CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-341

MEDICAL REVIEW(S)

Addendum to Clinical Safety Review
NDA 22341 (Victoza®, liraglutide injection)
Submission Received from Applicant 26 Oct 2009
Additional Calcitonin Shift Tables

Karen Murry Mahoney, MD, Clinical Reviewer
Division of Metabolism and Endocrinology Products
27 Oct 2009

On 26 Oct 2009, Novo Nordisk, the applicant for NDA 22341, submitted additional calcitonin analyses in response to a request from Dr. Hylton Joffe, Team Leader for Diabetes Products Team I in the Division of Metabolism and Endocrinology Products. These analyses include the five major Phase 3 diabetes trials which were included in the original NDA submission, and add data from two Phase 2 Japanese diabetes trials, preliminary data from a diabetes treatment trial versus exenatide, and preliminary data from a Phase 2 obesity treatment trial. Similarly to previous data presentations, the submitted shift tables show that the highest percentage of upward shifters occurs in the 1.8 mg liraglutide dose group, which is the highest proposed dose for marketing.

The following table summarizes the submitted data.

Summary of Specified Upward Shifts in Calcitonin (LOCF); Phase 3 Diabetes Trials, Two Phase 2 Japanese Diabetes Trials, Preliminary Data from Diabetes Treatment Trial vs Exenatide, and Preliminary Data from Phase 2 Obesity Trial

	LGT 0.6	LGT 1.2	LGT 1.8	PBO	AC	TC
Percentage of patients with shift from below the upper limit of normal to persistently[1] above the upper limit of normal, from baseline to Weeks 20/24/26/28[2]	1.1	1.0	1.9	0.8	1.1	1.0
Rate per 1000 patient-years of patients with shift from below the upper limit of normal to persistently[1] above the upper limit of normal, from baseline to Weeks 20/24/26/28[2]	23.2	22.9	41.8	20.7	23.7	22.7
Percentage of patients with shift from below the upper limit of normal to persistently[1] above the upper limit of normal, from baseline to Week 52[3] (voluntary unblinded extension data included)	0	0.6	1.3	0	1.0	0.7
Rate per 1000 patient-years of patients with shift from below the upper limit of normal to persistently[1] above the upper limit of normal, from baseline to Week 52[3] (voluntary unblinded extension data included)	0	6.9	14.1	0	10.9	8.1
Percentage of patients with shift from below the upper limit of normal to persistently[1] above the upper limit of normal, from baseline to Week 104[4] (all voluntary unblinded extension data)	0	0.3	0.6	0	0.6	0.5

Summary of Specified Upward Shifts in Calcitonin (LOCF); Phase 3 Diabetes Trials, Two Phase 2 Japanese Diabetes Trials, Preliminary Data from Diabetes Treatment Trial vs Exenatide, and Preliminary Data from Phase 2 Obesity Trial

	LGT 0.6	LGT 1.2	LGT 1.8	PBO	AC	TC
Rate per 1000 PY of patients with shift from below the upper limit of normal to persistently[1] above the upper limit of normal, from baseline to Week 104[4] (all voluntary unblinded extension data)	0	1.7	3.4	0	3.5	3.0
Percentage of patients who shifted from below the upper limit of normal to persistently above the upper limit of normal, all post-baseline observations	0.7	0.6	1.7	0.8	0.8	0.8
Percentage of patients who began with serum calcitonin <20 ng/L and who shifted to a serum calcitonin ≥ 20 ng/L at Week 20/24/26/28	0.2	0.1	0.5	0.1	0.4	0.3
Rate per 1000 PY of patients who began with serum calcitonin <20 ng/L and who shifted to a serum calcitonin ≥ 20 ng/L at Week 20/24/26/28	3.9	2.3	12.4	3.4	4.7	4.3
Percentage of patients who began with serum calcitonin <20 ng/L and who shifted to a serum calcitonin ≥ 20 ng/L at Week 52 (voluntary unblinded extension data included)	0.4	0	0.6	0	0.3	0.2
Rate per 1000 PY of patients who began with serum calcitonin <20 ng/L and who shifted to a serum calcitonin ≥ 20 ng/L at Week 52 (voluntary unblinded extension data included)	3.8	0	7.1	0	3.6	2.7
Percentage of patients who began with serum calcitonin <20 ng/L and who shifted to a serum calcitonin ≥ 20 ng/L at Week 104 (all voluntary unblinded extension data)	0.5	0	0	0	0.3	0.3
Rate per 1000 PY of patients who began with serum calcitonin <20 ng/L and who shifted to a serum calcitonin ≥ 20 ng/L at Week 104 (all voluntary unblinded extension data)	3.1	0	0	0	1.8	1.5
Percentage of patients who began with serum calcitonin <20 ng/L and who shifted to a serum calcitonin ≥ 20 ng/L, all post-baseline observations	0.5	0.6	1.1	0.3	0.5	0.4

Summary of Specified Upward Shifts in Calcitonin (LOCF); Phase 3 Diabetes Trials, Two Phase 2 Japanese Diabetes Trials, Preliminary Data from Diabetes Treatment Trial vs Exenatide, and Preliminary Data from Phase 2 Obesity Trial

	LGT 0.6	LGT 1.2	LGT 1.8	PBO	AC	TC

Source: Applicant's Table 2-3, NDA 22341 submission stamp date 26 Oct 2009, serial pg 9; and Table 2-4, serial pg 10.
1 "Persistently" is defined as having elevation in all calcitonin values obtained after baseline, up to the specified week
2 Includes measurements at Weeks 20/24/26/28 for the Phase 3 diabetes trials, two Phase 2 Japanese diabetes trials, preliminary data from a Phase 2 obesity trial and preliminary data from a diabetes trial vs exenatide
3 Includes data from a Phase 3 monotherapy diabetes trial; and voluntary unblinded extension data from a Phase 3 diabetes trial as add-on to metformin, two Phase 2 Japanese diabetes trials and preliminary data from a Phase 2 obesity trial. These data should be interpreted with caution, because the drop-out rate in extensions was high and differed between treatment groups.
4 Voluntary unblinded extension data from a Phase 3 monotherapy diabetes trial and a Phase 3 diabetes trial as add-on to metformin. These data should be interpreted with caution, because the drop-out rate in extensions was high and differed between treatment groups.

In a previous submission (25 Jun 2009), the applicant had stated that there were two liraglutide-treated patients (both treated with 1.8 mg/day) who began with a serum calcitonin <50 ng/L and shifted to >50 ng/L during study, and one comparator-treated patient. In the 26 Oct 2009, submission, the applicant states that there was only one liraglutide-treated patient (1.8 mg group) who exhibited this shift, and no comparator-treated patients. The 26 Oct 2009 submission did not discuss this discrepancy. In response (11 Nov 2009) to an inquiry regarding the difference, the applicant stated that the 25 Jun 2009 submission "contained an error".

Data provided for Weeks 52 and 104 should be interpreted with caution; most data at 52 weeks, and all data at 104 weeks, are from voluntary unblinded extensions. The drop-out rate in extensions was high, and differed between treatment groups, as discussed in the original clinical safety review (DARRTS 8 Aug 2009). The applicant has not submitted study reports for the diabetes trial versus exenatide and for the Phase 2 obesity trial, and therefore these data are preliminary. As in previous submissions, the mean and median changes in serum calcitonin are not large. Also as in previous submissions, the highest percentage of upward shifters occurs in the 1.8 mg liraglutide dose group, which is the highest proposed dose for marketing.

As discussed in the original clinical safety review, the clinical safety reviewer remains concerned about the strong animal carcinogenicity signal for liraglutide, and feels that the duration of blinded controlled human study has been inadequate to recommend marketing at this time. The clinical reviewer continues to recommend a long-term (≥3 year) double-blinded controlled study, which would include multiple biomarkers to further characterize liraglutide's effect on C-cells, prior to marketing.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/

KAREN M MAHONEY
11/17/2009

HYLTON V JOFFE
11/17/2009
See CDTL memorandum and addendum

11/3/09

DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	November 3, 2009
To:	John Bishai, Regulatory Project Manager, Division of Metabolic and Endocrine Products (DMEP)
From:	Brian Oscar Porter, M.D., Ph.D., M.P.H., Medical Reviewer
Through:	Susan Limb, M.D., Medical Team Leader
Through:	Badrul Chowdhury, M.D., Ph.D., Division Director
Subject:	Anti-drug antibody formation to liraglutide

General Information

NDA/IND#:	NDA 22341
Sponsor:	Novo Nordisk
Drug Product:	Liraglutide (Victoza®)
Request From:	John Bishai, Regulatory Project Manager, DMEP
Date of Request:	October 28, 2009
Date Received:	October 29, 2009
Date Due:	ASAP
Materials Reviewed:	Primary review of NDA 22341 by Clinical Review team; sections of NDA 22341 related to immunogenicity of drug product

Executive Summary

This is a Medical Officer Consultation Review requested by the Division of Metabolic and Endocrine Products (DMEP) from the Division of Pulmonary and Allergy Products (DPAP) for the drug liraglutide (NDA 22341). Liraglutide is an analogue of the glucose-dependent insulin secretagogue human glucagon-like-peptide-1 (GLP-1), which is engineered to resist degradation by endogenous peptidases and thus contribute to long-term glycemic control with a decreased risk of hypoglycemia. The NDA was submitted on May 23, 2008. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. The target age group is adults aged 18 years and older.

In pooled Phase III clinical trials, nearly 10% of liraglutide recipients formed anti-drug antibodies (ADA), of which ~50% cross-reacted with native GLP-1 and ~10% demonstrated neutralizing activity in a cell-based assay. Although an efficacy analysis of the treatment effect of ADA formation, GLP-1 cross-reactivity, and the presence of neutralizing ADA on glycosylated hemoglobin levels demonstrated no statistical impact of these factors on long-term glycemic control, the assay used to detect liraglutide-specific ADA is directly inhibited by the drug product itself. Although immunogenicity samples were drawn ≥5 days following last study drug administration, sampling was not done uniformly for all subjects in the Phase III

development program, resulting in an incomplete dataset, which may be biased toward false negative misclassification, potentially resulting in regression of group values toward the mean in both efficacy and safety analyses.

Thus, we recommend further evaluation of immunogenicity in the postmarketing stage. Potentially, the Sponsor could add ADA sampling to the already planned 9000 subject postmarketing trial for long-term cardiovascular outcomes. Alternatively, the Sponsor can conduct a designated clinical trial to assess adverse events associated with immunogenicity. While antibody levels may be obtained on a subset of patients from the proposed large Phase IV trial, we recommend sampling subjects following a liraglutide-free period of uniform and sufficient duration. This may necessitate periodic drug-withholding periods within the trial design in order to screen for ADA with maximal sensitivity. In addition, outcome measures in this trial should also include assessments relevant to the potential immunopathogenic mechanisms of ADA, not only in terms of reduced drug efficacy, but also in terms of organ-specific adverse events common to drug hypersensitivity reactions.

Background

Drug Product. Liraglutide is an analogue of human glucagon-like-peptide-1 (GLP-1), which is currently under review (NDA 22341; Sponsor: Novo Nordisk) for approval as a subcutaneously injected, once daily treatment for diabetes mellitus type 2. Native GLP-1 is a gut incretin hormone that induces glucose-dependent insulin secretion but has an extremely short half-life, due to rapid degradation by endogenous dipeptidyl-peptidase-4. As an analogue to GLP-1, liraglutide has an altered structure, which makes it more resistant to degradation, resulting in a longer half-life. As the insulin-secreting activity of liraglutide is glucose-dependent, the drug is designed to facilitate glycemic control with a decreased risk of hypoglycemia due to insulin over-secretion, as compared to other insulin secretagogues, such as sulfonylurea drugs.

Anti-drug Antibody Formation. A review of the information submitted by the Sponsor for NDA 22341 reveals that anti-drug antibodies (ADA) to liraglutide developed in nearly 10% of study drug recipients in four major Phase III clinical trials (Trials 1572, 1436, 1574, and 1697). Of these, approximately half displayed cross-reactivity with native GLP-1 (i.e., ~5% of liraglutide recipients tested), while roughly 10% (or 1-2% of the total sample) developed antibodies with neutralizing activity against liraglutide. In contrast to these liraglutide-specific ADA, antibodies formed against another GLP-1 analogue, exenatide (the only FDA-approved drug product in this class: NDA 21773), demonstrated no significant treatment-emergent cross-reactivity with either GLP-1 or glucagon. Liraglutide-specific ADA were detected using a radioimmune assay in which patient serum was adsorbed with radiolabeled liraglutide and then protein-extracted with polyethylene glycol. In turn, the amount of precipitated radioactivity (i.e., liraglutide bound-antibody) was expressed as a percentage of the total amount of radioactivity applied to the sample and could be used to quantify the level of ADA present in the sample. Assessment of GLP-1 cross-reactivity was done by taking patient serum bound with radiolabeled liraglutide and subsequently incubating it with excess unlabeled native GLP-1 protein to determine the extent to which GLP-1 competed off bound, radiolabeled liraglutide. Neutralizing activity of ADA was assessed using a cell-based assay in which a luciferase reporter gene construct was created using the human GLP-1 receptor and transfected into a rodent cell line. This construct allowed for the quantification of cyclic adenosine monophosphate (cAMP) in

response to binding by GLP-1 or an agonist, such as liraglutide. Thus, by incubating patient serum with a known amount of liraglutide prior to application to the cell line, the neutralizing activity of ADA could be measured as a function of their inhibitory activity against liraglutide-induced cAMP production.

Antibody Detection Assays and Efficacy Assessment. A primary concern with the assays described above is that the ADA detection assay is directly inhibited by the presence of drug product in patient serum. In other words, sensitivity of the detection assay is markedly diminished if sampling is done while levels of liraglutide are still detectable in the circulation, potentially resulting in false negative results. To address this concern, immunogenicity samples tested in the four Phase III trials were drawn ≥5 days following the last liraglutide dose. Of note, however, nonclinical animal studies in cynomolgus monkeys suggested ADA may interfere with liraglutide clearance and result in prolonged drug exposure. Thus, it is unclear whether a 5-day drug-free window is adequate to minimize misclassification bias in terms of ADA detection. With regard to drug efficacy, the treatment effects of ADA formation, GLP-1 cross-reactivity, and neutralizing antibody formation on glycosylated hemoglobin (HgbA1c, i.e., long-term glycemic control) were evaluated in separate ANCOVA models and found to have no statistical impact. Interestingly, mean HgbA1c levels were actually lower in the small group of patients with detectable neutralizing ADA (n=12). However, properly timed samples were not universally available for all subjects in these studies. Moreover, the number of liraglutide-recipients evaluated in the HgbA1c efficacy analysis (n=1174; ADA-positive=101) was lower than the total number of liraglutide-recipients included in ADA detection studies (n=2501; ADA-positive=160). Thus, the immunogenicity dataset gleaned from the Phase III trials appears incomplete. Moreover, a propensity for false negative misclassification in this dataset with regard to ADA detection would result in regression toward the mean in group values, potentially masking the impact of ADA on long-term drug effectiveness.

Safety Assessment. Although no serious adverse events emerged in relation to ADA formation, a comparison of adverse event profiles between subjects who developed anti-liraglutide antibodies versus seronegative patients revealed trends toward an increased incidence in several categories of adverse events in the ADA-positive group, including infections (especially of the upper and lower respiratory tract), injection site reactions, and musculoskeletal disorders (e.g., arthralgias). Again, false negative misclassifications would tend to regress these group values toward the mean and obscure actual underlying differences in adverse event rates associated with ADA formation. Thus, although there does not appear to be a significant safety signal among subjects who developed ADA, it remains concerning that over half of them displayed cross-reactivity to native GLP-1 and that the assays used for ADA detection have questionable accuracy, particularly at only 5 days following last study drug administration.

Recommendations

DMEP requests input from our Division regarding the potential impact of ADA on the approval of liraglutide and whether any additional studies should be required of the Sponsor to further explore safety and/or clinical efficacy issues of this drug, with respect to immunogenicity.

Given concerns over the accuracy of the ADA detection assay used, particularly as it relates to decreased sensitivity in the presence of circulating study drug, as well as the incomplete nature of the Phase III clinical trial immunogenicity dataset as reflected in both partial testing and a propensity for false negative misclassification, we recommend conducting a postmarketing trial of liraglutide recipients to more reliably delineate the incidence and implications of liraglutide-specific ADA formation. At present, the Sponsor plans to conduct a randomized, blinded, placebo-controlled postmarketing trial of 9000 type 2 diabetic patients at risk for cardiovascular complications, in order to discern the impact of study drug on cardiovascular related mortality and morbidity. Clinical immunogenicity could be evaluated in a subset of liraglutide recipients in this large Phase IV trial. Alternatively, potential adverse events associated with immunogenicity could be assessed in a separate postmarketing trial.

We note that antibody sampling in the Phase III trials after a 5-day drug-free period was only done after 6 months on study drug, while ADA formation against a similar drug product, exenatide, peaked at 6 weeks following drug initiation. Thus, assessing for antibody formation at more than one time point in the proposed study, including timepoints earlier than 6 months, would provide information on the kinetics of ADA formation. However, immunogenicity sampling must be sufficiently separated in time from last study drug receipt, as supported by the Sponsor's pharmacokinetic data. Given that liraglutide is administered as a once daily injection, this may necessitate recurrent periods of drug withholding at pre-planned points in the study, in order to draw immunogenicity samples only after a sufficient drug-free period, after which, study drug may be re-started for the purposes of completing the long-term cardiovascular outcomes study. A planned and uniformly executed immunogenicity evaluation would allow the Sponsor to robustly determine the effects of ADA formation on both the efficacy and safety profile of liraglutide, as such a study would capture immunogenicity data on the full dataset.

As mentioned in the Clinical Safety Review of NDA 22341, the DMEP Clinical Review Team already recommended that an assessment of immune-related adverse events also be done for the entire sample of the proposed cardiovascular outcomes postmarketing study, with which we concur. To facilitate correlation of observed immune-related adverse events to seroconversion, antibody levels could be obtained from a subset of patients in this trial. The number of patients sampled should take into account the overall rate of seroconversion (~10%), as well as the rates of seroconversion for neutralizing antibodies (~1-2%) and cross-reactive antibodies (~5%) observed in the Phase III clinical development program..

Although no major safety signals emerged in this dataset related to IgE-mediated immediate hypersensitivity events other than urticaria, ADA formation with documented cross-reactivity to an endogenous protein carries a potential risk not only of inactivation of the native protein, but also of antigen-antibody complex mediated disease, including immune complex deposition, serum sickness, or other systemic hypersensitivity syndromes. Thus, outcome measures in this postmarketing immunogenicity study should also address these immune mechanisms, including appropriate historical and physical assessments of target body systems (e.g., cutaneous and musculoskeletal manifestations), measuring complement levels as an index of immune complex mediated disease, and screening hepatic transaminases and renal function tests in the setting of systemic inflammatory findings.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22341	ORIG-1	NOVO NORDISK INC	VICTOZA (LIRAGLUTIDE)

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/s/

BRIAN PORTER
11/03/2009

SUSAN L LIMB
11/03/2009

SALLY M SEYMOUR
11/03/2009
for Badrul Chowdhury

ADDENDUM TO CLINICAL SAFETY REVIEW
NDA 22341 (Victoza®, liraglutide injection)
14 Aug 2009
Karen Murry Mahoney, MD, FACE

At the time of the original clinical safety review of liraglutide (DARRTS 7 Aug 2009), information from the applicant was pending regarding a patient who was treated with liraglutide and who had an event of "jaundice". On 12 Aug 2009, the applicant submitted the requested information.

Patient 212002 was a 45 year old woman who had a nonserious event of "jaundice" reported after 98 days of treatment with liraglutide. No further clinical history was available. However, the applicant provided laboratory data which suggests that this event was not clinically significant and may not have represented actual jaundice. Prior to the event, the patient had three separate sets of normal laboratory for serum alanine aminotransferase, aspartate aminotransferase and bilirubin, including normal values 4 days prior to the reported date of the event. At that time, her bilirubin was 0.16 mg/dL (upper limit of normal 1.28). Subsequent to the date of the event of "jaundice", all bilirubin levels and transaminase levels were normal on all seven subsequent collections over an additional 20 months. The closest post-event values were from samples collected 3 months after the event; there is a small possibility that the patient had an event of jaundice that rapidly resolved. However, liraglutide had not been discontinued, and despite its continued use for 20 months, multiple subsequent measures of liver function were normal, suggesting that liraglutide was not causative in a significant liver injury.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1		VICTOZA (LIRAGLUTIDE)

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KAREN M MAHONEY
08/14/2009

HYLTON V JOFFE
08/14/2009

CLINICAL REVIEW

Application Type	NDA
Submission Number	022341
Submission Code	N000
Letter Date	23 May 08
Stamp Date	23 May 08
PDUFA Goal Date	23 Mar 09
Reviewer Name	Lisa B. Yanoff, M.D.
Review Completion Date	22 Jul 09
Established Name	Liraglutide
(Proposed) Trade Name	Victoza
Therapeutic Class	GLP-1 analogue
Applicant	Novo Nordisk
Priority Designation	S
Formulation	Subcutaneous injection
Dosing Regimen	0.6, 1.2, and 1.8 mg daily
Indication	Treatment of type 2 diabetes
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

This document contains the clinical efficacy review for liraglutide, a human glucagon-like peptide (GLP-1) analogue that has been developed as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. The clinical safety review for liraglutide is contained in a separate document prepared by Dr. Karen Mahoney.

1.1 Recommendation on Regulatory Action

The recommendation for regulatory action in this review is based on a clinical review of efficacy only. Safety is addressed by Dr. Mahoney in her Clinical Review of Safety. For a comprehensive risk/benefit analysis that incorporates all known efficacy and safety information the reader is referred to the cross discipline team leader memo written by Dr. Joffe.

Based on my review of clinical efficacy, I recommend approval of liraglutide from a clinical efficacy perspective for the Sponsor's proposed indication and at the doses proposed by the Sponsor. There is substantial evidence of effectiveness from five pivotal phase 3 trials (randomized, double-blind, and controlled (some placebo-controlled and some active-controlled)) that are considered by this reviewer to be "adequate and well-controlled" and permit selection of an appropriate dosing regimen for the claimed indication in the general type 2 diabetic population as well as in special populations including various demographic subgroups, and those with renal or hepatic impairment.

1.2 Recommendation on Postmarketing Actions

From an efficacy standpoint there are no recommendations on postmarketing actions. The efficacy of liraglutide has been well-established in the premarketing development program.

1.2.1 Risk Management Activity

Please see Dr. Mahoney's clinical safety review

1.2.2 Required Phase 4 Commitments

Required phase 4 commitments, if any, are discussed in Dr. Mahoney's clinical safety review.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Liraglutide (proposed trade name Victoza®) is a new molecular entity in the class of drugs known as glucagon-like peptide (GLP-1) analogues that has been developed as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is administered by subcutaneous injection. The clinical efficacy of liraglutide was studied in adult (age ≥ 18 years) type 2 diabetic patients in five pivotal phase 3 trials. A total of 3978 patients were exposed to treatment in the phase 3 efficacy trials (2501 to liraglutide, 524 to placebo, and 953 to an active comparator). The overall number of patients in the safety database and extent of exposure are discussed in Dr. Mahoney's clinical safety review.

1.3.2 Efficacy

The five major efficacy trials investigated the benefits of liraglutide as:

Monotherapy (i.e. liraglutide alone) (52 week trial)

Add-on to one oral anti-diabetic drug (two 26 week trials)

- combination with metformin
- combination with a sulfonylurea (glimepiride)

Add-on to two oral anti-diabetic drugs (two 26 week trials)

- combination with a thiazolidinedione (TZD) (rosiglitazone) and metformin
- combination with an sulfonylurea (glimepiride) and metformin

The three above-listed scenarios, monotherapy (i.e. liraglutide alone), "add-on" to one oral anti-diabetic drug (i.e. combined with one other commonly used anti-diabetic drug), and "add-on" to two oral anti-diabetic drugs (i.e. combined with two other commonly used anti-diabetic drugs) represent the manner in which liraglutide will be used in the diabetic population because diabetes is a progressive disease that typically requires the stepwise addition of anti-diabetic agents (and ultimately insulin) to maintain adequate glycemic control. Therefore, this development program has adequately studied liraglutide in a large proportion of the potential conditions of its use by diabetic patients.

The five pivotal studies were "adequate and well-controlled." This reviewer identified no major problems with the efficacy studies including choice of endpoint, choice of control, adequacy of blinding, conduct of the studies, and appropriateness of statistical analyses.

The primary endpoint (i.e. primary efficacy variable) for all pivotal studies was change from baseline in hemoglobin A1c (HbA1c) (%) at the end of the double-blind treatment period. HbA1c is an appropriate endpoint for reasons discussed in section 6.1.2.1. The FDA draft guidance entitled Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf) states, "For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control."

Important secondary endpoints included other glycemic control parameters such as change in fasting plasma glucose at the end of the double-blind treatment period, as well as body weight change at the end of the double-blind treatment period.

The development program used both placebo and active comparators (meaning another anti-diabetic drug) for control groups in the phase 3 clinical trials. The monotherapy trial did not have a placebo group, but rather compared liraglutide with glimepiride, a commonly used sulfonylurea drug for the treatment of type 2 diabetes. The add-on trials used various active comparators that consisted of commonly used anti-diabetic therapies, mostly oral, but also insulin glargine in one trial. The active comparators dosages generally were adequate for supporting approval of liraglutide for the proposed indication. The full discussion of the adequacy of active comparator dosages is located in section 6 of this review.

Blinding was accomplished in all of the phase 3 trials (note exception below) by incorporating a placebo and/or a double-dummy technique in which active comparators were also blinded by the use of indistinguishable "dummy" comparators. (exception: the trial that compared liraglutide to insulin glargine included open-label insulin glargine because of the need for titration of insulin).

Conduct of the studies was appropriate with adherence to good clinical practices and full financial disclosures reported. Statistical analyses were appropriately performed; these are discussed more fully in the statistical review written by the Division of Biometrics.

This reviewer concludes that liraglutide is effective for the proposed indication: as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. This conclusion is based both on the quality of the phase 3 clinical trials conducted, as discussed in the previous paragraphs in this section, as well as the clinical importance of the findings of those trials. Based on the results of the trials, it can be concluded that liraglutide results in a clinically important placebo-corrected reduction in HbA1c of approximately 1% when used as monotherapy, as add-on to one other oral anti-diabetic agent, or as add-on to two other oral anti-diabetic agents. This reviewer did not identify any major limitations of the available clinical data

that would influence efficacy conclusions. Limitations of the development program are discussed in section 6.1.4.5.

There is a need for new antidiabetic drugs. There are now over 23 million patients diagnosed in the U.S. alone and over 170 million worldwide with more than 1.5 million new cases per year. Diabetes has a devastating impact on patients from diabetic microvascular complications including blindness, amputation, and the need for dialysis, as well as from cardiovascular disease. A vast number of diabetic patients do not reach glycemic targets due to limitations of current therapies. Furthermore, since diabetes is a chronic, progressive disease, there is usually the need for additional treatments to be added to the patients' regimens over time.
The results of the major clinical efficacy trials show that liraglutide has a clinically important effect on HbA1c compared to placebo and should be considered a useful addition to the diabetic drug armamentarium. Comparison studies with liraglutide and other anti-diabetic drugs that were conducted as part of the liraglutide development program suggest that liraglutide is at least as effective and in some cases, superior to, some other commonly used anti-diabetic drugs.

1.3.3 Safety

See Dr. Mahoney's safety review

1.3.4 Dosing Regimen and Administration

The applicant's proposed dosing regimen is as follows: For all patients liraglutide treatment should be initiated with a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on tolerability and/or clinical response and after at least one week at 1.2 mg, the dose can be increased to 1.8 mg to achieve maximum efficacy. This reviewer agrees with the Sponsor's proposal on the basis of evidence of efficacy provided in the phase 3 program. However, an alternative dosing regimen may be acceptable as described in the next paragraph.

