieved dropouts, and non-retrieved dropouts for Trials 1839 (Table 9), 1922 (Table 10) and 1923 (Table 11). Non-retrieved subjects are those that discontinued but did not return for a follow-up assessment. Note that the groups are not related to whether they have primary endpoint assessment. For example, some retrieved subjects have a non-fasting bodyweight measurement for week 56 and are considered to have a missing endpoint. Since these groups are defined by post-baseline events they do not preserve the integrity of randomization. The following differences were observed:

- The non-retrieved dropout group tended to be younger on average than either the completer or retrieved dropout groups. This observation was consistent across treatment arms and trials.
- Within a treatment arm and trial, the distribution of gender was reasonably similar across the groups. One possible exception is liraglutide 3.0 mg arm in Trial 1923, where males

Reference ID: 3627768

represented 16% of completers, 27% of retrieved dropouts, and 10% of non-retrieved dropouts.

- There were regional differences across the groups, with there being disproportionately more in the non-retrieved dropout group being from the US. This observation was consistent across treatment arms and trials.
- Subject disposition was associated with the groups, with the retrieved dropouts being more likely to have discontinued due to an adverse event than in the non-retrieved dropouts. This observation was consistent across treatment arms and trials.

Table 9. Demographic and baseline characteristics by completer and retrieved dropout status (Trial 1839)

	Liraglutide 3.0 mg			**Placebo**		
	Completers N=1789	**Retrieved Dropout N=195**	**Non-Retrieved Dropout N=503**	**Completers N=801**	**Retrieved Dropout N=108**	**Non-Retrieved Dropout N=335**
Age (years)						
Mean (SD)	46 (12)	46 (13)	41 (12)	46 (12)	46 (11)	42 (12)
Median (Q1, Q3)	47 (38, 55)	45 (36, 57)	39 (31, 51)	46 (38, 55)	47 (37, 55)	42 (32, 51)
≥ 65	100 (6%)	19 (10%)	17 (3%)	54 (7%)	6 (6%)	9 (3%)
Gender: Males	386 (22%)	40 (21%)	104 (21%)	180 (22%)	14 (13%)	79 (24%)
Race:						
White	1528 (85%)	175 (90%)	404 (80%)	696 (87%)	90 (83%)	275 (82%)
Black	167 (9%)	15 (8%)	60 (12%)	66 (8%)	11 (10%)	37 (11%)
Country: US	723 (40%)	83 (43%)	280 (56%)	334 (42%)	49 (45%)	170 (51%)
Weight (kg)						
Mean (SD)	106 (21)	105 (23)	107 (21)	107 (23)	103 (21)	106 (19)
Median (Q1, Q3)	103 (92, 117)	99 (90, 117)	104 (92, 118)	103 (91, 118)	99 (89, 113)	102 (92, 118)
BMI (kg/m^2)						
Mean (SD)	38 (6)	38 (7)	39 (6)	38 (7)	38 (6)	38 (6)
Median (Q1, Q3)	37 (33, 41)	37 (33, 42)	38 (34, 42)	37 (34, 42)	37 (33, 41)	38 (34, 41)
≥ 30	1739 (97%)	187 (96%)	495 (98%)	767 (96%)	105 (97%)	328 (98%)
HbA1c (%)						
Mean (SD)	5.6 (0.4)	5.5 (0.3)	5.5 (0.4)	5.6 (0.4)	5.6 (0.3)	5.5 (0.4)
Median (Q1, Q3)	5.6 (5.4, 5.9)	5.6 (5.3, 5.7)	5.5 (5.3, 5.8)	5.6 (5.3, 5.8)	5.6 (5.3, 5.8)	5.5 (5.3, 5.8)
≥ 8.5%	15.0 (0.8%)	4.0 (2.1%)	11.0 (2.2%)	5.0 (0.6%)	1.0 (0.9%)	4.0 (1.2%)
Subgroups						
With Pre-diabetes	1110 (62%)	121 (62%)	297 (59%)	505 (63%)	67 (62%)	185 (55%)
Without Pre-diabetes	679 (38%)	74 (38%)	206 (41%)	296 (37%)	41 (38%)	150 (45%)
Discontinuation						
Adverse event	-	104 (53%)	134 (27%)	-	16 (14%)	29 (9%)
Ineffective therapy	-	8 (4%)	15 (3%)	-	9 (8%)	27 (8%)
Non-compliance	-	9 (5%)	56 (11%)	-	8 (7%)	30 (9%)

D&E-Diet and Exercise; OAD-oral antidiabetic; Mono-Monotherapy; Combo-Combination therapy

Reference ID: 3627768

Table 10. Demographic and baseline characteristics by completer and retrieve dropout status (Trial 1922)

	Liraglutide 3.0 mg			Placebo		
	Completers N=324	**Retrieved Dropout N=36**	**Non-Retrieved Dropout N=63**	**Completers N=140**	**Retrieved Dropout N=23**	**Non-Retrieved Dropout N=49**
Age (years)						
Mean (SD)	55 (10)	58 (12)	53 (13)	56 (9)	57 (10)	50 (11)
Median (Q1, Q3)	56 (49, 62)	60 (54, 67)	53 (41, 62)	56 (50, 64)	55 (50, 65)	49 (45, 56)
≥ 65	59 (18%)	14 (39%)	12 (19%)	27 (19%)	6 (26%)	5 (10%)
Gender: Males	169 (52%)	17 (47%)	34 (54%)	63 (45%)	11 (48%)	23 (47%)
Race:						
White	270 (83%)	32 (89%)	51 (81%)	118 (84%)	21 (91%)	36 (73%)
Black	30 (9%)	2 (6%)	12 (19%)	16 (11%)	1 (4%)	10 (20%)
Country: US	157 (48%)	11 (31%)	39 (62%)	75 (54%)	7 (30%)	34 (69%)
Weight (kg)						
Mean (SD)	105 (21)	96 (19)	112 (27)	106 (21)	107 (15)	107 (24)
Median (Q1, Q3)	102 (90, 118)	91 (85, 109)	108 (95, 122)	105 (92, 117)	107 (96, 119)	105 (91, 119)
BMI (kg/m^2)						
Mean (SD)	37 (6)	35 (6)	38 (7)	37 (7)	37 (5)	37 (8)
Median (Q1, Q3)	36 (32, 41)	32 (30, 39)	38 (33, 41)	37 (32, 41)	36 (33, 41)	35 (31, 41)
≥ 30	287 (89%)	26 (72%)	58 (92%)	122 (87%)	21 (91%)	39 (80%)
HbA1c (%)						
Mean (SD)	7.9 (0.8)	8.0 (0.9)	8.1 (0.8)	7.8 (0.7)	8.2 (0.8)	8.2 (0.9)
Median (Q1, Q3)	7.7 (7.3, 8.4)	7.9 (7.1, 8.8)	8.0 (7.4, 8.6)	7.6 (7.3, 8.2)	8.0 (7.7, 8.7)	8.2 (7.4, 9.0)
≥ 8.5%	83 (26%)	15 (42%)	22 (35%)	30 (21%)	9 (39%)	20 (41%)
Subgroups						
D&E or OAD Mono	219 (68%)	26 (72%)	45 (71%)	95 (68%)	13 (57%)	39 (80%)
OAD Combo	105 (32%)	10 (28%)	18 (29%)	45 (32%)	10 (43%)	10 (20%)
Discontinuation						
Adverse event	-	22 (61%)	17 (27%)	-	3 (13%)	4 (8%)
Ineffective therapy	-	0 (0%)	0 (0%)	-	2 (9%)	1 (2%)
Non-compliance	-	3 (8%)	9 (14%)	-	3 (13%)	10 (20%)
Other	-	2 (6%)	14 (22%)	-	2 (9%)	10 (20%)
Withdrawal criteria	-	9 (25%)	23 (37%)	-	13 (57%)	24 (49%)

D&E-Diet and Exercise; OAD-oral antidiabetic; Mono-Monotherapy; Combo-Combination therapy

Reference ID: 3627768

Table 11. Demographic and baseline characteristics by completer and retrieve dropout status (Trial 1923)

	Liraglutide 3.0 mg			Placebo		
	Completers N=159	**Retrieved Dropout N=22**	**Non-Retrieved Dropout N=31**	**Completers N=146**	**Retrieve Dropout N=25**	**Non-Retrieve Dropout N=39**
Age (years)						
Mean (SD)	48 (11)	42 (13)	38 (12)	47 (10)	46 (13)	43 (11)
Median (Q1, Q3)	48 (39, 56)	41 (32, 50)	34 (29, 46)	47 (39, 56)	48 (37, 56)	44 (34, 51)
≥ 65	8 (5%)	2 (9%)	1 (3%)	9 (6%)	1 (4%)	0 (0%)
Gender: Males	25 (16%)	6 (27%)	3 (10%)	32 (22%)	6 (24%)	7 (18%)
Race:						
White	128 (81%)	18 (82%)	24 (77%)	132 (90%)	21 (84%)	32 (82%)
Black	24 (15%)	3 (14%)	5 (16%)	14 (10%)	4 (16%)	6 (15%)
Country: US	130 (82%)	17 (77%)	27 (87%)	113 (77%)	20 (80%)	35 (90%)
Weight (kg)						
Mean (SD)	101 (22)	97 (13)	98 (21)	97 (20)	109 (22)	98 (24)
Median (Q1, Q3)	99 (85, 110)	96 (88, 103)	98 (81, 112)	95 (83, 106)	110 (91, 131)	90 (81, 106)
BMI (kg/m^2)						
Mean (SD)	36 (6)	35 (5)	36 (6)	35 (5)	38 (7)	36 (7)
Median (Q1, Q3)	34 (32, 39)	34 (32, 37)	36 (30, 40)	34 (30, 38)	34 (33, 42)	34 (30, 38)
≥ 30	142 (89%)	17 (77%)	25 (81%)	118 (81%)	24 (96%)	29 (74%)
HbA1c (%)						
Mean (SD)	5.6 (0.4)	5.5 (0.5)	5.4 (0.4)	5.5 (0.4)	5.7 (0.4)	5.5 (0.4)
Median (Q1, Q3)	5.6 (5.3, 5.9)	5.7 (5.2, 5.8)	5.3 (5.0, 5.6)	5.5 (5.3, 5.7)	5.7 (5.5, 6.0)	5.5 (5.2, 5.8)
≥ 8.5%	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subgroups						
Co-morbid cond.	78 (49%)	11 (50%)	5 (16%)	69 (47%)	14 (56%)	13 (33%)
Non-comorbid cond.	81 (51%)	11 (50%)	26 (84%)	77 (53%)	11 (44%)	26 (67%)
Discontinuation						
Adverse event	-	13 (59%)	5 (16%)	-	11 (44%)	7 (18%)
Ineffective therapy	-	0 (0%)	0 (0%)	-	2 (8%)	0 (0%)
Non-compliance	-	1 (5%)	7 (23%)	-	0 (0%)	5 (13%)
Other	-	3 (14%)	7 (23%)	-	3 (12%)	12 (31%)
Withdrawal criteria	-	5 (23%)	12 (39%)	-	9 (36%)	15 (38%)

Reference ID: 3627768

3.2.2.2 Patient Demographic and Baseline Characteristics

Across trials differences in patient demographic and baseline characteristics were observed (Table 12) and reflective of the different obese and overweight populations that were studied. In the diabetes trial (1922) the subjects tended to be older on average compared to the trials that enrolled non-diabetics. In the OSA trial (Trial 3970) the subjects were the heaviest on average compared to subjects in the other trials.

Across trials the subjects were predominately White (74% to 98%). There were differences in the sex of subjects across trials. The frequency of males and females was equal in Trial 1922, greatly favored males in Trial 3970 (72%), and greatly favored females in Trials 1807, 1839, and 1923 (76% to 81%). At baseline, the average weight and BMI ranged between 97 to 118 kg and 34 to 39 kg/m^2, respectively.

Table 12. Patient demographic and baseline characteristics by trial

	1807 N = 564	**1839 N = 3731**	**1922 N = 846**	**1923 N = 422**	**3970 N = 359**
Age (years)					
Mean (SD)	46 (10)	45 (12)	55 (11)	46 (11)	49 (10)
Median (Q1, Q3)	46 (39, 54)	45 (36, 54)	56 (48, 63)	46 (38, 55)	50 (42, 56)
≥ 65	2 (0%)	205 (5%)	157 (19%)	21 (5%)	0 (0%)
Gender: Males	135 (24%)	803 (22%)	425 (50%)	79 (19%)	258 (72%)
Race:					
White	555 (98%)	3168 (85%)	705 (83%)	355 (84%)	265 (74%)
Black	6 (1%)	356 (10%)	98 (12%)	56 (13%)	69 (19%)
Country: US	0 (0%)	1639 (44%)	418 (49%)	342 (81%)	324 (90%)
Weight (kg)					
Mean (SD)	97 (13)	106 (21)	106 (21)	100 (21)	118 (24)
Median (Q1, Q3)	96 (88, 105)	103 (91, 118)	103 (91, 118)	97 (84, 110)	113 (100, 134)
BMI (kg/m^2)					
Mean (SD)	34 (3)	38 (6)	37 (7)	36 (6)	39 (7)
Median (Q1, Q3)	34 (32, 36)	37 (34, 42)	36 (32, 41)	34 (31, 39)	38 (34, 43)
≥ 30	538 (95%)	3621 (97%)	730 (86%)	355 (84%)	359 (100%)
≥ 35	207 (37%)	2426 (65%)	470 (56%)	191 (45%)	249 (69%)
≥ 40	4 (1%)	1241 (33%)	252 (30%)	88 (21%)	12 (36%)
HbA1c (%)					
Mean (SD)	5.6 (0.4)	5.6 (0.4)	7.9 (0.8)	5.6 (0.4)	5.6 (0.4)
Median (Q1, Q3)	5.6 (5.3, 5.8)	5.6 (5.3, 5.8)	7.8 (7.3, 8.5)	5.6 (5.3, 5.8)	5.7 (5.4, 5.9)
≥ 8.5%	9 (2%)	9 (0.2%)	241 (28%)	63 (13%)	1 (0.3%)
Subgroups					
With Pre-diabetes	-	2285 (61%)	-	-	-
Without Pre-diabetes	-	1446 (39%)	-	-	-
D&E or OAD Mono	-	-	582 (69%)	-	-
OAD Combo	-	-	264 (31%)	-	-
Co-morbid cond.	-	-	-	190 (45%)	-
Non-comorbid cond.	-	-	-	232 (55%)	-

D&E-Diet and Exercise; OAD-oral antidiabetic; Mono-Monotherapy; Combo-Combination therapy

Reference ID: 3627768

3.2.3 Statistical Methods

Sample Size: The sample size assumptions used for the Phase 3 Trials are described below. The trials, in particular Trial 1839, are over-sized for the efficacy endpoints to comply with safety considerations outlined in the Draft FDA Guidance on weight management. The Guidance recommends approximately 3,000 subjects are randomized to active doses and no fewer than 1,500 subjects are randomized to placebo.

For Trials 1839 and 1922:

- A placebo-adjusted difference of 5.82 kg and 3.36 kg for the 3.0 mg and 1.8 mg dose, respectively, and a standard deviation (SD) of 5.9 kg. These estimates were obtained from Trial 1807.
- The proportion of 5% and 10% responders was assumed to be 75% and 37% for the 3.0 mg dose respectively, 53% and 27% for the 1.8 mg dose respectively (Trial 1922), and 28% and 10% in placebo respectively. These estimates were obtained from Trial 1807.

For Trial 1923:

- A placebo-adjusted difference of 6% with SD of 11%. No justification for the expected mean difference was provided in the protocol. The SD was obtained from a study involving topiramate (Astrup et al.[1]).
- The proportion of subjects maintaining weight at randomization is 79% and 61% in the liraglutide and placebo group, respectively. A justification for these proportions was not provided in the protocol.

For Trial 3970:

- A difference of 6 events per hour assuming a SD of 17. The estimated SD was obtained from two randomized trials of OSA (Johansson et al.[2] [34] and Forster et al[3]33). For the expected difference the sponsor notes that no clinically relevant change in AHI has been established. The expected difference is based the expected difference in AHI when inducing a 6 kg difference between in weight loss, based on Trials 1807 and 1923.

Analysis Populations: All trials used the same definition for the analysis populations, with exceptions as described below:

Full analysis set (FAS): The FAS was the primary analysis population, and included all randomized subjects exposed to at least one dose of the trial product and with at least post-baseline assessment of body weight in Trials 1807 and 1923, or of any efficacy endpoint in Trials 1839 and 1922. The FAS in Trial 3970 was defined as all randomized subjects. This

[1] Astrup et al. Topiramate: Long-Term Maintenance of Weight Loss Induced by a Low-Calorie Diet in Obese Subjects. Obesity Research 2004; 12:1658-1669

[2] Johansson K et al. Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomized controlled trial: prospective observational follow-up study. BMJ 2011; 342:d3017.

[3] Foster GD et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med 2009; 169(17):1619-1626.

Reference ID: 3627768

population is consistent with the modified ITT population defined in the Draft FDA Guidance (Box 2).

Completers: The Completer population includes subjects in the FAS with a valid end of trial efficacy assessment.

Statistical methods for the primary efficacy endpoints:

Primary analysis models— Consistent with the Draft FDA Guidance for weight management, the primary analysis was performed on the FAS using LAO-OT to impute the endpoint if the subject was no longer on-treatment at the landmark visit. In Trial 1922 the analysis used the last available observation on treatment prior to glycemic rescue to impute the endpoint. Continuous primary endpoints were analyzed using an analysis of covariance (ANCOVA) model that included treatment, country, sex, baseline response, and randomization stratum as independent variables. Categorical endpoints were analyzed using a logistic regression model using the same independent variables.

In Trial 1922 using the pre-rescue on-treatment measurement has the potential to inflate the treatment effect based on the placebo group experiencing more rescue medication use overall which occurred earlier on average in the trial. With an abbreviated follow-up time the concern is that the full weight loss experience in the placebo group is truncated, resulting in under-estimate of the change from baseline.

Sensitivity analyses for the primary efficacy endpoints: In my opinion, the sponsor's sensitivity analyses used to assess the potential impact of missing data are inadequate. None of their analyses attempted to estimate the ITT effect at week 56 under a reasonable set of assumptions. Our recommended/preferred approach represent the missing week 56 response for subjects that prematurely discontinued using information from the subjects that also prematurely discontinued but returned for their week 56 assessment. This approach can be implemented only for Trials 1839, 1922 and 1923 because they retrieved dropouts. Additionally, I do not concur with the sponsor's definition/notion of missing data. Our notion is that all study subjects (if alive) have a weight at week 56, with their missing status being defined by whether or not the endpoint was assessed. Thus, the retrieved dropouts have a valid endpoint even though they were no longer receiving study drug. In the sponsor's investigation of missing data the majority of their analyses did not use a subject's actual off-treatment week 56 measurements. This approach has significant implications on the interpretation of treatment effect at week 56, as detailed for the sponsor's MMRM and imputation analysis below.

