CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-341

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	022341/0
Drug Name:	Victoza™ (liraglutide) injection
Indication(s):	Treatment of type 2 diabetes mellitus
Applicant:	Novo Nordisk Inc
Date(s):	Submission date: July 8, 2009 Review date: September 8, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Janice Derr, Ph.D.
Statistics Team Leader:	J. Todd Sahlroot, Ph.D.
Medical Reviewer	Karen M. Mahoney, M.D.
Medical Team Leader	Hylton Joffe, M.D.
Project Manager	John Bishai, Ph.D.

This memorandum is the statistical review of the protocol of Study 3748, which is proposed to evaluate the long-term effect of liraglutide on cardiovascular and other clinically important outcomes. A brief description of the statistical aspects of the design and proposed analysis is included at the end of this memo.

Statistical review comments, to be transmitted to the sponsor:

1. We agree with the calculations of the number of subjects needed in the study, subject to clinical input on the appropriateness of the assumption of a 1.8% event rate per year in this clinical population. Our understanding is that the study is designed to accumulate a total of approximately 611 adjudicated primary outcome events across the two study arms. Please confirm or clarify this total.

2. We have the following requests concerning the proposed interim assessment of efficacy:

   (a) The protocol should specify the number of events associated with the two proposed interim assessments. We assume that 50% of the expected number of events is approximately 306 and 75% is approximately 458. Please confirm or clarify this assumption.

   (b) The protocol should specify which efficacy outcome variable(s) will be assessed for superiority, using the modified Haybittle-Peto stopping boundary. If more than one outcome variable will be assessed, the protocol should provide more information about the protection of Type I error for the primary cardiovascular outcome variable.

(c) The protocol should specify how the interim analysis of efficacy and futility will be conducted, in order to maintain the appropriate study blind.

3. The statistical methods for the analysis of primary and supportive outcome data that are generally described in this protocol are acceptable. In addition, we request that you submit the more detailed statistical analysis plan with sufficient lead time prior to your analysis of data so that we may review the plan and send you our review comments.

4. Study 3748 presents an opportunity to gain further information concerning the comparison between liraglutide and placebo in longitudinal changes in serum calcitonin in this study population. We recommend that the study protocol include a detailed analysis plan for evaluating this relationship. This analysis plan should include a pre-specified statistical analysis model, along with additional supportive analyses and descriptive summaries.

Summary of the study design (not to be transmitted to the sponsor):

Title of Study: EX221-3748, "Liraglutide Effect and Action in Diabetes; Evaluation of cardiovascular outcome Results; A five-year, multi-centre, international, randomized, double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events" (LEADER).

Purpose: The primary purpose of this study is to determine the long-term effect of liraglutide on cardiovascular and other clinically important outcomes.

Trial design: Subjects with type 2 diabetes treated with 0, 1 or 2 oral anti-diabetes drugs (OAD) will, after a single-blind run-in period of a minimum of two weeks, be randomized (1:1) to receive liraglutide 1.8 mg once daily or equivalent placebo as an add-on to their standard of care treatment. The study will enroll approximately 9000 patients among type 2 diabetic subjects who are at high risk for cardiovascular events. The recruitment period is planned for 18 months, and intended maximum trial duration will be 60 months. The minimum duration of observation after randomization will be 42 months.

Number of subjects in the study: The number of subjects to be randomized in the study was estimated based on a time to first outcome using a log rank test on an intention-to-treat analysis and the following assumptions: a) a conservative range of primary outcome event rate of 1.8% per year; b) a 1 sided alpha of 0.025; c) uniform enrolment over 1.5 years with a maximum follow-up of 5 years (including the accrual period) ; d) a non-inferiority margin versus placebo of 1.3 for the upper limit of the 2-sided 95% confidence interval; e) a non-adherence rate of 10%; by the second year in trial and uniform thereafter; and f) 90% power to reject the null hypothesis that the hazard ratio is > 1.3.