The recommendation for approval for the Sponsor's proposed dosing regimen is based on review of efficacy only. However, if the overall risk benefit analysis shows a significant safety concern for the highest tested dose of liraglutide (1.8 mg daily), this reviewer concludes that the next highest tested dose of liraglutide (1.2 mg daily) has also shown substantial evidence of effectiveness from four phase 3 trials (four of the five trials mentioned above tested the 1.2 mg dose) that, as stated above, are considered by this reviewer to be "adequate and well-controlled" and would, in the situation of a safety concern for the 1.8 mg dose, recommend approval of a modified dosing regimen with a maximal approved dose of liraglutide of 1.2 mg daily.

1.3.5 Drug-Drug Interactions

Drug-drug interactions are discussed in Dr. Mahoney's review.

1.3.6 Special Populations

Subject Demographics

Comparison of the efficacy of liraglutide in sub-populations including various demographic sub-groups as well as various diabetes disease characteristics was assessed based on data from the five phase 3 trials. These analyses did not suggest that there were any subsets of the population that demonstrated differences with respect to the effectiveness, as measured by HbA1c, among treatments. Therefore, from an efficacy standpoint, there were no meaningful differences in efficacy across these demographic variables that would affect this product's use.

Renal and Hepatic Impairment

Based on clinical pharmacology data (including one pharmacokinetic study in patients with renal impairment and one pharmacokinetic study in patients with hepatic impairment) no dose adjustment is proposed for renal and hepatic impairment subjects (see section 5.1). The clinical pharmacology reviewer concluded the same. The clinical efficacy review of the phase 3 program also did not find evidence that dose adjustment should be recommended for patients with mild renal and hepatic impairment. However, the phase 3 trials did not enroll many subjects with moderate or severely impaired renal and hepatic function so there is limited efficacy data in these populations.

Pregnancy and Lactation

The use of liraglutide during pregnancy and lactation is primarily a safety issue. Please see Dr. Mahoney's review.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Product description

Liraglutide (Arg34Lys26-(N-ε-(γ-Glu (N-α-hexadecanoyl)))-GLP-1[7-37]) is a once-daily human GLP-1 analogue in which lysine at position 34 has been replaced with arginine, and palmitic acid has been attached via a glutamoyl spacer to lysine at position 26.

Established name and proposed trade name

The established name of this product is liraglutide. The proposed trade name is Victoza®. This trade name has been approved by the Division of Medication Error Prevention and Analysis (DMEPA).

Chemical class

Liraglutide is a new molecular entity.

Pharmacologic class

Liraglutide belongs to the class of anti-diabetic agents known as glucagon-like peptide-1 (GLP-1) analogues. Liraglutide is the second GLP-1 analogue to undergo FDA review as a New Drug Application (NDA). The other GLP-1 analogue, exenatide (trade name Byetta®) was approved as a treatment for type 2 diabetes mellitus in April, 2005 and is dosed subcutaneously twice daily. A once weekly formulation of exenatide (exenatide LAR) is currently under review by the Division of Metabolism and Endocrinologic Products (DMEP).

Discussion of the pharmacologic class (source: sponsor's clinical overview)
Oral glucose leads to greater insulin secretion than intravenous glucose despite equivalent increases in plasma glucose levels. This phenomenon, known as the incretin effect, is caused by gastrointestinal hormones released from the small intestine during a meal that stimulate insulin release from the pancreatic beta-cell in a glucose-dependent manner. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP; formerly known as gastric inhibitory peptide) are the two most important incretin hormones.

Studies with native GLP-1 have shown that the primary mechanisms of action are to:
- stimulate insulin secretion and decrease glucagon secretion in a physiological and glucose dependent manner
- delay gastric emptying
- reduce appetite

An important and possibly primary defect in type 2 diabetes may be an impaired incretin function. Patients with type 2 diabetes have reduced GLP-1 levels and a well-preserved insulin response to GLP-1. In contrast, patients with type 2 diabetes have normal or slightly increased GIP levels, but an impaired insulin response to GIP. These properties make GLP-1 a suitable candidate for the treatment of type 2 diabetes. However, due to the very short half-life of native GLP-1 ($t_{1/2}$ <1.5 minutes after i.v. administration) and short duration of action, the native hormone is not a useful therapeutic agent. The short half-life is due to rapid degradation by dipeptidyl peptidase-IV (DPP-IV). Therefore, GLP-1 analogues with a longer half-life are the target of drug development for the treatment of type 2 diabetes.

Applicant's proposed indication, dosing regimen, age group

The sponsor proposes liraglutide as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus.

The reader should be aware that DMEP is no longer issuing separate indications for specific combinations of drugs and biologics for the treatment of type 2 diabetes. The indication section in labeling is instead has been replaced by a single, simplified indication (Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus). If the risk/benefit profile is favorable when the drug is used in combination with other drugs, the study findings and conclusions will be described in the Clinical Studies section of the label, effectively providing support for the combination use in clinical practice. If the drug is not studied in combination with anti-hyperglycemic medications that are likely to be commonly co-administered with it in clinical practice, DMEP will require that the label contain a statement reflecting this limitation under "Important Limitations of Use".

The applicant's proposed dosing regimen is as follows:
For all patients liraglutide treatment should be initiated with a dose of 0.6 mg injected subcutaneously for at least one week, after which the dose should be increased to 1.2 mg. Based on clinical response and after at least one week at 1.2 mg, the dose can be increased to 1.8 mg to achieve maximum efficacy.

2.2 Currently Available Treatment for Indication

T2DM can be treated with a combination of proper diet, exercise, and the following classes of drugs, alone or in combination:

- Insulin and insulin analogues
- Sulfonylureas
- Biguanides
- Meglitinides
- Thiazolidinediones (TZDs)
- Inhibitors of alpha-glucosidase
- Analogues of Glucagon-like Peptide 1 (GLP-1)
- Synthetic analogues of human amylin

- Inhibitors of the enzyme dipeptidyl peptidase 4
- Bile acid sequestrants
- Dopamine agonists

Despite the number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an antidiabetic drug. Further, many of these drug classes have limited usefulness in certain populations. For example, metformin is not for use in patients with renal insufficiency and TZDs are not for use in many patients with congestive heart failure. Insulin and insulin analogues as well as sulfonylureas are often associated with hypoglycemia and weight gain. For these reasons, there is an unmet need for new antidiabetic therapies.

Table 2.1. Currently approved pharmacologic therapies for type 2 diabetes mellitus

Drug Class	Examples	Mechanism of action	Expected decrease in HbA1c (%)*	Pros	Cons
Biguanides	Metformin	Decreases hepatic glucose production Increases insulin sensitivity	1.5	Weight neutral Inexpensive	GI side effects Rare lactic acidosis Contraindicated in renal failure
Sulfonylureas	Glimepiride Glyburide Glipizide	Insulin secretagogue	1.5	Inexpensive	Hypoglycemia Weight gain
Thiazolidinediones	Rosiglitazone Pioglitazone	Increases insulin sensitivity	0.5-1.4	Lower risk of hypoglycemia	Fluid retention Weight gain Contraindicated in heart failure Expensive
Insulin	Lispro NPH insulin Glargine	Stimulates glucose uptake in muscle and adipose tissues	1.5-2.5	No dose limit Inexpensive Improved lipid profile	Injections Frequent monitoring Hypoglycemia Weight gain
Alpha-glucosidase inhibitors	Acarbose Miglitol	Slows GI absorption of carbohydrates	0.5-0.8	Weight neutral	Frequent GI side effects Three times/day dosing Expensive
Meglitinides	Repaglinide Nateglinide	Insulin secretagogue	1-1.5	Short duration	Three times/day dosing Expensive
Amylin analogues	Pramlintide	Slows gastric emptying Suppresses glucagon secretion Promotes satiety Decreases appetite	0.5-1.0	Weight loss	Three times/day dosing Frequent GI side effects Expensive Limited clinical experience
GLP-1 analogues	Exenatide	Stimulates glucose-dependent insulin release Slows gastric emptying Inhibits glucagon secretion Reduces food intake	0.5-1.0	Weight loss Theoretically lower risk of hypoglycemia	Frequent GI side effects Expensive Limited clinical experience Pancreatitis
DPP-IV inhibitors	Sitagliptin	Inhibits the enzyme DPP-IV prolonging the action of endogenous GLP-1 and GIP	0.5-0.8	Weight neutral Lower risk of hypoglycemia	Limited clinical experience Expensive Hypersensitivity reactions
Bile acid sequestrant	Colesevelam	Unknown	0.4-0.8	Favorable lipid effects	Frequent GI side effects
Dopamine agonist	Bromocriptine	Unknown	0.4-0.6	Weight neutral Minimal hypoglycemia	-

* Expected decrease in HbA1c is not placebo-corrected. Note: Part of the extent of reduction depends on the patient characteristics – e.g., baseline HbA1c etc.
GI = gastrointestinal; GLP-1 = glucagon-like peptide-1, DPP-IV = Dipeptidyl peptidase 4, GIP = glucose-dependent insulinotropic polypeptide

Source: Adapted from Stumvoll et al. (2005), Nathan et al. (2008), Cycloset prescribing information, and WelChol prescribing information

2.3 Availability of Proposed Active Ingredient in the United States

Liraglutide is not currently marketed in the United States.

2.4 Important Issues with Pharmacologically Related Products

Liraglutide is a member of the GLP-1 analogue class of antidiabetic therapies. Exenatide (marketed as Byetta®) is the only FDA approved member of this class. Effectiveness concerns regarding Byetta have stemmed from immunogenicity (i.e. patients who develop high titer antibodies to Byetta) with evidence of reduced effectiveness in about half of patients with high titer antibodies. However, the development of high titer antibodies is relatively rare (Byetta prescribing information). With liraglutide, antibody generation has been <15% in completed trials over 26 weeks, with no apparent attenuation of glycemic control in patients with high antibody titers. For a discussion of safety concerns that have arisen in this class see Dr. Mahoney's safety review.

2.5 Presubmission Regulatory Activity

This section summarizes important presubmission activities including major milestone interactions with the applicant and agreements made at each one focusing on clinical topics.

2.5.1 End-of-phase 2 meeting (face to face, 4 May 04)

Proposed Phase 3 Study Design and Indication discussion:

Discussion of Design
The Division agreed that the proposed trials and trial designs are adequate to support the indication of adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus, and that the comparator doses and the potential adjustment downwards are acceptable to support the above mentioned indication. The Division considered the statistical plan acceptable.

Endpoints
Primary endpoints were agreed upon and were adhered to by the sponsor. The sponsor asked if the Agency agreed that the described approach of assessing the improvement in beta cell function supports the indication. The Division stated that response to this question is deferred until review of the NDA submission. The sponsor was informed that consideration would be given based on submitted data, strength of the evidence, and the appropriateness of the endpoints as surrogates for delayed progression of type 2 diabetes.

Safety exposures and monitoring
The Division agreed upon the proposed number of patient exposures. Please see Dr. Mahoney's review for a discussion of safety exposures included in the NDA submission. Agreements were made on the proposal for antibody assessment and collection of adverse events. The plan for c-cell related monitoring in the phase 3 trials that are at least 6 months in duration was deemed acceptable by the Division.

2.5.2 Type C guidance (teleconference, 20 Sep 05)

The purpose of this meeting was to discuss initiation of the Phase 3 program for liraglutide in the context of concerns stemming from a 26 Feb 04 teleconference between the sponsor and the Division reporting the preliminary findings from the 2-year rat carcinogenicity studies. The sponsor stated that 2-year rat toxicity studies indicated an increased frequency of C-cell tumors of the thyroid. The discussion points included questions related to proceeding with phase 3 studies in light of these findings. Based upon the limited clinical information that was available at that time, the following agreements were reached

- The Division agreed it was acceptable to proceed cautiously into Phase 3a studies without calcitonin monitoring at 12 week intervals after unblinding of the data from the 14-week, European, Phase 2 Study NN2211-1571, provided that it yielded additional evidence of a lack of liraglutide effect on calcitonin release.
- The Division stated that the available information was not yet sufficient to rule out the potential human relevance of the rodent C-cell findings. The sponsor was advised that unstimulated calcitonin measurement is not particularly sensitive to detect C-cell hyperplasia in humans. The Division urged the sponsor to perform a pentagastrin stimulated calcitonin test on a subset of subjects in Phase 3a at baseline and at the end of the study.
- The Division concurred that the exclusion of patients with elevated calcitonin or family history of thyroid disease is not warranted.

A final discussion point was that the Division agreed upon the general design of an additional Phase 3 study – trial 1697 (see section 6.2.3.8.4 for a description of this trial).

2.5.3 Pre-NDA meeting (face to face, 5 Feb 08)

Non-clinical
A major discussion point was the rodent thyroid C-cell finding. The Sponsor stated that it was hypothesized that a non-genotoxic induction of the C-cell tumors occurs in rodents via a mechanism not relevant for humans and asked if the Agency agreed that this hypothesis had been substantiated. The Division stated that the proposed mechanism of action of rodent C-cell thyroid tumors and their clinical relevance was a review issue and agreement could not be given at that time. A similar discussion occurred with respect to calcitonin measurements, i.e. the Division stated that calcitonin measurements would be a review issue and did not agree that it could be definitively concluded at that time that treatment with liraglutide does not result in a clinically meaningful change in calcitonin secretion in humans.

Efficacy
The statistical analysis plan for efficacy was discussed and agreed upon at this meeting. The sponsor complied with the recommendations/plans in this NDA submission.

Safety
Discussion also focused on the strategy of safety evaluation for liraglutide. The sponsor generally complied with all FDA requests and, per Dr. Mahoney, any information requested by the safety reviewer was provided in a timely fashion.

Risk management plan
The topic of a risk management plan was raised. No formal agreements were reached at this pre-NDA meeting. It was deemed too early to determine whether the proposed program was acceptable. The Sponsor was encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP) if they believed that there were product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks.

Device
The Sponsor was encouraged to submit the proposed device (a working model of the same pre-filled pen which was used in the clinical trials) and all associated packaging, any usability studies performed on the pre-filled pen, the proprietary name and all associated labels and labeling for review as soon as available.

Pediatric studies
The status of pediatric investigation was discussed. At the End of Phase 2 Meeting, May 4, 2004, the Division agreed to the sponsor's plan to seek a waiver for subjects below —years and a deferral for older children. The sponsor reported plans to conduct a pharmacokinetic/pharmacodynamic trial in pediatric patients with type 2 diabetes including children of age 10 years and older. The Agency did not immediately agree with this plan but rather asked the sponsor to submit the proposal and all references to support the proposal and it would be reviewed. The sponsor outlined the proposed pediatric pharmacokinetic/pharmacodynamic trial and were informed that the study design as proposed, would not satisfy the requirement for pediatric assessment under the Pediatric Research Equity Act (PREA) because it would not adequately address the efficacy and safety of liraglutide in pediatric subjects, nor would this PK/PD proposal be sufficient to obtain pediatric exclusivity under the Best Pharmaceuticals for Children Act (BPCA). b(4)

2.6 Other Relevant Background Information

Regulatory actions in other countries

Liraglutide was approved by the European Medicines Agency (EMEA) on 30 Jun 09.

Per the EMEA website http://www.emea.europa.eu/humandocs/Humans/EPAR/victoza/victoza.htm
Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycemic control:
In combination with:
- Metformin or a sulfonylurea, in patients with insufficient glycemic control despite maximal tolerated dose of monotherapy with metformin or sulfonylurea.
In combination with:
- Metformin and a sulfonylurea or metformin and a thiazolidinedione in patients with insufficient glycemic control despite dual therapy.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See Dr. Mahoney's safety review.

3.2 Animal Pharmacology/Toxicology

See Dr. Mahoney's safety review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data used in this review are derived solely from studies performed by the Sponsor or designated contract organizations.

Clinical studies that were completed (total of 38) and for which reports were submitted at the time of NDA submission are summarized in tables in section 4.2. These include the extension phases of two of the phase 3 trials since data as of a cutoff date of 21 Feb 2008 were submitted to support long term safety of liraglutide. However, these trials were still ongoing at the time of NDA submission and are not used to support efficacy claims. In sum, there are a total of 40 trials listed in the tables. Of the 40 trials, two trials investigated liraglutide delivered by alternative routes of administration; NN2211-1464 (pulmonary administration) and NN9233-1898 (intranasal administration).

The clinical pharmacology development program was designed to evaluate the pharmacokinetic and pharmacodynamic properties of liraglutide and included 26 clinical pharmacology trials. The five long-term pivotal phase 3 trials were randomized, double-blind, double-dummy (including liraglutide and/or

oral anti-diabetic drug placebo) trials, providing long-term efficacy and safety data. Trial 1697 included an open-label comparator arm (insulin glargine + glimepiride + metformin). The double-blind period was 26 weeks in the combination trials and 52 weeks in the monotherapy trial (Trial 1573). Two of the therapeutic confirmatory trials have ongoing open-label extension periods (Trial 1573: 48 months extension and Trial 1572: 18 months extension), which provide additional long-term safety data.

There were also 6 ongoing trials at the time of NDA submission for which no full study reports were submitted. These include trials 1796, 1797, 1799, 1700 and 1701 (Japanese phase 3a trials) and NN8022-1807 (obesity extension trial). These trials are not listed in the tables below. However, safety information for some of these trials was submitted at the 120-day safety update per Dr. Mahoney, the safety reviewer.

4.2 Tables of Clinical Studies

Tables of Biopharmaceutics and Clinical Pharmacology Studies

Table 4.1. Biopharmaceutic Studies

Study Number	Objectives	Study Design	Study Population	Treatment, Route, Regimen, Dosage	Duration of Therapy	Relevance
1331	bioequivalence	Randomized, single-blind, cross-over	Healthy volunteers N=22	Single s.c. doses of 1 mg liraglutide formulation 2 and formulation 3	Single dose	Showed bioequivalence between phase 2 and 3 formulation
1636	bioequivalence	Randomized, double-blind, cross-over	Healthy volunteers N=24	Single s.c. doses of 0.75 mg liraglutide formulation 3 at pH7.7, 7.9, and 8.15	Single dose	Bioequivalence at differing pH values
1692	bioequivalence	Randomized, double-blind, cross-over	Healthy volunteers N=21	Single s.c. doses of 0.72 mg liraglutide formulation 4 and formulation 4 with final manufacturing process for drug substance	Single dose	Showed bioequivalence between phase 3a and 3b formulation
1693	bioequivalence	Randomized, double-blind, cross-over	Healthy volunteers N=22	Single s.c. doses of 0.71 mg liraglutide formulation 3 and formulation 4	Single dose	Showed bioequivalence between formulations

Table 4.2. Pharmacokinetic (PK) and Pharmacodynamic (PD) Studies

Study Number	Objectives	Study Design	Study Population	Treatment, Route, Regimen, Dosage	Duration of Therapy	Relevance
1745	PK and bioavailability	Randomized, open-label, cross-over	Healthy volunteers N=21	Three single s.c. doses of 0.6 mg liraglutide in the abdomen, thigh and upper arm, respectively	Single dose	Showed comparability at different injection sites
1149	PK, PD, and bioavailability	Randomized, double-blind, placebo-controlled, parallel-group, dose-escalation	Healthy volunteers N=72	Eight single s.c. doses of 1.25, 2.5, 5, 10, 12.5, 15, 17.5 or 20 µg/kg liraglutide	Single dose	Bioavailability of s.c. administration vs. i.v. in healthy subjects
1699	PK	Open-label	Healthy volunteers N=7	Single s.c. dose of 0.75 mg radio-labeled liraglutide	Single dose	Metabolite investigation
1189	PK and PD	Randomized, double-blind, placebo-controlled, parallel-group, dose-escalation trial	Healthy volunteers (N=30) and type 2 diabetics (N=4)	Initial single s.c. dose and subsequent once daily s.c. doses with dose escalation of 1.25, 5, 7.5, 10, and 12.5 µg/kg liraglutide	Single dose followed by 7 days	Dose finding
1327	PK	Open-label, parallel-group	Healthy volunteers young (N=16) and elderly (N=16)	Single s.c. dose of 1 mg liraglutide	Single dose	Pharmacokinetics in young vs. elderly
1329	PK	Open-label, parallel-group	Healthy volunteers and type 2 diabetics with normal renal function or renal impairment N=30	Single s.c. dose of 0.75 mg liraglutide	Single dose	Pharmacokinetics in renal impairment
1328	PK	Open-label, parallel-group	Healthy volunteers and type 2 diabetics with normal hepatic function or hepatic impairment N=24	Single s.c. dose of 0.75 mg liraglutide	Single dose	Pharmacokinetics in hepatic impairment
1644	Thorough QTc study	Randomized, double-blind, placebo-controlled, cross-over trial followed by open-label moxifloxacin (positive control)	Healthy volunteers N=58	Liraglutide: Once daily s.c. doses of 1.8 mg Moxifloxacin: Single p.o. dose of 400 mg	7 weeks	Cardiac safety

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1589	PD	Randomized, double-blind, balanced incomplete Latin square design trial with placebo and active control (glimepiride)	Type 2 diabetics N=46	Liraglutide: Once daily s.c. doses of 1.8 mg Glimepiride: Once daily p.o. dose of 1-4 mg Paracetamol (gastric emptying): Single p.o. dose of 1 g	4 weeks	Evaluate the effects on appetite in patients with type 2 diabetes of liraglutide vs. glimepiride or placebo
1332	PK and PD	Randomized, double-blind, placebo-controlled, cross-over	Type 2 diabetics N=13	Once daily s.c. doses of liraglutide 6 µg/kg of liraglutide	9-10 days	Effect of liraglutide on hormonal profiles, gastric emptying, and gluconeogenesis
1219	PK and PD	Randomized, double-blind, placebo-controlled, cross-over	Type 2 diabetics N=11	Single s.c. dose of 10 µg/kg of liraglutide	Single dose	Effect of liraglutide on pulsatile insulin secretion in type 2 diabetics
2063	PK and PD	Randomized, double-blind, placebo-controlled, cross-over	Healthy volunteers (N=10) and type 2 diabetics (N=10)	Single s.c. dose of 7.5 µg/kg of liraglutide	Single dose	PK information plus early PD evidence using hyperglycemic clamp procedure
1224	PK and PD	Randomized, double-blind, placebo-controlled, cross-over	Type 2 diabetics N=19	Single s.c. dose of 7.5 µg/kg of liraglutide	Single dose	Effect of liraglutide on hypoglycemic counter-regulation during stepwise hypoglycemic clamp in type 2 diabetics
1694	PK and PD	Randomized, double-blind, within dose group, placebo-controlled, dose escalation, multiple s.c. dose	Healthy volunteers (Japanese) N=24	Once daily s.c. doses of 15, 20 or 25 µg/kg of liraglutide, titrated in weekly steps of 5 µg/kg	5 weeks	Japanese PK and PD study
1551	PK and PD	Randomized, double-blind, placebo-controlled, dose escalation trial	Healthy volunteers (Japanese) N=24	Once daily s.c. doses of 5, 10 or 15 µg/kg of liraglutide, titrated in weekly steps of 5 µg/kg	3 weeks	Japanese PK and PD study
1326	PK and PD	Randomized, double-blind, placebo-controlled, dose escalation trial	Healthy volunteers (Japanese) N=32	Single s.c. dose of 2.5, 5, 10, or 15 µg/kg of liraglutide	Single dose	Japanese PK and PD study
1591	PK and PD	Randomized, double-blind, placebo-controlled, parallel-group	Type 2 diabetics (Japanese) N=15	Once daily s.c. doses of 5 or 10 µg/kg of liraglutide	14 days	Japanese PK and PD study

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1464	Bioavailability (pulmonary)	Randomized, cross-over	Healthy volunteers N=32	Single inhalation dose of 6, 12, and 24 µg/kg Single s.c. dose of 6 µg/kg	Single dose	Safety (counts towards total exposures)
1898	Bioavailability (intranasal)	Randomized, double-blind, placebo-controlled	Healthy volunteers N=12	Single intranasal dose of 2.5, 5, and 10 mg Single s.c. dose of 6 µg/kg	Single dose	Safety (counts towards total exposures)

Table 4.3. Drug Interaction Studies in Healthy Volunteers

Study Number	Objectives	Study Design	Study Population	Treatment, Route, Regimen, Dosage	Duration of Therapy	Relevance
1330	Ethinyl-estradiol and levonorgestrel interaction study	Randomized, double-blind, placebo-controlled, cross-over	Healthy post-menopausal women N=21	Once daily s.c. doses of 1.8 mg liraglutide. Single p.o. dose of 0.03 mg ethinylestradiol plus 0.15 mg levonorgestrel	3 week and single dose	Drug drug interaction safety
1608	Atorvastatin lisinopril griseofulvin and digoxin interaction study	Randomized, double-blind, placebo-controlled, two-way cross-over trial in two parts (A and B)	Healthy volunteers N=42 in Part A and N=28 in Part B	Liraglutide: Once daily s.c. doses of 1.8 mg Part A: Single p.o. doses of 40 mg atorvastatin and 20 mg lisinopril Part B: Single p.o. doses of 500 mg griseofulvin and 1 mg digoxin	4 weeks and single dose	Drug drug interaction safety
1698	Paracetamol interaction study	Randomized, double-blind, placebo-controlled, cross-over	Type 2 diabetics N=18	Liraglutide: Once daily s.c. doses of 1.8 mg Paracetamol: Single p.o. dose 1 g	3 weeks	Drug drug interaction safety

Tables of Efficacy and Safety Studies

Table 4.4. Phase 2 studies

Study Number	Objectives	Study Design	Study Population	Treatment, Route, Regimen, Dosage	Duration of Therapy	Relevance
1571	Efficacy and Safety	Randomized, double-blind, placebo-controlled, parallel-group	Type 2 diabetics (N=163) Healthy (N=12) (not dosed) Liraglutide 0.65 mg (N=40) Liraglutide 1.25 mg (N=42) Liraglutide 1.90 mg (N=41) Placebo (N=40)	Once daily s.c. doses of 0.65, 1.25 or 1.9 mg liraglutide	14 weeks	Dose finding study placebo-controlled
1310	Efficacy and Safety	Randomized, double-blind (open-label glimepiride), parallel-group. Placebo and active control (glimepiride)	Type 2 diabetics (N=190) Liraglutide 0.045 mg (N=26) Liraglutide 0.225 mg (N=24) Liraglutide 0.45 mg (N=27) Liraglutide 0.60 mg (N=30) Liraglutide 0.70 mg (N=28) Glimepiride (N=26) Placebo (N=29)	Liraglutide: Once daily s.c. doses of 0.045, 0.225, 0.45, 0.60, or 0.75 mg. Glimepiride: Once daily p.o. dose of 1-4 mg	12 weeks	Dose finding study placebo and active controlled
1499	Efficacy and Safety	Randomized, double-blind (metformin and glimepiride open-label), parallel-group. Active control (metformin and glimepiride)	Type 2 diabetics (N=144) Liraglutide (N=36) Liraglutide+metformin (N=36) Metformin (N=36) Metformin+glimepiride (N=36)	Liraglutide: Once daily s.c. doses of 2.0 mg (titrated in weekly steps of 0.5 mg) Metformin: bid, p.o. doses of 1 g Glimepiride: Once daily p.o. doses of 2-4 mg	5 weeks	Early evidence of efficacy as add-on therapy
1333	Efficacy and Safety	Randomized, double-blind, placebo-controlled, parallel-group	Obese, type 2 diabetics (N=33) Liraglutide (N=21) Placebo (N=12)	Liraglutide: Once daily s.c. doses of 0.6 mg	8 weeks	Efficacy in obese subjects
2072	Efficacy and Safety	Randomized, double-blind, parallel-group with active control (metformin)	Obese, type 2 diabetics (N=210) Liraglutide 0.045 mg (N=37) Liraglutide 0.225 mg (N=35) Liraglutide 0.45 mg (N=33) Liraglutide 0.60 mg (N=34) Liraglutide 0.75 mg (N=37) Metformin (N=34)	Liraglutide: Once daily s.c. doses of 0.045, 0.225, 0.45, 0.60, or 0.75 mg Metformin: bid, p.o., 1 g/day	12 weeks	Dose finding trial in obese type 2 diabetics
1334	Efficacy and Safety	Randomized, double-blind, placebo-controlled, parallel-group	Type 2 diabetics (Japanese) N=226 Liraglutide (N=180) Placebo (N=46)	Liraglutide: Once daily s.c. doses of 0.1, 0.3, 0.6, or 0.9 mg	14 weeks	Dose finding trial in Japanese type 2 diabetics