***Continuous endpoints (Sponsor's)*:** Below is a description of the sponsor's sensitivity analyses that are presented in this document. With the exception of the MMRM analyses the endpoint was analyzed using an ANCOVA model using the covariates in the primary analysis.

1. *Completers* –Subset analysis that includes subjects that did not have their endpoint imputed in the primary analysis.
2. *LOCF using last available observation (LAO)* – This is a traditional LOCF analysis that includes off-treatment measurement. Both fasting or non-fasting weight measurements were used. The analysis for Trial 1923 excluded post-rescue measurements.

Reference ID: 3627768

3. *Baseline observation carried forward (BOCF)* – This analysis carried baseline observation forward for subjects without a valid post-baseline assessment. Subjects had their week 56 response imputed using LAO-OT. This BOCF implementation is different than the traditional BOCF analysis, which imputes the baseline outcome value for participants who either dropout or having the primary endpoint missing. This analysis was applied to all randomized subjects. This analysis was not performed in Trial 1923.
4. *MMRM* –a longitudinal analysis of on-treatment fasting weights that set off-treatment measurements to missing. A contrast and 95% CI was constructed for the difference in percent weight change for liraglutide compared to placebo at week 56.
5. *Multiple imputation (MI)* – Off-treatment responses in both treatment groups were imputed assuming the distribution of their pre- and post- withdrawal values is the same as the distribution of placebo completers. Off-treatment follow-up measurements were not included in either the imputation or the analysis.

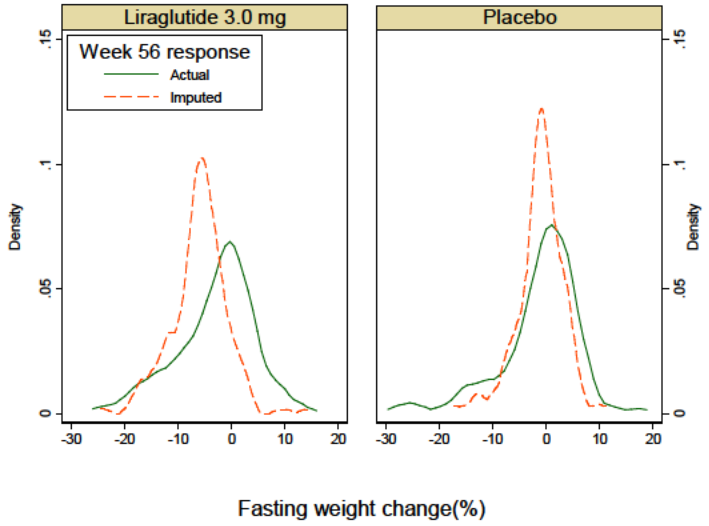
Comments on the limitation of the sponsor's MMRM and MI analysis:
MMRM—The MMRM model assumes missing data are missing at random. Under this assumption the statistical behavior of the missing data (given the observed responses and model covariates) is assumed to be the same as the observed data. Because the model uses only on-treatment observations, the model estimates the treatment effect at week 56 assuming all subjects in the FAS could adhere to randomized therapy, contrary to the fact that a sizable number could not. This analysis therefore attempts to estimate a treatment effect under conditions that were not observed in the clinical trials, nor could occur in clinical practice. Therefore, it is my opinion that the findings from this sensitivity analysis lack clinical relevance due to the underlying implausibility of achieving perfect treatment adherence.

Multiple imputation—The analysis anchors the imputed week 56 responses based on the placebo completers. Whether this is appropriate is debatable and was not justified by the sponsor. An assumption of their imputation model is, for a liraglutide treated subject, the on-treatment experiences are attributable to placebo and not the treatment received. Due to the sponsor's approach to missing data the implication of this assumption can be empirically evaluated. This was done for Trial 1839 by comparing the average imputed value with their actual value for the retrieved dropouts (Figure 9). It is evident that for liraglutide treated subjects the imputation model had them having greater average loss at week 56 than they actually did. The average decrease at week 56 from baseline was 6.1% based on the imputation, which was double the 3.0% average decrease that was actually observed and surprisingly greater than the 4.9% average decrease at the LAO-OT. For placebo the differences between imputed and observed values were not as dramatic. As a consequence of these findings, it is likely that this analysis will over-state the ITT effect at week 56.

Among the subjects in Trial 1839 without a week 56 measurement that had their primary endpoint imputed, it is not surprising that the imputation model had liraglutide treated subjects losing additional weight after going off-treatment. In particular, the average decrease at week 56 was 5.2% based on the imputation which was slightly greater than the 4.3% average decrease based on LAO-OT. For placebo the imputation model had subjects losing slightly more weight than LAO-OT, 1.3% vs. 1.0%.

Reference ID: 3627768

Figure 9. Kernel density plot (smoothed histogram) comparing the actual week 56 fasting weight change (%) with the average imputed value from the sponsor' MI analysis for subjects that discontinued and returned for a week 56 follow-up assessment (Trial 1839)



Source: FDA statistical reviewer

***Categorical endpoints*:** Below is a description of the sponsor's sensitivity analyses that are presented in this document. Instead of comparing event probabilities using the odds ratio metric from a logistic regression model as done by the sponsor, this review will present the risk difference due to the ease of interpretation. Unadjusted estimates will be provided along with asymptotic 95% confidence interval (CI).

1. *Completers* – See description above.

2. *Off-treatment as failures* (*FAIL*) – Subjects in the FAS without a valid week 56 assessment were classified as non-responders. This analysis is consistent with a sensitivity analysis described in the Draft FDA Guidance.

Sensitivity analyses for the primary efficacy endpoints done by FDA: Two sensitivity analyses were performed by FDA to attempt to estimate the ITT effect. This was not done in Trials 1807 and 3970 since subjects that prematurely discontinued were not asked to return for an assessment at the landmark visit. How subjects were handled was not uniform across trials due to the varying number of subjects that returned for a follow-up assessment after discontinuation. Additional details of the approaches are provided in the Appendix.

Due to the sponsor's unconventional BOCF algorithm, we also present, for completeness, results from a BOCF analysis that imputes the baseline outcome value for participants who either dropout or having the primary endpoint missing. This analysis is not done for Trial 1923 since baseline imputation may not be conservative due to the requirement that subjects lose 5% weight loss during the LCD run-in phase.

Reference ID: 3627768

Multiple imputation using retrieve dropout (MI-RD) – Our preferred approach imputes missing week 56 responses based on subjects that discontinued and had a week 56 fasting measurement. The imputation was done within groups defined by randomized treatment and the timing (month) of their last on-treatment measurement. Values were imputed using measurements from baseline and LAO-OT, when possible. This approach was not done for Trial 1923 and the liraglutide 1.8 mg arm in Trial 1922 due to the small number of retrieve dropouts; our preferred approach for Trial 1922 and comparison involving liraglutide 1.8 mg is described below.

For the continuous endpoints a total of 100 imputed datasets were created, and results were combined using Rubin's rule[4]. For the categorical endpoints response status was determined from the imputed continuous response. A total of 1000 imputed data sets were created. The imputed data were analyzed using a Beta-Binomial model with a uniform prior. For each imputed dataset a sample for each group was drawn from their respective posterior distribution, which thus incorporated imputation variability. Difference in probabilities was summarized using 50th, 2.5^{th} and 97.5^{th} percentiles of the distribution.

To understand the imputation analysis, the imputed week 56 response for Trial 1839 was compared to LAO-OT. Based on the weight gain after going off-treatment for liraglutide (Table 8) for retrieve dropouts, it is not surprising that our imputation model had liraglutide treated subjects gaining additional weight after going off-treatment. In particular, the average decrease at week 56 was 2.7% based on the imputation which was less than the 4.2% average decrease based on LAO-OT. Importantly, this trend is supported by the re-randomization period from this study, which found that subjects gained weight after switching from liraglutide to placebo for 12 weeks. The imputed values from our approach is notably different than the sponsor's imputation approach, which had them losing additional weight after going off-treatment. For placebo the imputation model had subjects losing slightly more weight than LAO-OT, 1.4% vs. 1.0%.

Retrieve dropout weighted analysis (RD-Weighted) – In this analysis subjects were assigned differential weights, which up-weighted the contribution of subjects that prematurely discontinued and returned for a week 56 measurement while those missing a week 56 measurement were assigned zero weight (and did not contribute to the analysis). A subject with an on-treatment or other week 56 measurement was assigned a weight of one. The degree to which a subject was up-weighted depended on their treatment group and the timing of their LAO-OT.

For the continuous endpoints the data were analyzed using a weighted ANCOVA model. For the categorical endpoints the weighted sample was analyzed using a Beta-Binomial model with a uniform prior. A total of 100,000 samples were taken for each treatment group, and the difference in probabilities was summarized using 50th, 2.5^{th} and 97.5^{th} percentiles of the distribution.

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[4] Rubin, D., *Multiple Imputation for Nonresponse in Surveys*, New York: Wiley & Sons (1987)

Reference ID: 3627768

Comments on the FDA analyses: The ideal scenario for estimating the treatment effect at week 56 would be to have data on all subjects at that time. Because we do not have complete endpoint ascertainment, we rely on the experiences of the retrieved dropouts to inform us of the experiences the non-retrieved dropouts may have had. This is also not optimal since the retrieved dropouts are not a random sample of the subjects that discontinued, making it unlikely that their experiences are statistically representative of the non-retrieved dropouts. However, it is our opinion that that the group that best reflects what happened to the non-retrieved dropouts at week 56, are the retrieved dropouts. For these reasons we cannot be assured that our analysis provides a statistical unbiased estimate of the treatment effect at week 56. However, it is my opinion that our analyses more faithfully captures the magnitude of the treatment effect at week 56 than the sponsor's primary analysis.

Approach to multiplicity: The Phase 3 trials (1839, 1922, 1923, 3970) individually preserved the study-wise type-I error at 5% by hierarchically testing the study endpoints according to their order in Table 3. Under this approach the statistical testing for an endpoint is performed only if the statistical test for the preceding endpoint in the hierarchy is statistically significant at the two-sided 5% level. For Trial 1922 that investigated two liraglutide doses, the hierarchy ordered the hypotheses for the 3.0 mg dose first followed by hypotheses for the 1.8 mg dose.

Approximately 15 to 20 secondary endpoints were prespecified for investigation in each of the Trials. None of the secondary endpoints, including those related to body composition in Trial 3970, were incorporated into the hierarchical testing sequence to preserve the study-wise type-I error.

For Trial 1807 the pairwise comparisons at week 20 between the separate liraglutide doses to placebo and orlistat were done using Dunnett's method for simultaneous confidence intervals. The nominal study-wise error was not preserved at the 5% level as a separate 5% alpha was used for the placebo comparison and the orlistat comparison.

3.2.4 Results

3.2.4.1 Trial 1807

Results from the analysis of primary endpoints at week 20 are shown below (Table 13). For both endpoints at week 20 only the 2.4 mg and 3.0 mg liraglutide doses had changes that were statistically significantly different than both placebo and orlistat, with the change for the 3.0 mg dose being more favorable. For the week 52 comparison (Table 14) the results should be interpreted extremely cautiously due to the likely bias resulting from a sizable number of subjects not consenting to the 84 week extension period. It is unclear what impact these subjects would have had if they continued in the study since they tended to have less favorable responses.

Reference ID: 3627768

Table 13. Analysis results for fasting weight change at week 20 in Trial 1807 (FAS, LOCF using LAO-OT)

Endpoint	Treatment Group	N	Adj. mean change from baseline / 5% response n (%)	Difference in means* / Risk difference Lira-Placebo (95% CI)	Difference in means* / Risk difference Orlistat-Placebo (95% CI)
Fasting weight change (kg)	Lira 3.0 mg	92	-7.2 kg	-4.4 kg (-5.9, -2.9)	-3.0 kg (-4.5, -1.4)
	Lira 2.4 mg	92	-6.3 kg	-3.5 kg (-5.0, -2.0)	-2.1 kg (-3.7, -0.6)
	Lira 1.8 mg	90	-5.5 kg	-2.8 kg (-4.3, -1.3)	-1.4 kg (-3.0, 0.2)
	Lira 1.2 mg	94	-4.8 kg	-2.1 kg (-3.6, -0.6)	-0.7 kg (-2.2, 0.9)
	Orlistat	95	-4.1 kg		
	Placebo	98	-2.8 kg		
5% responders	Lira 3.0 mg	92	70 (76%)	46.5% (33.9, 59.1)	31.9% (18.6, 45.1)
	Lira 2.4 mg	92	56 (61%)	31.3% (17.8, 44.7)	16.7% (2.5, 30.8)
	Lira 1.8 mg	90	18 (53%)	23.7% (10.0, 37.4)	9.1% (-5.2, 23.5)
	Lira 1.2 mg	94	49 (52%)	22.5% (9.0, 36.1)	7.9% (-6.3, 22.1)
	Orlistat	95	42 (44%)		
	Placebo	98	29 (30%)		

Source: FDA statistical reviewer
* Results for fasting weight are adjusted and for the 5% responder endpoint is unadjusted.

Table 14. Analysis results for fasting weight change at week 52 in Trial 1807 (FAS, LOCF using LAO-OT)

Endpoint	Treatment Group	N	Adj. mean change from baseline / 5% response n (%)	Difference in means / Risk difference Lira-Placebo (95% CI)	Difference in means / Risk difference Orlistat-Placebo (95% CI)
Fasting weight change (kg)	Lira 3.0 mg	92	-7.8 kg	-5.8 kg (-7.9, -3.7)	-3.8 kg (-6.0, -1.6)
	Lira 2.4 mg	92	-6.1 kg	-4.1 kg (-6.2, -2.0)	-2.2 kg (-4.4, -0.0)
	Lira 1.8 mg	90	-5.4 kg	-3.4 kg (-5.5, -1.2)	-1.5 kg (-3.7, 0.7)
	Lira 1.2 mg	94	-3.8 kg	-1.8 kg (-3.9, 0.4)	0.2 kg (-2.0, 2.4)
	Orlistat	95	-3.9 kg		
	Placebo	98	-2.0 kg		
5% responders	Lira 3.0 mg	92	68 (74%)	45.3% (32.7, 58.0)	28.6% (15.2, 42.1)
	Lira 2.4 mg	92	49 (53%)	24.7% (11.1, 38.3)	8.0% (-6.3, 22.3)
	Lira 1.8 mg	90	47 (52%)	23.7% (10.0, 37.3)	7.0% (-7.4, 21.3)
	Lira 1.2 mg	94	42 (45%)	16.1% (2.7, 29.6)	-0.6% (-14.8, 13.6)
	Orlistat	95	43 (45%)		
	Placebo	98	28 (29%)		

Source: FDA statistical reviewer

3.2.4.2 Trials 1839, 1922, and 1923

In each of the Phase 3 weight management trials all of the efficacy endpoints evaluated under the hierarchical testing sequence were statistically significant. To allow for a more fluid discussion of study findings the results will not be presented according to the pre-specified testing sequence. Furthermore, we caution contrasting results across trials since the trials differed in important way with respect to study design and study population.

Change in body weight: Results from the sponsor's primary analysis of the primary efficacy endpoint is shown in Table 15. In each of the Trials liraglutide 3.0 mg treated subjects had a statistically significant greater reduction in body weight change from baseline compared to

Reference ID: 3627768

placebo. For Trials 1839 and 1922 the confidence interval did not rule out the difference in average reduction for liraglutide compared to placebo of 5%.

In Trial 1922 the liraglutide 1.8 mg treated subjects had a statistically significant greater weight reduction compared to placebo, although the difference was not as large as the reduction observed for the 3.0 mg dose.

In our preferred analysis (MI-RD for Trials 1839 and 1922, and RD-Weighted for Trial 1923) the estimate of the ITT effect remained statistically significantly better than placebo (Table 16) but the magnitude of the estimated treatment effect was attenuated relative to the primary prespecified analysis. For Trial 1839 the estimated effect was 11% smaller and 15% smaller for Trials 1922 and 1923. In Trials 1839 and 1922 the findings from the MI-RD and RD-Weighted were reasonably aligned and were in-line with the FDA BOCF.

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

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

Source: FDA statistical reviewer

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

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

Source: FDA statistical reviewer

Responder endpoints: Results from the pre-specified primary analysis of the responder endpoints is shown in Table 15. In each trial for each of the two responder endpoints, the liraglutide 3.0 mg treated subjects had a statistically significant excess number of subjects respond compared to placebo. For Trials 1839 and 1922 the estimated proportion of liraglutide 3.0 mg treated subjects having a 5% response were notably greater than 35% and more than double the proportion in placebo.

Reference ID: 3627768

In Trial 1922 there was a statistically significantly greater number of 5% and 10% responders in the liraglutide 1.8 mg arm compared to placebo. The estimated proportion of 5% responders for the liraglutide 1.8 mg arm was just above 35% (36%) and more than double the proportion in placebo (14%).

In our preferred analysis the estimate of the ITT effect remained statistically significantly better than placebo (Table 18) but, similar to the findings from the continuous endpoint, the magnitude of the estimated treatment effect was attenuated relative to the primary prespecified analysis. The estimated risk difference for liraglutide 3.0 mg to placebo from the analysis is 28 per 100 in Trial 1839, and 31 per 100 in Trial 1922.

For Trials 1839 and 1922 this attenuation can be attributed the statistical model predicting a greater number placebo treated subjects having a 5% response compared to LAO-OT (Trial 1839: 34% vs. 27%; Trial 1922: 20% vs. 14%). For these two trials the estimated proportion of liraglutide 3.0 mg treated subjects having a 5% response remained above 35% and approximately double the proportion in placebo.

In the sensitivity analysis that that treated subjects that were off-treatment or had a missing week 56 response (FAIL), the estimated proportion of 5% responders for liraglutide 3.0 mg well above the 35% benchmark (1839: 54%; 1922: 45%) and more than double the proportion for placebo (1839: 24%; 1922: 11%).

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

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

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

Reference ID: 3627768

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

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

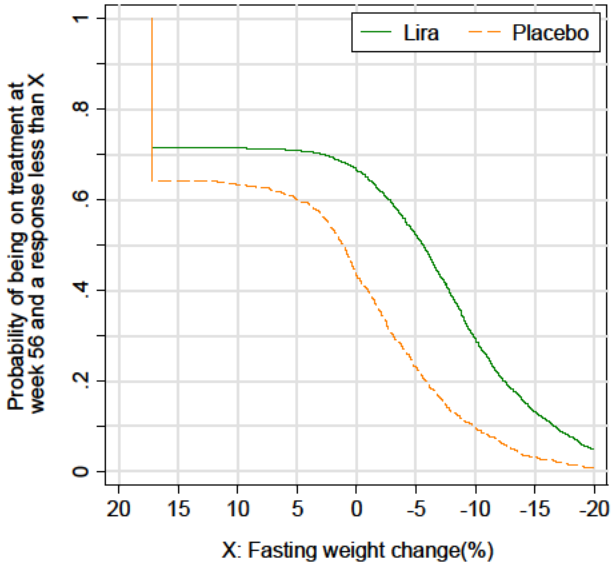
Source: FDA statistical reviewer

Cumulative distribution plots were constructed to allow investigating of different thresholds beyond those considered above. These figures are displayed below. Importantly, randomized subjects that were no longer on-treatment by week 56 and/or did not have an endpoint assessment were assigned the worst possible weight change. This resulted in the initial step in the curves and removes the problem problems introduced by using LOCF with LAO-OT.The expectation in such a plot is that if liraglutide was not efficacious the liraglutide curve would be similar or worse (due to potential adverse effects) than placebo over the changes from baseline that are considered meaning (e.g., > 5%). This was not what was observed, with the proportion of responders being greater in the liraglutide group.