Under the above assumptions, 8900 subjects need to be randomized to clearly evaluate the cardiovascular effects of liraglutide with high power.

Statistical review comment: I was able to recreate this calculation (approximately) using the statistical software East™5.2. The study is designed to accumulate a total of 611 adjudicated primary outcome events in both study arms combined.

Outcomes: The primary outcome is the first occurrence of either cardiovascular (CV) death, nonfatal myocardial infarction (MI) or nonfatal stroke. Secondary outcomes include an expanded composite of CV events, a composite microvascular outcome, and all-cause mortality. Among the other endpoints are serious adverse events and other medical events of special interest such as pancreatitis, neoplasms, thyroid disease and adverse events leading to treatment discontinuation. HbA1c and laboratory endpoints such as calcitonin are also included as other endpoints.

Assessment: Pre-treatment clinical visits are planned for screening, the start of run-in, and randomization (baseline). Visits during the treatment period are planned for week 2, then months 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60. Assessments include composite cardiovascular and microvascular outcomes, all-cause mortality, individual components of the composite cardiovascular and microvascular outcomes, weight and waist-to-hip ratio, sustained normoglycaemia without severe hypoglycaemia, cognitive function, serious adverse events and

other medical adverse events of special interest (pancreatitis, neoplasm, thyroid-related events, adverse events leading to treatment discontinuation), blood pressure and heart rate, as well as selected laboratory parameters: blood lipids, HbA1c and selected safety parameters (including calcitonin, amylase and lipase).

Data Monitoring Committee (DMC): An independent external DMC will be constituted for the trial to perform ongoing safety surveillance at pre-defined time points, and to provide advice to the sponsor during the conduct of the trial as whether to continue, modify or terminate the trial as necessary. The DMC will evaluate all relevant safety information un-blinded. Clear evidence of net harm with respect to total mortality, cancer, hospitalizations or other variables identified by the DMC based on emerging data from this or other studies, that is consistent over time and across subgroups would justify a recommendation to stop the trial early.

Event Adjudication Committee (EAC): An external EAC will be constituted for the trial to perform ongoing adjudication, standardization and assessment of pertinent events in an independent and blinded manner, including cardiovascular death, acute coronary syndrome, stroke, cardiac insufficiency requiring acute hospitalization, pancreatitis, and all neoplasms.

Evaluability of subjects for analysis: The sponsor describes their intention to maximize adherence to the study protocol, and to follow up with subjects who prematurely discontinue their assigned treatment.

Statistical considerations: The sponsor plans to prepare a more detailed statistical analysis plan, which will be finalized before the database is released. No analyses of unmasked or between-group data is planned before the database is closed or released, except for confidential analyses performed to support the deliberations of the independent Data Monitoring Committee.

Interim analysis of efficacy data: The sponsor plans two interim analyses of efficacy data, after 50% and 75% of the expected number of primary cardiovascular outcome events have occurred. They plan to use a modified Haybittle-Peto stopping boundary such that if the difference in event rates between groups is greater than 4 standard deviations for the first interim analysis, and 3 standard deviations for the second and this difference is confirmed by a second analysis 3 months later, the trial may be terminated early. The sponsor notes that alpha spending associated with these criteria is very small; and for this reason they plan to evaluate the final primary analysis will be done at a 1 sided alpha=0.025.

The sponsor also notes that the trial may also be stopped early if there is clear evidence of futility with respect to demonstrating non-inferiority. At the time of the two formal interim analyses, there will be an interim futility calculation of the conditional power to demonstrate non-inferiority of liraglutide versus placebo on the primary outcome at the end of this trial. If in the judgment of the DMC this conditional power is unreasonably low (e.g. < 10%), they may recommend early stopping.

Statistical review comments:

- *Based on a total of 611 events, the interim analyses of efficacy will take place after 50% (approximately 306) and 75% (approximately 458) events have occurred.*
- *"Efficacy endpoints" in this study include the primary and secondary cardiovascular, microvascular and all-cause mortality endpoints, and individual components of the*

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