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1807	Efficacy and Safety	Randomized, double-blind (orlistat open-label) trial with placebo and active control (orlistat)	Healthy obese subjects (N=564) Liraglutide 1.2 mg (N=95) Liraglutide 1.8 mg (N=90) Liraglutide 2.4 mg (N=93) Liraglutide 3.0 mg (N=93) Orlistat (N=95)	Liraglutide: Once daily s.c. doses of 1.2, 1.8, 2.4, or 3.0 mg Orlistat: tid, p.o. doses of 120 mg	20 weeks	Evaluation of safety of liraglutide at higher doses up to 3.0 mg

Table 4.5. Phase 3 key efficacy studies

Study Number	Objectives	Study Design	Study Population	Treatment, Route, Regimen, Dosage	Duration of Therapy	Relevance
1573	Efficacy and safety and population PK	Randomized, double-blind, parallel-group with active control (glimepiride)	Type 2 diabetics (N=745) Liraglutide 1.2 mg (N=251) Liraglutide 1.8 mg (N=246) Glimepiride (N=248)	Liraglutide: Once daily s.c. doses of 1.2 mg or 1.8 mg Glimepiride: Once daily p.o. 8 mg/day	52 weeks	Efficacy and safety of liraglutide as monotherapy
1572	Efficacy and safety	Randomized, double-blind, parallel-group with placebo and active control (glimepiride)	Type 2 diabetics (N=1087) Liraglutide 0.6 mg + metformin (N=242) Liraglutide 1.2 mg + metformin (N=240) Liraglutide 1.8 mg + metformin (N=242) Metformin (N=121) Metformin + glimepiride (N=242)	Liraglutide: Once-daily s.c. doses of 0.6, 1.2, or 1.8 mg in combination with metformin Metformin: p.o. bid, 2 g/day Glimepiride: p.o. daily 4 mg/day	26 weeks	Efficacy and safety of liraglutide as add-on therapy to metformin
1436	Efficacy and safety	Randomized, double-blind, parallel-group with placebo and active control (rosiglitazone)	Type 2 diabetics (N=1040) Liraglutide 0.6 mg + glimepiride (N=233) Liraglutide 1.2 mg + glimepiride (N=228) Liraglutide 1.8 mg + glimepiride (N=234) Glimepiride (N=114) Glimepiride + rosiglitazone (N=231)	Liraglutide: Once-daily s.c. doses of 0.6, 1.2, or 1.8 mg in combination with glimepiride Glimepiride: p.o. daily 4 mg/day Rosiglitazone: p.o. daily, 4 mg/day	26 weeks	Efficacy and safety of liraglutide as add-on therapy to glimepiride
1574	Efficacy and safety	Randomized, double-blind, parallel-group, placebo-controlled	Type 2 diabetics (N=530) Liraglutide 1.2 mg + metformin + rosiglitazone (N=177) Liraglutide 1.8 mg + metformin + rosiglitazone (N=178) Metformin + rosiglitazone (N=175)	Liraglutide: Once-daily s.c. doses of 0.6, 1.2, or 1.8 mg in combination with metformin and rosiglitazone Metformin: p.o. bid, 2g/day Rosiglitazone: p.o. bid, 8 mg/day	26 weeks	Efficacy and safety of liraglutide as add-on therapy to metformin and rosiglitazone
1697	Efficacy and safety	Randomized, double-blind, parallel-group with placebo and active control (insulin glargine)	Type 2 diabetics (N=576) Liraglutide 1.8 mg + glimepiride + metformin (N=230) Glimepiride + metformin (N=114) Insulin glargine + glimepiride + metformin (N=232)	Liraglutide: Once daily s.c. doses of 1.8 mg in combination with glimepiride and metformin Glimepiride: p.o. daily, 4 mg/day Metformin: p.o. bid, 2 g/day Insulin glargine (100 IU/mL): s.c. daily, individual titration	26 weeks	Efficacy and safety of liraglutide as add-on therapy to metformin and glimepiride

Table 4.6. Extension studies						
Study Number	**Objectives**	**Study Design**	**Study Population**	**Treatment, Route, Regimen, Dosage**	**Duration of Therapy**	**Relevance**
1573 extension 1	Efficacy and safety	Randomized, open-label, parallel-group extension trial with active control (glimepiride)	Type 2 diabetics (N=440) Liraglutide 1.2 mg (N=149) Liraglutide 1.8 mg (N=154) Glimepiride (N=137)	Liraglutide: Once daily s.c. doses of 1.2 mg or 1.8 mg Glimepiride: Once daily p.o. 8 mg/day	Cutoff date 21 Feb 2008 approx. 18 months	Long term safety data
1572 extension 1	Efficacy and safety	Randomized, open-label, parallel-group extension trial with active control (glimepiride)	Type 2 diabetics (N=780) Liraglutide 0.6 mg + metformin (N=184) Liraglutide 1.2 mg + metformin (N=178) Liraglutide 1.8 mg + metformin (N=174) Metformin (N=61) Metformin + glimepiride (N=183)	Liraglutide: Once-daily s.c. doses of 0.6, 1.2, or 1.8 mg in combination with metformin Metformin: p.o. bid, 2 g/day Glimepiride: p.o. daily 4 mg/daily	Cutoff date 21 Feb 2008 approx. 18 months	Long term safety data

4.3 Review Strategy

For the clinical efficacy review, the five phase 3 pivotal studies were emphasized. The phase 2 studies were evaluated as supportive data in the clinical efficacy review. The long term extension studies were not complete at the time of NDA submission, and therefore, were not reviewed to support efficacy. Literature was not relied on to support efficacy since liraglutide is a new molecular entity.

Review strategy for the safety review is described in Dr. Mahoney's review.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) inspected two sites for this NDA.

Andrew Lewin, M.D. was selected because he enrolled a relatively large number of subjects. At this site, for Protocol NN2211-1574, 34 subjects were screened, 26 subjects were enrolled, and eleven subjects completed the study. There were no deaths or serious adverse events reported. An audit of all 34 subjects' records, including informed consent documents was conducted. No regulatory violations were

noted. No under-reporting of adverse events was detected. The DSI inspector concluded that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

[redacted] was selected because [redacted] reported disclosable financial information (see section 4.6 Financial Disclosures). At this site, [redacted] subjects were screened, [redacted] subjects were enrolled, and [redacted] subjects completed the study. There were [redacted] reported. [redacted] subjects on placebo discontinued due to lack of efficacy. An audit of 10 subjects' records was conducted. No regulatory violations were noted. No under-reporting of adverse events was detected. The DSI inspector concluded that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication. b(6)

4.5 Compliance with Good Clinical Practices

The clinical studies were conducted in accordance with ethical standards including informed consent from all subjects.

All attempts were made to adhere to protocol guidelines. Furthermore, an individual subject's compliance to the protocol was scrutinized prior to database release and subjects with violations to the protocol that were considered to affect the efficacy assessments were excluded from the "per protocol" analysis sets (see section 6). Analyses using per protocol sets were used to support the primary intention to treat analyses. Reasons for being excluded from the per protocol analysis set included not having an evaluable HbA1c at the final study visit, not meeting all inclusion criteria, or meeting exclusion criteria, not meeting randomization criteria, or subjects with HbA1c values taken at baseline more than three days apart from the date of the first dose of study medication, among others. For the primary efficacy endpoint in all 5 pivotal phase 3 studies, the per protocol analyses supported the primary intention to treat analyses. Specific protocol violations and study design procedural deviations are discussed within the context of each trial design (section 6).

4.6 Financial Disclosures

Most, but not all investigators who enrolled subjects in phase 2/3 studies submitted financial disclosure forms. None of the clinical investigators were direct employees of NovoNordisk. Any deficiencies or disclosable information are discussed in the following paragraphs.

Several investigators for the phase 2 study [redacted] from [redacted] did not submit financial disclosure forms and these investigators enrolled a total of [redacted] subjects. [redacted] investigators from this study had some financial disclosure to report. [redacted] (enrolled subjects) reported that NovoNordisk had recently given a grant of £50,000 to the [redacted] b(6)

[redacted] (enrolled subjects) disclosed that the [redacted] with which [redacted] is affiliated is supported by grants from NovoNordisk. Since the year 2000, [redacted] reports 2 million pounds in grant money given to this facility. [redacted] (enrolled [redacted] subjects) disclosed two grants from

NovoNordisk in the amount of £25,000 each to [redacted] involved but that are unrelated to the current application. Therefore, a total of [redacted] out of a total of [redacted] subjects in study [redacted] were enrolled by investigators with a possible financial conflict of interest. b(6)

Several investigators enrolling a total of [redacted] subjects for the phase 2 study [redacted], which consisted of [redacted] randomized subjects in total, did not submit financial disclosure information. It appears that financial disclosure information was often not obtained for this trial. Of the investigators that did submit financial information [redacted] of them (enrolling [redacted] subjects total) reported disclosable information, [redacted] of which received grants and/or honoraria totaling over $100,000. b(6)

These two phase 2 studies ([redacted] studies) were not pivotal in the evaluation of efficacy and safety of liraglutide and therefore, have little impact on the overall conclusions of this review.

[redacted] investigators participating in phase 3 pivotal studies disclosed potential conflicts of interest:

- [redacted] was a [redacted] for two of the pivotal trials. He disclosed receiving over $25,000 in payments for [redacted] and over $50,000 for [redacted] He enrolled [redacted] subjects in trial [redacted] and [redacted] subjects in trial [redacted]
- [redacted] (disclosed owning over 7,000 shares of Novo Nordisk stock valued at over $50,000) was a [redacted] for two of the five pivotal trials. He enrolled [redacted] subjects in trial [redacted] and [redacted] subjects in trial [redacted]

b(6)

Any potential bias from these [redacted] investigators will have minimal, if any, affect on liraglutide's efficacy and safety conclusions, because the number of affected patients is a very small fraction of the total number of patients in the phase 2/3 clinical development program, the studies were double-blinded and controlled, and the primary endpoint (HbA1c) was objective. Further, [redacted] was inspected by the Division of Scientific Investigations and no irregularities were found (see section 4.4 Data Quality and Integrity). b(6)

5 CLINICAL PHARMACOLOGY

For a full review of clinical pharmacology information relevant to this NDA the reader is referred to Clinical Pharmacology Review by Dr. Manoj Khurana, Ph.D. Per the executive summary of Dr. Khurana's review, the Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted in support of NDA 22-341 for liraglutide and found it acceptable, pending an acceptable resolution of the deficiencies found in the Division of Scientific Investigation with regards to the bio-analytical method. According to Dr. Khurana these deficiencies have been resolved at the time of this review and a memo documenting the resolution is forthcoming. Key findings from Dr. Khurana's review are summarized in sections 5.1, 5.2 and 5.3 below.

5.1 Pharmacokinetics

Liraglutide was studied in healthy subjects and T2DM patients to determine pharmacokinetic properties.

Absorption, Distribution, Metabolism, and Excretion

Liraglutide has a pharmacokinetic and pharmacodynamic profile in humans suitable for once daily administration. Following subcutaneous administration, absorption is slow, reaching maximum concentration 8-12 hours post dosing. Mean maximum concentration was 9.4 nmol/L for a single subcutaneous dose of 0.6 mg of liraglutide. At 1.8 mg, the average steady state concentrations reached 33.7 nmol/L. Exposure was lower following s.c. administration of liraglutide in the thigh compared to abdomen, however, the observed difference in bioavailability between injection sites was minor and not considered by the sponsor to be of clinical relevance and therefore all injection sites (including the upper arm) could be used interchangeably in the pivotal clinical trials. The clinical pharmacology reviewer Dr. Khurana agreed with this conclusion. The mean liraglutide apparent clearance was 0.7 L/hour and apparent volume of distribution was 12.5 L after a single subcutaneous dose of 0.7 mg. Liraglutide was eliminated with an average half-life of 13 hours suggesting that liraglutide follows a flip-flop pharmacokinetics after subcutaneous administration - a situation where the half-life is observed to be longer after subcutaneous administration than that observed with the intravenous route. This suggests that the absorption process is slower than the elimination process. The dose-proportionality assessment revealed that liraglutide exposure increased in proportion to the increase in dose up to 20 μg/kg (equivalent to 1.8 mg dose based on 90 kg median weight in Phase 3 trials). There was slight accumulation (RA of 1.4- 1.5) after multiple once daily subcutaneous administrations. The absolute bioavailability of liraglutide following subcutaneous administration is approximately 55% at 5 μg/kg. In Trial 1745, the relative bioavailability of liraglutide after s.c. administration in the thigh, upper arm and abdomen was estimated as relative ratios of $AUC_{0-\infty}$ for liraglutide after administration at the various sites. The relative bioavailability of liraglutide after s.c. administration was estimated to 0.81 in thigh versus abdomen, 0.90 in upper arm versus abdomen and 1.11 in upper arm versus thigh. Liraglutide is extensively bound to plasma protein (>98%).

In vitro and in vivo metabolism and excretion studies demonstrated that liraglutide is fully metabolized in the body by sequential cleavage of the peptide with no excretion of liraglutide, i.e. neither renal nor biliary excretion are major routes of clearance, and only very limited excretion of closely related metabolites in the feces or urine occurred in all tested animal species and humans. No unique human metabolite was found. Liraglutide was metabolized by dipeptidyl peptidase 4 (DPP-IV) and neutral endopeptidase (NEP) in similar positions in the peptide as observed for native GLP-1.

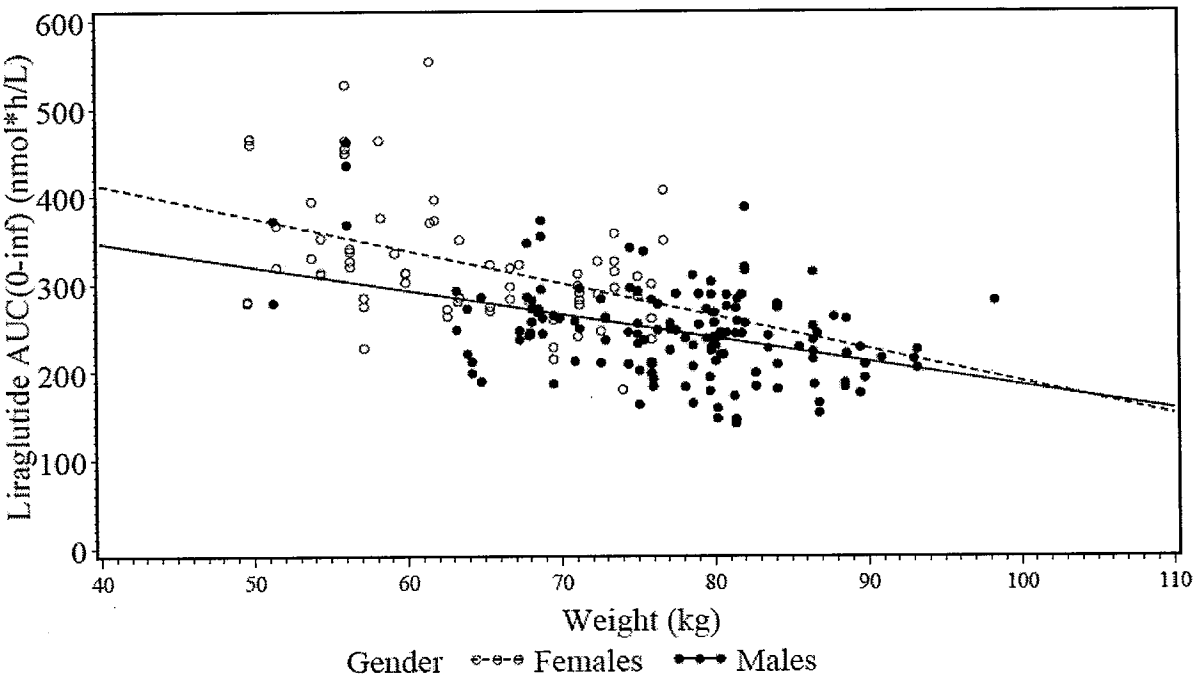
The potential inhibitory effect of liraglutide on the important human drug metabolizing cytochrome P450s was examined *in vitro* using human liver microsomes. Data suggested that liraglutide at concentrations up to 100 μM did not inhibit or only very slightly inhibited all the human cytochrome P450s studied (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2D6, CYP2C19, CYP2E1 and CYP3A4). Thus, liraglutide is not expected to cause any drug-drug interactions related to inhibition of cytochrome P450s. Dr. Khurana concurred with this assessment in his review.

Pharmacokinetic effects of drug-demographic and drug-disease interactions

Body weight and BMI

Several studies including the population pharmacokinetic analysis investigated the effect of body weight and BMI on the pharmacokinetics of liraglutide. Most of the evidence suggested that the effect of body weight on exposure was statistically significant with higher body weight associated with lower exposure (inverse relationship). See figure 5.1 below. However, the effect of BMI was not significant. Weight but not BMI was found to be a significant predictor of clearance of liraglutide. According to the clinical pharmacology reviewer Dr. Khurana, although weight was found to affect clearance, the effect does not appear to be clinically relevant. Considering that steady state exposures, resulting from 1.2 and 1.8 mg doses, were in the maximal response region of the exposure-relationship for the primary efficacy variable (HbA1c) (see section 5.3), these differences are not clinically meaningful to warrant a dose-adjustment.

Figure 5.1. Scatter plot of dose adjusted AUC0-∞ vs. body weight following single dose liraglutide in healthy subjects (trials 1331, 1636, 1692, 1693, and 1745)



Sex

The effect of sex on the pharmacokinetics of liraglutide was investigated in several trials. In a single-dose trial (1327) the mean liraglutide plasma profiles indicated that female subjects had higher plasma concentrations than male subjects. The difference appeared to be primarily explained by difference in body weight between females and males, i.e. no statistically significant difference between males and females was demonstrated for AUC0-t for liraglutide when corrected for body weight. In addition, no statistically significant differences between females and males were observed for other pharmacokinetic endpoints.

Age
The effect of age on the pharmacokinetics of liraglutide was investigated in the single dose trial, Trial 1327 and based on the population pharmacokinetics from Trial 1573. Liraglutide AUC0-t was declared equivalent in young and elderly subjects after a single 1 mg dose. There was no effect of age on other pharmacokinetic endpoints.

Race/Ethnicity
The impact of race and ethnicity on pharmacokinetics of liraglutide was investigated using the population pharmacokinetic data from Trial 1573. Five racial groups (White, Asian, Black, Hawaiian, and 'Other') and two ethnic categories (Hispanic and non-Hispanic) were investigated. In an analysis of covariance including body weight and gender, race and ethnicity were not significantly associated with pharmacokinetic variables.

Renal and Hepatic Impairment
The pharmacokinetics of a single s.c. dose of 0.75 mg liraglutide administered in the abdomen in subjects with renal impairment was evaluated in Trial 1329. Subjects with four different grades of renal impairment (based on creatinine clearance estimated by the Cockcroft-Gault formula) were compared against subjects with normal renal function. Overall on average, the AUC0-∞ of liraglutide was around 19 - 35% lower in the renally impaired subjects than the normal subjects. However, equivalence was demonstrated for maximum concentration (Cmax) a subjects with moderate renal impairment (creatinine clearance greater than 30 but less than or equal to 50 mL/minute). Total apparent clearance varied slightly across the renal groups; however, no trend with respect to renal function was seen.

The pharmacokinetics of a single s.c. dose of 0.75 mg liraglutide injected in the thigh was evaluated in subjects with hepatic impairment in Trial 1328. Subjects with three different grades of hepatic impairment (classified according to the Child-Pugh scores) were compared against subjects with normal hepatic function. Severe hepatic impairment was found to have an impact on the liraglutide pharmacokinetics in terms of around a two-fold increase in clearance and 42% lower mean AUC0-∞ of liraglutide. The reason for this finding is unknown, but could possibly be attributed to lower albumin levels found in hepatic impairment, as a statistically significant positive relationship between albumin concentration and liraglutide exposure (AUC0-∞) was observed.

No dose adjustment is proposed by either the sponsor or by Dr. Khurana, the clinical pharmacology reviewer, for renal and hepatic impairment subjects.

Pharmacokinetic effects of drug-drug interactions

Please see Dr. Mahoney's review for a discussion of drug-drug interactions.

5.2 Pharmacodynamics

Please refer to section 4.2 for tables of pharmacodynamic studies submitted with this NDA and to Dr. Khurana's Clinical Pharmacology Review for details of the pharmacodynamic investigations. Results of pharmacodynamic studies were consistent with the proposed mechanism of action of liraglutide. The pharmacodynamic effects of liraglutide on glucodynamics were demonstrated. Liraglutide administration resulted in increased insulin secretion in response to glucose. There was a significant reduction in post-prandial glucose over a 24 hour period, slight increase in post-prandial insulin and significant post-prandial glucagon suppression. There was also a substantial increase in the first phase insulin secretion as assessed during a hyperglycemic clamp.

Please see Dr. Mahoney's review (section 7.1.12) for a discussion of the thorough QTc study.

5.3 Exposure-Response Relationships

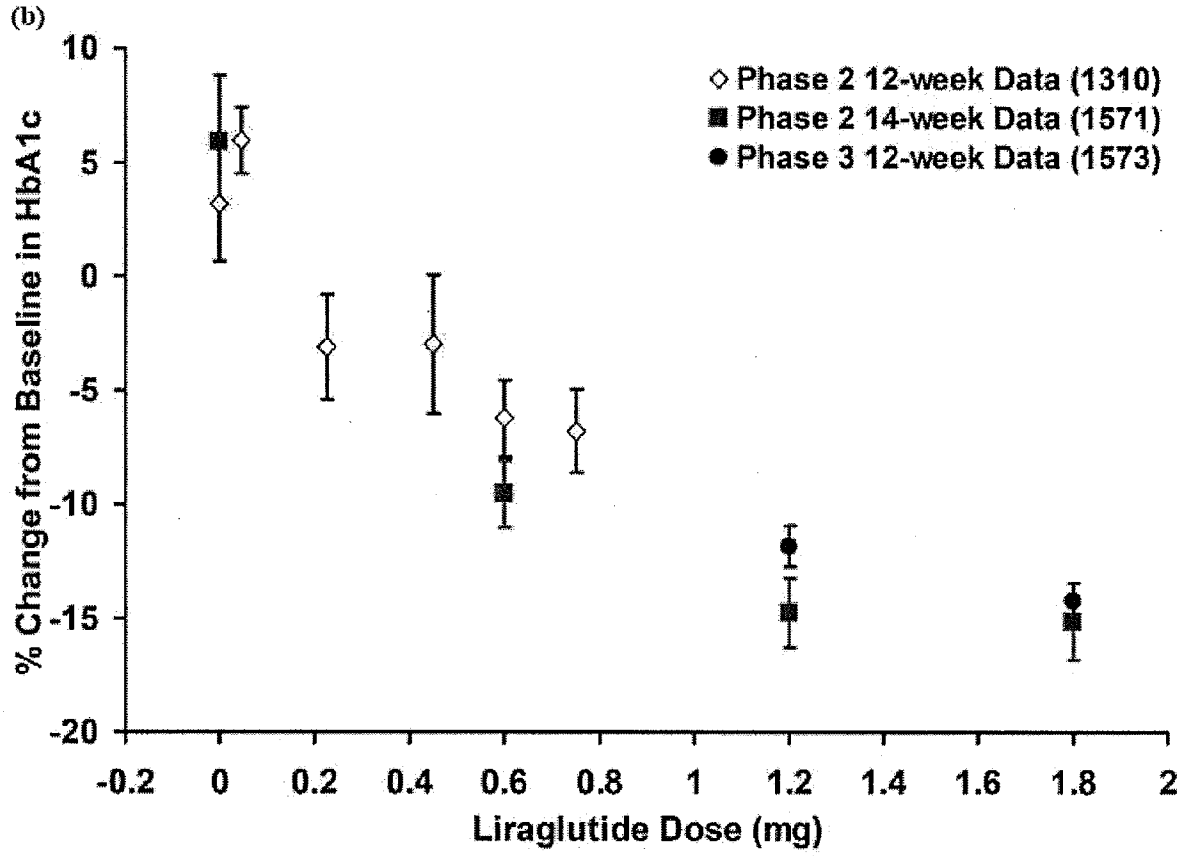
According to the end-of-phase 2 meeting minutes, there was no specific determination of dose selection for the phase 3 program, although the Division did state that it found the phase 2 clinical pharmacology program including doses tested during phase 2 acceptable. Therefore, the selection of the three doses tested in the phase 3 program, 0.6, 1.2 and 1.8 mg was determined by the sponsor based on results of phase 2 studies, specifically trial 1571 (source: sponsor's summary of clinical efficacy, section 1.3.6).

Monotherapy studies were used to evaluate the exposure-response relationship of liraglutide. Because the maximal mean reduction in HbA1c from baseline with liraglutide is achieved by week 12, the 12 week data for the phase 2 (study 1310 and 1571) and phase 3 (trial 1573) monotherapy studies could be compared. A graphic examination of these data (figure 5.1 below) showed that the response with 0.6 mg was in reasonable proximity to half the maximal response. Graphical analysis of pooled dose-response data from phase 2 and 3 studies showed that liraglutide treatment is associated with a dose dependent reduction in HbA1c from baseline. The maximal effect is achieved at 1.2 mg dose with a numerical advantage of 1.8 mg over 1.2 mg with regards to maximal HbA1c reduction. The consistent findings of multiple studies and the identification of what appears to be the maximal effective dose for HbA1c lowering (i.e. flattening of the curve) provide evidence for adequacy of the clinical assessment and this reviewer agrees these three doses were a reasonable choice for the phase 3 clinical trials.

According to Dr. Khurana's review, in the phase 2 program, there was a considerable overlap in the exposures for 1.2 mg and 1.8 mg doses so the two doses could not be differentiated using a dose response analysis. In patients with body weight 160 kg the expected mean average concentration (Cavg) is 9 nmol/L and 13 nmol/L using 1.2 mg and 1.8 mg dose, respectively. However, the liraglutide concentration response (% change from baseline HbA1c) suggests that maximum effect is achieved at or above 7 nmol/L liraglutide concentration (see Dr. Khurana's review **Fig. 15a**). This was consistent for the Phase 3 data where the liraglutide concentrations ranged from 5 nmol/L to 45 nmol/L (see Dr. Khurana's review **Fig. 15b**). Hence, Dr. Khurana inferred that the proposed doses provide adequate liraglutide exposures over the body weight range of 40-160 kg and the sponsor's proposed fixed dose titration is acceptable from clinical pharmacology perspective.

The clinical efficacy implications of these findings are discussed further in section 8.1 Dosing Regimen and Administration.

Figure 5.1: Dose dependent increase in effectiveness of liraglutide based on Mean(±SE) % change from baseline in HbA1c from 12-week Phase 2 trial (1310), 14-week Phase 2 trial (1571) and 12-week data from the 52-week Phase 3 trial (1573).



Source: Dr. Khurana's Clinical Pharmacology Review, page 29

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor is seeking approval for liraglutide as an adjunct to diet and exercise to achieve glycemic control in patients with type 2 diabetes mellitus.