This plot also enables one to answer the following question regarding a treatment decision: For a patient considering treatment with liraglutide for 56 weeks, how likely are they to stay on treatment for the intended duration and experience a change in fasting weight of a certain degree. Such a question could not be answered from a plot using LAO-OT.

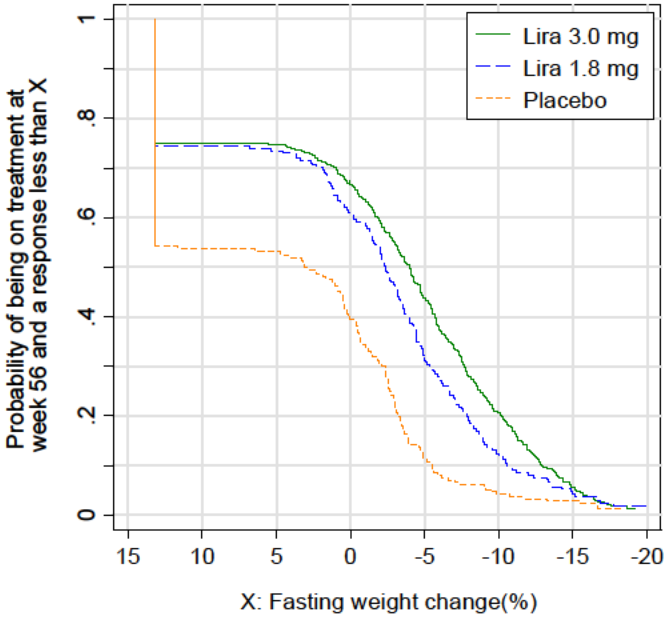
Reference ID: 3627768

Figure 10. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1839)



Source: FDA statistical reviewer

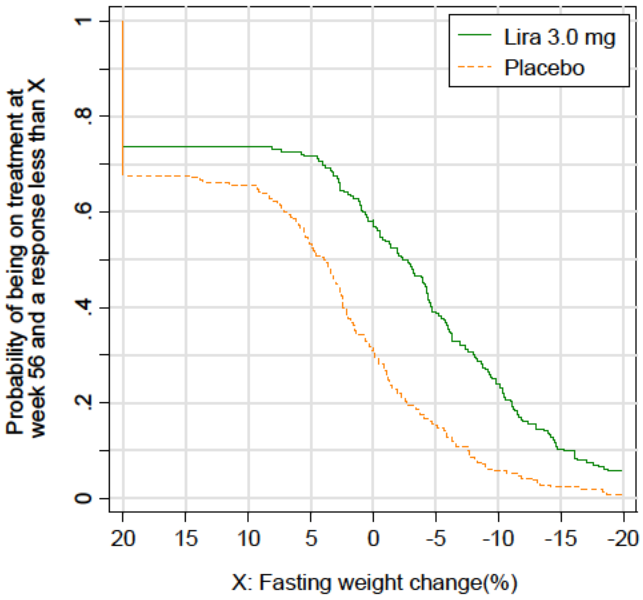
Figure 11. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1922)



Source: FDA statistical reviewer

Reference ID: 3627768

Figure 12. Empirical distribution plot of being on-treatment and fasting weight change (%) at week 56 (all randomized, Trial 1923)



Source: FDA statistical reviewer

Re-randomization Period in Trial 1839: A total of 701 subjects without pre-diabetes in the liraglutide group were re-randomized to liraglutide or placebo for an additional 12 weeks. At the end of the re-randomization period, subjects that were switched to placebo gained on average an additional 2.9% of their weight at week 56 compared to an increase of 0.7% for those that stayed on liraglutide (Table 19). The excess weight gain of 2.2% for placebo with 95% CI (1.8, 2.6) excludes zero.

Table 19. Analysis of re-randomization period (Trial 1839)

Treatment Group	N	Week 56 mean (kg) (SD)	Adj. mean change from week 56	Difference in adj. mean change; Liraglutide-Placebo (95% CI)
Liraglutide 3.0 mg	349	94 (21.5)	0.7%	-2.2% (-2.6, -1.8)
Placebo	347	94 (20.9)	2.9%	

Onset of T2DM in Trial 1839: The sponsor's briefing document for the September 11, 2014 advisory committee presented interim results for the development of T2DM. The counts are based on the overall sample and not those with pre-diabetes. Recall that the 4th co-primary endpoint for this study is the onset of T2DM in subjects with pre-diabetes at week 160. The sponsor reported that in the liraglutide group 4 subjects (0.2%) developed T2DM compared to 14 (1.1%) with placebo. Despite the small number of events, the lowering of the frequency of T2DM provides some evidence of the possible clinical benefit of liraglutide. This finding may not be surprising giving that liraglutide is approved for the treatment of T2DM. However, the presentation of interim results will present non-trivial multiplicity issues for the analysis and interpretation of the 160 week data.

Reference ID: 3627768

Secondary Endpoints

***Body Composition*:** Across trials, the liraglutide group had statistically significant reductions in the three secondary endpoints related to body composition. The excess reduction for the liraglutide group on these endpoints is in agreement with the reduction in the primary endpoint.

***Glucose*:** In Trial 1922 that was done in subjects with T2DM, both the 3.0 mg and 1.8 mg liraglutide arms had statistically significant reduction in HbA1c. The excess decrease in HbA1c was 0.9% and 0.7% compared to placebo for the 3.0 mg and 1.8 mg liraglutide dose, respectively. In the other trials the reduction was statistically significantly lower in the liraglutide group, although the magnitude of the decrease was notably smaller than in the 1922 (Trial 1839: 0.2%; Trial 1923: 0.3%). The clinical relevance of modest changes in glycemic parameters in a non-diabetic population is unclear.

***Lipids*:** Across trials, the liraglutide group had consistently had lower levels of triglycerides, LDL cholesterol and total cholesterol and increased HDL cholesterol. Based on these findings, the liraglutide arms did not appear to adversely affect these biomarkers.

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

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

FPG-Fasting Plasma Glucose

Reference ID: 3627768

3.2.4.3 Trial 3970

Results from the analysis of the primary efficacy endpoint (AHI) and the secondary body weight endpoints are shown in Table 20. For on-treatment changes in AHI up until week 32, liraglutide treated subjects had a statistically significant greater reduction from baseline relative to placebo; the excess reduction was -6.1 events/per hour with 95% CI (-11.0, -1.2). It is unclear whether changes of this magnitude are clinically meaningful since clinically relevant changes in AHI have not been established.

For the weight endpoints, compared to placebo by week 32 using LOCF with LAO-OT, the liraglutide treated subjects experienced an additional decrease in body weight of 4.2%, and an estimated additional 27.7 and 21.7 subjects per 100 treated that would have had weight reductions of at least 5% and 10%, respectively.

Table 20. Analysis results for change in AHI (events/hour) and secondary weight endpoints in Trial 3970 (FAS, LOCF using LAO-OT)

Endpoint	Treatment Group	N	Adj. mean change from baseline/ response n (%)	Diff. in means* Lira-Placebo (95% CI)
AHI	Liraglutide 3.0 mg	168	-12.2	-6.1 (-11.0, -1.2)
	Placebo	166	-6.1	
% change	Liraglutide 3.0 mg	175	-5.7%	-4.2% (-5.2, -3.1)
	Placebo	178	-1.6%	
5% responders	Liraglutide 3.0 mg	175	81 (46%)	27.7% (18.4, 37.1)
	Placebo	178	33 (19%)	
10% responders	Liraglutide 3.0 mg	175	41 (23%)	21.7% (15.2, 28.3)
	Placebo	178	3 (2%)	

Source: FDA statistical reviewer
* Results for AHI and fasting weight change (%) are adjusted and the responder endpoints are unadjusted.

3.3 Evaluation of Safety

The reader is referred to the following reviews for safety evaluations. The meta-analysis of cardiovascular events was reviewed by Dr. Rongmei Zhang of the Division of Biometrics VII. Other safety events were reviewed by Dr. Julie Golden of the Division of Metabolism and Endocrinology Products.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Comparison of the primary efficacy endpoint is summarized separately for the three phase 3 weight management trials in the table below.

The factors considered for the subgroup analyses include intrinsic factors (sex, age, race, region, weight, BMI) and study-specific factors. Study specific factors are the stratification factors, which were only evaluated in the study that used them as a stratification factor. These include pre-diabetes status (Trial 1839), baseline HbA1c (Trial 1922), background OAD treatment (Trial 1922), and co-morbidity status (Trial 1923).

Reference ID: 3627768

Subgroup analysis on the percent change in the fasting weight was conducted using the ANCOVA model used for the primary analysis with LOCF using the LAO-OT. Effect estimates were obtained from the model being fit within the individual level that defined the subgroup. Formal tests for interaction were not performed. The analysis was performed separately for each trial.

Across trials two factors that consistently favored one level over another were sex and weight. Females experienced more favorable weight reductions than males, and subjects that weighed less at baseline (below the sample median) lost more weight than those that weighed more at baseline (above the sample median). Because females tend to weigh less on average than males, it is possible that the effect observed for sex could be described, in part, by differences in baseline weight. The extent to which this does, however, is unclear.

Table 21. Results from subgroup analysis of fasting weight change (%, FAS with LOCF using LAO-OT)

		1839	**1922**	**1923**
Factor	**Level**	**Lira 3.0 mg - Pla. (95% CI)**	**Lira 3.0 mg - Pla. (95% CI)**	**Lira 3.0 mg - Pla. (95% CI)**
Sex	Female	-5.9% (-6.4, -5.4)	-4.9% (-6.0, -3.8)	-6.8% (-8.5, -5.2)
	Male	-3.5% (-4.4, -2.6)	-3.0% (-4.3, -1.7)	-2.7% (-5.3, -0.2)
Age	< 65 y.o.	-5.4% (-5.9, -5.0)	-3.8% (-4.7, -2.8)	-5.7% (-7.1, -4.3)
	≥ 65 y.o.	-4.7% (-6.6, -2.9)	-5.6% (-7.6, -3.6)	-10.6% (-19.3, -1.9)
Race	White	-5.8% (-6.9, -4.7)	-2.4% (-4.3, -0.5)	-5.6% (-8.8, -2.5)
	Non-White	-5.4% (-5.8, -4.9)	-4.3% (-5.2, -3.3)	-6.1% (-7.7, -4.5)
Region	Non-US	-5.2% (-5.8, -4.7)	-3.9% (-5.1, -2.7)	-8.8% (-12.2, -5.3)
	US	-5.6% (-6.3, -4.9)	-4.0% (-5.2, -2.8)	-5.4% (-6.9, -3.8)
Weight	≤ median	-5.9% (-6.5, -5.3)	-4.5% (-5.7, -3.3)	-7.0% (-9.1, -5.0)
	> median	-4.8% (-5.4, -4.2)	-3.3% (-4.5, -2.1)	-5.0% (-7.0, -3.0)
BMI	< 30 kg/m^2	-6.5% (-9.0, -4.1)	-4.6% (-6.7, -2.5)	-7.0% (-10.5, -3.5)
	≥30, < 40 kg/m^2	-4.5% (-5.3, -3.8)	-4.4% (-6.1, -2.7)	-5.1% (-8.2, -2.0)
	≥ 40 kg/m^2	-5.8% (-6.4, -5.3)	-3.8% (-5.0, -2.7)	-6.2% (-8.0, -4.4)
Pre-Diabetes	With	-5.5% (-6.1, -5.0)	-	-
	Without	-5.3% (-6.0, -4.5)	-	-
Background	D&E/Mono OAD	-	-3.9% (-4.9, -2.8)	-
	Combo OAD	-	-4.1% (-5.7, -2.6)	-
HbA1c	< 8.5%	-	-4.6% (-5.6, -3.5)	-
	≥ 8.5%	-	-2.5% (-3.8, -1.1)	-
Co-morbidity	Yes	-	-	-6.4% (-8.6, -4.2)
	No	-	-	-5.9% (-7.8, -4.0)

Reference ID: 3627768

5 SUMMARY AND CONCLUSIONS

5.1 Summary and Conclusions

The primary endpoint in four trials was change in body weight from baseline to either week 20 or week 56, and change in AHI from baseline to week 32 in the fifth. In all of the trials they included a liraglutide 3.0 mg arm. In three Phase 3 weight management trials designed to evaluate to change in body weight at liraglutide 56 weeks, the liraglutide 3.0 mg group had statistically significantly greater decreases in fasting body weight than placebo. This finding was consistent across both the sponsor's primary analysis and our preferred analysis (Table 1) that attempted to address shortcomings of the primary analysis.

I have concern that the sponsor's primary analysis exaggerates the treatment effect at week 56. The issue is their analysis imputes the response at the landmark visit using the last available observation while on-treatment and ignores measurements taken while off study drug. From an empirical evaluation it was found that the LAO-OT for the retrieved dropouts poorly describes their response at the landmark visit; the liraglutide group consistently gained weight after going off-treatment, and the placebo group consistently lost slightly more weight.

Based on our preferred analysis, the estimated average excess reduction in fasting weight was 4.8% in a non-diabetic population (Trial 1839) and 3.4% in the T2DM population (Trial 1922). After an initial weight loss using a LCD in Trial 1923, the estimated average excess reduction was 5.3%.

An interaction appears to exist for sex, with females consistently experienced more favorable weight reductions than males. This is also important as two of the three Phase 3 weight management trials had disproportionately more females (~80%).

The main statistical issues in this are:

- The use of LAO-OT to impute the response at the landmark visit in the sponsor's primary analysis. When an off-treatment measurement was available the analysis still used the LAO-OT.
- None of the sponsor's sensitivity analyses attempted to estimate the treatment effect at week 56 under a reasonable set of assumptions.

5.2 Recommendations for Labeling

Below are high-level recommendations for the label included with the NDA submission. For reference, Study 1 in the label corresponds to Trial 1839, Study 2 corresponds to Trial 1922, Study 3 corresponds to Trial 3970, and Study 4 corresponds to Trial 1923.

- The estimates of the weight loss at the landmark visit should not be (b) (4) Our recommendation is the estimates are derived from a statistical model that is in-line with the key feature of our analyses (i.e., represent the missing data based on the experiences of the retrieved dropouts). This cannot be done for Trial 3970 due to the fact that the study did not include retrieved dropouts.

Reference ID: 3627768

- The cumulative distribution plots should be derived using the same statistical model that will be used to summarize the primary endpoint.
- The difference in responders should be summarized using the risk difference (b) (4)
- Findings from the 1.8 mg dose should be presented for Trial 1922.
- (b) (4) .

Reference ID: 3627768

A. Appendix

A.1 Supportive Material

Definition of obstructive apnea and hypopnea events per study protocol (Section 3.2)

Apnea Rules
Score an apnea when all of the following criteria are met:

- There is a drop in the peak thermal sensor excursion by ≥90% of baseline
- The duration of the event lasts at least 10 seconds
- At least 90% of the event's duration meets the amplitude reduction criteria of apnoea

Hypopnea Rules
Score a hypopnea if all of the following criteria are met:

- The nasal pressure signal excursions (or those of the alternative hypopnea sensor) drop by ≥30% of baseline
- The duration of this drop occurs for a period lasting at least 10 seconds
- There is a ≥4% desaturation from pre-event baseline
- At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea

Details of the FDA sensitivity analyses

MI-RD –The imputation was done within groups defined by randomized treatment and the timing (month) of their last on-treatment measurement. In Trial 1839 the visits were grouped by month as follows: 0 to 1, 2 to 3, 4 to 6, 7 to 9, after 10. In Trial 1922 the visits were grouped based on whether the last on-treatment measurement was on or before month 5. For subjects in the FAS the imputation model, fit within each group, included baseline and last on-treatment measurement. Imputation for randomized subjects excluded from the FAS was done as follows. These subjects were first grouped with the subjects that had their last on-treatment measurement during the first time period (Trial 1839: 0 to month 1; Trial 1922: 0 to month 5). In the first step the missing week 56 response was imputed using only their baseline measurement. Next, the distribution of imputed values was centered per subject around their baseline measurement (i.e., MI version of BOCF). Stata program code for the analysis is provided in the section below.