The pivotal phase 3 studies in support of these indications are reviewed in sections 6.1.3.7 (monotherapy), 6.1.3.8 (combination therapy with one oral antidiabetic drug [OAD] and combination therapy with two OADs).

6.1.1 Methods

The primary clinical data used in the review of efficacy came from five therapeutic confirmatory trials which investigated the benefits of liraglutide as:

- monotherapy (Trial 1573)
- combination with metformin (Trial 1572)
- combination with an SU (glimepiride) (Trial 1436)
- combination with a TZD (rosiglitazone) and metformin (Trial 1574)
- combination with an SU (glimepiride) and metformin (Trial 1697)

Tables 6.1 and 6.2 summarize liraglutide's efficacy trials. Please also refer to section 4.2 Tables of Clinical Studies for details of the efficacy trials including study designs, dosages, and treatment durations. A total of 3978 patients were exposed to treatment in the therapeutic confirmatory trials (2501 to liraglutide, 524 to placebo, and 953 to an active comparator). In addition to the therapeutic confirmatory trials, six therapeutic exploratory trials (Trials 1571, 1310, 1333, 2072, 1499 and 1334 (Japan)) provide some additional relevant efficacy data. These trials enrolled a total of 966 patients. Open-label extension studies (1572 – extended to 18 months to a total of 2 years and 1573 – extended to 48 months for a total of 5 years) are not used to support efficacy claims and therefore, not reviewed in this section, but are used to support long-term safety and are discussed by Dr. Mahoney in her Clinical Safety Review.

Table 6.1
Overview of Efficacy Data for Liraglutide

Source of data	Details
Phase 2 dose or regimen selection	**6 studies** 2 placebo-controlled dose finding trials (dose selection) (1571, 1310) Liraglutide vs. placebo for body weight reduction (1333) Active control (metformin) dose finding trial (2072) Individual dose titration w/add on to metformin (1499) Placebo-controlled dose finding Japanese trial (1334)
Phase 3 confirmatory trials	**5 studies** 1 monotherapy phase 3 trial (1573) 2 add-on combination therapy with one OAD studies (1572, 1436) 2 add-on combination therapy with two OADs studies (1574, 1697)

Source: Summary of Clinical Efficacy

Table 6.2
Overview of Treatment Regimens in the Therapeutic Confirmatory Trials

Study		Liraglutide Doses / regimens				
Trial	**Weeks**	**Lira 0.6**	**Lira 1.2**	**Lira 1.8**	**Placebo**	**Comparator**
1573	52	-	X + placebo (glimepiride)	X + placebo (glimepiride)	-	Glimepiride 8 mg + placebo (lira)
1572	26	X + placebo (glimepiride) + metformin 2 g	X + placebo (glimepiride) + metformin 2 g	X + placebo (glimepiride) + metformin 2 g	X + placebo (glimepiride) + metformin 2 g	Glimepiride 4 mg + placebo (lira) + metformin 2 g
1436	26	X + placebo (rosi) + glimepiride 4mg	X + placebo (rosi) + glimepiride 4 mg	X + placebo (rosi) + glimepiride 4 mg	X + placebo (rosi) + glimepiride 4 mg	Rosi 4 mg + placebo (lira) + glimepiride 4 mg
1574	26	-	X + metformin 2 g + rosi 8 mg	X + metformin 2 g + rosi 8 mg	X + metformin 2 g + rosi 8 mg	-
1697	26	-	-	X + glimepiride 4 mg + metformin 2 g	X + glimepiride 4 mg + metformin 2 g	Insulin glargine + glimepiride 4 mg + metformin 2 g

Doses of metformin and glimepiride could be adjusted in trial 1572 (metformin 1.5 – 2 g), trial 1436 (glimepiride 2 - 4 mg) and trial 1697 (glimepiride 2 – 4 mg)
Rosi = rosiglitazone; Lira = liraglutide

Source: Summary of Clinical Efficacy, Table 1-1, section 2.7.3

6.1.2 General Discussion of Endpoints

This section provides an overview of the endpoints used in the five phase 3 trials which were mostly similar among the trials. Aspects unique to individual trials are discussed in the sections relating to study design of each trial (starting with section 6.1.3.7).

6.1.2.1 Primary Efficacy Variable

The primary efficacy variable for all key studies was change from baseline in HbA1c (%) at the end of the double-blind treatment period. HbA1c is an appropriate endpoint because

a) HbA1c is a widely-accepted, objective, surrogate measure of glycemic control that correlates well with mean blood glucose over the preceding 1-3 months (Nathan DM 1984).
b) The National Glycohemoglobin Standardization Program (NGSP) has established and promulgated standardized assays for HbA1c based on data from the Diabetes Control and

Complications Trial (DCCT). Use of standardized methodology has reduced inter-laboratory coefficients of variation to <5% (College of American Pathologists 1999; Goldstein 1982).

c) HbA1c has excellent reliability, predicts several diabetes-specific complications, and provides the current basis for treatment decisions (American Diabetes Association 2008).
d) Lowering HbA1c reduces microvascular complications in patients with type 1 and type 2 diabetes (Diabetes Control and Complications Trial Research Group 1993, UK Prospective Diabetes Study (UKPDS) Group 1998) and possibly macrovascular complications in patients with type 1 diabetes (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group 2005).

For these reasons, the FDA draft guidance entitled Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf) states, "For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control."

The percentage of subjects who reached the pre-defined target for HbA1c of <7% and HbA1c of ≤ 6.5% was also examined. These are clinically appropriate endpoints because

e) The American Diabetes Association (ADA) currently recommends a target HbA1c of roughly 7% for non-pregnant adults in general with diabetes. Lowering HbA1c to an average of 7% has been shown to reduce microvascular and possibly macrovascular complications of diabetes. Since pregnant subjects are excluded from these clinical trials, <7% is an appropriate endpoint for these trials (ADA 2008).
f) The AACE (American Association of Clinical Endocrinologists) recommended target for HbA1c is ≤ 6.5% (http://www.aace.com/public/awareness/stateofdiabetes/FactsAboutA1C.pdf)

HgA1c was measured by a National Glycohemoglobin Standardization Program certified high-performance liquid chromatography assay at a central laboratory.

6.1.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints included

a. Body weight
b. Other measures of glycemic control (fasting plasma glucose, plasma glucose profiles)
c. Biomarkers of beta-cell function
d. Fasting glucagon
e. Blood pressure
f. Lipid profile
g. Cardiovascular effects
h. Waist and hip circumference
i. Patient-reported outcome

j. DXA scan for body composition (sub-study)
k. Frequently sampled intravenous glucose tolerance test (FSIGT) (sub-study) 1573 only
l. Calcium stimulation test (sub-study) 1573 only
m. Liraglutide antibodies 1573 only
n. CT scan for visceral and subcutaneous adiposity as well as liver to spleen attenuation ratio for hepatic steatosis assessment 1572 only

Reviewer's comment: not all of these secondary endpoints are included in this review because they are not used to support approval of the primary indication and are not intended to be included in the product label.

Details of Secondary Endpoints:

Key secondary endpoints:

Body weight and Beta cell sparing effect:
Change in body weight was a key secondary endpoint in all five therapeutic confirmatory trials, meaning that the trials were powered to evaluate changes in both HbA1c and body weight. In addition, "beta-cell sparing" effect (evaluated on the basis of HbA1c trend after nadir) was a key secondary endpoint in the 52 week monotherapy Trial 1573. The slope of the HbA1c by time profile after nadir was analyzed and compared between treatment arms in Trial 1573. This endpoint is assumed to reflect the long-term effect of treatment on beta-cell function.

Reviewer's comment: HbA1c trend after nadir is not a validated method of assessing beta-cell sparing effect. Past practices of the Division have been to not allow information about beta cell sparing into the label.

Other reviewed secondary endpoints:

Fasting plasma glucose – measured at visits with a colorimetric assay kit using the glucose oxidase method at the central laboratory.

Self-measured 7- and 8-point plasma glucose profiles and post-prandial glucose. Subjects were asked to perform two consecutive days of 8-point plasma glucose profiles at the start, middle, and end of trial 1573 which consisted of measuring glucose at the time points: before each meal, 90 minutes after the start of each meal, at bedtime and at 3 am +/- 30 minutes. (note: regular calibration of glucose meters was left up to study participants). Calculated endpoints were mean prandial increments of glucose and mean post-prandial glucose (PPG). Mean post-prandial glucose was determined by obtaining a patient-measured glucometer reading taken 90 minutes after the start of each meal and then by taking the average of the measurement after each meal.

Reviewer's comment: It is more rigorous to obtain PPG data in a clinic setting after a standardized meal or oral glucose tolerance test. When measured at home there are issues of compliance (e.g., did patients measure at the right times) and also less accuracy with glucometers vs. lab measures in a clinic. Therefore, this reviewer has concerns about including the PPG, as

obtained by the applicant, in the label. The Division is in the process of considering whether PPG data (even those obtained appropriately) should be included in labeling for diabetes products because of concerns about inappropriate promotion about potential reduction in diabetes complications, and because the relevance to physicians is unclear for medications that cannot be titrated based on PPG.

Beta-cell function, insulin sensitivity, and fasting glucagon: measured by the central laboratory using fasting insulin, fasting C-peptide, proinsulin to insulin ratio, HOMA-B and HOMA-IR with formulas as follows:
HOMA-B = 20×fasting serum insulin (μU/mL)/(fasting plasma glucose (mmol/L) – 3.5)
HOMA-IR = fasting serum insulin (μU/mL)×fasting plasma glucose (mmol/L)/22.5
In trial 1573, an insulin-modified frequently-sampled intravenous glucose tolerance test (FSIGT) was done for a subset of subjects at randomization and after 52 weeks of treatment.

Reviewer's comment: these are useful but non-validated measures of beta cell function and should not be included in labeling.

Blood pressure - As effects on blood pressure were observed in the Phase 2 exploratory trials, the evaluation methods used in the confirmatory trials followed guidelines for evaluating effects of agents used to treat blood pressure.

Body composition was assessed in a subset of subjects (Trials 1573 and 1572) at randomization and end of trial using dual-energy x-ray absorptiometry (DXA). The DXA scans were analyzed centrally by a specialist who was blinded with regard to treatments and the change in body composition from baseline to end of trial was calculated.

Metabolic syndrome prevalence (NCEP ATPIII criteria) – meeting at least three of the following:
Abdominal obesity (Waist Circumference)
- Men >102 cm (>40 in)
- Women >88 cm (>35 in)

Triglycerides ≥150 mg/dL
High-density lipoprotein cholesterol
- Men <40 mg/dL
- Women <50 mg/dL

Blood pressure ≥130/85 mmHg
Fasting glucose ≥110 mg/dL

Cardiovascular disease markers: (plasminogen activator inhibitor-1 (PAI-1), N-terminal B-type natriuretic peptide (NT-proBNP) and highly sensitive C-reactive protein (hsCRP).)

Reviewer's comment: most of these are non-validated markers of CVD.

Lipid profile (fasting)
Free fatty acids (FFA)
Low-density lipoprotein-cholesterol (LDL-C)

Total cholesterol (TC)
Very low-density lipoprotein-cholesterol (VLDL-C)
Triglycerides (TG)
High-density lipoprotein-cholesterol (HDL-C)
Apolipoprotein B (ApoB)

Liraglutide antibodies: measured at several time points in study 1573.

6.1.2.3 Overview of Statistical Methods

See Dr. Derr's statistical review for more discussion.

Randomization: At the time of randomization subjects were stratified with respect to their previous OAD (monotherapy or combination therapy) or diet/exercise therapy.

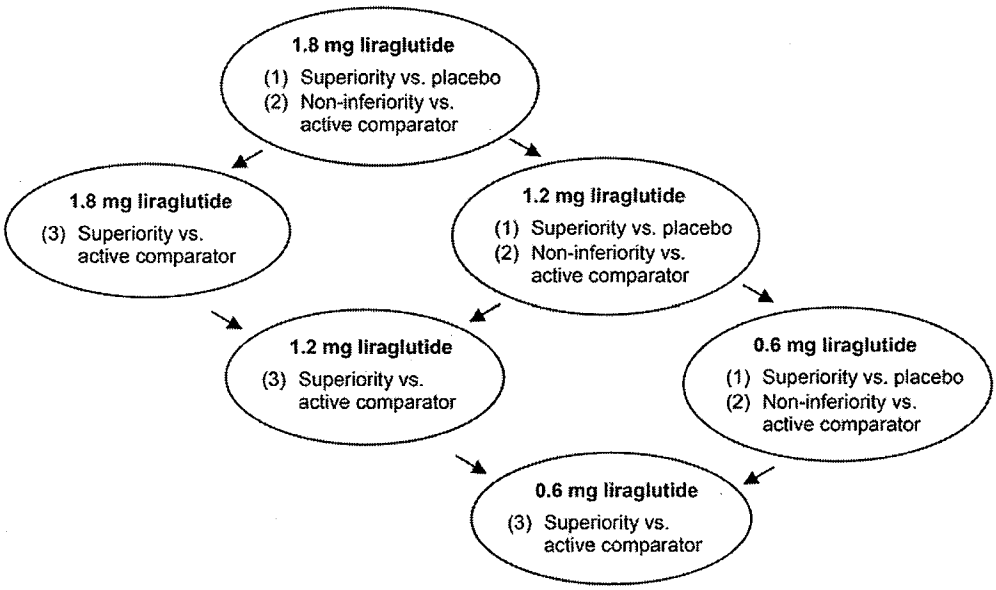
Efficacy Assessments:
The efficacy assessments for all key phase 3 trials were mostly based on the Intent-to-Treat (ITT) population, which consisted of all patients who were randomized and exposed to at least one dose of trial product

For these trials, the Sponsor also defined a per-protocol population (PP) consisting of patients in the primary ITT population who completed the trial and had no major protocol deviations. The PP population was used for supportive analyses.

For all five therapeutic confirmatory trials, the HbA1c change from baseline was analyzed using an analysis of covariance (ANCOVA) model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline HbA1c value as covariate. The primary endpoint was analyzed for both the ITT analysis set and the PP analysis set. For tests of superiority, the ITT analysis set was considered the primary test and the PP supportive, whereas for tests of noninferiority (noninferiority margin of 0.4%) the two analysis sets were considered of equal importance. In analyses based on the ITT analysis set, post-baseline missing values were replaced using last observation carried forward (LOCF). Furthermore, a sensitivity analysis without imputation was also done.

All five therapeutic confirmatory trials employed a hierarchical testing procedure in order to protect the overall type I error rate (Figure 6.1 below).

Figure 6.1 – Hierarchical Testing Procedure for Phase 3 Studies



An ANCOVA model similar to that described above was used for analyses of the key secondary efficacy variable - body weight. The model included treatment, country, and previous antidiabetic treatment as fixed effects and baseline body weight as the covariate. The other secondary endpoints were analyzed for the ITT analysis set using the same ANCOVA model as described above. For change in body weight, no claim was made unless the noninferiority claim could be made for change in HbA1c relative to the placebo in each trial (or if no placebo the active comparator). Multiplicity correction was not applied to the secondary endpoint analyses.

Analysis of Treatment Effect-by-Factor Interaction

Based on the primary analysis, a number of exploratory analyses were done to evaluate if observed treatment effect was consistent across selected sub-populations. The analyses were done using the standard ANCOVA, but with the addition of the respective baseline characteristic (e.g. sex) and baseline characteristic by treatment interaction as fixed effects. The following baseline characteristics were evaluated:

- Demographic differences between groups of subjects
  - sex (female, male)
  - age (<65 years, 65–75 years, ≥75 years)
  - ethnicity (Hispanic/Latino, not Hispanic/Latino)
  - race (American Indian/Alaska Native, Asian/Native Hawaiian/Pacific Islander, Black/African American, White)
  - BMI (<25 kg/m^2, 25–29.9 kg/m^2, 30–34.9 kg/m^2, ≥35 kg/m^2)
  - body weight (<90 kg, ≥90 kg)
- Disease
  - baseline HbA_{1c} (≤9.5%, >9.5%)
  - duration of diabetes (<10 years, ≥10 years)
  - serum albumin (<75th percentile, ≥75th percentile)
  - serum creatinine (<75th percentile, ≥75th percentile)

– serum alanine aminotransferase (ALT), (<75th percentile, ≥75th percentile)
– serum aspartate aminotransferase (AST), (<75th percentile, ≥75th percentile)
• Previous anti-diabetic treatment (diet, OAD monotherapy, OAD combination therapy)
• Concomitant drug interaction (albumin- and protein-bound drugs)
The analyses were based on individual data from the five therapeutic confirmatory trials and on pooled data from the four 26-week combination therapy trials (Trial 1572, 1436, 1574 and 1697).

6.1.3 Study Design

The five pivotal phase 3 efficacy study protocols are reviewed in sections 6.1.3.7 and 6.1.3.8 [section 6.1.3.7: monotherapy (one trial), section 6.1.3.8: combination therapy with one OAD (two trials) and combination therapy with two OADs (two trials)]. Six phase 2 studies relevant for efficacy are discussed in section 10. The five therapeutic confirmatory trials were similar in design. All trials were randomized, parallel group, multi-center trials in which the therapeutic response to liraglutide was compared with that of placebo and/or a specific active comparator drug.

The designs of the five major studies supporting effectiveness for the proposed indication are adequate and well controlled in that:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocols for the study and in the report of their results. In addition, the protocols contain a description of the proposed methods of analysis, and the study reports contain a description of the methods of analysis ultimately used.

(2) The studies use designs that permit a valid comparison with a control to provide a quantitative assessment of drug effect. The protocols for the study and report of results describe the study designs precisely.

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables. In the case of the five pivotal studies, assignment is by randomization, with stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data since the majority of the studies are double-blind.

(6) The methods of assessment of subjects' response are well-defined and reliable. HbA1c is an objective, surrogate measure of glycemic control (see section 6.1.2).

(7) There is an analysis of the results of the study adequate to assess the effects of the drug (see section 6.1.2.1 and also Dr. Derr's Statistical Review).

6.1.3.1 Dose Selection

Fixed dose levels of liraglutide were used in all five therapeutic confirmatory trials. Doses could be administered in the three sites (thigh, abdomen, and upper arm) interchangeably. Based on the phase 2 dose range finding trial, Trial 1571, three dose levels of liraglutide were chosen for the program of therapeutic confirmatory trials: 0.6, 1.2, and 1.8 mg administered as a once-daily s.c. injection, but not all dose levels were evaluated in every trial. In trial 1310, a 12-week, multi-center, multi-national, seven-arm parallel-group trial with five doses of liraglutide (0.045, 0.225, 0.45, 0.60 or 0.75 mg/day, s.c., double-blind) versus placebo (s.c., double-blind) or glimepiride (1 or 2 mg, p.o., open-label) in subjects with type 2 diabetes mellitus showed the estimated dose for half-maximal effect on glycemic control parameters (such as fasting plasma glucose and glucose profiles), ED50, was 0.76 mg. As in the 14-week dose range finding trial (Trial 1571) involving 163 subjects with type 2 diabetes, significant improvement in glycemic control at all 3 tested dose levels (0.65, 1.25 and 1.9 mg/day) and a significant reduction in body weight at the highest dose level were observed. These data formed the rationale for the planned dose levels in the phase 3a program (0.6, 1.2 and 1.8 mg/day). The slight apparent difference in dose levels between the NN2211-1571 trial and the phase 3a program was due to a change in the way liraglutide content is declared, i.e. the dose levels were actually similar.

See section 10.1 - Review of Individual Study Reports for details of the phase 2 dose finding studies.

6.1.3.2 Duration of treatment

The duration of treatment for all pivotal trials was 26 weeks, except Trial 1573, in which subjects were treated for 52 weeks.

6.1.3.3 Inclusion, and Exclusion Criteria – Phase 3 Trials

The inclusion, exclusion, and randomization criteria were similar across the five trials. Therefore, a summary is presented below. Any important differences are highlighted in the specific study reviews.

Inclusion Criteria [(a)]
- Informed consent obtained before any trial-related activities
- Diagnosed with type 2 diabetes mellitus
- Age 18–80 years (both inclusive)
- Body mass index [(b)] $\leq$45.0 kg/m^2

With respect to previous antidiabetic therapy and baseline HbA1c, the inclusion criteria differed among trials, reflecting the different treatment combinations being studied:

• Trial **1573** included subjects treated with diet/exercise or one OAD for at least two months. If treated with an OAD the dose was to be no *more* than half maximal dose, except subjects previously treated with metformin 1500 mg or pioglitazone 30 mg were also eligible.
HbA1c at screening: 7.0–11.0% for subjects on diet/exercise treatment and 7.0–10.0% for subjects on OAD therapy.
• Trials **1572** and **1436** included subjects treated with OAD(s) for at least 3 months.
HbA1c at screening: 7.0–11.0% for subjects on OAD monotherapy and 7.0–10.0% for subjects on OAD combination therapy.
• Trial **1574** included subjects treated with OAD(s) and/or exenatide for at least 3 months.
HbA1c at screening: 7.0–11.0% for subjects on OAD monotherapy or exenatide therapy alone and 7.0–10.0% for subjects on combination therapy including OADs and/or exenatide.
• Trial **1697** included subjects treated with OAD(s) for at least 3 months.
HbA1c at screening: 7.5–10.0% for subjects on OAD monotherapy and 7.0–10.0% for subjects on OAD combination therapy.

Exclusion Criteria
• Previous participation in the randomized phase of the trial
• Treatment with insulin within the last 3 months prior to trial (except for short-term treatment with insulin in connection with intercurrent illness at the discretion of the investigator) Note: this criterion did apply to trial 1697 – the trial comparing liraglutide to insulin glargine.
• Impaired liver function, defined as alanine aminotransferase or aspartate aminotransferase [(c)] ≥2.5 times upper limit of normal based on analysis from central laboratory
• Impaired renal function, defined as serum creatinine ≥125 µmol/L (≥1.4 mg/dL) for males [(d)] and ≥110 µmol/L (≥1.24 mg/dL) for females [(e)] based on analysis from central laboratory
• Clinically significant, active (over the past 12 months) disease of the gastrointestinal, pulmonary, neurological, genitourinary or hematological system that might confound the results of the study or pose additional risk in administering the study drug [(f)]
• Clinically significant active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure (New York Heart Association class III and IV)
• Proliferative retinopathy or maculopathy requiring acute treatment
• Uncontrolled treated/untreated hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg)
• Subjects known to be Hepatitis B surface antigen or Hepatitis C antibody positive
• Cancer (except basal cell skin cancer or squamous cell skin cancer) or any clinically significant disease or disorder, except for conditions associated to type 2 diabetes, which could interfere with the results of the trial
• Recurrent major hypoglycemia or hypoglycemic unawareness [(g)]
• Known or suspected allergy to trial product(s) or related products
• Use of any drug (except for OADs), which could interfere with glucose levels (e.g. systemic corticosteroids)
• Receipt of any investigational drug within the 4 weeks prior to this trial
• Known or suspected abuse of alcohol or narcotics
• Mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation

• Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice)
• Any contraindications to concomitant OAD and/or insulin treatment [h]

a For inclusion criteria related to diabetes therapy and baseline HbA1c, see below.
b Body mass index ≤ 40.0 kg/m2 in Trial 1572.
c Aspartate aminotransferase only included in Trials 1573 and 1574.
d ≥152 µmol/L (≥1.7 mg/dL) in Trial 1573 and ≥135 µmol/L (≥1.53 mg/dL) in Trials 1572 and 1697.
e ≥152 µmol/L (≥1.7 mg/dL) in Trial 1573.
f Only Trials 1573 and 1574.
g Hypoglycemic unawareness was not an exclusion criterion in Trial 1572.
h Glimepiride and metformin in Trial 1572, glimepiride and rosiglitazone in Trial 1436, metformin and rosiglitazone in Trial 1574 and glimepiride, metformin and insulin glargine in Trial 1697.

6.1.3.4 Run-in periods and forced dose escalation periods

All trials utilized standardized and widely accepted treatment regimens during a run-in phase to provide a uniform baseline of treatment prior to addition of liraglutide, placebo, or active comparator drug (Table 6.3). The run-in period (before randomization) was used to increase and maintain the dose level of some of the concomitant OADs. Subjects already treated with the relevant OAD could advance directly to the maintenance period. The specified maintenance period was mandatory for all subjects.

Table 6.3
Run in Period for Phase 3 Trials

Trial 1572	Metformin to 2 g (3 weeks titration, 3 weeks maintenance)
Trial 1436	Glimepiride to 4 mg (2 weeks titration, 2 weeks maintenance)
Trial 1574	Metformin to 2 g and rosiglitazone to 8 mg (2 weeks titration, 6 weeks maintenance)
Trial 1697	Metformin to 2 g and glimepiride to 4 mg (3 weeks titration, 3 weeks maintenance)

For all trials, the randomized treatment period included an initial period of forced dose escalation to reach the intended daily dose level. The main reason for dose escalation for liraglutide was because starting at the full dose of liraglutide resulted in increased gastrointestinal adverse effects.

• For subjects randomized to 1.2 or 1.8 mg liraglutide/day, an initial dose of 0.6 mg/day was used during the first week, followed by 1 or 2 weeks after which the dose was increased by 0.6 mg per week.
• For Trial 1573, four weeks of forced dose escalation with glimepiride to reach 8 mg/day.
• For Trial 1572, three weeks of forced dose escalation with glimepiride to reach 4 mg/day.

Reviewer's comments: The run in period for most of these trials was sufficient to reach steady state, but generally too short to be reflected in the baseline Hba1c values, although by the end of the run-in period subjects had some relatively low HbA1c values (i.e. < 6.0%) at the baseline

measurement. Nonetheless, as a result of the short run-in period, the within group changes from baseline in HbA1c may overestimate the true effect but between group changes from baseline in HbA1c should be unaffected, assuming that patients were well balanced between treatment groups as a result of randomization.

6.1.3.5 Randomization Criteria – Therapeutic Confirmatory Trials

Randomization occurred after the run-in period of background therapy as indicated in Table 6.4 for each trial. Subjects also were required to meet FPG criteria in order to be randomized.

Table 6.4
Randomization Criteria for Phase 3 Trials

Trial	Background therapy	FPG
1573		FPG 7.0–13.9 mmol/L (126–250 mg/dL) if on diet/exercise therapy or FPG ≤12.2 mmol/L (220 mg/dL) if on single OAD
1572	Daily use of 2000 mg metformin for at least three weeks	FPG in the range 7.0–12.8 mmol/L (126–230 mg/dL
1436	Daily use of 4 mg glimepiride for at least two weeks	FPG in the range 7.0–12.8 mmol/L (126–230 mg/dL).
1574	Daily use of 2000 mg metformin and 8 mg rosiglitazone for at least 3 weeks	FPG in the range 7.5–12.8 mmol/L (135–230 mg/dL).
1697	Daily use of 4 mg glimepiride and 2000 mg metformin for at least 3 weeks	FPG in the range 7.5–12.8 mmol/L (135–230 mg/dL).

6.1.3.6 Withdrawal and rescue

No glycemic rescue medication (e.g. other diabetes drugs) was permitted during the studies – subjects with an unsatisfactory therapeutic effect (see withdrawal criteria) were discontinued from the trial. Subjects were expected to be withdrawn from the study if FPG became above a pre-determined value for three consecutive days and confirmed by a central laboratory (See Table 6.5 – FPG Criteria). Subjects could also be withdrawn if background therapy needed to be adjusted beyond the approved range. For example for trial 1572, if a subject required down-titration to below 1500 mg per day then he or she would be discontinued from the trial (See Table 6.5 – Background Therapy Criteria).

Table 6.5
Criteria for Withdrawal for Therapeutic Confirmatory Trials

Trial	FPG Criteria	Background Therapy Criteria

1573	FPG > 240 mg/dL after week 8 FPG > 220 mg/dL after week 28	
1572	FPG > 239 mg/dL after week 8	If titrated to less than 1500 mg metformin or more than 2000 mg metformin.
1436	FPG > 239 mg/dL after week 8	If dosed with less than 2 mg/day or greater than 4 mg/day glimepiride.
1574	FPG > 240 mg/dL after week 8	Dose adjustment not specified. Protocol states that "subjects needed to be on metformin and rosiglitazone throughout the study"
1697	FPG > 239 mg/dL after week 8	If being dosed with less than 1.8 mg liraglutide daily (after uptitration), less than 2000 mg metformin daily, or less than 2 mg or more than 4 mg glimepiride daily

6.1.3.7 Individual Trial Design - Liraglutide as monotherapy

6.1.3.7.1 (Liraglutide 1.8) vs. (Liraglutide 1.2) vs. (Glimepiride)

One monotherapy study was conducted in both patients with drug-naive diabetes (diet/exercise therapy only) and patients on one oral antidiabetic medication at less than half the maximum dose for at least two months.

Trial 1573: Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on Glycemic Control of Liraglutide versus Glimepiride in Type 2 Diabetes [A Fifty-Two Week (with Fifty-Two Week Open-Label Extension) Double-Blind, Multicenter, Randomized, Parallel Study to Investigate Safety and Efficacy] Trial 1573

Hypothesis: Liraglutide (1.8 mg once daily) will provide glycemic control [as measured by glycosylated hemoglobin (HbA1c)] as good as that achieved with glimepiride (8 mg once daily) after 52 weeks in subjects with type 2 diabetes previously treated with diet/exercise or a single oral antidiabetic agent at not more than the half-maximal recommended dose for at least two months.

Reviewer's comments: non-inferiority to glimepiride is a rational study design choice because glimepiride is an approved treatment for type 2 diabetes that has a mechanism of action as an insulin secretagogue. The dose being used in this study is the maximum FDA approved therapeutic dose.

This was a multicenter (117 centers in the United States and Mexico), randomized, double-blind, double-dummy, parallel, active-controlled study. A total of 746 patients with type 2 diabetes were randomized in a 1:1:1 ratio to:

Liraglutide 1.2 mg sc qd
Liraglutide 1.8 mg sc qd

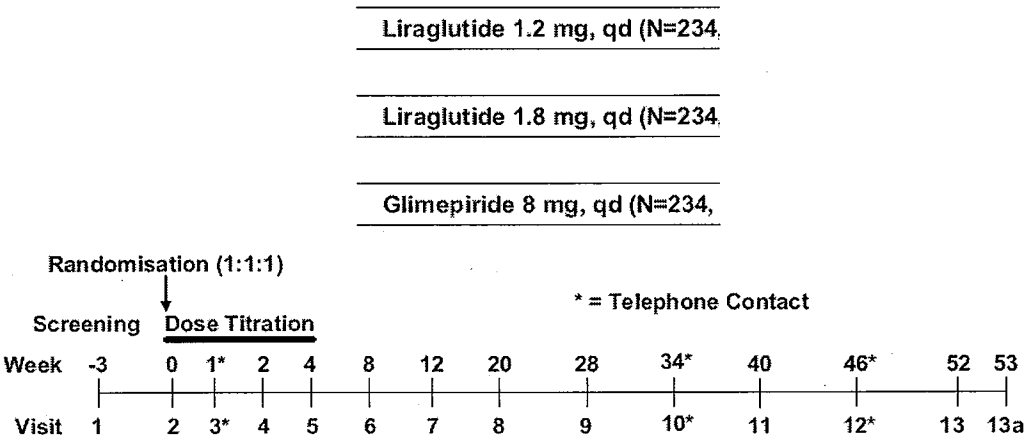
Glimepiride 8 mg po qd

In addition to the 746 subjects, one of the sites (site 507), with 11 randomized subjects (<2% of randomized subjects), was excluded from ITT and safety analyses due to GCP compliance issues.

Procedures:

At week 0 (visit 2) subjects were asked to discontinue use of current OADs after screening, upon randomization, and before initiation of study drugs.

Figure 6.2 – Procedures for Trial 1573



Reviewer's comments: There appears to have been no washout period of OADs prior to randomization and the baseline measurement of HbA1c. This may bias results in that it could lead to underestimation of the within group primary efficacy variable (change in HbA1c from baseline to endpoint) in the patients taking OADs prior to randomization in a direct comparison to diet/exercise patients because of the expectation of the HbA1c to "drift back to baseline" among the subjects who were enrolled in the trial on OADs and then taken off those OADs at randomization. Note: This lack of washout period may also have affected the secondary endpoint of change in body weight. The change in HbA1c relative to comparator should be unaffected by the lack of washout.

6.1.3.7.2 Fifty-two week open label extension period

The open label portion of the study started after the last subject had completed the 52-week double-blind portion of the study. The primary efficacy variable was change in HbA1c from baseline to week 76. Four hundred forty (440) patients (60%) continued into the open-label portion of this trial and 53.9% completed 18 months of the voluntary study by the cutoff date of February 21, 2008.

Reviewer's comment: The extension period was unblinded and its data were not used to support efficacy claims, although these data may provide supportive information on durability of effect.

6.1.3.8 Individual Trial Designs - Liraglutide as Combination Therapy

6.1.3.8.1 (Liraglutide + Metformin) vs. (Placebo + Metformin) vs. (Glimepiride + Metformin)

Trial 1572: Liraglutide Effect and Action in Diabetes (LEAD-2) Effect on glycemic control after once daily administration of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomized, active control, parallel-group, multicenter, multinational trial with an 18 months extension period.

Hypothesis: Combination therapy of liraglutide and metformin will provide glycemic control (as measured by glycosylated hemoglobin [HbA1c]) significantly better than metformin monotherapy, and at least as good as or better than that achieved by metformin and glimepiride combination therapy in subjects with type 2 diabetes.

This was a multicenter (170 centers in 21 countries), double-blind, double-dummy, randomized, study. Subjects with type 2 diabetes inadequately controlled on OADs (HbA1c 7.5-11% inclusive) were randomized in a 2:2:2:1:2 ratio to:

Liraglutide active (0.6 mg/day) + glimepiride placebo + metformin (1.5-2.0 g/day)
Liraglutide active (1.2 mg/day) + glimepiride placebo + metformin (1.5-2.0 g/day)
Liraglutide active (1.8 mg/day) + glimepiride placebo + metformin (1.5-2.0 g/day)
Liraglutide placebo + glimepiride placebo + metformin (1.5-2.0 g/day)
Liraglutide placebo + glimepiride (4 mg/day) + metformin (1.5-2.0 g/day)

Dose Adjustments:
After randomization the dose level of metformin could, at the discretion of the investigator, be decreased to a minimum of 1500 mg /day in case of unacceptable hypoglycemia or other adverse events. Likewise, the metformin dose could be increased again to 2000 mg/day. If a dose level less than 1500 mg/day or more than 2000 mg/day was required, the subject had to be withdrawn from the trial (see also section 6.1.3.6 Withdrawal and rescue).

Reviewer's comment: Although the maximum recommended dose of metformin is 3,000 mg daily, the 2000 mg dose used in this trial is considered the maximally/near-maximally efficacious dose (Garber 1997) and is commonly used in trials of antidiabetic medications.

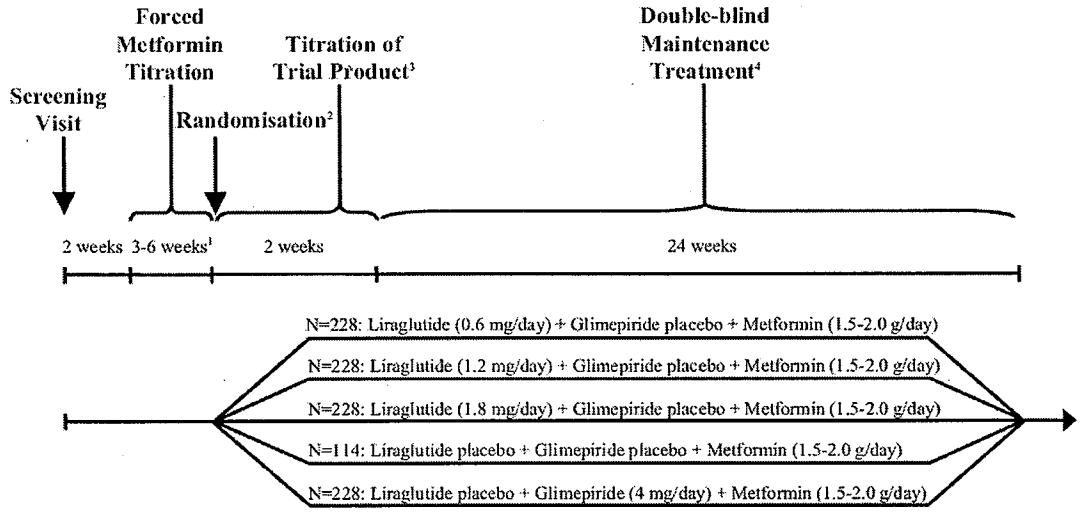
The doses of liraglutide and glimepiride were to be maintained throughout the trial.

Inclusion criteria differed from those presented in section 6.1.3.3 in that:

1. Body mass index (BMI) ≤ 40.0 kg/m^2

Procedures: Each subject underwent a screening visit at week 0 and then an open forced metformin titration period of 3-6 weeks. Depending on randomization criteria being met, subjects were then randomized to a 2 week double-blind up-titration of liraglutide and glimepiride (active and/or placebo) (Figure 6.3).

Figure 6.3 – Procedures for Trial 1572



Reviewer's comment: The protocol permitted an increase in metformin dosage within 3-6 weeks prior to the baseline HbA1c measurement. Improved glycemic control resulting from this regimen change would not be fully reflected in the baseline HbA1c measurement (HbA1c represents glycemic control over the prior three months). This could lead to over-estimation of the within group primary efficacy variable (change in HbA1c from baseline to endpoint) in these patients because some of the improvement in HbA1c during the double-blind treatment period would be attributable to the recent increase in metformin dosage. Therefore, the change in HbA1c should be reported relative to placebo.

Study Design Procedural Deviations

b(4)

The NGSP Level I certification for testing of HbA1c at [redacted] expired 1 September 2006. Thereafter, [redacted] had a Level II certification. The majority of samples analyzed at [redacted] after 1 September 2006 were reanalyzed at [redacted] (NGSP Level I certified) at a later time point. However, for a number of samples there was no material left and it was therefore not possible to perform the reanalysis at [redacted] (subjects 401009, 401012, 401013, 401014, 401015, 401016, 401017, 401018, 402015, 402016, 402018, 402019, 403008, 403010, 403011, 403012, 403014, 403016, 403018, 403019 and 403020 at Visit 3, subjects 401002, 401003, 401004, 401005, 402001, 402004, 402005, 403001, 403002, 403003, 403005, 403006, 404001, 404002, 404003, 404005, 404006, 404008, 404010, 404011, 404013, 404014, 404019 and 404020 at Visit 7, subject 404002 at Visit 8 and subjects 402004, 402019, 403016 and 403019 at Visit 10 which was the visit during which the final HbA1c measurement used for efficacy analyses was obtained) and for another few samples the

analysis at [redacted] was not performed because the samples were hemolyzed (subjects 401002 and 401005 at Visit 10). For all these samples, the results from the analysis at [redacted] (NGSP Level II certified) were used. The Sponsor concluded that this approach would not influence the results of the study. b(4)

Reviewer's comment: This reviewer agrees that this protocol deviation is not likely to have affected study results because the number of affected samples from visit 3, (the visit at which the baseline HbA1c measurement was obtained) was only 21, and the number of affected samples from visit 10, the study endpoint visit (the visit at which the final HbA1c measurement for analysis of the primary efficacy endpoint was obtained) was only 6. This small number of affected samples is unlikely to have resulted in altered study results.

18 month extension period of trial 1572
This report aimed to fulfill the FDA request to present data following longer exposure time for a large number of subjects. At Visit 10 at 26 weeks after randomization, all subjects were asked to confirm their continued participation in an 18-month, voluntary, open-label treatment extension period. Subjects who continued into the extension period were unblinded to treatment assignment at their first visit at the site after database release and continued the treatment regimen they had been randomized to in the blinded part of the trial. Data from the extension trial are used to support safety (see Dr. Mahoney's Clinical Safety Review).

6.1.3.8.2 (Liraglutide + glimepiride) vs. (placebo + glimepiride) vs. (rosiglitazone + glimepiride)

Trial 1436: Liraglutide Effect and Action in Diabetes (LEAD-1): Effect on glycemic control after once daily administration of liraglutide in combination with glimepiride versus glimepiride monotherapy versus glimepiride and rosiglitazone combination therapy in subjects with type 2 diabetes

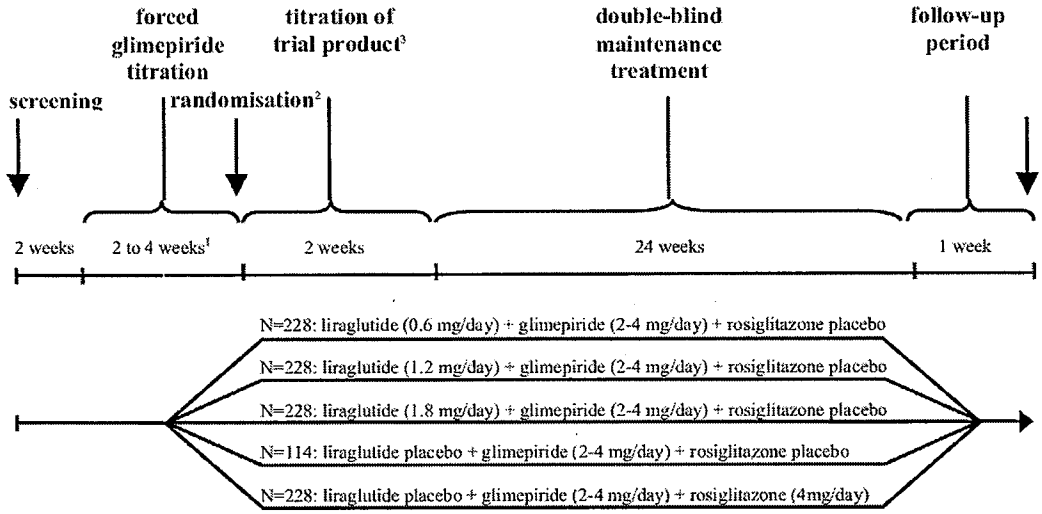
The rationale for this trial was to demonstrate that the addition of liraglutide to existing sulfonylurea (SU) therapy, glimepiride, provides additional improvements in glycemic control. Furthermore, the rationale was to compare liraglutide in combination with glimepiride to glimepiride monotherapy and to rosiglitazone, a thiazolidinedione (TZD), in combination with glimepiride.

This was a 6 month, multicenter (116 centers in 21 countries), randomized, double-blind, double-dummy, active control, five armed parallel group study. 1041 subjects were randomized in a 2:2:2:1:2 ratio to:
Liraglutide active (0.6 mg/day) + glimepiride (2-4 mg/day) + rosiglitazone placebo
Liraglutide active (1.2 mg/day) + glimepiride (2-4 mg/day) + rosiglitazone placebo
Liraglutide active (1.8 mg/day) + glimepiride (2-4 mg/day) + rosiglitazone placebo
Liraglutide placebo + glimepiride (2-4 mg/day) + rosiglitazone placebo
Liraglutide placebo + glimepiride (2-4 mg/day) + rosiglitazone (4mg/day)

Procedures (Figure 6.4):

Study procedures included a screening visit followed by a 2 – 4 week forced glimepiride titration up to 4 mg/day prior to randomization. Subjects that were evaluated as being eligible at the screening visit were to discontinue their usual OAD(s) and commence an open 2-week run-in period with forced titration of glimepiride therapy increasing to 4 mg/day followed by a 2-week maintenance period. Subjects on current glimepiride therapy could go through a modified titration period or advance directly to the 2-week maintenance period at the discretion of the investigator. The doses of glimepiride (open-label) could be reduced from 4 mg/day to 3 or 2 mg/day (minimum) after randomization in the event of unacceptable hypoglycemia or other adverse events. Subjects who required less than 2 mg glimepiride were discontinued from the trial (see Table 6.5).

Figure 6.4 – Procedures for Trial 1436



Reviewer's comments: The usual maintenance dose of glimepiride is 2-4 mg daily. Therefore, this study's 4 mg background glimepiride dose is appropriate. Because sulfonylureas have similar efficacy, results from this trial should also apply to patients using maintenance doses of other sulfonylureas.

The protocol permitted an increase in glimepiride dosage within 3-6 weeks prior to the baseline HbA1c measurement. Improved glycemic control resulting from this regimen change would not be fully reflected in the baseline HbA1c measurement (HbA1c represents glycemic control over the prior three months). This could lead to over-estimation of the within group primary efficacy variable (change in HbA1c from baseline to endpoint) in these patients because some of the improvement in HbA1c during the double-blind treatment period would be attributable to the recent increase in glimepiride dosage. Therefore, the change in HbA1c should be reported relative to placebo. The baseline value of HbA1c is really a reflection of the decreasing effects of OADs used prior to study entry and the increasing effects of glimepiride.

6.1.3.8.3 (Liraglutide + Rosiglitazone + Metformin) vs. (Placebo + Rosiglitazone + Metformin)

Trial 1574: Liraglutide Effect and Action in Diabetes (LEAD-4): Effect on Glycemic Control of Liraglutide in Combination with Rosiglitazone plus Metformin versus Rosiglitazone plus Metformin in Type 2 Diabetes (A Twenty-Six Week Double-Blind Parallel Trial to Investigate Safety and Efficacy)

The primary efficacy objective was to assess and compare the additive effect (as assessed by change in HbA1c) of two doses of liraglutide (liraglutide 1.2 mg and liraglutide 1.8 mg) in combination with rosiglitazone and metformin versus the combination of rosiglitazone and metformin, on glycemic control after 26 weeks in subjects with type 2 diabetes.

Hypothesis: Liraglutide (1.8 mg once daily) in combination with rosiglitazone (4 mg twice daily) plus metformin (1000 mg twice daily) will provide glycemic control (as measured HbA1c) better than that achieved with the combination of rosiglitazone (4 mg twice daily) and metformin (1000 mg twice daily) in subjects with type 2 diabetes.

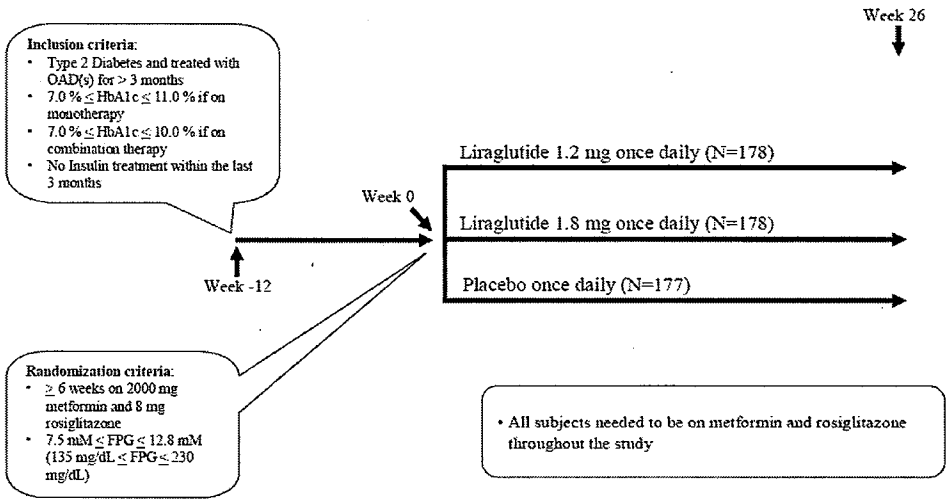
This was a multicenter (96 centers in the United States and Canada), randomized, double-blind, placebo-controlled study. A total of 533 patients with type 2 diabetes inadequately controlled on OAD(s) (HbA1c 7.0-11%) were randomized in a 1:1:1 ratio to:

Liraglutide 1.2 mg qd + rosiglitazone 4 mg bid + metformin 1000 mg bid
Liraglutide 1.8 mg qd + rosiglitazone 4 mg bid + metformin 1000 mg bid
Liraglutide placebo + rosiglitazone 4 mg bid + metformin 1000 mg bid

Study procedures (Figure 6.5):
Subjects who satisfied inclusion and exclusion criteria underwent a 9-week forced titration period (3 week dose escalation with 6 week dose maintenance) with rosiglitazone (starting at 4 mg once daily and increasing to 4 mg twice daily within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 1000 mg twice daily). Subjects who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) were eligible for randomization after a 6-week run-in period. Subjects who did not tolerate the final dose were not randomized into the trial. Once randomized, all groups underwent a double-blinded forced titration period with liraglutide (active or placebo) in order to achieve their final doses. All subjects started on 0.6 mg liraglutide (active or placebo). The dose was increased to 1.2 mg after one week. Subjects randomized to receive the highest dose had their dose of liraglutide (or placebo) increased to 1.8 mg/day one week later.

Reviewer's comment: The mandatory maintenance period with rosiglitazone 8 mg and metformin 2000 mg prior to randomization was 6 weeks. Improved glycemic control resulting from this 6 week period would not be fully reflected in the baseline HbA1c measurement (HbA1c represents glycemic control over the prior three months).

Figure 6.5 – Procedures for Trial 1574



6.1.3.8.4 (Liraglutide + glimepiride + metformin) vs. (placebo + glimepiride + metformin) vs. (insulin glargine + glimepiride + metformin):

Trial 1697: Liraglutide Effect and Action in Diabetes (LEAD-5): Effects on glycemic control after once daily administration of liraglutide in combination with glimepiride and metformin versus glimepiride and metformin combination therapy, and versus insulin glargine added to glimepiride and metformin combination therapy in subjects with type 2 diabetes. A six-month randomized, double-blind, parallel-group, multicenter, multinational trial with an open-label treat-to-target insulin glargine control arm.

Study rationale: The purpose of this trial was to demonstrate that the addition of liraglutide to existing metformin and SU therapy (glimepiride) provided additional improvements in glycemic control, and furthermore to compare the addition of liraglutide with that of insulin glargine to subjects treated with metformin and SU therapy (glimepiride).

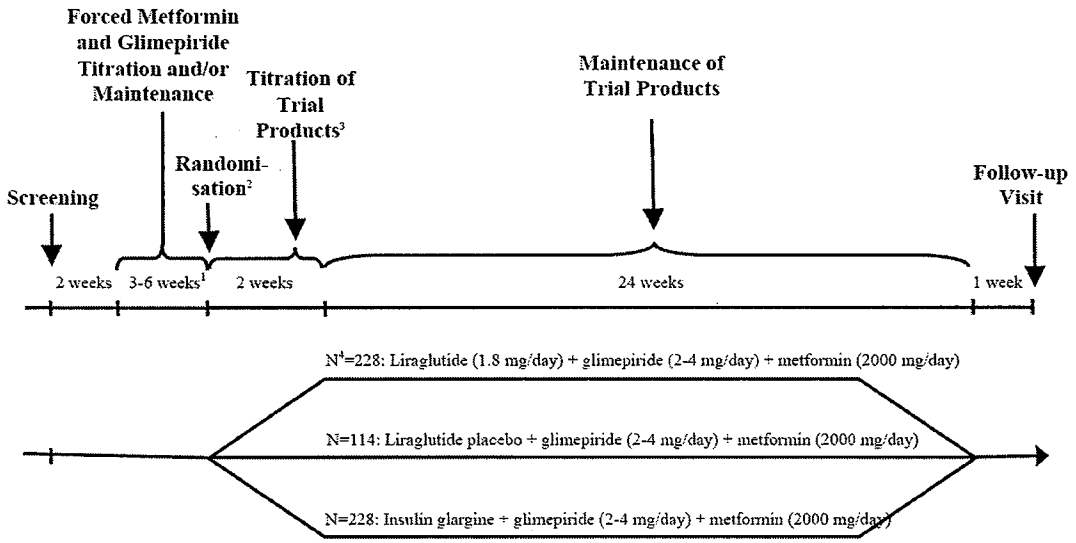
This was a multicenter (107 centers in 17 countries), randomized, double-blind, placebo-controlled study. A total of 581 patients with type 2 diabetes were randomized in a 2:1:2 ratio to:

Liraglutide 1.8 mg sc qd + OAD
Liraglutide placebo + OAD
Open label glargine + OAD

Study procedures (Figure 6.6)
Randomization took place after a run-in period including a 3-week forced metformin and glimepiride titration period followed by a maintenance period of 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. After randomization, the subjects underwent a 2-week period of titration with liraglutide for reaching a daily

dose of 1.8 mg liraglutide in the last week. After this 2-week titration period, a 24-week maintenance period commenced, during which doses of liraglutide/liraglutide placebo and metformin were fixed, although glimepiride and insulin glargine doses could be adjusted. The dose of insulin glargine was to be adjusted by the subject 2 times weekly, based on self-measured fasting plasma glucose using a glucose meter on the day of titration, and following a titration guideline (Table 6.6).

Figure 6.6 – Procedures for Trial 1697



The starting dose of insulin glargine was to be numerically equivalent to the mean FPG value in mmol/L measured for the purpose of randomization at the clinic using a glucose meter. For example, if the mean FPG was 12 mmol/L, the initial dose of insulin glargine was 12 IU. However, as the brand of glucometer used in the trial (Optiset) worked in increments of 2 IU it was necessary to round off to the nearest unit, e.g. if 10.9 then 10 IU and if 11.1 then 12 IU.

Table 6.6
Guideline for Titration of Insulin Glargine

Self-measured FPG	Increase in insulin glargine dose (IU)
≤ 5.5 mmol/L (≤ 100 mg/dL) Target	No adjustment
> 5.5 and < 6.7 mmol/L (> 100 and < 120 mg/dL)	0-2 IU[a]
≥ 6.7 mmol/L (≥ 120 mg/dL)	2 IU
[a]According to the individualized recommendation by the investigator at the previous visit for example depending on whether the subject has experienced hypoglycemia	
Source: Trial 1697 report, Table 9-3, page 48	

For this particular trial, with regard to the titration of insulin glargine done according to the titration guideline, it was decided that no subjects could be excluded from the PP analysis set due to inadequate

titration, as only the starting dose of glargine was specified in the protocol and the subsequent titration was managed by the subject.

Reviewer's comments: **the baseline value for HbA1c was determined at visit 3 at the same time as randomization. This visit occurred at a minimum of 3 weeks and a maximum of 6 weeks after discontinuation of pre-study OADs and initiation of the study drugs of metformin and glimepiride at visit 2. The baseline HbA1c will reflect pre-study OAD doses as well as the metformin and glimepiride initiated at study entry.**

The starting dose of glargine seems very low and would result in inadequate therapy. However the titration guideline would allow the glargine dose to reach clinically effective levels over time. At the end of 26 weeks this reviewer would expect the glargine dosed in this manner to be a fair comparator to liraglutide.

All subjects treated with insulin glargine were instructed to measure their fasting plasma glucose frequently for the purpose of insulin glargine titration. This behavior might encourage greater compliance.