RD-Weighted – Subjects with a week 56 assessment that were not a retrieve dropout were assigned an analysis weight of one. Subjects without a week 56 assessment were assigned an analysis weight of 0. The retrieve dropouts were assigned weights that depended on the time of their last on-treatment observation and randomized treatment. Specifically, the analysis weight assigned to a subject that was a retrieve dropout in group *i* was $(A_i + B_i)/A_i$ where A_i is the number of retrieve dropouts in the group and B_i is the number of subjects in the group with the missing endpoint. For Trial 1839 and 1922 the timing used to define the groups was based on the MI-RD analysis (see above). In Trial 1923 the visits were grouped based on whether the last on-treatment measurement was on or before month 4

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A.2 Additional Tables and Figures

Figure 14. Kaplan-Meier plot time-to-discontinuation—Adverse Event (Trial 1839)

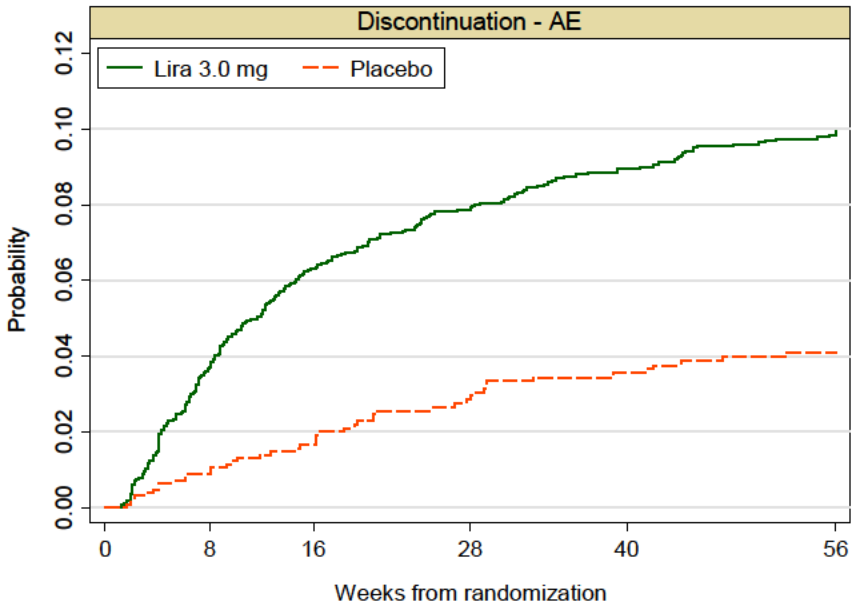


Figure 15. Kaplan-Meier plot time-to-discontinuation—Adverse Event (Trial 1922)

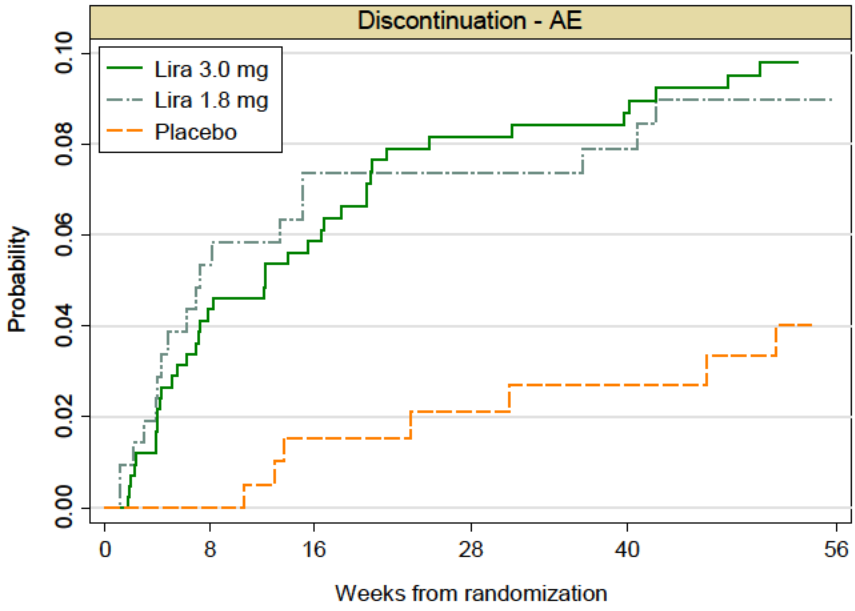
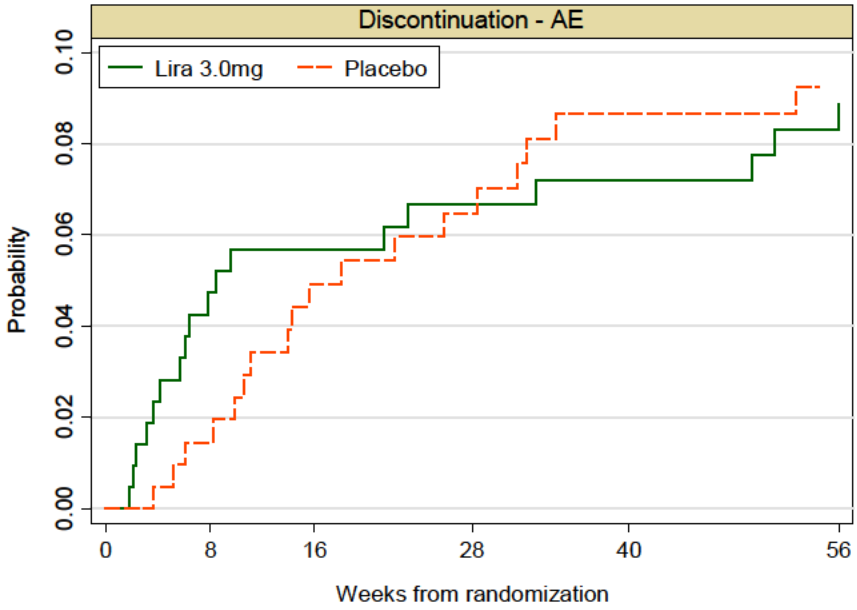


Figure 16. Kaplan-Meier plot time-to-discontinuation—Adverse Event (Trial 1923)



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BRADLEY W MCEVOY
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MARK D ROTHMANN
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I concur

THOMAS J PERMUTT
09/15/2014
I concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	206321
Drug Name:	liraglutide 3.0 mg injection
Indication:	Adjunct to diet and exercise for chronic weight management in adult patients with an initial BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with comorbidities
Applicant:	Novo Nordisk, Inc.
Date(s):	December 20, 2013 (Submission Date)
	October 20, 2014 (PDUFA Goal Date)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII (DBVII)
Statistical Reviewer:	Rongmei Zhang, PhD.
Concurring Reviewers:	Mat Soukup, PhD., Statistics Team Leader, DBVII
	Aloka Chakravarty, PhD., Division Director, DBVII
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Julie Golden, MD, Medical Officer, DMEP
	James Smith, MD, Medical Team Leader, DMEP
Project Manager:	Patricia Madara, DMEP

Keywords: weight management, cardiovascular safety, meta-analysis, Cox proportional hazards

Table of Contents

LIST OF TABLES **3**

LIST OF FIGURES **4**

1 EXECUTIVE SUMMARY **5**

2 INTRODUCTION **6**

2.1 PRODUCT DESCRIPTION AND REGULATORY BACKGROUND 6
2.2 CLINICAL TRIAL OVERVIEW 7
2.3 DATA SOURCES 8

3 STATISTICAL SAFETY EVALUATION **9**

3.1 DATA AND ANALYSIS QUALITY 9
3.2 CARDIOVASCULAR META-ANALYSIS IN WEIGHT MANAGEMENT 9
3.2.1 Designs of Trials Included in WM Meta-analysis *9*
3.2.2 Endpoints and Adjudication *11*
3.2.3 Statistical Methodology *12*
3.2.4 Patient Disposition, Demographic and Baseline Characteristics *14*
3.2.5 Analysis Findings *19*
3.3 CARDIOVASCULAR META-ANALYSIS IN TYPE 2 DIABETES MELLITUS 22
3.3.1. Designs of Trials Included in T2DM Meta-analysis *22*
3.3.2. Statistical Methodology *22*
3.3.3. Demographics *23*
3.3.4. Analysis Findings *23*

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS **26**

4.3. GENDER, RACE, AGE, AND GEOGRAPHIC REGION 26
4.4. OTHER SPECIAL/SUBGROUP POPULATIONS 27
4.5. LIRAGLUTIDE DOSE 28

5. SUMMARY AND CONCLUSIONS **28**

5.3. COLLECTIVE EVIDENCE AND STATISTICAL ISSUES 28
5.4. CONCLUSIONS AND RECOMMENDATIONS 29

APPENDIX I. COMPLETED CONTROLLED PHASE 2 AND 3 TRIALS AND EXTENSIONS IN THE T2DM DEVELOPMENT PROGRAMS TO BE INCLUDED IN THE ANALYSIS **31**

APPENDIX II. OVERVIEW OF UNCONTROLLED PHASE 2 AND 3 TRIALS AND EXTENSIONS IN TO BE EXCLUDED IN THE T2DM MAIN META-ANALYSIS. **32**

APPENDIX III. DISTRIBUTION OF DEMOGRAPHIC CHARACTERISTICS IN THE T2DM META-ANALYSIS. **33**

SIGNATURE DISTRIBTUION LIST **34**

Reference ID: 3626734

LIST OF TABLES

Table 1: Phase 2 and 3 clinical trials in the liraglutide weight management. 8
Table 2: Subjects switched treatment in the WM program. 13
Table 3: Pre-specified analyses in WM meta-analysis 13
Table 4: Trial Withdrawal Rates by trial and overall in the WM meta-analysis. 15
Table 5: Distribution of Demographic Characteristics in the WM meta-analysis. 18
Table 6: Distribution of Cardiovascular Risk Factors in the WM meta-analysis 19
Table 7: Summary of MACE overall and by trial in the WM primary analysis. 19
Table 8: Summary of first MACE by trial, treatment group, and type of events in the WM primary analysis. 20
Table 9: Pre-specified analyses in WM meta-analysis 21
Table 10: Summary of MACE overall and by trial in the T2DM main analysis. 24
Table 11: Summary of First MACE by trial, treatment group, and type of events in the T2DM meta-analysis[a]. 25
Table 12. MACE for subgroups gender, age, and geographic region. 27
Table 13 MACE for subgroups BMI, smoking status, history of CV disease, diabetes and hypertension. 28

Reference ID: 3626734

LIST OF FIGURES

Figure 1: Estimated probability of withdrawal by time across trials. 16
Figure 2: Estimated probability of withdrawal due to adverse event (AE) by time across trials. 16
Figure 3: Forest Plot of WM Primary Analysis of MACE across all trials. 21
Figure 4: Forest plot of T2DM on-treatment meta-analysis of MACE across all trials*.....26

Reference ID: 3626734

1 EXECUTIVE SUMMARY

This is a statistical safety review of a cardiovascular (CV) meta-analysis report submitted in New Drug Application, NDA 206321 (stamp date: December 20, 2013) for liraglutide 3.0 mg injection. The proposed indication is "adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of at least one weight related comorbidity". Prior to this submission, liraglutide was approved by the FDA in January 2010 for the treatment of type 2 diabetes mellitus (T2DM), and is currently marketed at doses up to 1.8 mg/day under the brand name, Victoza®.

The meta-analysis was conducted to investigate the effect of treatment with liraglutide for weight management (WM) compared to a pooled comparator group (placebo and active comparators) on cardiovascular (CV) safety. Per prior agreement with the FDA, there was no pre-specified risk margin to rule out for this meta-analysis in weight management. The primary endpoint was major adverse cardiovascular events (MACE), a composite endpoint comprising non-fatal myocardial infarction, non-fatal stroke, or CV death. The events were either prospectively or post hoc adjudicated, by an independent and blinded Event Adjudication Committee (EAC), which was governed under a charter.

The meta-analysis of CV safety included five WM trials (one phase 2 and four phase 3 clinical trials). The primary CV meta-analysis was performed using an *on treatment* population, which included all subjects exposed to a minimum of one dose of trial drug and included events occurring up to 30 days after last drug date. The primary analysis was a time-to-event analysis based on a Cox proportional hazard model stratified by trial with treatment (liraglutide vs. comparator) as a fixed effect.

There were a total of 5908 subjects included in the primary analysis, 3872 were randomized to liraglutide and 2036 were randomized to the comparator group. There were 17 (0.3%) confirmed MACE by the event adjudication committee, 8 (0.2%) for liraglutide and 9 (0.4%) for comparators. In the primary analysis using an "on treatment" censoring scheme, the estimated hazard ratio and two-sided 95% confidence interval for liraglutide vs. comparators was 0.40 (0.15, 1.05). Several sensitivity analyses including the analysis using an "on study" censoring scheme were conducted and the results were consistent with the primary analysis.

In addition, a meta-analysis of T2DM trials was conducted to support the findings from the WM meta-analysis. The results from the T2DM meta-analysis were consistent with the WM meta-analysis.

Based on the submitted WM meta-analysis, there was no apparent increase in CV risk identified in the liraglutide group compared to the comparator group. However, there are several limitations associated with this meta-analysis that need to be carefully considered. First, a limited number of MACE were observed in the WM program with relatively short treatment exposure times included in the meta-analysis. This limits the ability to make inferences on CV safety

Reference ID: 3626734

beyond one year of treatment with liraglutide. In addition, subjects enrolled in the WM trials may be at low risk of cardiovascular disease (9.0% a history of CV disease, 93.5% less than 65 years old, 14.5% diabetes, 2.9% hypertension, 14.9% smokers), which limits the ability to identify CV events in the trials included in the meta-analysis. Therefore, the current available data cannot be generalized to more at risk populations and caution is advised in interpreting findings from a meta-analysis with few events.

Note that the approval letter of liraglutide for T2DM (Victoza®) states that Novo Nordisk (NN)is required to conduct a post-marketing clinical trial to evaluate the effect of liraglutide on the incidence of major adverse cardiovascular events in patients with T2DM[1]. This trial might provide useful data to further assess the CV risk with liraglutide in subjects at sufficiently high risk of CV events with extended duration of follow-up. However, the lower dose of liraglutide for T2DM (1.8mg/day) may limit the ability to directly extrapolate the results from this trial to the liraglutide dose 3.0mg/day in the WM indication. Therefore, if liraglutide 3.0 mg is approved for the WM indication, the recommendation is that further assessment of risk of CV events be conducted through post-marketing studies if further characterization of the CV risk is needed for the WM indication.

2 INTRODUCTION

2.1 Product Description and Regulatory Background

Liraglutide is an acylated human glucagon-like peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1. The Applicant, Novo Nordisk (NN), submitted a New Drug Application, NDA 206321, for approval of liraglutide 3.0 mg injection for the treatment of weight management on December 20, 2013.

The proposed indication[2] for liraglutide 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.

According to the proposed label submitted by the Applicant, liraglutide 3.0 mg is to be administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, thigh or upper arm. The injection site and timing can be changed without dose adjustment. To improve gastro-intestinal tolerability, for all patients, the proposed starting dose is 0.6 mg, which is to be increased in increments of 0.6 mg up to 3.0mg with at least one week between intervals.

[1] See the FDA approved letter for NDA 022341.
[2] See annotated proposed labeling by the applicant.

Reference ID: 3626734

Prior to this submission, liraglutide was approved by the FDA in January 2010 for the treatment of type 2 diabetes mellitus (T2DM), and is currently marketed for this indication at doses up to 1.8 mg/day, under the brand name Victoza®.

This is a statistical safety review for the cardiovascular meta-analysis included in the weight management NDA submission. The cardiovascular (CV) assessment requirements for obesity drugs and biologics were discussed on the Endocrinologic and Metabolic Drugs Advisory Committee (AC) Meeting in March 2012. The majority of the AC members recommended that obesity drugs without a theoretic risk or signal for CV harm should be required to rule out a certain degree of excess CV risk prior to approval[3]. The trials included in the WM meta-analysis were not prospectively designed to assess CV risk because the liraglutide WM program was developed before the 2012 AC meeting. Therefore, per agreements with the FDA, the WM meta-analysis, which is the subject of this statistical review, was not conducted to rule out a pre-specified CV risk margin. Details regarding the CV meta-analysis approach were discussed with the Division of Metabolism and Endocrinology Products (DMEP) and reflected in the pre-NDA Meeting Minutes (September 10, 2013), and a teleconference (September 19, 2013), where the Agency provided guidance regarding the proposed approaches for assessing CV risk for liraglutide for obesity and agreed with the sponsor's proposal.

The CV meta-analysis for liraglutide was conducted based on the agreed upon Statistical Analysis Plan (SAP) dated November 10, 2013. The primary objective of the meta-analysis is to investigate the effect of treatment with liraglutide for weight management on CV safety, compared to a pooled comparator group (placebo and active comparators). The submission also included a supportive meta-analysis based on T2DM trials to support the WM meta-analysis (see Section 3.2.2 of this review for more details).

2.2 Clinical Trial Overview

Three development programs involving treatment with liraglutide were included in the meta-analysis conducted by NN. The WM meta-analysis included trials from liraglutide in WM development program (NN8022). The T2DM meta-analysis included trials of liraglutide from two T2DM development programs, NN2211 and NN9535.

Table 1 gives an overview of all phase 2 and 3 trials conducted by NN included in the WM meta-analysis. All five trials conducted in the WM program were randomized, double-blinded, placebo-controlled, and parallel-group designs. Except Trial 1922, all trials in the WM program excluded subjects with T2DM at baseline.

An overview of all phase 2-3 trials included in the T2DM meta-analysis is given in the Appendix I. All uncontrolled trials, uncontrolled extensions, and uncontrolled treatment groups were

[3] Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting, March 28-29, 2012. http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303352.pdf

Reference ID: 3626734

excluded from this meta-analysis (see Appendix II for the list of trials excluded). A total of 20 trials were included in the T2DM meta-analysis.

Table 1: Phase 2 and 3 clinical trials in the liraglutide weight management.

Trial ID/ Phase	Treatment duration/Trial period	Trial Design/randomization	Population	N (safety analysis set[a])
1807 Phase 2	Main (20 weeks) Jan. 10, 2007-Sept. 13, 2007 Extension (weeks 20-104 weeks) June 20, 2007-Apr. 30, 2009	Randomized, double-blind, placebo-controlled, six-armed parallel-group with an open label orlistat comparator arm. Randomization: 1:1:1:1:1:1 Weeks 20-52 (single-blinded): Subjects continued on their randomized treatment Weeks 52-104 (open-label): Liraglutide/placebo-treated subjects switched to liraglutide 2.4 mg and then gradually changed to 3.0 mg. Orlistat-treated subjects continued on orlistat. 2-week follow-up period after trial completion.	BMI: 30-40 kg/m^2. T2DM excluded	564 total Lira 1.2 mg: 95 Lira 1.8 mg: 90 Lira 2.4 mg: 93 Lira 3.0 mg: 93 Placebo: 98 Orlistat 120 mg: 95
1839 Phase 3	Main (56 weeks) and a re-randomization period (12 weeks) June 1, 2011-ongoing	Randomized, double-blinded, placebo-controlled, parallel-group trial. Randomization: 2:1 Subjects without pre-diabetes at screening: after completion of 56 weeks, lira-treated subjects were re-randomized to either lira or placebo in the following 12 weeks; placebo-treated subjects continued on placebo.	BMI: ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidemia or hypertension. T2DM excluded	3723 total Lira 3.0 mg: 2481 Placebo: 1242
1922 Phase 3	56 weeks June 1, 2011-Jan. 25, 2013	Randomized, double-blinded, placebo-controlled, three-armed, parallel-group trial. 12-week follow-up period after treatment completion. Randomization: 2:1:1	BMI: ≥30 kg/m^2 with T2DM	844 total Lira 1.8 mg: 210 Lira 3.0 mg: 422 Placebo: 212
1923 Phase 3	56 weeks Oct. 30, 2008-Sept. 1, 2010	Randomized, double-blinded, placebo-controlled, parallel-group trial. 12-week follow-up period after treatment completion. Randomization: 1:1	BMI: ≥30 kg/m^2 or ≥27 kg/m^2 with dyslipidemia or hypertension. T2DM excluded	422 total Lira 3.0 mg: 212 Placebo: 210
3970 Phase 3	32 weeks June 7, 2012-June 17, 2013	Randomized, double-blinded, placebo-controlled, parallel-group trial. 2-week follow-up period after treatment completion. Randomization: 1:1	BMI: ≥30 kg/m^2 with moderate or severe OSA. T2DM excluded	355 total Lira 3.0 mg: 176 Placebo: 179

Lira: liraglutide; BMI: body mass index; OSA: obstructive sleep apnea; T2DM: type 2 diabetes mellitus;
N: number of subjects randomized and received at least one dose of trial drug.
[a]: safety analysis set was defined as all randomized subjects receiving at least one dose of trial drug.
Source: created by the reviewer from Table 1-1 in the sponsor's report for Integrated Summary of Safety.

2.3 Data Sources

The NDA was submitted electronically and included integrated datasets comprising each of the trials included in the CV meta-analysis. The data was not submitted in CDISC standardized format. However, the submission included Study Data Reviewers Guide and data definition files that provided description of datasets content.

EDR location: \\Cdsesub1\evsprod\NDA206321\0001\m5\datasets.

Reference ID: 3626734

The following integrated datasets were used to perform statistical analyses in this review:

- "mace.xpt" which contains the time to event analysis variables.
- "s.xpt" which contains the demographic and disposition data
- "sae.xpt" which contains the subject adverse event
- "cvadj.xpt" which contains the cardiovascular events adjudication results
- "svis.xpt" which contains the subject information for each visit

A discussion of data quality is provided in Section 3.1 of this review.

3 STATISTICAL SAFETY EVALUATION

This is a statistical safety review that focuses on the CV safety meta-analysis for liraglutide in the weight management (WM) program. The T2DM meta-analysis is summarized to support the results from the WM meta-analysis. Please refer to separate statistical review by Dr. Bradley McEvoy for overall efficacy and safety evaluation.

3.1 Data and Analysis Quality

Using the submitted data and the data definition files, the reviewer was able to perform and reproduce all major findings included in the Applicant's CV meta-analysis study report. No major data quality issue was found.

3.2 Cardiovascular Meta-Analysis in Weight Management

3.2.1 Designs of Trials Included in WM Meta-analysis

The cut-off date for trials to be included in the meta-analysis is July 2, 2013, determined by the data base lock (DBL) date of the latest completing trial (NN8022-3970) in the WM program. The extension part (104 weeks) of the phase 3 trial NN8022-1839 is still ongoing. Using such a cut-off date, the WM CV meta-analysis includes one phase 2 dose-finding trial (trial NN8022-1807, duration 20 weeks with an 84-week extension) and four confirmatory phase 3 trials (trials NN8022-1839[56 weeks, main], NN8022-1822[56 weeks], NN8022-3970[32 weeks], and NN8022-1923[56 weeks]).

Summaries for each of the trials included in the meta-analysis (completed and ongoing) are provided below.

<u>NN8022-1807 main</u>: The main trial was a phase 2, 20-week, randomized, double-blinded, placebo-controlled, six-armed parallel-group, multi-center, multi-national trial. An open-label orlistat arm, representing an approved obesity treatment, was included as a reference treatment. Obese subjects (BMI $\geq$ 30 kg/m^2) without type 2 diabetes were randomized in a 1:1:1:1:1:1 manner, to receive one of the four doses of liraglutide (1.2 mg, 1.8mg, 2.4mg or 3.0mg once daily), placebo or orlistat treatment (120mg 3 times daily). The randomization was stratified

Reference ID: 3626734

based on gender. The main trial consisted of a screening visit, a 2-week single-blind placebo run-in period, a 4-week dose escalation period, a 16 week maintenance period, and a post-trial follow-up visit 4 to 10 days after Visit 12 for subjects not wishing to enter the extension period. The main trial was initiated on January 10, 2007 and completed on September 17, 2007.

NN8022-1807 extension: All subjects completing the 20 weeks treatment in the main trial were offered the opportunity to be enrolled in the extension period. A new informed consent for participation in the 84-week extension period was obtained before entering the extension period. (1) During weeks 20-52, subjects and investigators remained blinded to liraglutide/placebo treatment but the sponsor was unblinded. (2) After week 52, the trial was open-label (subjects, investigators and the sponsor were all unblinded). All subjects treated with liraglutide or placebo were initially treated with liraglutide 2.4 mg in the open-label period, but then all were gradually changed to treatment with liraglutide 3.0 mg. Subjects treated with orlistat in the main trial remained unchanged during the entire extension period. The extension trial was initiated on June 20, 2007 and completed on April 30, 2009.

NN8022-1839**:** A randomized, double-blinded, placebo controlled, parallel group, multi-center, multinational trial. Non-diabetic, obese subjects (BMI $\geq$ 30 kg/m^2) or overweight (BMI $\geq$ 27 kg/m^2) subjects with comorbidities (treated or untreated hypertension and/or dyslipidaemia) were randomized in a 2:1 manner to receive either liraglutide 3.0 mg or placebo. The randomization was stratified based on pre-diabetes status at screening (based on FPG[4], OGTT[5], and HbA_{1c}[6]) and BMI at baseline (BMI $\geq$ 30 kg/m^2, BMI < 30 kg/m^2).

Subjects classified at screening as not having pre-diabetes were randomized to 56 weeks of treatment, followed by a 12-week re-randomized treatment period and a 2-week follow-up period. In the re-randomized period, subjects treated with liraglutide 3.0 mg were re-randomized in a 1:1 manner to either continue treatment with liraglutide 3.0mg or to switch to placebo; subjects treated with placebo continued on placebo. Subjects classified at screening as having pre-diabetes were randomized to 160 weeks treatment (followed by a 12-week off drug/placebo observational follow-up period). The trial was initiated on June 1, 2011 and is still ongoing.

NN8022-1922: A 56-week, randomized, double-blind, placebo-controlled, three-armed, parallel-group, multi-center, multi-national trial. Obese or overweight subjects (BMI $\geq$ 27 kg/m^2) with type 2 diabetes were randomized in a 2:1:1 manner to receive liraglutide 3.0mg, liraglutide 1.8mg, or placebo. The trial consisted of a screening visit (up to 2 weeks before randomization), a 2- to 4- week of dose escalation period, a 52- to 54- week maintenance period, and a 12-week observational off-drug follow up period. The trial was initiated on June 1, 2011 and completed on January 25, 2013.

NN8022-1923: A 56-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, multi-national trial. Non-diabetic, obese subjects (BMI $\geq$ 30 kg/m^2) or overweight (BMI

[4] FPG: Fasting Plasma Glucose
[5] OGTT: Oral Glucose Tolerance Test
[6] HbA_{1c}: Hemoglobin A1C

Reference ID: 3626734

≥ 27 kg/m^2) subjects with comorbidities (treated or untreated hypertension and/or dyslipidaemia) were first treated with a low calorie diet (total energy intake 1200-1400 kcal/day) in the run-in period lasting up to 12 weeks. Subjects who lost at least 5% screening body weight (start run-in) after 4 weeks and up to 12 weeks during the run-in period were randomized in a 1:1 manner to receive either liraglutide 3.0 mg or placebo for 56 weeks. At the time of randomization, subjects were stratified based on co-morbidity status, i.e., presence or absence of treated or untreated hypertension or dyslipidaemia. Subjects were instructed by a nutritionist to follow a standard energy-restricted diet (500 kcal deficit). The trial consisted of a 12-week run-in period before randomization, a 4-week dose-escalation period, a 52-week maintenance period, and a 12 week off-drug follow-up period. The trial was initiated on October 30, 2008 and completed on September 1, 2010.

NN8022-3970: A 32-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center, and multi-national trial. Non-diabetic, obese subjects (BMI ≥ 30 kg/m^2) with moderate or severe Obstructive Sleep Apnoea (OSA) were randomized in a 1:1 manner to receive either liraglutide 3.0 mg or placebo. The trial consisted of a 2-week screening period, a 4-week dose escalation period, a 28-week maintenance period, and 2-week follow-up period. Throughout the trial period, both groups were counselled by a dietitian on a 500 kcal/day-deficit diet and encouraged to exercise for a minimum of 150 min/week. The trial was initiated on June 7, 2012 and completed on June 17, 2013.

3.2.2 Endpoints and Adjudication

The pre-specified primary endpoint for the CV meta-analysis is a composite endpoint consisting of non-fatal myocardial infarction, non-fatal stroke, or CV death. This endpoint is referred to as MACE throughout this statistical review. In addition to assessment of MACE, all-cause mortality was assessed as a key safety endpoint.

The WM trials were not designed to capture a pre-specified number of CV events as there was no requirement to rule out a certain degree of excess CV risk.

Prospective external, independent, blinded, adjudication by an Event Adjudication Committee (EAC) was established in the WM program when the phase 3 trial NN8022-1923 was ongoing, which means that events from trials NN8022-1839, NN8022-1922, NN8022-3970 were prospectively adjudicated, whereas for trial NN8022-1923 events were adjudicated after trial completion but using the same vendor and process for identification and adjudication. As per agreement with the DMEP[7], *post hoc* adjudication has been conducted for all trials in which MACE were not prospectively adjudicated. In the WM program, this includes phase 2 dose-finding trial (NN8022-1807).

[7] Type C meeting, September 19, 2012, final minutes issued February 5, 2013

Reference ID: 3626734

Events sent for adjudication were identified by either the investigator (reported as a MESI[8]) or by a search for specified MedDRA preferred terms, not initially reported as MESIs, and submitted to the external vendor which performed independent blinded adjudication according to the EAC charter. In addition, all fatal cases were evaluated to determine cause of death (cardiovascular, not cardiovascular, and unknown).

3.2.3 Statistical Methodology

The main effect measure discussed throughout this review is the hazard ratio (pooled liraglutide doses relative to pooled comparator arms) for the outcomes defined in Section 3.2.2. A hazard ratio of one is indicative of equivalent rates between the two treatment groups, a hazard ratio greater than one is indicative of higher rate in the liraglutide treatment group compared to comparator, and vice versa for a hazard ratio less than one.

3.2.3.1 Analysis Populations and Censoring

The safety analysis set was defined as all randomized subjects receiving at least one dose of trial drug. This set was utilized for all analyses conducted in this review based on the following two analysis populations.

On treatment (primary): This analysis population was defined as all subjects from the safety analysis set with a censoring window of up to 30 days after last drug date for the trials and extensions. This population was used as the primary population for the WM meta-analysis. Subjects not experiencing an event in the treatment period or within 30 days after last dose were censored at last treatment date plus 30 days.

On study (sensitivity): This analysis population was defined as all subjects from the safety analysis set including information from the duration of the trial including extensions and off-drug period (applicable for trials 1922, 1923 and 1839). For those prematurely withdrawn subjects, censoring was at last date on drug plus 30 days follow-up or the date of their follow-up visit which ever came last. For those subjects entering the 12 week off drug follow-up period, censoring was at 12 weeks after last drug date, or on the last follow-up date which ever came last.

In the WM program, two trials (NN8022-1807 and NN8022-1839) had subjects switching treatment, referred to as switchers (see Table 2). These switchers were censored on the date of switching in the analyses using “on treatment” and “on study” populations. However, any event that occurred in the first 30 days after switch of treatment will be counted as an event with previous treatment.

[8] MESI: medical events of special interest

Reference ID: 3626734

Table 2: Subjects switched treatment in the WM program.

Trial	Background medication	Liraglutide (mg/day)	Comparator	Phase	Trial Duration (weeks)	Randomised # of subjects
1807 ext2[a]	N/A	Subjects randomised to placebo but switched to liraglutide 2.4 and later 3.0 in ext2	N/A	2	52	62
1839 re-randomi-sation[a]	N/A	Subjects randomised to liraglutide but re-randomised to placebo		3a	12	350

ext = extension. N/A = not applicable.

a Events occuring in the first 30 days after switch of treatment are included in the primary analysis but with treatment being the previous treatment

Source: Applicant's Statistical Analysis Plan for meta-analysis Table 1-3.

Reviewer's Comment:
In addition to the analysis populations mentioned above, the applicant also defined "on treatment with switch" and "on study with switch" populations. In studies in which subjects receive a sequence of different treatments, there may be "carry-over" effect between treatments, which biases the estimate of treatment effects. Therefore, we do not perform any analysis using "on treatment with switch" or "on study with switch" populations in our review.

3.2.3.2 Pre-Specified Statistical Analyses

The primary WM meta-analysis was based upon time-to-event methodologies using trials in the WM program. The primary endpoint, MACE, was analyzed using a Cox proportional hazards model stratified by trial with a fixed effect for treatment. The hazard ratio and corresponding 95% confidence interval of liraglutide group vs. a pooled comparator (placebo or active comparator) were estimated. The primary population is *on treatment*. Table 3 provides the pre-specified primary and sensitivity analyses that were performed and replicated by the reviewer.

In addition, all-cause mortality was analyzed in a model similar to the one used in the primary analysis.

Table 3: Pre-specified analyses in WM meta-analysis

Primary Analysis	**Analysis Population**
Censoring at last treatment date +30 days	On treatment
Sensitivity Analysis	**Analysis Population**
Including off-drug follow-up periods	On study
Liraglutide comparing to placebo	On treatment
Liraglutide 3.0mg comparing to placebo	On treatment
Liraglutide 3.0mg comparing to comparator	On treatment

Source: created by the reviewer (modified applicant's CV meta-analysis report Table 4-1).

Reference ID: 3626734

3.2.3.3 Additional Statistical Analyses Conducted by the Reviewer

The impact of withdrawals due to CV related adverse events on the meta-analysis were investigated.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

There were a total of 5908 subjects included in the WM meta-analysis. Among the 5908 subjects, 3872 were randomized to liraglutide and 2036 were randomized to the comparator group (1941 placebo and 95 orlistat).

In the liraglutide group, most subjects were randomized to the 3.0 mg dose (n=3384, 87.4%), compared to the 1.2 mg dose (n=95, 2.5%), the 1.8 mg dose (n=300, 7.8%), and the 2.4 mg dose (n=93, 2.4%). In the comparator group, most subjects were randomized to the placebo (n=1941, 95.3%), compared to the active control orlistat (n=95, 4.7%)

3.2.4.1 Patient Disposition

The withdrawal rate overall and broken down by the primary reason of withdrawal is shown in Table 4. The overall withdrawal rate was slightly lower in the liraglutide group than in the comparator group (30.3% vs. 36.3%). This was consistent for all trials except trial 3970 where the rate was higher in the liraglutide group than in the comparator group (23.9% vs. 20.7%). In the liraglutide group, the three most common reasons for withdrawal were Others (10.3%), adverse events (AEs) (9.8%), and withdrawal criteria (4.4%); in the comparator group, the three most common reasons were Others (16.5%), withdrawal criteria (9.2%), and AEs (4.3%). The withdrawal rate due to AE was higher in the liraglutide group than that in the comparator group overall (9.8% vs. 4.3%).

Reference ID: 3626734

Table 4: Trial Withdrawal Rates by trial and overall in the WM meta-analysis.

Trial	*N*	*Withdrawal Reason*						*All Combined*
		AE n(%)	**Did not Participate n(%)[a]**	**Ineffective therapy n(%)**	**Non-compliance n(%)**	**Other n(%)**	**Withdrawal Criteria n(%)**	**n(%)**
1807								
Liraglutide	371	42(11.3)	50(13.5)	11(3.0)	20(5.4)	72(19.4)	--	195(52.6)
Comparator	193	9(4.7)	24(12.4)	7(3.6)	9(4.7)	52(26.9)	--	101(52.3)
1839								
Liraglutide	2481	240(9.7)	--	37(1.5)	64(2.6)	275(11.1)	107(4.3)	709(28.6)
Comparator	1242	47(3.8)	--	23(1.9)	41(4.4)	227(18.3)	104(8.4)	456(36.7)
1922								
Liraglutide	632	59(9.3)	--	1(0.2)	21(3.3)	26(4.1)	61(9.7)	168(26.6)
Comparator	212	7(3.3)	--	3(4.1)	14(6.6)	12(5.7)	41(19.3)	77(36.3)
1923								
Liraglutide	212	18(8.5)	--	0(0.0)	9(4.2)	15(7.1)	17(8.0)	59(27.8)
Comparator	210	18(8.6)	--	2(1.0)	6(2.9)	19(9.0)	24(11.4)	70(33.3)
3970								
Liraglutide	176	20(11.4)	--	2(1.1)	6(3.4)	12(6.8)	2(1.1)	42(23.9)
Comparator	179	6(3.4)	--	1(0.6)	5(2.8)	25(14.0)	0(0.0)	37(20.7)
Overall								
Liraglutide	3872	379(9.8)	50(1.3)	37(1.0)	120(3.1)	400(10.3)	169(4.4)	1173(30.3)
Comparator	2036	87(4.3)	24(1.2)	50(2.5)	75(3.7)	335(16.5)	187(9.2)	740(36.3)

[a] Only apply to trial 1807,
Source: created by the reviewer using dataset "s.xpt".

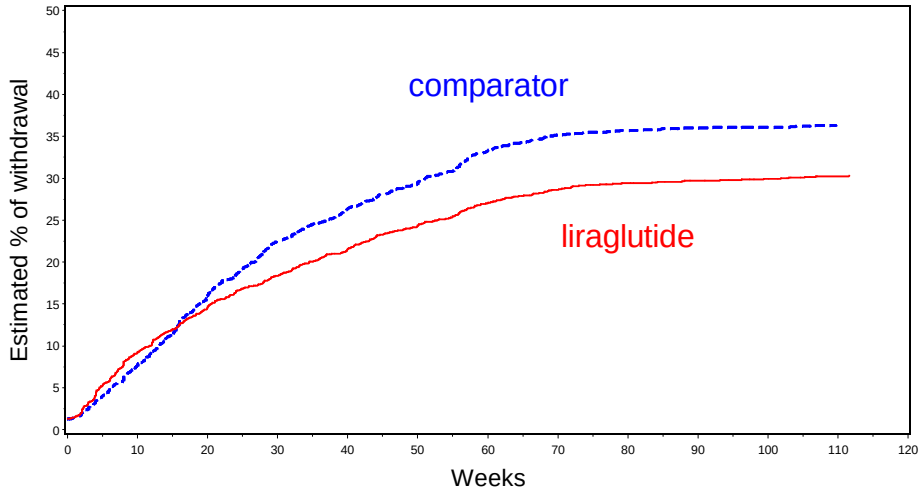
The probability of withdrawal and the probability of withdrawal due to AE over time on treatment are shown in Figure 1 and Figure 2, respectively. Within about 16 weeks of treatment, the probability of withdrawal was higher in the liraglutide group than the comparator group. After 16 weeks, the probability of withdrawal was higher in the comparator group than the liraglutide group. The probability of withdrawal due to AE was constantly higher in the liraglutide group than that in the comparator group over time on treatment.

Among the AE withdrawals (379[9.8%] in the liraglutide group vs. 87 [4.3%] in the comparator group), the reviewer investigated the proportion of CV related AE withdrawals using sae.xpt. In this reviewer's analysis, the subjects were identified to have CV related AE if in the dataset sae.xpt, the subjects had any AE in one of the five AE classes: *Cardiac arrhythmia (F_CV_ARR), Cardiovascular disorders (F_CV_CV), Cardiac failure (F_CV_HF), ECF related (F_ECG), Tachycardia (F_TACHY).* By using this definition, withdrawal due to CV related AE was similar in the ligraglutide and comparator groups [9(0.2%) in the liraglutide vs. 10(0.5%) in the comparator].