Study Design Protocol deviations: The Sponsor lists two study design protocol deviations b(4)
1) As the NGSP Level I certification for testing of HbA1c at ——— expired at the end of August 2006, a transfer of HbA1c analyses from ——— to the ——— laboratory in ——— was done for all samples from sites in ——— as of 17 September 2006. Samples analyzed at ——— between the end of August and until the transfer to ——— (Level II analysis) were reanalyzed at ——— for HbA1c unless there was no sample material left, which was the case for 8 subjects (817003, 817004, 817009, 817010, 818015, 819023, 820009 and 820010). There were 52 subjects from sites in ——— total although it is not reported how many of these subjects were affected by the protocol deviation (e.g. had samples dating from 17 September 2006).
2) There was a discrepancy between the laboratory and the protocol's conversion factor between µmol/L and mg/dL for serum creatinine; the limits in mg/dL for the exclusion criteria regarding impaired renal function (exclusion criterion no. 4) were ≥1.53 mg/dL for males and ≥1.24 mg/dL for females. This information was included in the amendment to central laboratory specifications

Reviewer's comment: **Potentially 52 subjects out of a total of 581 (10%) randomized subjects would be affected by this protocol deviation. The Sponsor did not report if the samples were appropriately transferred and handled and did not report if HbA1c values obtained at ——— were similar to the results obtained from reanalysis at ——— However, this reviewer and the statistical reviewer believe that the overall assessment of efficacy in the liraglutide development program would not be significantly affected by this deviation (note: this issue is not addressed in the written Statistical Review which was formalized before this issue came to light, but was discussed in person with Dr. Derr). This deviation could, however, have labeling implications as clinical data are presented separately for each trial in the label. Therefore, the Sponsor was asked on 23 Jul 2009 to provide the following:** b(4)

1. A reanalysis of the primary efficacy endpoint (change in HbA1c at the end of 26 weeks) for trial

1697 excluding the subjects whose samples had to be reanalyzed due to the protocol deviation and excluding the 8 subjects who did not have enough sample material left to perform the reanalysis at Toronto.

2. An assessment of the inter-laboratory differences in HbA1c levels of samples that were assayed by both laboratories.

The responses submitted on 29 Jul 2009 were as follows:

1. We looked into the 52 subjects randomized in trial 1697 described above. These were all randomized in ——. In comparison to the original ITT population we excluded 51 subjects (1 subject did not have any samples reanalyzed in ——— and 50 subjects had at least one post-baseline sample reanalyzed in ———). The remaining subject (820005) – did not have any post baseline values and was therefore not included in the original analysis (and was also not included in the revised analysis). We analyzed the primary endpoint change in HbA_{1c} at the end of 26 weeks using the same model as described originally – excluding the 51 subjects. To facilitate comparison to the original results we performed the same three analyses ITT with LOCF, ITT without imputation, and the PP population. b(4)

The ANCOVA results for the ITT with LOCF population showed that liraglutide+OADs lowered HbA1c by -1.29% (vs. -1.33% in the original analysis), glargine+OADs by -1.10% (vs. -1.09% in the original analysis), and placebo+OADs by -0.25% (vs. -0.24% in the original analysis). The tests of superiority were similar to the original analysis, i.e. liraglutide+OADs was superior to both the glargine+OADs group and the placebo+OADs group.

2. We looked into the inter-laboratory differences by plotting the average vs. the difference (so called Bland-Altman plot), and also performed a statistical analysis. We found a difference between the mean of HbA_{1c} values from the two analysis of -0.56 (95%CI: [-0.60; -0.52]; p<0.0001) with results at —— being lower than at —— b(4)

Reviewer's comment: Although there appears to be lower mean HbA1c values at —— compared to ——— the mean changes from baseline were not sensitive to excluding the subjects whose samples had to be reanalyzed due to the protocol deviation. Therefore, the overall efficacy conclusions are not affected by the protocol deviation. b(4)

6.1.3.9 Study design conclusions:

Based on review of the study designs, this reviewer concludes that the designs are adequate to provide assessment of benefit in patients with type 2 diabetes mellitus, are of adequate duration to allow for such conclusions, allow for generalizability of results (excepting severely ill diabetics with high HbA1c levels as well as advanced cardiovascular disease and other excluded populations, i.e. renal and hepatic failure), and that the doses studied in the pivotal Phase 3 trials were adequate based on the findings in Phase 2.

6.1.4 Efficacy Findings

See Dr. Derr's statistical review for additional information.

6.1.4.1 Monotherapy Trial

Trial 1573 - (liraglutide 1.2 + placebo) vs. (liraglutide 1.8 + placebo) vs. (glimepiride + placebo)

6.1.4.1.1 Demographic and baseline features of the monotherapy population

There was one monotherapy trial. The trial compared two doses of liraglutide to an active comparator (glimepiride in this case). The screening characteristics and the key efficacy parameters at baseline of randomized subjects are summarized in Table 6.7 and Table 6.8, respectively.

The study population was roughly half male and half female, had a mean age of 53 years (range 19-79), was 77% White and 12% Black or African and 10% other races, and had a mean BMI of 33 kg/m^2. The mean duration of diabetes was 5.4 years with a mean HbA1c of 8.3% at screening. Roughly two-thirds of the subjects were treated previously with monotherapy while the other one-third was previously treated with diet and exercise and hence were drug naïve. There were no reported differences between randomization groups with respect to baseline parameters.

Table 6.7
Trial 1573 - Screening Characteristics and Demographic Features of all Randomized Subjects

All randomized subjects (N)	247	251	248
	Lira 1.8	**Lira 1.2**	**Glimepiride**
Sex N (%)			
Male	121 (48.99)	117 (46.61)	133 (53.63)
Female	126 (51.01)	134 (53.39)	115 (46.37)
Age (years)			
Mean (SD)	52.0 (10.8)	53.7 (11.0)	53.4 (10.9)
Ethnicity N (%)			
Hispanic or Latino	87 (35.22)	81 (32.27)	93 (37.50)
Not Hispanic or Latino	160 (64.78)	170 (67.73)	155 (62.50)
Race N (%)			
White	186 (75.30)	200 (79.68)	192 (77.42)
Black or African American	30 (12.15)	34 (13.55)	30 (12.10)
Native Hawaiian/Pacific Islander	2 (0.81)	0 (0.00)	0 (0.00)
American Indian – Alaska Native	0 (0.00)	0 (0.00)	0 (0.00)
Asian	12 (4.86)	5 (1.99)	9 (3.63)
Other	17 (6.88)	12 (4.78)	17 (6.85)

BMI (kg/m^2)			
Mean (SD)	32.8 (6.3)	33.2 (5.6)	33.2 (5.6)
Duration of diabetes (years)			
Mean (SD)	5.3 (5.1)	5.2 (5.5)	5.6 (5.1)
Previous anti-diabetic treatment, N (%)			
Diet/exercise	87 (35.22)	91 (36.25)	94 (37.90)
Monotherapy	160 (64.78)	160 (63.75)	154 (62.10)
HbA1c at screening (%)			
Mean (SD)	8.3 (1.1)	8.3 (1.0)	8.4 (1.2)
Source: Table 11-1, Trial 1573 report			

At randomization the subjects were similar with regards to HbA1c, fasting plasma glucose, and blood pressure.

Table 6.8 **Trial 1573 - Key Efficacy Parameters of All Randomized Subjects**			
All randomized patients (N)	233	228	234
	Liraglutide 1.8	**Liraglutide 1.2**	**Glimepiride**
HbA1c (%)			
N	247	251	248
Mean (SD)	8.19 (1.08)	8.18 (1.05)	8.23 (1.06)
Fasting plasma glucose (mmol/L)			
N	236	239	242
Mean (SD)	9.5 (2.6)	9.3 (2.6)	9.5 (2.6)
Diastolic BP (mmHg)			
N	247	251	248
Mean (SD)	78.8 (8.4)	78.5 (8.3)	79.5 (8.6)
Systolic BP (mmHg)			
N	247	251	248
Mean (SD)	128.1 (13.9)	127.6 (14.3)	130.0 (16.1)
Source: Table 11-2, Trial 1573 report			

6.1.4.1.2 Participation and withdrawals in the monotherapy population (disposition of patients)

Participation and withdrawals in the monotherapy trial are summarized in table 6.9. Although 746 subjects were randomized, one did not receive any treatment. In addition to the 746 subjects, one site with 11 subjects was not included in the ITT analysis set due to GCP compliance issues. As a result, there are 745 subjects in the analysis and tables.

Table 6.9 **Trial 1573 - Subject Disposition**			
	Liraglutide 1.8	**Liraglutide 1.2**	**Glimepiride**
Subjects	N (%)	N (%)	N (%)
Randomized	247 (100.0)	251 (100.0)	248 (100.0)
Exposed (ITT Analysis Set)	246 (99.6)	251 (100.0)	248 (100.0)
Withdrawals	74 (30.0)	89 (35.5)	96 (38.7)
Adverse Events	18 (7.3)	25 (10.0)	15 (6.0)
Ineffective therapy	9 (3.6)	15 (6.0)	25 (10.1)
Non-compliance with protocol	11 (4.5)	11 (4.4)	5 (2.0)
Other	36 (14.6)	38 (15.1)	51 (20.6)
Completers	173 (70.0)	162 (64.5)	152 (61.3)
PP Analysis Set	154 (62.3)	142 (56.6)	130 (52.4)
Source: Table 10-1, trial 1573 report			

Reviewer's comment: 11 subjects removed from a sample size of 746 would not be expected to alter efficacy results.

Overall, 65.3% of subjects completed the trial (64.5% in the liraglutide 1.2 mg arm, 70.0% in the liraglutide 1.8 mg arm, and 61.3% in the glimepiride arm. The difference in completion rates seemed to be based on a higher rate of therapeutic failure in the glimepiride arm. Early in the study, however, there was a higher withdrawal rate in the liraglutide groups compared with glimepiride. For example, during month 1 the dropout rate was 24.7% in the lira 1.8 group, 25.8% in the lira 1.2 group, and 14.6% in the glimepiride group. The majority of the subjects in the liraglutide treatment groups that withdrew from the study early due to an adverse event, withdrew due to a gastrointestinal system related adverse event. Details of withdrawals due to adverse events are discussed in detail in Dr. Mahoney's Clinical Safety Review. At 52 weeks, the discontinuation rate due to unsatisfactory therapeutic effect was lowest for the liraglutide 1.8 mg group (3.6%), intermediate for the liraglutide 1.2 mg group (6.0%), and highest for the glimepiride group (10.1%).

Reviewer's comment: Handling of dropouts was addressed in Dr. Derr's statistical review. Per Dr. Derr there was no compromise of the efficacy assessment due to the somewhat high dropout rate. It was also concluded that the lower and dose-dependent discontinuation due to unsatisfactory therapeutic effect in the liraglutide 1.8 mg groups was evidence for efficacy of liraglutide.

6.1.4.1.3 Adequacy of comparator drug dosages used

In this study (1573) the active comparator was glimepiride 8 mg once daily in the morning. This is the maximal recommended dose of glimepiride.

Reviewer's comments: The glimepiride group was adequately exposed to an effective glimepiride dosage.

6.1.4.1.4 Primary efficacy variable for the monotherapy population

Table 6.10 summarizes the changes in HbA1c from baseline using the ITT analysis set.

Table 6.10
Trial 1573 - Summary of Change in HbA1c (%), ITT Population

	Lira 1.8	Lira 1.2	Glimepiride
ITT Analysis Set			
Baseline			
N	246	251	248
Mean (SD)	8.19 (1.085)	8.18 (1.054)	8.23 (1.062)
Week 52 completers			
N	170	159	150
Mean (SD)	6.97 (1.091)	7.16 (1.225)	7.54 (1.111)
Change from Baseline to Week 52 completers			
N	170	159	150
Mean (SD)	-1.22 (1.134)	-0.93 (1.261)	-0.55 (1.130)
End of Treatment LOCF			
N	234	236	241
Mean (SD)	7.17 (1.229)	7.46 (1.345)	7.80 (1.242)
Change from Baseline to End of Treatment LOCF			
N	234	236	241
Mean (SD)	-1.01 (1.277)	-0.73 (1.333)	-0.44 (1.165)

Source: Table 11-3, trial 1573 report

This trial used a non-inferiority design with the pre-defined non-inferiority margin of 0.4% change in HbA1c. A hierarchical testing procedure was used to test for non-inferiority and then superiority (see section 6.1.2.3 statistical methods).

Reviewer's comment: The non-inferiority margin of 0.4% change in HbA1c is standard for diabetes trials. The hierarchical testing procedure was used to reduce the type 1 error rate. Dr. Derr's statistical review identified no concerns with this procedure.

Mean change in HbA1c from baseline to end of treatment was analyzed in the ITT analysis set with LOCF using an ANCOVA model (Table 6.11). The adjusted mean decrease in HbA1c value from baseline to end of treatment was 1.14% in the liraglutide 1.8 mg group, 0.84% in the liraglutide 1.2 mg group, and 0.51% in the glimepiride group (*note: these are not placebo adjusted percentages as there was no placebo group in this trial*). Treatment with liraglutide at both the 1.8 and 1.2 mg dose was superior to treatment with glimepiride, and there was also a significantly greater decrease in HbA1c values for liraglutide 1.8 mg compared to liraglutide 1.2 mg. The ANCOVA model was also performed on the PP analysis set (Table 6.12) and for the ITT analysis set without imputation (Table 6.13) with similar results.

Table 6.11
Trial 1573 - ANCOVA of Primary Endpoint – Change in HbA1c (%), (LOCF) ITT population

Treatment/comparison	**Estimates**			
Least Square Means	N	LS Mean	SE	
Lira 1.8	234	-1.136	(0.081)	
Lira 1.2	236	-0.843	(0.080)	
Glimepiride	241	-0.513	(0.077)	
Estimated Treatment Differences	**LS Mean**	**95% CI**		**p-value**
Lira 1.8 - Glimepiride	-0.623	-0.826 – (-0.421)		<.0001
Lira 1.2 - Glimepiride	-0.329	-0.531 – (-0.127)		0.0014
Lira 1.8 – Lira 1.2	-0.294	-0.497 – (-0.091)		0.0046

The estimates are from an ANCOVA model with treatment, country, and previous OAD treatment as fixed effects and baseline value as a covariate.

Source: Table 11-4, trial 1573 report

Table 6.12
Trial 1573 - ANCOVA of Primary Endpoint – Change in HbA1c (%), PP population

Treatment/comparison	**Estimates**			
Least Square Means	N	LS Mean	SE	
Lira 1.8	154	-1.311	(0.087)	
Lira 1.2	142	-1.049	(0.088)	
Glimepiride	130	-0.662	(0.089)	
Estimated Treatment Differences	**LS Mean**	**95% CI**		**p-value**
Lira 1.8 - Glimepiride	-0.649	-0.875 – (-0.423)		<.0001

Lira 1.2 - Glimepiride	-0.387	-0.617 – (-0.157)	0.0010
Lira 1.8 – Lira 1.2	-0.262	-0.482 – (-0.042)	0.0196
Source: EOT Table 14.2-5-8, trial 1573 report			

Table 6.13
Trial 1573 - ANCOVA of Primary Endpoint – Change in HbA1c (%), (no imputation) ITT population

Treatment/comparison	**Estimates**		
Least Square Means	N	LS Mean	SE
Lira 1.8	170	-1.289	(0.087)
Lira 1.2	159	-1.044	(0.089)
Glimepiride	150	-0.662	(0.088)
Estimated Treatment Differences	**LS Mean**	**95% CI**	**p-value**
Lira 1.8 – Glimepiride	-0.627	-0.853 – (-0.402)	<.0001
Lira 1.2 – Glimepiride	-0.383	-0.612 – (-0.154)	0.0011
Lira 1.8 – Lira 1.2	-0.245	-0.466 – (-0.023)	0.0304
Source: EOT Table 14.2-5-9, trial 1573 report			

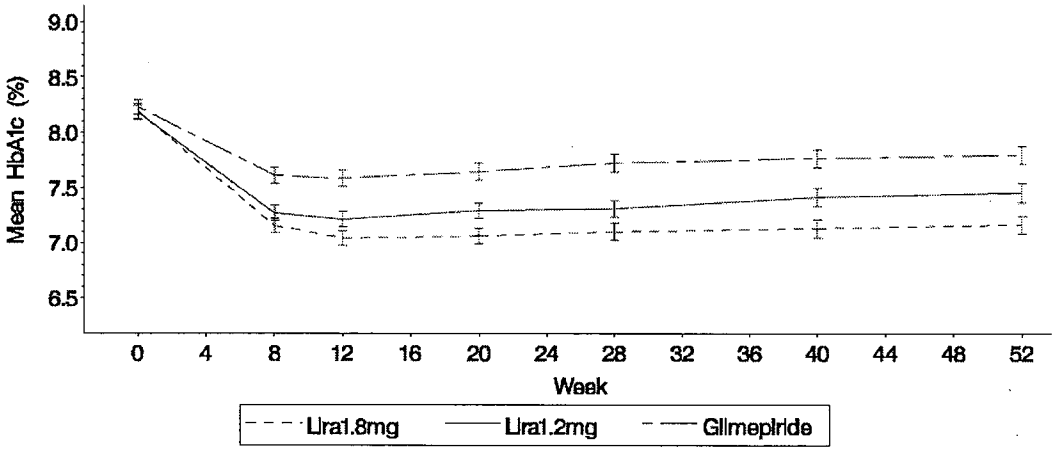
Reviewer's comments: **Both of the liraglutide doses resulted in clinically meaningful reductions in HbA1c.**

For the HbA1c endpoint, the ITT with LOCF, ITT without imputation, and PP results were similar, supporting robustness of the efficacy results. As expected the PP analysis set shows the greatest efficacy for all groups.

The -0.513% mean HbA1c reduction with glimepiride is lower than expected. For comparison, in two 14-week placebo controlled studies in 720 subjects, the average net reduction in HbA1c for patients treated with 8 mg Amaryl once daily was 2.0% compared with placebo-treated patients. (Amaryl label, 2005). Several possible explanations for the lower-than-expected response to glimepiride are differing trial populations, starting HbA1c levels, duration of diabetes, etc. Also, trial 1573 was not a placebo controlled trial, whereas the trial cited in the Amaryl label was placebo controlled.

A plot of the mean HbA1c values over time by treatment for the ITT analysis set with LOCF is presented in Figure 6.7.

Figure 6.7 – Trial 1573 - Mean HbA1c (%) Over Time by Treatment, ITT with LOCF



Source: Figure 11-1, Trial 1573 report

Reviewer's comments: The figures show that the greatest impact on HbA1c occurred between 8 and 12 weeks with a leveling off of HbA1c that remains stable up to 52 weeks, suggesting persistence of effect of liraglutide. Also, according to these data, the persistence of effect is dose-dependent with the error bars for the 1.2 mg and 1.8 mg not overlapping throughout the trial and possibly appearing more separated at 52 weeks than at 28 weeks. As this was the only 52 week trial these findings may be important in determining which dose(s) should be approved since the other four pivotal studies (all 26 weeks in length) show equivalence in efficacy between the 1.2 and 1.8 mg doses.

6.1.4.1.5 Supplementary Analyses of the Primary Efficacy Variable HbA1c

6.1.4.1.5.1 Percentage of subjects achieving HbA1c targets

The percentage of subjects achieving HbA1c targets (ADA target <7% and AACE target ≤6.5%) were compared between the treatments (Table 6.14).

Table 6.14
Trial 1573 - Summary of subjects reaching HbA1c target of good glycemic control at week 52

	Liraglutide 1.8	Liraglutide 1.2	Glimepiride
	N (%)	N (%)	N (%)
Week 52 HbA1c < 7% (completers)	99 (58.2)	85 (53.5)	50 (33.3)
Week 52 HbA1c <7% (LOCF)	119 (50.9)	101 (42.8)	67 (27.8)

Week 52 HbA1c ≤6.5% (completers)	76 (44.7)	60 (37.7)	30 (20.0)
Week 52 HbA1c ≤6.5% (LOCF)	88 (37.6)	66 (28.0)	39 (16.2)
Source: Table 11-5 Trial 1573 report			

Statistical analysis by logistic regression using the ITT with LOCF population showed that the percentage of subjects achieving ADA and AACE targets was significantly greater in the liraglutide groups as compared to the glimepiride group (Table 6.14 and Table 6.15, respectively). Also, significantly more subjects in the liraglutide 1.8 mg group achieved the ≤ 6.5% target than liraglutide 1.2 mg. Logistic regression analyses using the ITT population with no imputation were similar to the findings for the < 7% target and for the ≤ 6.5% target except that there was no significant difference between the liraglutide 1.8 mg and the liraglutide 1.2 mg treatment groups for the percentage of subjects achieving the ≤ 6.5% target (p=0.0812).

Table 6.14
Trial 1573 - Logistic Regression of Subjects Reaching HbA1c < 7%, ITT (LOCF)

	Comparison after 52 weeks of treatment			
Treatment/comparison	**N**	**Estimates n (%)**	**95% CI**	
Proportions				
Lira 1.8	234	119 (50.9)	44.3 – 57.4	
Lira 1.2	236	101 (42.8)	36.4 – 49.4	
Glimepiride	241	67 (27.8)	22.2 – 33.9	
Odds Ratio		**95% CI**		**p-value**
Lira 1.8 - Glimepiride	2.92	1.94 – 4.39		<.0001
Lira 1.2 - Glimepiride	2.01	1.34 – 3.02		0.0007
Lira 1.8 – Lira 1.2	1.45	0.98 – 2.14		0.0629
Odds ratio is from logistic regression with treatment as fixed effect and baseline HbA1c value as a covariate				
Source: Table 11-6 trial 1573 report				

Table 6.15
Trial 1573 - Logistic Regression of Subjects Reaching HbA1c ≤ 6.5%, ITT (LOCF)

	Comparison after 52 weeks of treatment			
Treatment/comparison	**N**	**Estimates n (%)**	**95% CI**	
Proportions	234	88 (37.6)	31.4 – 44.2	
Lira 1.8	236	66 (28.0)	22.3 – 34.2	
Lira 1.2	241	39 (16.2)	11.8 – 21.5	
Glimepiride				

Odds Ratio		95% CI	p-value
Lira 1.8 - Glimepiride	3.32	2.11 – 5.22	<.0001
Lira 1.2 - Glimepiride	2.04	1.29 – 3.25	0.0025
Lira 1.8 – Lira 1.2	1.62	1.08 – 2.45	0.0208
Odds ratio is from logistic regression with treatment as fixed effect and baseline HbA1c value as a covariate			
Source: Table 11-7 trial 1573 report			

Reviewer's comments: The difference between liraglutide 1.2 mg and 1.8 mg was statistically significant for the AACE goal comparison (which is more stringent) but not the ADA goal comparison (although no corrections were made to avoid type 1 error in this analysis). Further, the difference between liraglutide 1.2 mg and 1.8 mg was not significant in an ANCOVA done with no imputation for the AACE target. Clinically, this suggests there may not be an important difference between 1.2 mg and 1.8 mg as monotherapy in the percent of patients reaching goals of HbA1c lowering.

The logistic regression did not exclude subjects who had HbA1c below target at baseline. However, the mean and range of HbA1c were similar among groups at baseline making the probability that the groups were imbalanced at baseline for the percentage with HbA1c already below goal very small.

6.1.4.1.5.2 Change in HbA1c by Previous Treatment

The Sponsor reports that previous treatment (diet/exercise versus monotherapy) indicated a greater decrease in HbA1c for subjects previously treated with diet and exercise in all treatment groups (Table 6.16).

Table 6.16
Trial 1573 - Summary of Change in HbA1c (%) by Previous Treatment, ITT Population – Treatment by Previous Treatment Interaction

	Lira 1.8		Lira 1.2		Glimepiride	
	Baseline	Change	Baseline	Change	Baseline	Change
Diet/exercise						
N	87	79	91	84	94	91
Mean (SD)	8.59 (1.29)	-1.60 (1.29)	8.43 (1.29)	-1.19 (1.40)	8.59 (1.25)	-0.88 (1.23)
Range						
Monotherapy						
N	159	155	160	152	154	150

b(4)

Mean (SD)	7.97 (0.89)	-0.71 (1.16)	8.04 (0.86)	-0.47 (1.23)	8.01 (0.87)	-0.17 (1.04)	b(4)
Range							
Treatment by Previous Treatment Interaction	**p=0.6747**						
Source: Table 14.2-5-3, Trial 1573 report							

Reviewer's comment: Although the subjects with previous treatment of diet/exercise appear to have a greater decrease in HbA1c, the treatment by previous treatment interaction term p-value is non-significant. Therefore, this reviewer has concerns about a claim of greater efficacy in previous diet/exercise treated patients being included in the product label. Also, the previously treated with monotherapy group had an insufficient washout period (see section 6.1.3.7 methods trial 1573) so the lesser effect in the monotherapy group is possibly due to loss of effect from the prior agent. Another possible explanation for this finding is regression to the mean since glimepiride may also more effective among patients with previous diet/exercise therapy.

6.1.4.1.5.3 Treatment effect on selected subgroups

Further supplementary analyses of HbA1c were performed to investigate the treatment effect on selected subgroups. There was no reported notable effect on change in HbA1c due to country, gender, race, ethnicity, age (as a continuous variable), and BMI (as a continuous variable) (data not shown).

Reviewer's comment: Statistical power is too low to answer the questions regarding demographics from individual trials. These questions are better answered by pooling data from the add-on indication trials, or by newly designed trials.

6.1.4.1.6 Additional Exploratory Analyses Related to HbA1c

The Sponsor conducted the following additional exploratory analyses for HbA1c reduction

- Age categories (<65, ≥ 65, ≥ 70, ≥ 75)
- Disease severity (quartiles of HbA1c, and HbA1c ≤ 9.5% and >9.5%)
- Baseline body weight and BMI categories
- Baseline hypertension and hyperlipidemia (presence or absence)

The Sponsor did not perform formal statistical comparisons between subgroups because patients were not allocated to these subgroups by randomization.

Liraglutide at both 1.8 mg and 1.2 mg doses appeared to reduce HbA1c to a similar extent regardless of age group, although the sample size for the ≥ 75 age group was small (n=40).

A summary of change in HbA1c by baseline quartiles suggested a greater decrease in HbA1c with higher baseline HbA1c in all three treatment groups. This was similar to the result of change in HbA1c by baseline HbA1c categories (HbA1c $\leq$ 9.5% and HbA1c >9.5%).

Reviewer's comment: This finding may reflect regression to the mean and is commonly seen with other anti-diabetic medications.

The inclusion of baseline body weight as covariate in the ANCOVA model used for analysis of HbA1c was similar with respect to superiority of liraglutide to glimepiride for change in HbA1c as compared to the analyses performed without baseline body weight as covariate. This result was similar when BMI was used as a covariate in the ANCOVA model. A summary of change in HbA1c at the end of the study by BMI subgroups indicates slightly less change in HbA1c in the higher BMI subgroup for subjects treated with liraglutide.

A summary of change in HbA1c at the end of the study by whether or not a subject had hypertension or hyperlipidemia indicates that these conditions had no impact on change in HbA1c during the study.

6.1.4.1.7 Secondary efficacy variables for the monotherapy population

6.1.4.1.7.1 Fasting Plasma Glucose (FPG)

All groups had a mean decrease in FPG from baseline to 52 weeks, with the greatest mean decrease occurring in the liraglutide 1.8 mg group (1.42 mmol/L); the liraglutide 1.2 mg group had a decrease of 0.84 mmol/L, and the glimepiride group had the smallest decrease (0.29 mmol/L) (Table 6.17). The mean decreases in FPG values in the liraglutide groups were significantly greater than in the glimepiride group, and the decrease in FPG was significantly greater in the liraglutide 1.8 mg group compared with the 1.2 mg group, as shown by ANCOVA analysis using the ITT population with both LOCF and no imputation. In conventional units, the mean decreases were 25.6 mg/dL for liraglutide 1.8 mg, 15.2 for liraglutide 1.2 mg, and 5.3 for glimepiride. As expected, for completers the decreases were greater at 32.6, 17.2, and 7.2 mg/dL respectively for liraglutide 1.8 mg, liraglutide 1.2 mg, and glimepiride.

Table 6.17
Trial 1573 - ANCOVA of Change in FPG (mg/dL), (LOCF) ITT population

Treatment/comparison	**Estimates**			
Least Square Means	N	LS Mean	SE	
Lira 1.8	230	-25.6	3.5	
Lira 1.2	234	-15.2	3.5	
Glimepiride	242	-5.3	3.3	
Estimated Treatment Differences	**LS Mean**	**95% CI**		**p-value**

Lira 1.8 - Glimepiride	-20.3	-29.1 – (-11.5)	<0.0001
Lira 1.2 - Glimepiride	- 9.9	-18.7 – (-1.1)	0.0270
Lira 1.8 – Lira 1.2	-10.4	-19.2 – (-1.5)	0.0223
The estimates are from an ANCOVA model with treatment, country, and previous OAD treatment as fixed effects and baseline value as a covariate.			
Source: Table 11-15 and EOT Table 14.2-7-7, trial 1573 report			

Reviewer's comment: These data support the primary efficacy indication. One caveat is that these p values are not adjusted for multiple comparisons and no method has been implemented to reduce the type 1 error rate.