Reference ID: 3626734

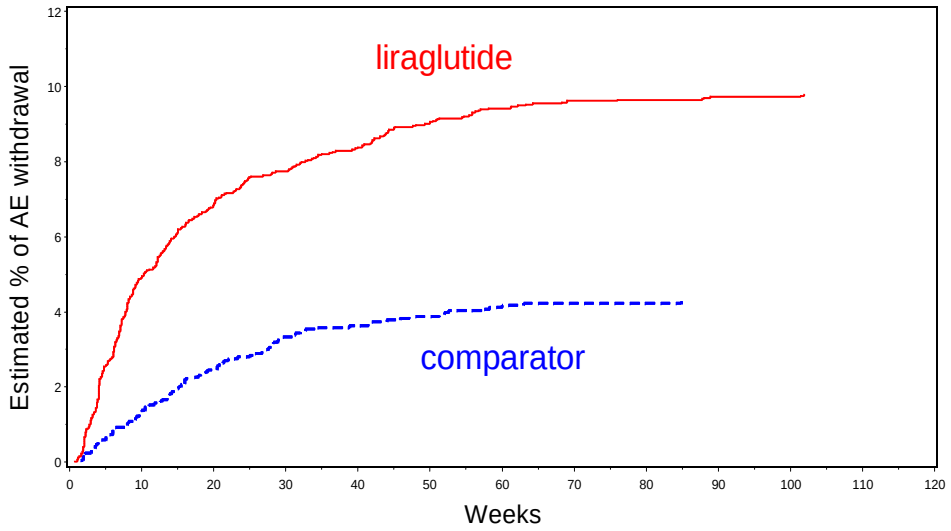
Reviewer's Comment:
Note that the probabilities of withdrawals in Figures 1 and 2 are estimated from the pooled data across all trials, which do not account for trial level difference. Therefore, caution is advised when interpreting these figures.

Figure 1: Estimated probability of withdrawal by time across trials.



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

Figure 2: Estimated probability of withdrawal due to adverse event (AE) by time across trials.



Source: created by the reviewer using dataset "s xpt" and "sae.xpt".

Reference ID: 3626734

3.2.4.2 Demographics and CV Risk Factors

The distributions for demographic characteristics were generally similar between liraglutide and comparator groups in the WM meta-analysis (see Table 5). Overall, subjects had a mean age of 46.9 years (range18−82 years), a mean BMI of 37.6 kg/m^2 (range 25.7-77.2 kg/ m^2), and 28.9% of subjects had a BMI of at least 40 kg/ m^2. The majority of subjects (71.3%) were women. Most of the subjects were white (85.3%) and 9.8% were Black or African American. Most of the subjects were enrolled in sites in the EU or North American.

Reference ID: 3626734

Table 5: Distribution of Demographic Characteristics in the WM meta-analysis.

Demographic	*Liraglutide* 1.2mg n=95	1.8mg n=300	2.4mg n=93	3.0mg n=3384	ALL n=3872	*Comparator* Orlistat n=95	Placebo n=1941	ALL N=2036
Sex, n(%)								
Male	22(23.2)	130(43.3)	22(23.7)	935(27.6)	**1109(28.6)**	22(23.2)	567(29.2)	**589(28.9)**
Female	73(76.9)	170(56.7)	71(76.3)	2449(72.4)	**2763(73.4)**	73(76.9)	1374(70.8)	**1447(71.1)**
Age, in years								
Mean (SD)	47.2(9.7)	52.1(11.6)	45.0(11.1)	46.6(12.2)	**47.0(12.2)**	45.9(9.1)	46.6(11.8)	**46.5(11.7)**
Range	23.0-65.0	18.0-82.0	21.0-65.0	18.0-79.0	**18.0-82.0**	27.0-3.0	18.0-78.0	**18.0-78.0**
Age, n(%)								
less than 65	94(99.0)	266(88.6)	92(98.9)	3152(93.1)	**3604(93.1)**	95(100.0)	1825(94.0)	**1920(94.3)**
[65,75)	1(1.0)	32(10.7)	1(1.1)	215(6.4)	**249(6.4)**	0(0.0)	113(5.8)	**113(5.5)**
Over 75	0(0.0)	2(0.7)	0(0.0)	17(0.5)	**19(0.5)**	0(0.0)	3(0.2)	**3(0.2)**
BMI, in kg/m2								
Mean(SD)	34.2(2.7)	36.3(6.1)	34.6(2.8)	37.9(6.4)	**37.6(6.2)**	33.8(2.7)	37.8(6.5)	**37.6(6.4)**
Range	22.4-40.0	27.1-67.6	29.1-39.9	27.0-77.2	**27.0-77.2**	29.4-40.4	25.7-75.3	**25.7-75.3**
BMI, n(%)								
Less than 30	5(5.3)	38(12.7)	2(2.2)	149(4.4)	**194(5.0)**	9(9.5)	117(6.0)	**126(6.2)**
[30,35)	57(60.0)	114(38.0)	53(57.0)	1142(33.70)	**1366(35.3)**	55(57.9)	633(32.6)	**688(33.8)**
[35,40)	33(34.7)	83(27.7)	38(40.9)	1038(30.7)	**1192(30.8)**	30(31.6)	606(31.2)	**636(31.2)**
Over 40	0(0.0)	65(21.7)	0(0.0)	1055(31.2)	**1120(28.93)**	1(1.0)	585(30.1)	**586(28.8)**
Race, n(%)								
White	94(99.0)	264(88.0)	91(97.9)	2845(84.1)	**3294(85.1)**	93(97.9)	1651(85.1)	**1744(85.7)**
Black	0(0.0)	29(9.7)	1(1.1)	348(10.3)	**378(9.8))**	1(1.1)	202(10.4)	**203(10.0)**
Asian	0(0.0)	4(1.3)	0(0.0)	115(3.4)	**119(3.1)**	0(0.0)	53(2.7)	**53(2.6)**
Amer. Ind	0(0.0)	0(0.0)	0(0.0)	9(0.3)	**9(0.23)**	1(1.1)	4(0.2)	**5(0.3)**
Pac. Island	0(0.0)	0(0.0)	0(0.0)	5(0.15)	**5(0.1)**	0(0.0)	4(0.2)	**4(0.2)**
Other	1(1.1)	3(1.0)	1(1.1)	60(1.77)	**65(1.7)**	0(0.0)	26(1.3)	**26(1.3)**
Region, n(%)								
African	0(0.0)	17(5.7)	0(0.0)	47(1.4)	**64(1.7)**	0(0.0)	22(1.1)	**22(1.1)**
Asia	0(0.0)	0(0.0)	0(0.0)	78(2.3)	**78(2.0)**	0(0.0)	38(2.0)	**38(1.9)**
Australia and Oceania	0(0.0)	0(0.0)	0(0.0)	45(1.3)	**45(1.2)**	0(0.0)	20(1.0)	**20(1.0)**
EU	95(100.0)	174(58.0)	93(100.0)	952(28.1)	**1314(33.9)**	95(100.0)	537(27.7)	**632(31.0)**
Europe (non-EU)	0(0.0)	14(4.7)	0(0.0)	304(9.0)	**318(8.2)**	0(0.0)	126(6.5)	**126(6.2)**
North America	0(0.0)	95(31.7)	0(0.0)	1802(53.3)	**1897(49.0)**	0(0.0)	1121(57.8)	**1121(55.1)**
South America	0(0.0)	0(0.0)	0(0.0)	156(4.6)	**156(4.0)**	0(0.0)	77(4.0)	**77(3.8)**

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

The distributions for CV risk factors were generally similar between liraglutide and comparator groups (see Table 6). Overall, among the 5908 subjects, 14.3% had diabetes, 14.0% were current smokers, and 9.0% had a history of CV disease at baseline.

Reference ID: 3626734

Table 6: Distribution of Cardiovascular Risk Factors in the WM meta-analysis

Demographic	*Liraglutide* 1.2mg n=95	1.8mg n=300	2.4mg n=93	3.0mg n=3384	ALL n=3872	*Comparator* Orlistat n=95	Placebo n=1941	ALL N=2036
Diabetes Cat.								
Diabetes	0(0.0)	210(70)	0(0.0)	422(12.5)	**632(16.3)**	0(0.0)	212(10.9)	**212(10.4)**
Normal Glycaemia	43(45.3)	44(14.7)	48(51.6)	1129(33.4)	**1264(32.7)**	45(47.4)	676(34.8)	**721(35.4)**
Pre-diabetes	52(54.7)	46(15.33)	45(48.39)	1833(54.2)	**1976(51.0)**	50(52.6)	1053(54.3)	**1103(54.2)**
CV history, n(%)								
Yes	2(2.1)	36(12.0)	2(2.2)	311(9.2)	**351(9.1)**	8(8.42)	172(8.9)	**180(8.8)**
No	93(97.9)	264(88.0)	91(97.8)	3073(90.8)	**3521(90.9)**	87(91.6)	1769(91.1)	**1856(91.2)**
Hypertension, n(%)								
Yes	27(28.4)	169(56.3)	19(20.4)	1296(38.3)	**1511(39.0)**	16(16.8)	755(38.9)	**771(37.9)**
No	68(71.6)	131(43.7)	74(79.6)	2088(61.7)	**2361(61.0)**	79(83.2)	1186(61.1)	**1265(62.1)**
Smoking, n(%)								
Current	17(17.9)	49(16.3)	17(18.3)	484(14.3)	**567(14.6)**	21(22.1)	294(15.2)	**315(15.5)**
Never	78(82.1)	183(61.0)	76(81.7)	2082(61.5)	**2419(62.5)**	74(77.9)	1207(61.2)	**1281(62.9)**
Previous	0(0.0)	68(22.7)	0(0.0)	818(24.2)	**886(22.9)**	0(0.0)	440(22.7)	**440(21.6)**

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

3.2.5 Analysis Findings

3.2.5.1 Descriptive MACE Statistics

Table 7 provides a summary of MACE overall and broken down by trial and treatment group for the WM meta-analysis. Based on the primary censoring scheme ("on treatment"), a total of 17 MACE were observed: 8 (0.2%) in liraglutide group and 9 (0.4%) in the comparators group.

Table 7: Summary of MACE overall and by trial in the WM primary analysis.

Trial	Liraglutide Arms 1.2mg n/N(%)	1.8mg n/N(%)	2.4mg n/N(%)	3.0mg n/N(%)	All n/N(%)	Comparator Arms Orlistat n/N(%)	Placebo n/N(%)	All n/N(%)
1807	0/95(0.0)	0/90(0.0)	0/93(0.0)	0/93(0.0)	**0/371(0.0)**	0/95(0.0)	0/98(0.0)	**0/193(0.0)**
1839	-	-	-	3/2481(0.1)	**3/2481(0.1)**	-	3/1242(0.2)	**3/1242(0.2)**
1922	-	3/210(1.4)	-	2/422(0.5)	**5/632(0.8)**	-	3/212(1.4)	**3/212(1.4)**
1923	-	-	-	0/212(0.0)	**0/212(0.0)**	-	1/210(0.5)	**1/210(0.5)**
3970	-	-	-	0/176(0.0)	**0/176(0.0)**	-	2/179(1.1)	**2/179(1.1)**
Overall	0/95(0.0)	3/300(1.0)	0/93(0.0)	3/3384(0.1)	**8/3872(0.2)**	0/95(0.0)	9/1941(0.5)	**9/2036(0.4)**

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

Table 8 provides the number of percentage of MACE by trial, treatment group, and type of events in the WM primary analysis. Few events for each of the individual components of MACE were reported though, in general, balanced between the two groups.

Reference ID: 3626734

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

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

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

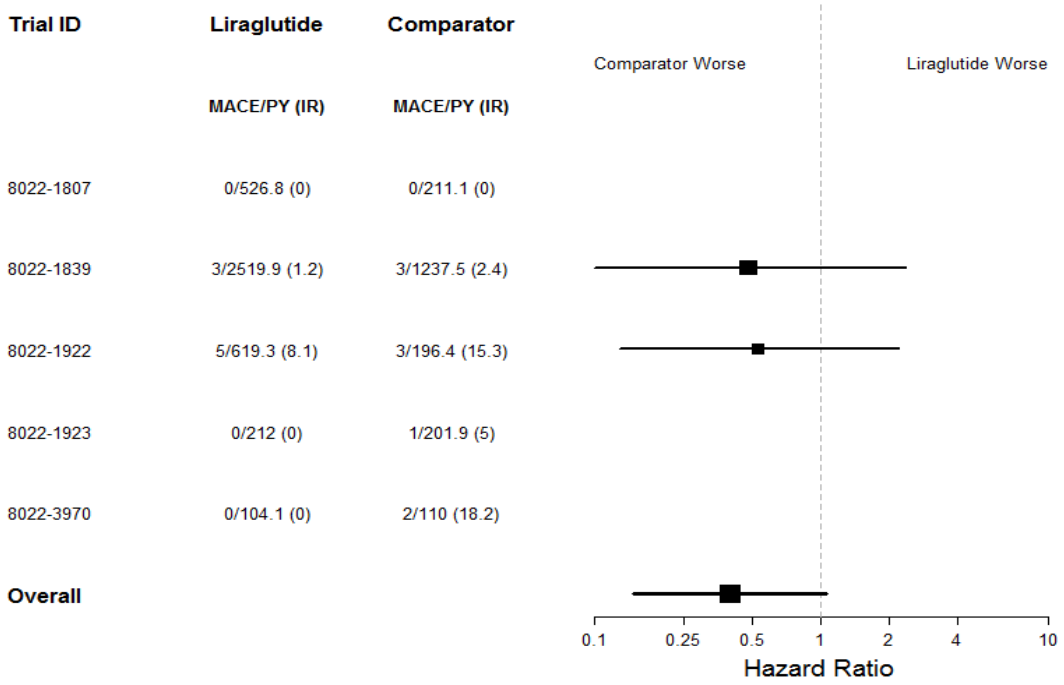
3.2.5.2 Meta-analysis of MACE Results

Results of Pre-Specified Analyses

The forest plot shown in Figure 3 illustrates the trial level and overall estimated hazard ratio (HR) and 95% confidence interval (CI) for the primary analysis of MACE. The overall estimated HR was 0.40 with 95% CI (0.15, 1.05). Note that this finding is mainly driven by trials 8022-1839 and 8022-1922 as the remaining trials did not contribute events to one of the treatment arms or both arms.

Reference ID: 3626734

Figure 3: Forest Plot of WM Primary Analysis of MACE across all trials.



IR = incidence rate per 1,000PY, PY=patient-years.
Source: created by the reviewer using dataset "mace xpt".

The results of the pre-specified primary and sensitivity analyses are shown in Table 9. Two more events were identified in the liraglutide group during the off-drug periods in trials 8022-1839 and 8022-1922. This resulted in an estimated HR and 95% CI of 0.49 (0.20, 1.23). The results of other sensitivity analyses were also consistent with the primary analysis.

Table 9: Pre-specified analyses in WM meta-analysis

Primary Analysis	Analysis Population	Liraglutide MACE	Comparator MACE	Hazard Ratio (95%CI)
Censoring at last treatment date +30 days	On treatment	8	9	0.40(0.15,1.05)
Sensitivity Analysis				
Including off-drug follow-up periods	On study	10	9	0.49(0.20,1.23)
Liraglutide comparing to placebo	On treatment	8	9	0.40(0.15,1.05)
Liraglutide 3.0mg comparing to placebo	On treatment	5	9	0.31(0.10,0.92)
Liraglutide 3.0mg comparing to comparator	On treatment	5	9	0.31(0.10,0.92)

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

Results of Additional Sensitivity Analyses Performed by the Reviewer

One patient in trial 8022-1839 (subject id "203020") who was randomized with liraglutide had a non-fatal stroke on October 12, 2012. This patient started to take drug on July 12, 2011 (first drug date), and stopped treatment on August 6, 2012 (end of treatment date). The event occurred after the 56-week visit, and after 30 days of the end of treatment. As such, this event was not counted in the primary analysis nor the sensitivity including off-drug follow-up period, because

Reference ID: 3626734

the "off-drug follow-up period" for trial 8022-1839 defined by the Applicant referred to the 12-week off-drug period following the 104-week extension. A sensitivity analysis was then performed by the reviewer including this event. In this analysis, the numbers of MACE were 11 for liraglutide vs. 9 for the comparator group. The estimated HR with 95% CI was 0.54 (0.22, 1.34).

An additional sensitivity analysis was performed to assess the impact of withdrawal due to CV related AEs on the primary analysis results. Among the 19 withdrawal due to CV related AEs (see Section 3.2.5.2), three of them were counted as MACE in the primary analysis. In this sensitivity analysis, the numbers of MACE were 15 for liraglutide vs. 18 for the comparator group. The estimated HR with 95% CI was 0.39 (0.19, 0.79).

3.2.5.3 All-cause Mortality Results

There were four *on-treatment* deaths (one in the liraglutide group and three in the comparator group) due to all causes across all trials in the WM meta-analysis. The estimated HR for all-cause mortality was 0.19 with 95% CI (0.02, 1.85). Because of the small number of events, caution is advised when interpreting all-cause mortality results.

3.3 Cardiovascular Meta-Analysis in Type 2 Diabetes Mellitus

3.3.1. Designs of Trials Included in T2DM Meta-analysis

The T2DM meta-analysis included all intermediate and long term trials (phase 2 and 3) in T2DM program[9] conducted by NN which included one or more treatment arms with liraglutide and with DBL prior to the DBL of trial NN8022-3970 (July 2, 2013). A total of 20 T2DM trials were included in this meta-analysis with durations ranging between 5 weeks and 104 weeks. A summary of the trials included in the supportive T2DM meta-analysis is shown in Appendix I. All uncontrolled trials, uncontrolled extensions, and uncontrolled treatment groups were excluded from this meta-analysis (see Appendix II for the list of trials excluded).

Reviewer's Comment:
Trial 1332 was excluded in the reviewer's analysis because of the small sample size (n=13) and short treatment duration (1-2 weeks).

3.3.2. Statistical Methodology

Similar to the WM meta-analysis, the endpoints analyzed were MACE and all-cause mortality. The supportive T2DM meta-analysis analysis was performed using the "on treatment" analysis

[9] Refer to a joint clinical/statistical review of cardiovascular events and thyroid tumors performed by Dr. Mahoney, and Dr. Derr in 2009 before the approval of liraglutide for T2DM for more details. The review can be found in FDA briefing materials for Endocrinologic and Metabolic Drugs Advisory Committee Meeting, April 2, 2009.

Reference ID: 3626734

population. All analyses were based on Cox proportional hazards models, each stratified by trial, with treatment (liraglutide or comparator) as a fixed effect.

3.3.3. Demographics

There were total 8233 subjects included in the T2DM meta-analysis, 5498 in liraglutide group and 2735 in the comparator group.

The distributions for demographic characteristics were generally similar between liraglutide and comparator groups in the T2DM meta-analysis (see Appendix III). Subjects had a mean age of 56.1 years (range 19-85 years), a mean BMI of 29.8 kg/ m^2 (range 14.5-47.8 kg/ m^2). 56.7% of the subjects were males and 43.3% were females. Most of the subjects were White (58.1%) or Asian (33.3%). Among 8233 subjects, 13.3% of them had a history of CV disease at baseline [709 (12.9%) in the liraglutide group and 387(14.1%) in the comparator group].