The proposed label states that [redacted] These values do not seem to have come from this trial and do not appear to be placebo-corrected. b(4)

6.1.4.1.7.2 Proportion of subjects achieving FPG targets

Logistic regression was performed to determine if there was a difference in the number of subjects achieving target FPG values of 90 – 130 mg/dL in the LOCF-ITT population at 52 weeks of treatment. Subjects treated with liraglutide were significantly more likely to achieve these FPG targets than the subjects treated with glimepiride (Table 6.18). Approximately 41% of subjects in the liraglutide 1.8 mg group and 38% in the liraglutide 1.2 mg group reached the FPG target as compared to 22% in the glimepiride treatment group. There was no significant difference between the two liraglutide doses.

Table 6.18
Trial 1573 - Logistic Regression of Subjects Achieving FPG Target Values, ITT (LOCF)

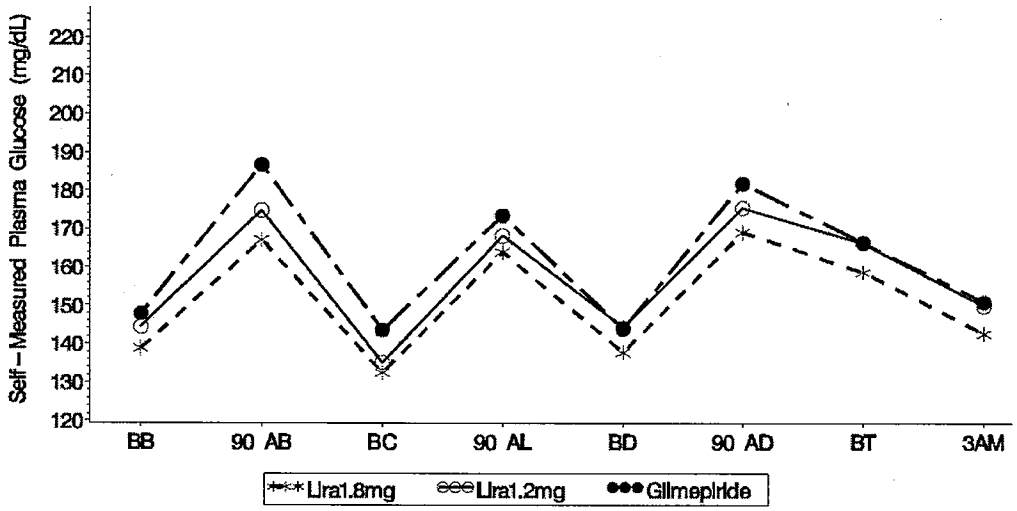
Treatment/comparison	**N**	**Estimates n (%)**	**95% CI**	
Proportions				
Lira 1.8	239	99 (41.4)	35.1 – 48.0	
Lira 1.2	245	92 (37.6)	31.5 – 43.9	
Glimepiride	248	55 (22.2)	17.2 – 27.9	
Odds Ratio		**95% CI**		**p-value**
Lira 1.8 - Glimepiride	3.28	2.12 – 5.07		<.0001
Lira 1.2 - Glimepiride	2.33	1.51 – 3.60		0.0001
Lira 1.8 – Lira 1.2	1.40	0.94 – 2.10		0.0991
Odds ratio is from logistic regression with treatment as fixed effect and baseline FPG value as a covariate				
Source: Table 11-16 trial 1573 report				

Reviewer's comment: **These results are consistent with the analyses of subjects reaching HbA1c targets.**

6.1.4.1.7.3 8-Point Self-Measured Glucose Profiles

This endpoint is discussed here because this variable is mentioned in the proposed product label. At baseline the three groups had similar glucose profiles. [redacted] b(4)

Figure 6.8
Trial 1573 - 8-Point Profiles of Self-Measured Plasma Glucose Profiles at Week 52 (ITT with LOCF analysis population)



Source: Figure 11-5, Trial 1573 report

Reviewer's comment: **The glucose profiles do suggest a glucose decrease at all 8 time points for the liraglutide group, but the figures do not show error bars, and no statistical analysis was reported. Data from glucose profiles have not been included in labeling for other anti-diabetic drugs to date.**

6.1.4.1.7.4 Post-prandial glucose

Post-prandial glucose was patient-measured by glucometer 90 minutes after the start of each meal. The adjusted mean reduction in post prandial glucose due to liraglutide 1.8 mg across all three daily meals was 37.4 mg/dL using the ITT population with LOCF. The reduction was 40.7 mg/dL for completers. ANCOVA showed that liraglutide 1.8 mg was significantly better at lowering mean post-prandial glucose than glimepiride (adjusted mean change -12.9 mg/dL, p=0.0038). There were no other significantly different comparisons (i.e. liraglutide 1.2 mg was not better than glimepiride and liraglutide 1.8 mg was not better than liraglutide 1.2 mg). Similar results were obtained when analyzing completers. When analyzed by meal, there were similar results: the mean decrease in the liraglutide 1.8 mg group was significantly greater than the reduction seen in the glimepiride group, except at lunch. In addition, the decrease for the liraglutide 1.2 mg group was significantly greater than the glimepiride group at breakfast (p=0.03).

Reviewer's comment: These analyses of each meal are not adjusted for multiple comparisons, nor is the study powered for these analyses. The subsequent analyses in this section suffer from a similar problem. In the product label it states "[redacted] These reported values were generated from other trials (the value 31 mg/dL may come from the liraglutide 0.6 mg arm in trial 1572. The 49 mg/dL value seems to come from the liraglutide 1.8 mg+glimepiride arm in trial 1436) and are discussed in section 6.1.4.2.6.2.

b(4)

6.1.4.1.7.5 Body weight

ANCOVA analysis was performed with the ITT analysis set using both the LOCF method (Table 6.19) and 52 week completer values. The LOCF method showed that both liraglutide groups resulted in a significantly greater negative weight change (-2.454 kg for liraglutide 1.8 mg and -2.048 kg for liraglutide 1.2 mg) than the glimepiride group which showed a mean increase in weight of 1.123 kg. The difference between the liraglutide groups was not significant. The 52 week completer analysis showed similar results.

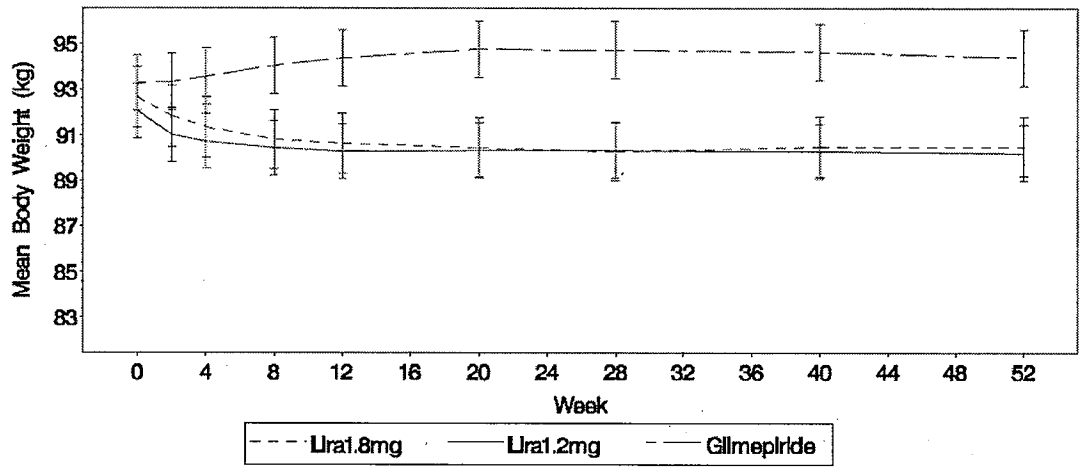
Table 6.19
Trial 1573 - ANCOVA of Change in Body Weight (kg), ITT population with LOCF

Treatment/comparison	**Estimates**			
Least Square Means	N	LS Mean	SE	
Lira 1.8	240	-2.454	0.282	
Lira 1.2	245	-2.048	0.281	
Glimepiride	248	1.123	0.269	
Estimated Treatment Differences	**LS Mean**	**95% CI**		**p-value**

Lira 1.8 - Glimepiride	-3.577	-4.281 – (-2.873)	<0.0001
Lira 1.2 - Glimepiride	-3.171	-3.872 – (-2.471)	<0.0001
Lira 1.8 – Lira 1.2	-0.406	-1.111 – 0.299	0.2584
The estimates are from ANCOVA model with treatment, country and previous OAD treatment as fixed effects and baseline value as a covariate			
Source: Table 11-9, trial 1573			

Plots of the LOCF values of mean body weight over time are presented in Figure 6.9. Weight loss in the liraglutide treatment groups primarily occurred in the first 12 weeks, with a slight increase in the later part of the trial. Body weight in the glimepiride group increased slightly during the first 20 weeks, and then remained steady throughout the trial.

Figure 6.9 - Trial 1573 - Mean Body Weight over Time by Treatment, ITT (LOCF)



Source: Figure 11-2, Trial 1573 report

Percentage change in body weight was -2.5 % for the liraglutide 1.8 mg group, -2.2 % for the liraglutide 1.2 mg group and +1.3 % for the glimepiride group. In the liraglutide group, 24.4 % of subjects gained weight, 47.2% lost 0-5% of their body weight, 20.7% lost 5-10% of their body weight, and 5.3% lost more than 10% of their body weight. The percentages were similar in the liraglutide 1.2 mg group (26.3%, 49.8%, 16.7%, and 4.8% in each of the four categories of weight change, respectively). A greater percentage of subjects achieved a weight loss of 5% or more in the liraglutide 1.8 mg group vs. the glimepiride group (OR 6.6, CI 3.5 – 12.3). A greater percentage of subjects achieved a weight loss of 5% or more in the liraglutide 1.2 mg group vs. the glimepiride group as well (OR 5.1, CI 2.7 – 9.6). A greater percentage of subjects achieved a weight loss of 10% or more in the liraglutide 1.8 mg group vs. the glimepiride group (OR 7.1, CI 1.6 – 31.6), and a greater percentage of subjects achieved a weight loss of 10% or more in the liraglutide 1.2 mg group vs. the glimepiride group (OR 6.4, CI 1.4 – 29.0). There was no difference in the percentage of subjects who lost 5% or more or 10% or more of body weight between the two liraglutide treatment groups.

Reviewer's comment: While the weight change in the liraglutide groups was statistically significantly different from the comparator (mostly because the comparator induced weight gain), the absolute percentage weight loss in the liraglutide groups is less than that seen with already FDA approved drugs for obesity. The summary of distribution of body weight change percentage showed that about a quarter of subjects actually gained weight while on liraglutide therapy and about half lost less than 5% of body weight.

Further analyses were performed to determine if nausea contributed to the greater weight loss seen in the liraglutide groups. Subjects were categorized based upon the number of days nausea was reported in the early phase of the trial (up to 8 weeks of treatment) and in the late phase (after 8 weeks of treatment). The Sponsor reports that slightly greater weight loss was observed in the subjects who experienced nausea, but all liraglutide-treated groups demonstrated a mean weight loss.

6.1.4.1.7.6 Measures of beta-cell function and insulin resistance

Five endpoints were related to β-cell function and insulin secretion (fasting insulin, fasting C-peptide, pro-insulin to insulin ratio, HOMA index of β-cell function, and HOMA index of insulin resistance).

Fasting insulin values from baseline to end of treatment showed a decrease in the liraglutide group compared with the glimepiride group (adjusted mean difference -22.7 pmol/L, p=0.025). There were no differences in C-peptide values among treatment groups (all were decreased). The pro-insulin to insulin ratio (calculated from fasting insulin and fasting pro-insulin) decreased in both liraglutide treatment groups, and increased slightly in the glimepiride group. However, ANCOVA analysis of the estimated mean changes in the ratios demonstrated that the differences between the liraglutide groups and the glimepiride group were not statistically significant.

B-cell function was assessed by HOMA. ANCOVA analysis demonstrated no difference between the treatment groups. Insulin resistance as measured by HOMA-IR was reduced in the liraglutide treatment groups compared with the glimepiride group in an ANCOVA model using the LOCF –ITT population (lira 1.8 vs. glimepiride adjusted mean difference -2.2%, 95% CI -3.5 – (-0.9), p=0.0011, lira 1.2 vs. glimepiride adjusted mean difference -1.5%, 95% CI -2.8 – (-0.2), p=0.0249, lira 1.8 vs. lira 1.2 adjusted mean difference not significant). Similar results were observed in an analysis performed with Week 52 values, although the differences were not significant.

Reviewer's comment: Using the completer-ITT (i.e. no imputation) analysis set the results were not statistically significant calling into question the robustness of these efficacy results. Measures of beta-cell function and insulin resistance, including HOMA, have not yet risen to the level of inclusion in labeling primarily because they are not fully validated surrogates.

6.1.4.1.7.7 Blood Pressure

Observed mean systolic blood pressure (SBP) values decreased from baseline to end of treatment in all three treatment groups. The decreases occurred after 2-4 weeks of treatment and were maintained to the end of the treatment period. ANCOVA, including baseline value as a covariate, of change in SBP with the LOCF-ITT analysis set showed that liraglutide lowered SBP significantly more than glimepiride. The liraglutide 1.8 mg group had an adjusted mean reduction in SBP of 3.64 mmHg (from a mean baseline of 128 mmHg), the liraglutide 1.2 mg group a mean reduction of 2.12 mmHg (baseline: 128 mmHg) and the glimepiride group a mean reduction of 0.69 mmHg (baseline: 130 mmHg). The difference between the reduction in SBP from liraglutide 1.8 mg and glimepiride was statistically significant (2.95 mmHg, p = 0.0117). Using the completer-ITT (i.e. no imputation) analysis set the results were not statistically significant (mean adjusted difference between liraglutide 1.8 and glimepiride -2.72, 95% CI -5.5 – 0.03, p=0.05). For diastolic BP there were no differences between treatment groups.

The proportions of subjects reaching targets of a diastolic blood pressure below 80 mmHg and a SBP below 130 mmHg was compared between the liraglutide groups and the glimepiride group using a chi-square test. Using LOCF, 42.1% of subjects in the liraglutide 1.8 mg group, 41.2% of subjects in the liraglutide 1.2 mg group, and 34.7% of subjects in the glimepiride group reached this target. These differences were not statistically significant and the results were similar when performing the analysis on Week 52 values.

Reviewer's comment: **Using the completer-ITT (i.e. no imputation) analysis set the results were not statistically significant calling into question the robustness of these blood pressure efficacy results. However, in this case there appears to be a trend comparing liraglutide 1.8 mg to glimepiride (p=0.05). On the other hand, using a dichotomous variable (subjects reaching targets of diastolic BP below 80 mmHg and a systolic BP below 130 mmHg) and chi-square test, there were still no differences among treatment groups.**

The data listings of concomitant medication that may have an effect on blood pressure, medications known as anti-diuretics, and medications for edema were not presented. Therefore, possible confounding by anti-hypertensive medications added or adjusted during the trial cannot be ruled out.

6.1.4.1.7.8 Fasting lipid profile

There were no clinically important changes in total cholesterol over the 52 week study period and no significant differences among treatment groups.

Reviewer's comment: **Similar data were seen in the other trials that are discussed in the next sections with some trials showing improvements in one or two lipid related variables but no overall consistent picture of lipid improvements. Since a change in lipid profile is not the**

proposed indication of liraglutide and changes in lipid profile are not discussed in labeling, this variable will *not* be discussed in the next sections (the sections presenting the efficacy data for the other phase 3 trials.)

6.1.4.1.7.9 Metabolic Syndrome Prevalence

The proportion of subjects having metabolic syndrome at the end of the trial were compared between the liraglutide groups and glimepiride group using a chi-square test. At baseline, 72.0% of the subjects in the liraglutide 1.8 mg group, 79.6%% in the liraglutide 1.2 mg group, and 76.4% in the glimepiride group were classified as having metabolic syndrome. At the end of trial, 66.5% of the subjects in the liraglutide 1.8 mg group, 73.4% in the liraglutide 1.2 mg group, and 78.4% in the glimepiride group were classified as having metabolic syndrome. The Sponsor did not report which component(s) of the metabolic syndrome drove these differences. The final proportion of subjects with metabolic syndrome in the liraglutide 1.8 mg group was significantly lower than the glimepiride group (p=0.004), but the liraglutide 1.2 mg group did not reach a statistically significant difference from the glimepiride group (0.2) Also there was no difference between the two liraglutide doses (p=0.1).

Reviewer's comment: The label states that liraglutide reduces the occurrence of metabolic syndrome. Note that this finding is not dose dependent and that this analysis for this secondary endpoint was not corrected for type 1 error. Also, this finding was not consistently found across the Phase 3 program as will be discussed in later sections.

6.1.4.2 Combination therapy trials with one OAD (Trials 1572 and 1436)

Trials 1572 and 1436 evaluated 26 weeks of treatment with liraglutide in combination with one OAD (metformin in Trial 1572 and glimepiride in Trial 1436). Both trials assessed three liraglutide dose levels (0.6, 1.2 and 1.8 mg), compared with placebo (the OAD alone) and compared with another OAD (active comparator). In Trial 1572 the active comparator was glimepiride (+metformin), and in Trial 1436 it was rosiglitazone (+glimepiride).

6.1.4.2.1 Demographic features of the combination therapy with one OAD population

The screening demographic and diabetes-related characteristics of the randomized subjects in the pivotal add-on with one OAD studies are summarized in table 6.20.

The treatment arms within each trial were generally well matched with regard to baseline demographics. The two trials also had mostly similar baseline characteristics between them. Trial 1572 studied a total of 1091 subjects (58% male and 42 % female) subjects, and trial 1436 studied a total of 1041 subjects (49.4% male and 50.6% female); the percentage of men was higher in trial 1542. The mean age of

subjects was similar in trials 1572 and 1436 (mean age 57 and 56.1 years, respectively), the mean BMI in trial 1572 was 31 kg/m^2 and in trial 1436 the mean BMI was 29.9 kg/m^2, also similar.

In trial 1572 the mean HbA1c was 8.4% with a mean duration of diabetes of 7.4 years. Similarly, in trial 1436 the mean HbA1c was 8.4% with a mean duration of diabetes of 7.9 years. The racial distribution was somewhat different between the two trials. In trial 1572, the majority of subjects (87%) were white with 9% of subjects being Asian or Pacific Islanders. In trial 1436 the majority of subjects (64.4%) were white, albeit a smaller percentage of white subjects than in trial 1572, while 32.4% of subjects were Asian/Pacific Islanders and 2.8% of subjects were black. In both trials approximately one-third of the randomized subjects had been using OAD monotherapy prior to participation in the trial, while the other two-thirds had been using OAD combination therapy. [note: prior OAD (monotherapy vs. combination therapy) was a randomization stratum in both trials]. At screening BMI appeared similar across groups and between the two trials.

Table 6.20 –
Screening Characteristics and Demographic Features of all Randomized Subjects in the add-on therapy with one OAD population

	Trial 1572 – 26 weeks					**Trial 1436 – 26 weeks**				
	Lira0.6 + Met	**Lira 1.2 + Met**	**Lira 1.8 + Met**	**Pbo + Met**	**Met + Glim**	**Lira0.6 +Glim**	**Lira1.2 +Glim**	**Lira1.8 +Glim**	**Pbo + Glim**	**Rosi +Glim**
All randomized subjects (N)	242	241	242	122	244	233	228	234	114	232
Sex N (%)										
Male	151 (62.4)	129 (53.5)	142 (58.7)	73 (59.8)	140 (57.4)	126 (54.1)	102 (44.7)	124 (53.0)	53 (46.5)	109 (47.0)
Female	91 (37.6)	112 (46.5)	100 (41.3)	49 (40.2)	104 (42.6)	107 (45.9)	126 (55.3)	110 (47.0)	61 (53.5)	123 (53.0)
Age (years)										
Mean (SD)	56.0 (10.5)	57.2 (9.3)	56.8 (9.4)	56.2 (9.4)	57.4 (8.8)	55.7 (9.9)	57.7 (9.0)	55.6 (10.0)	54.7 (10.0)	56.0 (9.8)
Race N (%)										
White	202 (83.5)	211 (87.6)	214 (88.4)	107 (87.7)	216 (88.5)	154 (66.1)	143 (62.7)	145 (62.0)	77 (67.5)	151 (65.1)
Black	4 (1.7)	9 (3.7)	5 (2.1)	3 (2.5)	5 (2.0)	7 (3.0)	7 (3.1)	9 (3.8)	1 (0.9)	5 (2.2)
Asian/Pacific Islander	31 (12.8)	19 (7.9)	18 (7.4)	9 (7.4)	21 (8.6)	72 (30.9)	78 (34.2)	79 (33.8)	35 (30.7)	73 (31.5)
American Indian – Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	5 (2.1)	2 (0.8)	5 (2.1)	3 (2.5)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
						0 (0.0)	0 (0.0)	1 (0.4)	1 (0.9)	3 (1.3)
BMI (kg/m2)										
Mean (SD)	30.5 (4.8)	31.1 (4.8)	30.9 (4.6)	31.6 (4.4)	31.2 (4.6)	30.0 (5.0)	29.8 (5.1)	30.0 (5.1)	30.3 (5.4)	29.4 (4.8)
Duration of diabetes (years)										
Mean (SD)	7.0	6.8 (4.9)	7.8 (5.2)	7.9	7.8 (5.3)	7.7 (5.0)	8.1 (5.5)	7.8	7.8	8.0

	(4.8)			(5.9)				(5.6)	(5.3)	(5.6)
Previous anti-diabetic treatment, N (%)										
Monotherapy	81 (33.5)	91 (37.8)	83 (34.3)	41 (33.6)	89 (36.5)	71 (30.5)	71 (31.1)	63 (26.9)	37 (32.5)	73 (31.5)
Combination therapy	161 (66.5)	150 (62.2)	159 (65.7)	81 (66.4)	156 (63.5)	162 (69.5)	157 (68.9)	171 (73.1)	77 (67.5)	159 (68.5)
HbA1c at screening (%)										
Mean (SD)	8.4 (0.9)	8.3 (0.9)	8.3 (0.9)	8.4 (1.0)	8.4 (0.9)	8.4 (0.9)	8.4 (0.9)	8.5 (0.9)	8.4 (0.9)	8.3 (0.9)
Source: [Study 1572 Table 11-1], [Study 1436 Table 11-2]										

The mean baseline values of selected efficacy parameters (HbA1c, FPG, and blood pressure) of the randomized population in the add-on with one OAD studies are summarized in table 6.21. These values were comparable between all treatment arms.

Table 6.21
Selected Baseline Efficacy Parameters Subjects in the add-on therapy with one OAD population

	Trial 1572 – 26 weeks					**Trial 1436 – 26 weeks**				
	Lira 0.6 + Met	**Lira 1.2 + Met**	**Lira 1.8 + Met**	**Pbo + Met**	**Met + Glim**	**Lira 0.6 +Glim**	**Lira1.2 +Glim**	**Lira1.8 +Glim**	**Pbo +Glim**	**Rosi +Glim**
All randomized subjects (N)	242	241	242	122	244	233	228	234	114	232
HbA1c (%)										
N	240	238	240	122	239	227	228	229	111	229
Mean (SD)	8.4 (0.9)	8.3 (1.0)	8.4 (1.0)	8.4 (1.1)	8.4 (1.0)	8.4 (1.0)	8.5 (1.1)	8.5 (0.9)	8.4 (1.0)	8.4 (1.0)
Fasting plasma glucose (mg/dL)										
N	239	237	236	117	237	231	224	229	111	229
Mean (SD)	10.2 (2.4)	9.9 (2.3)	10.1 (2.3)	10.0 (2.3)	10.0 (2.6)	10.0 (2.4)	9.8 (2.7)	9.7 (2.4)	9.5 (2.0)	9.9 (2.5)
Diastolic BP (mmHg)										
N	242	240	242	122	243	233	228	233	114	232
Mean (SD)	79.9 (8.2)	79.9 (9.5)	79.4 (7.7)	80.7 (9.0)	79.5 (8.3)	80.1 (8.3)	80.1 (8.8)	80.6 (8.6)	80.7 (8.9)	80.1 (8.4)
Systolic BP (mmHg)										
N	242	240	242	122	243	233	228	233	114	232
Mean (SD)	131	132	131	135	132 (15.9)	130.9	133.1	132.4	131.3	132.5

	(13.8)	(14.4)	(14.1)	(15.8)		(15.9)	(15.2)	(16.1)	(15.3)	(14.6)

Source: [Study 1572 Table 11-1], [Study 1436 Table 11-2]

6.1.4.2.2 Participation and withdrawals in the combination therapy population (disposition of subjects)

Participation and withdrawals in the pivotal add-on with one OAD treatment groups are summarized in table 6.22. At 26 weeks, the completion rates for the liraglutide groups (78.9-91.0%) were higher than the control groups (60.7-72.8%) and similar to the active comparator groups (83.6-86.1%). As expected, withdrawal rates for these 26-week trials are lower than withdrawal rates for the 52-week monotherapy trial. Withdrawals due to adverse events are discussed in Dr. Mahoney's Clinical Safety Review. Withdrawals due to ineffective therapy were higher in the control groups compared to the liraglutide groups and to the active comparator groups.

Approximately 25-30% of the withdrawn subjects were withdrawn from the trial during the first month and the overall withdrawal rate decreased over time. The withdrawal rate over time showed a similar trend for all treatment groups.

Reviewer's comment: See Dr. Derr's statistical review for more comment on the effect of withdrawals on the efficacy evaluation.

Table 6.22
Subject Disposition (add-on therapy with one OAD trials) (randomized subjects)

	Trial 1572 26 weeks					Trial 1436 26 weeks				
	Lira0.6 +met	**Lira1.2 +met**	**Lira1.8 +met**	**Met**	**Met +glim**	**Lira0.6 +glim**	**Lira1.2 +glim**	**Lira1.8+glim**	**Glim**	**Rosi +glim**
Total randomized (N)	242	241	242	122	244	233	228	234	114	232
Exposed	100%	99.6%	100%	99.2%	99.2%	100%	100%	100%	100%	99.6%
Withdrawals	14.0%	18.3%	21.1%	39.3%	13.9%	10.7%	14.0%	9.0%	27.2%	16.4%
Adverse Events	4.5%	9.5%	12.0%	1.6%	3.3%	2.1%	4.8%	3.8%	5.3%	3.0%
Ineffective therapy	7.9%	3.3%	5.4%	23.8%	3.7%	5.2%	3.5%	3.0%	17.5%	6.9%
Non-compliance with protocol	0.8%	1.7%	1.7%	3.3%	2.0%	1.3%	2.2%	1.3%	1.8%	2.6%
Other	0.8%	3.7%	2.1%	10.7%	4.9%	2.1%	3.5%	0.9%	2.6%	3.9%
Completers	86.0%	81.7%	78.9%	60.7%	86.1%	89.3%	86.0%	91.0%	72.8%	83.6%
PP analysis set	80.2%	77.6%	74.8%	58.2%	82.8%	81.1%	82.0%	86.3%	64.9%	78.4%

Source: [Trial 1572 Table 10-1], [Trial 1436 Table 10-1]

6.1.4.2.3 Adequacy of comparator drug dosages used in the key add-on with one OAD studies

6.1.4.2.3.1 Trial 1572

The comparator in this study was glimepiride 4 mg qd. Additionally subjects were on background therapy of 1.5 – 2 g metformin daily.