3.3.4. Analysis Findings

3.3.4.1. Descriptive MACE Statistics

Table 10 provides the summary of MACE overall and broken down by trial and treatment group. Seven of the 20 trials had no MACE events. The overall incidence was about 0.6% (0.5% in liraglutide group and 0.8% in the comparators group). Table 11 provides the summary of individual components of MACE overall and broken down by trial and treatment group. For each individual component of MACE (i.e., non-fatal MI, non-fatal stroke, and CV death) across all trials, the incidence in the liraglutide group was lower than the comparator group. Across all the trials, CV death only occurred in the comparator group. Given the small number of events for individual components, caution is advised when interpreting these results.

Reference ID: 3626734

Table 10: Summary of MACE overall and by trial in the T2DM main analysis.

Trial	Liraglutide n/N(%)	Comparator n/N(%)
NN2211-1310	1/135(0.7)	0/55(0.0)
NN2211-1333	0/21(0.0)	0/12(0.0)
NN2211-1334	0/180(0.0)	0/46(0.0)
NN2211-1436	4/695(0.6)	1/114(0.9)
NN2211-1499	0/72(0.0)	0/72(0.0)
NN2211-1571	0/123(0.0)	0/40(0.0)
NN2211-1572	6/724(0.8)	3/363(0.8)
NN2211-1573	1/497(0.2)	2/248(0.8)
NN2211-1574	0/355(0.0)	0/175(0.0)
NN2211-1697	2/230(0.9)	6/346(1.7)
NN2211-1700	4/268(1.5)	2/132(1.5)
NN2211-1701	0/176(0.0)	1/88(1.14)
NN2211-1796	2/697(0.3)	0/231(0.0)
NN2211-1797	1/233(0.4)	4/231(1.7)
NN2211-1799	0/16(0.0)	0/33(0.0)
NN2211-1860	2/439(0.5)	2/217(0.9)
NN2211-2072	1/175(0.6)	0/34(0.0)
NN2211-3924	1/240(0.4)	0/120(0.0)
NN2211-3925	1/127(0.8)	2/130(1.5)
NN9535-1821	0/95(0.0)	0/46(0.0)
Overall	**26/5498(0.5)**	**23/2735(0.8)**

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

Reference ID: 3626734

Table 11: Summary of First MACE by trial, treatment group, and type of events in the T2DM meta-analysis[a].

Trial		N	MACE n[b](%)	non-fatal MI n(%)	non-fatal Stroke n(%)	CV death n(%)
NN2211-1310	Liraglutide	135	1(0.7)	0(0.0)	1(0.7)	0(0.0)
	Comparator	55	0(0.0)	0(0.0)	0(0.0)	0(0.0)
NN2211-1436	Liraglutide	695	4(0.6)	4(0.6)	0(0.0)	0(0.0)
	Comparator	114	1(0.1)	1(0.1)	0(0.0)	0(0.0)
NN2211-1572	Liraglutide	724	6(0.8)	5(0.7)	1(0.1)	0(0.0)
	Comparator	363	3(0.8)	3(0.8)	0(0.0)	0(0.0)
NN2211-1573	Liraglutide	497	1(0.2)	1(0.2)	0(0.0)	0(0.0)
	Comparator	248	2(0.8)	2(0.8)	0(0.0)	0(0.0)
NN2211-1697	Liraglutide	230	2(0.9)	1(0.4)	1(0.4)	0(0.0)
	Comparator	346	6(1.7)	4(1.2)	2(0.6)	2(0.6)
NN2211-1700	Liraglutide	268	4(1.5)	3(1.1)	1(0.4)	0(0.0)
	Comparator	132	2(1.5)	0(0.0)	2(1.5)	0(0.0)
NN2211-1701	Liraglutide	176	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	Comparator	88	1(1.1)	0(0.0)	1(1.1)	0(0.0)
NN2211-1796	Liraglutide	697	2(0.3)	1(0.1)	1(0.1)	0(0.0)
	Comparator	231	0(0.0)	0(0.0)	0(0.0)	0(0.0)
NN2211-1797	Liraglutide	233	1(0.4)	0(0.0)	1(0.4)	0(0.0)
	Comparator	231	4(1.7)	3(1.3)	1(0.4)	1(0.4)
NN2211-1860	Liraglutide	439	2(0.5)	2(0.5)	0(0.0)	0(0.0)
	Comparator	219	2(0.9)	0(0.0)	0(0.0)	2(0.9)
NN2211-2072	Liraglutide	175	1(0.6)	0(0.0)	1(0.6)	0(0.0)
	Comparator	34	0(0.0)	0(0.0)	0(0.0)	0(0.0)
NN2211-3924	Liraglutide	240	1(0.4)	0(0.0)	1(0.4)	0(0.0)
	Comparator	120	0(0.0)	0(0.0)	0(0.0)	0(0.0)
NN2211-3925	Liraglutide	127	1(0.8)	0(0.0)	1(0.8)	0(0.0)
	Comparator	130	2(1.5)	1(0.8)	1(0.8)	0(0.0)
Overall[c]	**Liraglutide**	**5498**	**26(0.5)**	**17(0.3)**	**9(0.2)**	**0(0.0)**
	Comparator	**2735**	**23(1.0)**	**14(0.5)**	**7(0.3)**	**5(0.2)**

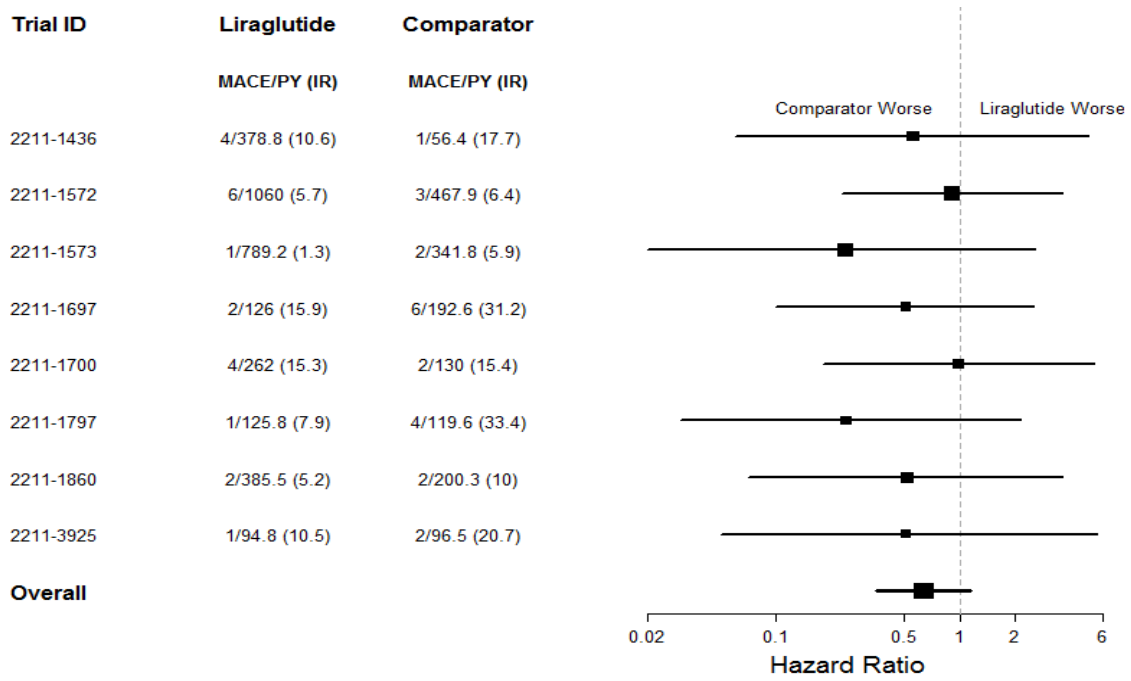
[a]: Only the 13 trials who had MACE events are shown in this table.
[b]: The number of unique subjects experienced first occurrence of MACE and its components, respectively. The counts of individual components don't necessarily add up to that of MACE since one subject may have experienced more than one component events.
[c]: The overall number of subjects and incidence for liraglutide and comparator in the total 20 trials.
Source: Created by the reviewer using dataset "mace xpt".

3.3.4.2. Meta-analysis of MACE Results

The forest plot shown in Figure 4 illustrates the trial level and overall estimated hazard ratio (HR) and 95% confidence interval (CI) for the T2DM meta-analysis. The overall estimated HR was 0.64 with 95% CI (0.35, 1.15). This finding is consistent with the results for the WM meta-analysis

Reference ID: 3626734

Figure 4: Forest plot of T2DM on-treatment meta-analysis of MACE across all trials*.



*Only the trials that contributed events to the analysis were shown in this forest plot.
Source: created by the reviewer using dataset "mace xpt".

3.3.4.3. All-cause Mortality Results

There were 16 deaths (8 in the liraglutide group and 8 in the comparator group) due to all causes across all trials in the T2DM meta-analysis. The estimated HR for all-cause mortality was 0.55 with 95% CI (0.20, 1.51).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section summarizes the results of analyses for MACE within subgroups for the WM meta-analysis utilizing the "on treatment" analysis population. Note that all subgroups are based on pre-treatment measurements. With no pre-specified subgroup of interest and the limited number of MACE observed in the overall analysis, results are presented descriptively only in this section as HR calculations would be subject to few events within a subgroup and large confidence intervals.

4.3. Gender, Race, Age, and Geographic Region

Table 12 provides the descriptive MACE statistics by gender, race, age, and geographic region. Note that for race and region these subgroups were re-categorized into two categories due to the small number of events. More detailed categories for race and region can be found in Table 5 in Section 3.2.4.2.

Reference ID: 3626734

Table 12. MACE for subgroups gender, age, and geographic region.

Subgroup	Liraglutide n/N(%)	Comparator n/N(%)	All n/N(%)
Sex			
Male	7/1109(0.6)	9/589(1.5)	16/1698(0.9)
Female	0/2763(0.0)	1/1447(0.1)	1/4210(<0.1)
Age			
< 65	7/3604(0.2)	8/1920(0.4)	15/5524(0.3)
≥65	1/268(0.4)	1/116(0.9)	2/384(0.5)
Race[a]			
White	6/3294(0.2)	9/1744(0.5)	15/5038(0.3)
Black	1/378(0.3)	0/203(0.0)	1/581(0.2)
Other[b]	0/198(0.0)	0/88(0.0)	0/286(0.0)
Region			
North America	4/1897(0.2)	6/1121(0.5)	10/3018(0.3)
EU	4/1314(0.3)	3/632(0.5)	7/1946(0.4)
Other[c]	0/661(0.0)	0/283(0.0)	0/944(0.0)

n=number of subjects with MACE; N= number of subjects in safety analysis set
[a]: Two subjects had missing values of RACE (not included in the category of "Other"), one for liraglutide and one for comparator group. The subject with a missing value of RACE in the liraglutide group had a MACE event.
[b]: "Other" under RACE includes Asian, American Indian, Pacific Islander, and Other.
[c]: "Other" under Region includes Europe (non-EU), South American, Asia, Africa, and Australia and Oceania.
Source: created by the reviewer using datasets "mace xpt" and "s.xpt".

4.4. Other Special/Subgroup Populations

Table 13 provides the descriptive MACE statistics by BMI, smoking status, history of CV disease, diabetes and hypertension.

Reference ID: 3626734

Table 13 MACE for subgroups BMI, smoking status, history of CV disease, diabetes and hypertension.

Subgroup	Liraglutide n/N(%)	Comparator n/N(%)	All n/N(%)
BMI			
< 30	3/194(1.5)	2/126(1.6)	5/320(1.6)
[30, 35)	4/1366(0.3)	5/688(0.7)	9/2054(0.4)
[35,40)	0/1192(0.0)	1/636(0.2)	1/1828(0.5)
≥ 40	1/1120(0.1)	1/586(0.2)	2/1706(0.1)
Smoking			
Current	2/567(0.4)	3/315(1.0)	5/882(0.6)
Never	3/2419(0.1)	1/1281(0.1)	4/3700(0.1)
Previous	3/886(0.3)	5/440(1.1)	8/1326(0.7)
CV history			
Yes	3/351(0.1)	3/180(1.7)	6/531(1.1)
No	5/3521(0.1)	6/1856(0.3)	11/5377(0.2)
Diabetes			
Diabetes	5/632(0.1)	3/212(1.4)	8/844(1.0)
Normal-Glycaemia	1/1264(0.1)	1/721(0.1)	2/1985(0.1)
Pre-diabetes	2/1976(0.1)	5/1103(0.5)	7/3079(0.2)
Hypertension			
Yes	6/1511(0.4)	4/771(0.5)	10/2282(0.4)
No	2/2361(0.1)	5/1265(0.4)	7/3626(0.2)

n=number of subjects with MACE; N= number of subjects in safety analysis set
Source: created by the reviewer using datasets “mace xpt” and “s.xpt”.

4.5. Liraglutide Dose

As shown in Section 3.2.5.1 Table 7, the majority of the subjects in the liraglutide group were treated with the 3.0mg dose (3384, 87.4%). The majority of the subjects in the comparator group were treated with placebo (1941, 95.3%).

Two sensitivity analyses restricted to liraglutide 3.0mg were previously shown in Section 3.2.5.2 Table 9.

5. SUMMARY AND CONCLUSIONS

5.3. Collective Evidence and Statistical Issues

The cardiovascular risk meta-analysis for liraglutide, which is the subject of this statistical safety review, was conducted based on the agreed upon Statistical Analysis Plan (SAP) for meta-analysis dated November 10, 2013. The primary objective of the meta-analysis was to investigate the effect of treatment with liraglutide for weight management, compared to a pooled comparator group (placebo and active comparators), on cardiovascular safety. Per agreements with the

Reference ID: 3626734

Agency, there was no pre-specified risk margin to rule out for this meta-analysis. The agreed upon primary endpoint was major adverse cardiovascular events (MACE), a composite endpoint comprising non-fatal myocardial infarction, non-fatal stroke, or CV death. The events were either prospectively or post hoc adjudicated, by an independent Event Adjudication Committee (EAC), which was governed under a charter. The primary analysis population (on treatment) was defined as the all randomized subjects receiving at least one dose and included events occurring up to 30 days after last drug date. The weight management meta-analysis included one phase 2 and four phase3 trials. The pre-specified primary statistical analysis used a Cox proportional hazards model stratified by trial.

In the weight management meta-analysis, there were 5908 subjects, 3872 were randomized to liraglutide and 2036 were randomized to the comparator group. There were 17 confirmed MACE by the event adjudication committee, 8 for liraglutide and 9 for comparators. The estimated hazard ratio and two-sided 95% confidence interval for liraglutide vs. comparators was 0.40 (0.15, 1.05).

To support the meta-analysis in weight management, this review includes a meta-analysis of 20 T2DM trials which included all intermediate and long term trials (phase 2 and 3). The analysis of the T2DM trials was also based on the on-treatment population. There were a total of 8233 subjects included in the T2DM meta-analysis, 5498 in liraglutide group and 2735 in the comparator group. There were 49 confirmed MACE by the event adjudication committee, 26 for liraglutide and 23 for comparators. Using a Cox proportional hazards model stratified by trial, the estimated hazard ratio and two-sided 95% confidence interval for liraglutide vs. comparators was 0.64 (0.35, 1.15).

5.4. Conclusions and Recommendations

This statistical review investigates the effect of treatment with liraglutide on CV risk for weight management compared to a pooled comparator group (active control and placebo) through a meta-analysis of 5 weight management trials. Using the pre-specified primary Cox proportional hazards model for the primary end point (MACE), the estimated hazard ratio and two-sided 95% confidence interval for liraglutide vs. comparators were 0.40 (0.15, 1.05). A supportive meta-analysis of the MACE endpoint was conducted for liraglutide in T2DM, which yielded results consistent with the results for weight management meta-analysis.

Based on the submitted WM meta-analysis, there was no apparent increase in CV risk identified in the liraglutide group compared to the comparator group. However, there are several limitations associated with this meta-analysis that need to be carefully considered. First, a limited number of MACE were observed in the WM program with relatively short treatment exposure times included in the meta-analysis. This limits the ability to make inferences on CV safety beyond one year of treatment with liraglutide. In addition, subjects enrolled in the WM trials may be at low risk of cardiovascular disease (9.0% a history of CV disease, 93.5% less than 65 years old, 14.5% diabetes, 2.9% hypertension, 14.9% smokers), which limits the ability to identify CV events in the trials included in the meta-analysis. Therefore, the current available

Reference ID: 3626734

data cannot be generalized to more at risk populations and caution is advised in interpreting findings from a meta-analysis with few events.

Note that the approval letter of liraglutide for T2DM (Victoza®) states that Novo Nordisk (NN) is required to conduct a post-marketing clinical trial to evaluate the effect of liraglutide on the incidence of major adverse cardiovascular events in patients with T2DM[10]. This trial might provide useful data to further assess the CV risk with liraglutide in subjects at sufficiently high risk of CV events with extended duration of follow-up. However, the lower dose of liraglutide for T2DM (1.8mg/day) may limit the ability to directly extrapolate the results from this trial to the liraglutide dose 3.0mg/day in the WM indication. Therefore, if liraglutide 3.0 mg is approved for the WM indication, the recommendation is that further assessment of risk of CV events be conducted through post-marketing studies if further characterization of the CV risk is needed for the WM indication.

[10] See the FDA approved letter for NDA 022341.

Reference ID: 3626734

Appendix I. Completed controlled phase 2 and 3 trials and extensions in the T2DM development programs to be included in the analysis.

Programme	Trial	Background medication	Liraglutide (mg)	Comparator	Phase	Treatment Duration (weeks)	Random-isation	Random-ised (# of subjects)
Victoza®	1310	N/A	0.045,0.225, 0.45, 0.60, 0.75	Placebo, glimepiride	2	12	1:1:1:1:1:1:1	193
Victoza®	1332	N/A	6 µg/kg	Placebo	2	1-2	1:1	13
Victoza®	1333	N/A	0.6	Placebo	2	8	2:1	35
Victoza®	1334	N/A	0.1, 0.3, 0.6, 0.9	Placebo	2	14	1:1:1:1:1	226
Victoza®	2072	N/A	0.045,0.225, 0.45, 0.60, 0.75	Metformin	2	12	1:1:1:1:1:1	210
Victoza®	1499	Metformin (switched to metformin placebo at randomisation in 1 of 4 treatment arms)	Maximum tolerated dose (2.0 mg at the most)	Placebo, glimepiride	2	5	1:1:1:1	144
Victoza®	1571	N/A	0.65,1.25, 1.90	Placebo	2	12	1:1:1:1	165
Victoza®	1436	Glimepiride	0.6, 1.2, 1.8	Placebo , rosiglitazone[a]	3a	26	2:2:2:2:1:2	1041
Victoza®	1572	Metformin	0.6, 1.2, 1.8	Placebo, glimepiride	3a	26	2:2:2:1:2	1091
Victoza®	1572 ext (OL)¤	Metformin	0.6, 1.2, 1.8	Placebo, glimepiride	3a ext	78		780
Victoza®	1573	Diet/exercise	1.2, 1.8	Glimepiride	3a	52	1:1:1	746
Victoza®	1573 ext1 (OL)	Diet/exercise	1.2, 1.8	Glimepiride	3a ext	52		440
Victoza®	1573 ext2 (OL)	Diet/exercise	1.2, 1.8	Glimepiride	3a ext	52		
Victoza®	1574	Metformin + Rosiglitazone	1.2, 1.8	Placebo	3a	26	1:1:1	533
Victoza®	1697	Metformin + glimepiride	1.8	Insulin glargine, Placebo	3a	26	2:2:1	581
Victoza®	1700	Diet/exercise	0.9	Glibenclamide	3a	24	2:1	411
Victoza®	1700 ext	Diet/exercise	0.9	Glibenclamide	3a ext	28		
Victoza®	1701	SU	0.6, 0.9	Placebo	3a	24	1:1:1	267
Victoza®	1701 ext	SU	0.6, 0.9	Placebo	3a ext	28		267
Victoza®	1796	Metformin	0.6, 1.2, 1.8	Glimepiride	3b	16	1:1:1:1	929
Victoza®	1797	Metformin, SU,	1.8	Exenatide	3b	26	1:1	464

Reference ID: 3626734

Programme	Trial	Background medication	Liraglutide (mg)	Comparator	Phase	Treatment Duration (weeks)	Random-isation	Random-ised (# of subjects)
		metformin+SU						
Victoza®	1799	Diet/exercise, metformin	1.8	Placebo, glimepiride	3b	12	1:1:1	49
Victoza®	1860	Metformin	1.2, 1.8	Sitagliptin	3b	26	1:1:1	665
Victoza®	1860 ext1	Metformin	1.2, 1.8	Sitagliptin	3b ext	26		497
Victoza®	3924	Glinide, metformin, or α-GI	0.9	+ 1 additional OAD	3b	52	2:1	363
Victoza®	3925	Insulin (basal, pre-mixed or basal-bolus)	0.9	Placebo	3b	36	1:1	257
Semaglutide (NN9535)	1821	Metformin, diet/exercise	1.2, 1.8	Placebo Semaglutide[b]	2	12	1:1:1:1: 1:1:1:1:1	411

ext = extension, N/A = not applicable, SU = sulfonylurea, OL=open label.

a. The rosiglitazone treatment arm will be excluded from the analysis.

b. The 5 semaglutide treatment arms (N=270 subjects) will be excluded from the analysis.

Source: Applicant's meta-analysis study report Table 1-6.
Note: In Reviewer's analysis, trial 1332 was excluded.

Appendix II. Overview of uncontrolled phase 2 and 3 trials and extensions in to be excluded in the T2DM main meta-analysis.

Trial	Background medication	Liraglutide (mg/day)	Comparator	Phase	Trial Duration (weeks)	Randomised # of subjects
1797 ext1	Metformin, SU, metformin+SU	1.8	N/A	3b ext	14	389
1797 ext2	Metformin, SU, metformin+SU	1.8	N/A	3b ext	38	334
1860 ext2	Metformin	1.2, 1.8	N/A	3b ext	26	419
1842	Metformin	1.8, 1.8 +insulin detemir, 1.8 in non-randomised subjects	N/A	3b	26	323 + 499 non-randomised +166 early withdrawals
1842 ext1	Metformin	1.8, 1.8 + insulin detemir, 1.8 in non-randomised subjects	N/A	3b ext	26	262 + 461 non-randomised

ext = extension. N/A = not applicable, SU=sulphonylurea.
Source: Applicant's meta-analysis study report Table 1-4

Reference ID: 3626734

Appendix III. Distribution of Demographic Characteristics in the T2DM meta-analysis.

Demographic	Liraglutide n=5458	Comparator N=2735
Sex, n(%)		
Male	3087(56.2)	1577(57.7)
Female	2411(43.8)	1158(42.3)
Age, in years		
Mean (SD)	55.9(10.1)	56.4(10.1)
Range	21.0-84.7	19.0-82.7
Age, n(%)		
less than 65	4352(79.2)	2130(77.9)
[65,75)	1020(18.6)	532(19.4)
Over 75	126(2.3)	73(2.7)
BMI, in kg/m2		
Mean(SD)	29.7(5.7)	30.0(5.7)
Range	15.7-47.8	14.5-46.7
BMI, n(%)		
Less than 30	3079(56.0)	1428(52.2)
[30,35)	1365(24.8)	767(28.0)
[35,40)	751(13.6)	380(13.9)
Over 40	300(5.5)	155(5.7)
Race, n(%)		
White	3100(56.4)	1681(61.5)
Black	224(4.1)	97(3.5)
Asian	1892(34.4)	846(30.9)
American Indian or Alaska Native	6(0.1)	3(0.1)
Pacific Islander	4(0.1)	2(0.1)
Other	272(5.0)	106(3.9)

Source: created by the reviewer using dataset “mace xpt” and “s xpt”

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Primary Statistical Reviewer: Rongmei Zhang
Date:

Concurring Reviewers: Mat Soukup, Team Leader DBVII, Aloka Chakravarty, Division Director DBVII

Cc:
Julie Golden, Medical Officer, DMEP
James Smith, Medical Team Leader, DMEP
Jean-Marc Guettier, Division Director, DMEP
Patricia Madara, Project Manager, DMEP
Janelle Charles, Statistical Reviewer, DBVII
Mat Soukup, Team Leader, DBVII
Aloka Chakravarty, Division Director, DBVII
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ALOKA G CHAKRAVARTY
09/12/2014

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	206321
SERIAL NO.:	
DATE RECEIVED BY THE CENTER:	December 20, 2013
DRUG NAME:	Saxenda (liraglutide for obesity)
DOSAGE FORM:	
INDICATION:	
SPONSOR:	Novo Nordisk
REVIEW FINIHSED:	June 19, 2014
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D.
NAME OF PROJECT MANAGER:	Pat Madara

Meiyu Shen, PhD, Mathematical Statistician

Concur:

Yi Tsong, Ph.D.
Division Director, DBVI

TABLE OF CONTENTS

1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE 3

1.1 Introduction and Background 3

1.2 Data and design 3

1.3 The sponsor's statistical analysis 4

1.3.1 Sponsor's statistical modeling of focal C-cell hyperplasia 4

1.3.2 Sponsor's statistical modeling of Adenoma 4

1.4 Review's comments on the sponsor's statistical analyses 4

1.5 Conclusions and Recommendation 5

Reference ID: 3528238

1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1.1 Introduction and Background

On April 22, 2014, Division of Metabolism and Endocrinology Products in Office of New Drug requested the CMC statistical team in Office of Biostatistics to evaluate statistical methods used in study 409.SqA.2058 appropriate for a nonclinical study. The nonclinical study report 409.SqA.2058 is titled "Liraglutide: Statistical analysis of the correlation between initial calcitonin change and focal C-cell hyperplasia and adenoma scores from study NN204163/NN204310 and NN205119."

1.2 Data and design

The relation between early calcitonin change during the first 28 days of treatment (measured as difference between day 28 level and pretreatment level) and terminal proliferative C-cell changes observed in study NN204163/NN204310 was investigated by the sponsor.

There are two types of terminal proliferative C-cell changes. One is focal C-cell hyperplasia and the other is C-cell adenoma.
The focal C-cell hyperplasia was scored as an ordered categorical variable (with the categories 0, 1, 2). C-cell adenoma was scored as a binary variable with the response 0 (absence) or 1 (presence).

The study was performed in 360 male rats (180 young and 180 aged). At start of the treatment period, the young rats were approximately 2 months old and the aged rats were approximately 8 months old. These are referred to as young and aged rats, respectively. The animals were assigned to one of four treatments vehicle, 0.075, 0.25 or 0.75mg/kg/day liraglutide. For the present analysis, data from the control and high dose animals were assessed as data on C-cell changes was confined to these groups. The animals were sacrificed after various duration of treatment as outlined in Table 1.

Table 1 Design of study N204163, each cell in the table represents a subgroup with different combinations of age, treatment and duration of treatment

Age-class	Age-class Aged (approximately 8 months old at start of dosing)		Young (approximately 2 months old at start of dosing)	
Treatment	Vehicle (0 mg/kg/day)	High dose (0.75 mg/kg/day)	Vehicle (0 mg/kg/day)	High dose (0.75 mg/kg/day)
Days of dosing	Number of animals	Number of animals	Number of animals	Number of animals
28	9	10		
119	10	9		
210	10	10	10	10
301	14	12	8	10
392			10	10
483			11	11

Reference ID: 3528238

1.3 The sponsor's statistical analysis

1.3.1 Sponsor's statistical modeling of focal C-cell hyperplasia

The sponsor treated the focal C-cell hyperplasia was a continuous variable although the focal C-cell hyperplasia was scored as an ordered categorical variable (with the categories 0, 1, 2).

First the sponsor obtained the correlation between the early calcitonin change and the focal C-cell hyperplasia score for each subgroup in Table 1 by fitting the data by linear model in which the focal C-cell hyperplasia is the dependent variable and the early calcitonin change is the predictor variable.
Initially the within subgroup correlation between the calcitonin change and the focal C-cell hyperplasia score, and the regression of the hyperplasia score on the calcitonin change, was estimated separately for each of the 16 subgroups.

Second, the sponsor tested the hypothesis of equal regression parameters in all 16 subgroups (this hypothesis is equivalent to the test of the hypothesis of equal correlation). If this hypothesis was not rejected, a common regression coefficient for all subgroups, and a common correlation for all subgroups were estimated.

Third, the sponsor imputed the missing value from the average if one of the measurements on day 28 and day 14 prior to start of treatment was missing for a rat. The sponsor imputed the missing value from the existing value and from the average difference between pre and post dosing measurement for the relevant treatment group and age group if one of the pre or post measurements on day 28 was missing for a rat.

1.3.2 Sponsor's statistical modeling of Adenoma

The sponsor analyzed adenoma as a binary variable by a logistic regression analysis with calcitonin change as a regression variable and with separate levels for each of the 8 vehicle subgroups, and a separate treatment effect for each of the 8 subgroups treated with liraglutide and a common effect of the regression parameter.

Let π denote the probability of observing an adenoma score equal to 1, and let logit(π) denote $\log(\pi/(1-\pi))$ then the sponsor's logistic model for the example is:

$$\text{logit}(\pi) = \mu_{\text{subgroup}} + \gamma_{\text{treatment(subgroup)}} + \delta^*(\ln(\text{calcitonin Day 28}) - \ln(\text{calcitonin pretreatment})).$$

1.4 Review's comments on the sponsor's statistical analyses

The statistical reviewer has the following comments for focal C-cell hyperplasia:

1) The sponsor did not state whether the purpose of the statistical analysis of the correlation between early calcitonin change during the first 28 days of treatment (measured as difference between day 28 level and pretreatment level) and terminal proliferative C-cell changes is to identify early calcitonin change as the statistically significant factor or predict the terminal proliferative C-cell changes by early calcitonin change.

Reference ID: 3528238

2) If the purpose is to identify the statistically significant factor, modeling terminal proliferative C-cell changes as categorical variable is statistically sound approach. The sponsor's statistical analysis of focal C-cell hyperplasia (the categorical variable) as continuous variable is not scientifically justified.

   On the other hand, If the purpose is to predict the terminal proliferative C-cell changes by early calcitonin change, The correlation of between focal C-cell hyperplasia and the calcitonin change is so small as shown in Table 2 here (Table 5 in the sponsor's report) that validity of use of this model for prediction is in question regardless of the validity of treating focal C-cell hyperplasia (the categorical variable) as continuous variable.

   Table 2 Within subgroup correlation coefficient (r) between focal C-cell hyperplasia score and calcitonin change for age group "aged"

Age group "aged" Correlation r	**Treatment**	
	Liraglutide	Vehicle
days of dosing		
28	-0.34	
119	-0.46	-0.16
210	0.20	-0.09
301	0.54	0.30

3) Pooling among 16 groups is not correct by hypothesis testing of correlation from 16 linear regressions from 16 subgroups.
4) Missing data is not important issue here given the above fundamental frauds.

The statistical reviewer has the following comments for adenoma:
The sponsor didn't justify why a common effect of the regression parameter is reasonable.

1.5 Conclusions and Recommendation

In summary, the sponsor did not have any study objective and the sponsor's analysis of correlation between early calcitonin change during the first 28 days of treatment (measured as difference between day 28 level and pretreatment level) and terminal proliferative C-cell changes is neither useful nor appropriate for a nonclinical study.

Reference ID: 3528238

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/s/

MEIYU SHEN
06/19/2014

YI TSONG
06/19/2014

STATISTICS FILING CHECKLIST FOR NDA 206321
Liraglutide for obesity

Filing meeting: February 6, 2014
Statistical reviewer: Bradley W. McEvoy

NDA Number: 206321 **Applicant: Novo Nordisk** **Stamp Date: 12/20/2013**

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

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ YES_____

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				Review issue
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	See comment below
Appropriate references for novel statistical methodology (if present) are included.			X	standard methodology used
Safety data organized to permit analyses across clinical trials	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA

in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Internal comment:
The interim analysis performed in the Phase 2b trial 1807 at week 52 is not a traditional interim analysis as it was 32 weeks after the end of the main treatment period and the follow-up time after week 20 was optional.

Comment: None at present

Bradley W. McEvoy — January 22, 2014
Reviewing Statistician — Date

Mark Rothmann — January 22, 2014
Supervisor/Team Leader — Date

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/s/

BRADLEY W MCEVOY
02/20/2014

MARK D ROTHMANN
02/20/2014
Concur

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 206-321
Product Name:	Saxenda (liraglutide) 3.0mg injection
Indication(s):	Adjunct to diet and exercise for chronic weight management in adult patients with an initial BMI ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 with comorbidities.
Applicant:	Novo Nordisk Inc.
Dates:	Date submitted: December 20, 2013 PDUFA due date: October 20, 2014
Review Priority:	Standard
Biometrics Division:	VII
Statistical Reviewer:	Rongmei Zhang, Ph. D.
Concurring Reviewers:	Mat Soukup, Ph.D.
Medical Division:	DMEP
Clinical Team:	Julie Golden, M.D., Medical Officer James Smith, M.D., Team Leader
Project Manager:	Patricia Madara

1. Brief Summary of Controlled Clinical Trials

Liraglutide is a human glucagon-like peptide-1 (GLP-1) agonist. The Applicant filed the submission for approval of liraglutide 3.0 mg for the treatment of weight management. The proposed indication is "adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of ≥ 30 kg/m2 or ≥ 27 kg/m2 in the presence of at least one weight related comorbidity". Prior to this submission, liraglutide was approved by the FDA in January 2010 for the treatment of type 2 diabetes mellitus, and is currently marketed at doses up to 1.8 mg/day under the brandname, Victoza®.

The Applicant conducted a meta-analysis to investigate the effect of treatment with liraglutide for weight management compared to a pooled comparator group (placebo and active comparators) on cardiovascular (CV) safety. The primary endpoint was time from first drug date to first occurrence of major adverse cardiovascular events (**MACE**), defined as non-fatal myocardial infarction, non-fatal stroke, or CV death. The events were either prospectively or post hoc adjudicated, by an independent Event Adjudication Committee (EAC), which was governed under a charter.

The primary meta-analysis (**weight management**) included five weight management trials (one phase 2 and four phase 3 clinical trials, see Table 1). In addition, the Applicant conducted a **T2DM** meta-analysis which included trials from liraglutide and semaglutide in T2DM (see Table 1-5 on page

Reference ID: 3454425

14 from the Applicant's statistical analysis plan), and a combined **weight management** and **T2DM** meta-analysis which included trials from both analyses.

Table 1 Completed controlled phase 2–3 trials including extensions in the liraglutide in weight management development program to be included in the primary analysis

Trial	Population	Liraglutide (mg/day)	Comparator	Phase	Trial Duration (weeks)	Rando-misation	Rando-mised subjects (N)
1807	Obese non-diabetic	1.2, 1.8, 2.4, 3.0	Placebo, orlistat	2	20	1:1:1:1:1:1	564
1807 ext1	Obese non-diabetic	1.2, 1.8, 2.4, 3.0	Placebo, orlistat	2	32		398
1807 ext2	Obese non-diabetic	2.4/3.0 (excl. subjects randomised to placebo)	Orlistat	2	52		294
1922	Obese or overweight T2DM Metformin, TZD, SU, or any combination of the three	1.8, 3.0	Placebo	3a	56	1:2:1	846
1923	Obese non-diabetic or overweight non-diabetic with co-morbidities	3.0	Placebo	3a	56	1:1	422
1839	Obese non-diabetic or overweight non-diabetic with co-morbidities	3.0	Placebo	3a	56	2:1	3731
3970	Obese non-diabetic with moderate to severe OSA	3.0	Placebo	3a	32	1:1	359

ext = extension, SU = sulphonylurea, T2DM = type 2 diabetes, TZD = thiazolidinedione, OSA=obstructive sleep apnoea.

Source: Applicant's Statistical analysis plan for meta-analysis, Table 1-5 (page12)

The primary CV meta-analysis was performed using an *on treatment* population, which included all subjects exposed to a minimum of one dose of trial drug and included events occurring up to 30 days after last drug date. The primary endpoint was analyzed using a Cox proportional hazard model stratified by trial with treatment (liraglutide vs. comparator) as the explanatory variable.

According to the report, there were 5908 subjects included in the primary analysis (i.e. weight management trials), 3872 were randomized to liraglutide and 2036 were randomized to the comparator group. Note that 14 randomized subjects were excluded due to not receiving any dose. There were 17 confirmed MACE by the event adjudication committee, 8 for liraglutide and 9 for comparators. The estimated hazard ratio and two-sided 95% confidence interval for liraglutide vs. comparators are 0.40 (0.15, 1.05).

Reviewer Comments:

The reviewer was able to use the integrated safety dataset, "mace.xpt", that was included in the NDA submission to verify the overall number of confirmed MACE and the number of randomized subjects in both treatment arms, in the primary analysis (weight management on treatment population). Using this dataset, the reviewer was also able to replicate the Applicant's estimated HR and 95% CI for MACE in the primary analysis. No other analyses were attempted at the time of this filing review, but will be addressed during the course of the statistical safety review of cardiovascular safety.

Reference ID: 3454425

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes.
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	Not applicable.
Appropriate references for novel statistical methodology (if present) are included.	Not applicable.
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Not applicable.

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\cdsesub1\evsprod\NDA206321\0000\m5\datasets\iss\analysis\legacy\datasets\
Dataset structure (e.g., SDTM or ADaM)	ADaM
List the dataset(s) that contains the primary endpoint(s)	MACE.xpt
Are the define files sufficiently detailed?	Yes.
Based on the *analysis datasets*, can results of the primary endpoint(s) be reproduced?	Yes.
Are there any concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	None at this time
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			

Reference ID: 3454425

Content Parameter	Yes	No	NA	Comments
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		X		The Applicant's CV meta-analysis did not investigate MACE for such subgroups. However, the electronic datasets include such information to run analyses.
Data sets in EDR are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Any other deficiency that on their face render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements		X		

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes, the application is fileable.

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Information Requests

None

5.2. Information Requests/Review Issues

None

Reference ID: 3454425

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/s/

RONGMEI ZHANG
02/14/2014

MATTHEW J SOUKUP
02/18/2014