Reviewer's comment: Although the maximal allowed dose of glimepiride is 8 mg qd, 4 mg qd is close to the maximally effective dose. Therefore, the dose of 4 mg qd is adequate. The background metformin exposure was also adequate.

6.1.4.2.3.2 Trial 1436

The comparator in this study was rosiglitazone 4 mg qd. Additionally, subjects were on background therapy of 2-4 mg glimepiride qd.

Reviewer's comment: Rosiglitazone 8 mg qd is the maximal FDA approved dose. Therefore, in this trial the highest proposed doses of liraglutide are being compared to the half maximal dose of rosiglitazone calling into question the adequacy of the active comparator dosage in this trial. The choice of active comparator dose was based on manufacturer's recommendations and the approved doses at the time in the regions where the trial was conducted (21 non-U.S. sites). This explains the difference in rosiglitazone doses between Trial 1436 (4 mg/day) and Trial 1574 (8 mg/day) (The design of Trial 1574 is discussed in section 6.1.3.8.3) However, use of the full 8 mg per day dose of rosiglitazone is often limited in clinical practice by side effects such as edema and weight gain limiting the usefulness of the highest dose. Therefore, rosiglitazone 4 mg daily as a comparator may have real world significance.

Background glimepiride exposure was adequate.

6.1.4.2.4 Primary efficacy variable for the add-on with one OAD population

Analyses of the changes in HbA1c from baseline to the end of the trials for liraglutide groups compared with placebo and active comparator groups (ITT with LOCF) for the add-on with one OAD populations are summarized in table 6.23. For the HbA1c endpoint, analyses using the ITT population with LOCF and the PP population were consistent across studies, supporting robustness of results. Unless otherwise noted, this section presents efficacy data using the ITT population with the LOCF method.

Table 6.23
Analysis of HbA1c (%) Change from Baseline at 26 weeks (add-on therapy with one OAD trials)

				Placebo			#Comparator		
	N	Baseline HbA1c unadjusted mean (SD)	*Adjusted mean change in HbA1c (SEM)	Mean difference from comparator	95% CI	p value	Mean difference from comparator	95% CI	p value
Trial 1572 Metformin add-on									
Lira 0.6	239	8.4 (0.9)	-0.70 (0.067)	-0.78	-0.99 ; -0.57	<.0001	0.29	0.12 ; 0.46	0.0009
Lira 1.2	232	8.3 (1.0)	-0.97 (0.069)	-1.06	-1.27 ; -0.85	<.0001	0.01	-0.16 ; 0.19	0.8775
Lira 1.8	236	8.4 (1.0)	-1.00 (0.066)	-1.09	-1.30 ; -0.88	<.0001	-0.02	-0.19 ; 0.15	0.8592
Placebo	120	8.4 (1.0)	0.08 (0.090)						
Comparator	234	8.4 (1.0)	-0.99 (0.068)						
Trial 1436 Glimepiride add-on									
Lira 0.6	224	8.4 (1.0)	-0.60 (0.071)	-0.83	-1.07 ; -0.60	<.0001	-0.16	-0.35 ; 0.02	0.0857
Lira 1.2	223	8.5 (1.1)	-1.08 (0.072)	-1.31	-1.54 ; -1.08	<.0001	-0.64	-0.82 ; -0.45	<.0001
Lira 1.8	226	8.5 (0.9)	-1.13 (0.072)	-1.36	-1.60 ; -1.13	<.0001	-0.69	-0.88 ; -0.51	<.0001
Placebo	107	8.4 (1.2)	0.23 (0.100)						
Comparator	224	8.4 (1.0)	-0.44 (0.071)						

Comparator in trial 1572 is glimepiride and in trial 1436 is rosiglitazone
The p-values correspond to a two-sided test for superiority on a 5% significant level (statistical significance for p <0.05).
*The change in HbA1c was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline HbA1c as covariate
Test for non-inferiority with switch to superiority if non-inferiority is shown.
Non-inferiority is concluded if the upper limit of the 95% confidence interval for the treatment difference is below 0.4% i.e. non-inferiority to comparator is shown for all liraglutide groups, except for the 0.6mg liraglutide group in trial 1572.
A hierarchical testing procedure is used.

Source: Tables 3-2, 3-3 Summary of Clinical Efficacy

In summary, subjects treated with liraglutide at doses of 0.6, 1.2 or 1.8 mg plus one additional OAD improved glycemic control as indicated by a significant decrease in their HbA1c. The placebo groups had small increases in HbA1c (0.08% to 0.23%) over the 26 week treatment periods despite the background therapy. In study 1572, relative to placebo+metformin, liraglutide 0.6 mg+metformin lowered HbA1c by -0.78%, liraglutide 1.2 mg+metformin lowered HbA1c by -1.06%, and liraglutide

1.8 mg+metformin lowered HbA1c -1.09%. In study 1436, relative to placebo+glimepiride, liraglutide 0.6 mg+glimepiride lowered HbA1c by -0.83%, liraglutide 1.2 mg+glimepiride lowered HbA1c by -1.31%, and liraglutide 1.8 mg+glimepiride lowered HbA1c -1.36%.

ANCOVA showed that in both trials, liraglutide in combination with one OAD was superior to treatment with the same OAD alone (i.e. the placebo-controlled arms of the study) (all $p<.0001$). The results for the active comparator arms were as follows: In trial 1572, liraglutide at doses of 1.2 and 1.8 mg in combination with metformin was non-inferior to treatment with metformin+glimepiride. In trial 1436, liraglutide at doses of 1.2 and 1.8 mg in combination with glimepiride was superior to treatment with glimepiride + rosiglitazone, and liraglutide 0.6 mg in combination with glimepiride was non-inferior to glimepiride + rosiglitazone.

Reviewer's comments: **These trials support efficacy of liraglutide 1.2 mg and 1.8 mg over placebo when added to one OAD.**

Concerning clinical importance: The HbA1c reductions for the 1.2 and 1.8 mg doses were greater than 1% over placebo in both trials. Therefore, when added to one OAD liraglutide can be expected to have an important clinical impact.

Concerning dose selection: Both trials show liraglutide at the higher two doses outperforming the 0.6 mg dose. However, the higher two doses seem roughly equally effective based on the HbA1c % reduction relative to placebo in both trials. Note: among the 5 major efficacy trials reviewed in this document, only the monotherapy trial showed liraglutide 1.8 mg to be superior to 1.2 mg.

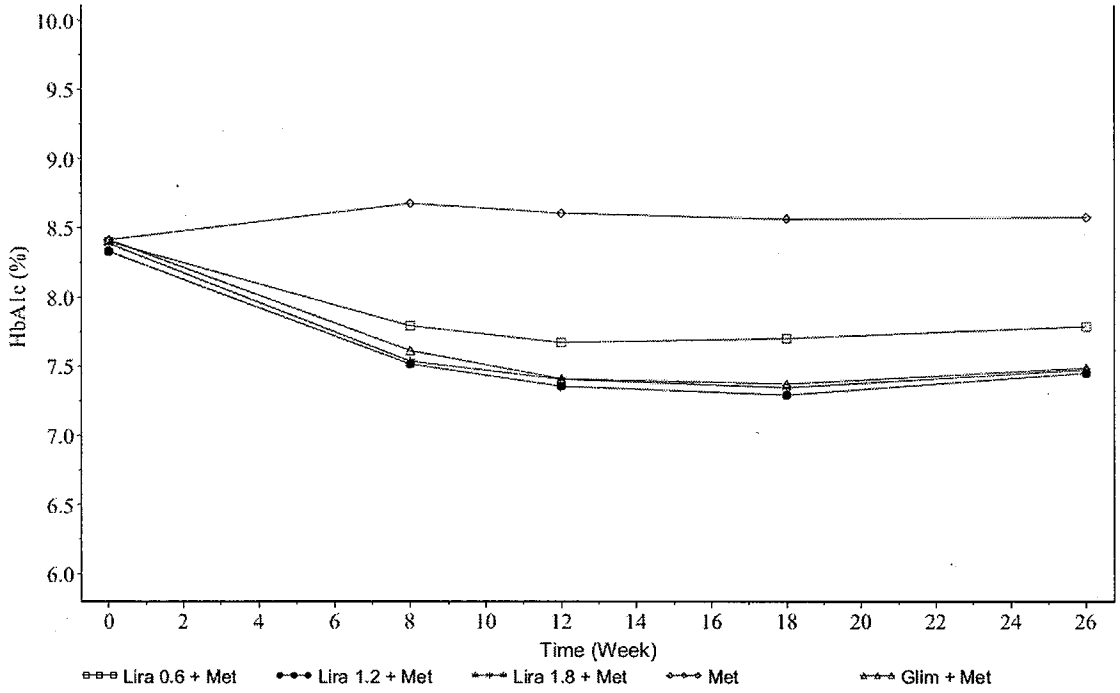
Concerning the active comparator arms: Liraglutide added to metformin was non-inferior to glimepiride added to metformin, and at the 0.6 mg dose liraglutide was slightly worse than glimepiride added to metformin. Liraglutide at both the 1.2 and 1.8 mg doses added to glimepiride was better than rosiglitazone added to glimepiride. However, the rosiglitazone dose in this trial was only 4 mg qd. Therefore, one should be cautious in concluding that liraglutide is superior to rosiglitazone given at the maximal FDA approved dose of 8 mg. Based on these two trials, taking into account the dose selection of the active comparator rosiglitazone, this reviewer concludes that liraglutide is at least non-inferior to both of the active comparators at an HbA1c margin of 0.4% when added to one OAD.

A plot of mean HbA1c by treatment and week for the treatment groups for trial 1572 is shown in 6.10 and for trial 1436 in figure 6.11. Overall, in the liraglutide and active comparator groups, the decrease in HbA1c was evident after 8–12 weeks of treatment in both trials.

In trial 1572 there was a decrease in mean HbA1c from baseline to 12 weeks of treatment in all 3 liraglutide groups and in the glimepiride+metformin group. In the metformin group, HbA1c increased from baseline to 8 weeks of treatment and then decreased to close to the baseline level at 12 weeks of treatment. In the period from 12 weeks of treatment to end of treatment, mean HbA1c remained essentially unchanged in all 5 treatment groups.

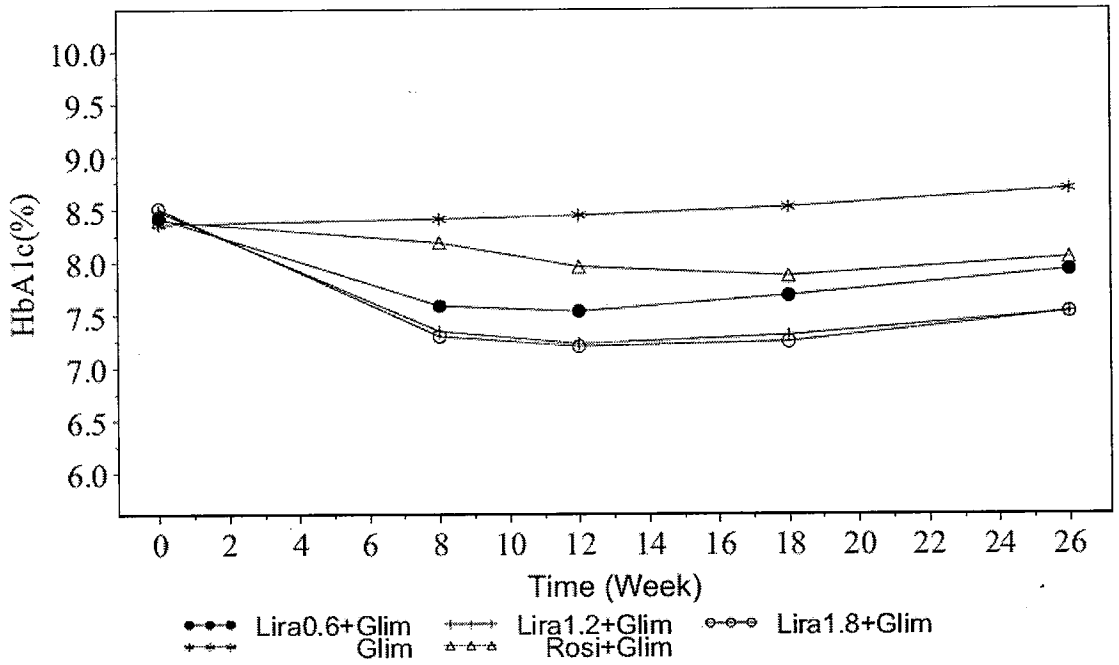
In trial 1436 there was a decrease in mean HbA1c from baseline to 12 weeks of treatment in all 3 liraglutide treatment groups and in the rosiglitazone+glimepiride treatment group, with the greatest decrease seen for liraglutide 1.2 mg+glimepiride and liraglutide 1.8 mg+glimepiride treatment. In the period from 12 weeks of treatment to end of treatment, mean HbA1c remained relatively unchanged to slightly increased in the 3 liraglutide treatment groups. In the rosiglitazone+glimepiride treatment group HbA1c appeared to continue to improve past 12 weeks, although a slight increase in mean HbA1c was seen at the end of the trial. No change in mean HbA1c during the trial was apparent in the glimepiride treatment group.

Figure 6.10 - Trial 1572 Plot of Mean HbA1c by Treatment and Week (LOCF, ITT)



Source: Figure 11-1, Trial 1572 report

Figure 6.11 - Trial 1436 Plot of Mean HbA1c by Treatment and Week (LOCF, ITT)



Source: Figure 11-1, Trial 1436 report

Reviewer's comment: The HbA1c lowering effect of the 1.2 mg and 1.8 mg liraglutide doses appear to be maintained until the end of the 26 week trial although somewhat less so in trial 1436. These findings suggest sustainability of the liraglutide effect when added to one OAD.

6.1.4.2.5 Supplementary Analyses of the Primary Endpoint HbA1c

6.1.4.2.5.1 Percentage of subjects achieving HbA1c targets

The percentages of subjects reaching the pre-defined HbA1c targets (ADA target < 7% and AACE target ≤ 6.5%) at Week 26 are summarized in Table 6.24 and Table 6.25, respectively. In Trial 1572, significantly more subjects reached both the ADA and the AACE targets with liraglutide (0.6, 1.2 or 1.8 mg) combined with metformin than with metformin alone. Similarly, in Trial 1436, significantly more subjects reached both the ADA and the AACE targets with liraglutide + glimepiride than with glimepiride alone.

For Trial 1572, the percentage of subjects reaching the ADA target with liraglutide 1.2 and 1.8 mg (+ metformin) did not differ significantly from the glimepiride + metformin group. With liraglutide 0.6 mg + metformin significantly fewer subjects reached the target compared with the glimepiride + metformin group. The same pattern was observed with respect to the percentage of subjects reaching the AACE target. For Trial 1436, the percentage of subjects achieving the ADA target with liraglutide 1.2 and 1.8 mg (+ glimepiride) was significantly higher than with rosiglitazone + glimepiride. With liraglutide at the 0.6 mg dose there was no difference. The same pattern was observed with respect to the percentage of subjects reaching the AACE target.

Reviewer's comment: These results appear similar to the primary efficacy variable in that liraglutide + OAD was better than placebo + OAD for both trials, but with the active comparators, liraglutide added to metformin was not better than glimepiride added to metformin, and at the 0.6 mg dose was actually slightly worse than metformin + glimepiride, while liraglutide at both the 1.2 and 1.8 mg doses added to glimepiride was better than rosiglitazone added to glimepiride. The same caveat that was mentioned in section 6.1.4.2.3.2 applies regarding the comparison with half maximal rosiglitazone dose.

Although no statistical comparison of liraglutide 1.2 mg vs. liraglutide 1.8 mg was reported, the percentage of subjects reaching the ADA target in both trials was higher in the liraglutide 1.8 mg group compared with the 1.2 mg group lending support to the conclusion of greater efficacy for the 1.8 mg dose over the 1.2 mg dose when added on to one OAD. For the AACE target this distinction was less clear since in trial 1436 the percentages reaching target for the 1.8 mg group and the 1.2 mg group were similar.

Table 6.24
Percentage of Subjects Reaching ADA Target (HbA1c < 7%) at 26 weeks (add-on therapy with one OAD trials)
Logistic Regression

				Placebo			Comparator		
	N	% of Subjects Reaching Target	(SEM)	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Trial 1572 Metformin add-on									
Lira 0.6	67	28.03	0.144	4.13	2.05 ; 8.30	<.0001	0.63	0.41 ; 0.97	0.0357
Lira 1.2	82	35.34	0.137	5.86	2.92 ; 11.72	<.0001	0.89	0.58 ; 1.36	0.5947
Lira 1.8	100	42.37	0.132	8.97	4.48 ; 17.94	<.0001	1.36	0.90 ; 2.07	0.1467
Placebo	13	10.83	0.294						
Comparator	85	36.32	0.136						
Trial 1436 Glimepiride									

add-on									
Lira 0.6	54	24.11	0.156	5.17	2.26 ; 11.81	<.0001	1.21	0.75 ; 1.96	0.4350
Lira 1.2	77	34.53	0.141	10.10	4.44 ; 22.99	<.0001	2.37	1.48 ; 3.79	0.0003
Lira 1.8	94	41.59	0.135	15.96	7.01 ; 36.36	<.0001	3.74	2.35 ; 5.97	<.0001
Placebo	8	7.48	0.368						
Comparator	49	21.88	0.162						
Comparator in trial 1572 is glimepiride and in trial 1436 is rosiglitazone The estimates are obtained from a logistic regression with treatment as fixed effect and baseline HbA1c value as a covariate.									
Source: Table 3-6, Summary of Clinical Efficacy									

Table 6.25
Percentage of Subjects Reaching AACE Target (HbA1c ≤ 6.5%) at 26 weeks (add-on therapy with one OAD trials)
Logistic Regression

				Placebo			Comparator		
	N	**% of Subjects Reaching Target**	**(SEM)**	**Odds Ratio**	**95% CI**	**p value**	**Odds Ratio**	**95% CI**	**p value**
Trial 1572 Metformin add-on									
Lira 0.6	27	11.30	0.204	3.62	1.28; 10.30	0.0157	0.40	0.23; 0.69	0.0009
Lira 1.2	46	19.83	0.165	7.19	2.60; 19.93	0.0001	0.80	0.49; 1.29	0.3566
Lira 1.8	58	24.58	0.151	10.5	3.82; 28.97	<.0001	1.16	0.73; 1.86	0.5223
Placebo	5	4.17	0.457						
Comparator	52	22.22	0.157						
Trial 1436 Glimepiride add-on									
Lira 0.6	28	12.50	0.202	4.67	1.53; 14.28	0.0068	1.43	0.76; 2.69	0.2680
Lira 1.2	48	21.52	0.163	10.5	3.50; 31.36	<.0001	3.20	1.77; 5.80	0.0001
Lira 1.8	48	21.24	0.163	11.7	3.90; 35.21	<.0001	3.59	1.98; 6.50	<.0001
Placebo	4	3.74	0.510						
Comparator	22	9.82	0.225						
Comparator in trial 1572 is glimepiride and in trial 1436 is rosiglitazone The estimates are obtained from a logistic regression with treatment as fixed effect and baseline HbA1c value as a covariate.									
Source: Table 3-7, Summary of Clinical Efficacy									

6.1.4.2.5.2 Treatment effect on selected subgroups

All analyses were performed using the ITT population with LOCF to test for significant interactions.

Treatment by Pre-Treatment Interaction

In both trials the decrease in HbA1c from baseline to end of treatment in all groups was greater in those subjects having received previous OAD monotherapy, representing an add-on scenario, compared with those subjects having received previous OAD combination therapy, representing a switch scenario. Note: in the metformin group, there was a lowering in HbA1c in subjects having received OAD monotherapy, while there was an increase in HbA1c in subjects having received OAD combination therapy.

Reviewer's comment: This finding may be due to inadequate washout of previous OAD. Further, in both trials, the differences between treatment groups with respect to change in HbA1c did not depend on previous OAD therapy (non-significant treatment by previous treatment interaction).

Treatment by Country Interaction
For trial 1572, from the statistical analysis, differences between treatment groups with respect to change in HbA1c did not significantly depend on country (non-significant treatment by country interaction).

For trial 1436, the difference between treatment groups with respect to change in HbA1c did demonstrate a statistically significant country interaction, meaning that the differences between treatment groups with respect to change in HbA1c differed between the countries (p=0.0048).

Reviewer's comment: The primary analysis for the primary efficacy variable included country as a fixed-effect in the model (i.e. the effect of country was accounted for in the primary efficacy analyses).

Treatment by Gender Interaction
There was no statistically significant treatment by gender interaction on HbA1c in either trial.

Treatment by Race Interaction
For trial 1572, differences between treatment groups with respect to change in HbA1c did not significantly depend on race (non-significant treatment by race interaction).

For trial 1436, there was no apparent difference in change in HbA1c from baseline to end of treatment for liraglutide among the different racial subgroups. The statistical analysis did, however, show a significant HbA1c treatment by race interaction (p value was 0.0026), meaning that the differences between treatment groups with respect to change in HbA1c differed between races.

Reviewer's comment: The statistical reviewer concluded that across the five Phase 3 studies, the average HbA1c response to liraglutide was not consistently affected by race or ethnicity. Most of the p-values of the interactions of race/ethnicity with treatment group were greater than 0.1. In the opinion of the statistical reviewer, the few p-values that were less than 0.1 (such as in this case)

were not consistent across studies and do not indicate an important effect of race on the efficacy of liraglutide.

Treatment by Age Group Interaction
This analysis investigated if the differences between treatment arms in change in HbA1c were dependent on age group (< 65 years and ≥ 65 years). From the statistical analysis, the differences between treatment groups with respect to change in HbA1c did not significantly depend on age group (non-significant treatment by age group interaction).

Treatment by BMI Group Interaction
This analysis investigated whether there was an interaction between the effect of treatment group and the effect of BMI group (BMI < 25 kg/m^2, 25 kg/m^2 ≥ BMI < 30 kg/m^2, 30 kg/m^2 ≥ BMI < 35 kg/m^2 and BMI ≥ 35 kg/m^2) on change in HbA1c. There was no statistically significant treatment by BMI group interaction on change in HbA1c in either trial.

6.1.4.2.5.3 Selected Exploratory Analyses

Relationship between Renal and Hepatic Impairment and Change in HbA1c

To investigate whether renal or hepatic impairment had any influence on the treatment effects seen on change in HbA1c, change in HbA1c was summarized by baseline creatinine level (reflecting renal impairment), by baseline alanine aminotransferase (ALT) level and by baseline aspartate aminotransferase (AST) level (the latter two reflecting hepatic impairment). The Sponsor noted that the degree of impairment was limited as exclusion criteria restricted the entry of subjects with significant impairment. The differences between the treatment groups for change in HbA1c did not appear to depend on baseline creatinine, baseline ALT, or baseline AST status in either trial.

Reviewer's comment: This reviewer agrees with the Sponsor that these analyses are limited because of the exclusion criteria. In addition the chosen measures of renal and hepatic impairment are not optimal. Estimated glomular filtration rate (GFR) or creatinine clearance for assessment of renal impairment may have been a better choice. In terms of hepatic impairment, tests of synthetic function (e.g., bilirubin, INR, etc.) may be more reflective of hepatic impairment. E.g., patients with cirrhosis may have very little elevation in transaminases because little tissue is left. However, in this trial which excluded patients with medical comorbidities such as cirrhosis, tests of synthetic function may not have been helpful.

6.1.4.2.6 Secondary efficacy variables for the add-on with one OAD population

Secondary glycemic control parameters were changes in fasting plasma glucose and post-prandial plasma glucose.

6.1.4.2.6.1 Fasting plasma glucose (FPG)

Table 6.26 summarizes the changes in FPG for the add-on to one OAD studies. The greatest decreases were seen for the two higher dose liraglutide groups which were quite similar to each other.

Liraglutide vs. placebo: In both trials, changes in FPG in the three liraglutide groups were significantly different from the placebo groups in favor of liraglutide.

Liraglutide vs. comparator: In trial 1572, changes in FPG in the three liraglutide groups+metformin were comparable to (i.e. not statistically different from) the glimepiride+metformin group. When the analyses were performed on the data set where no imputation had been performed differences between the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups and the glimepiride+metformin group were statistically significant in favor of liraglutide. In trial 1436, the two higher doses of liraglutide performed better than the comparator rosiglitazone, both when added to glimepiride.

Table 6.26
ANCOVA of Change in Mean Fasting Plasma Glucose (FPG) (mg/dL) (add-on therapy with one OAD trials)

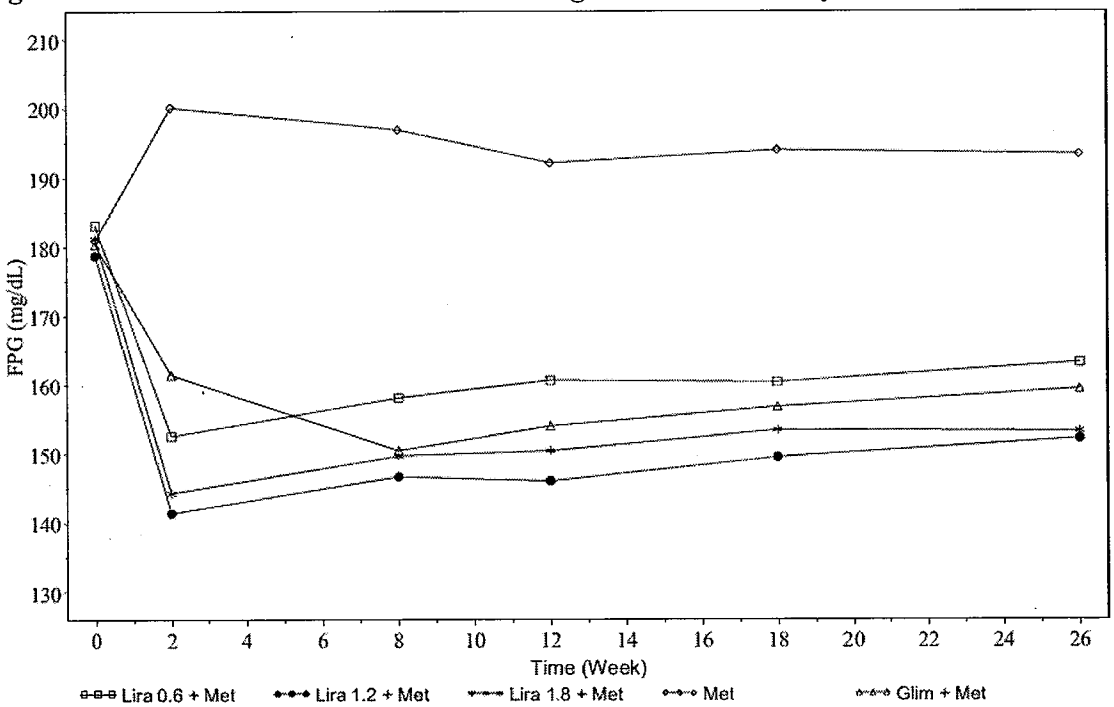
				Placebo			#Comparator		
	N	Baseline FPG un-adjusted mean (SD)	*Adjusted mean change in FPG (SE)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value
Trial 1572 Metformin add-on									
Lira 0.6	238	183.1 (43.6)	-20.3 (2.789)	-27.59	-38.3; -16.9	<.0001	3.16	-5.7; 12.1	0.8079
Lira 1.2	234	178.8 (42.0)	-29.4 (2.864)	-36.67	-47.3; -26.0	<.0001	-5.92	-14.8; 3.0	0.3047
Lira 1.8	235	181.2 (41.5)	-30.3 (2.787)	-37.58	-48.2; -26.9	<.0001	-6.83	-15.7; 2.0	0.1845
Placebo	116	181.0 (41.4)	7.24 (3.814)						
Comparator	234	180.4 (46.2)	-23.5 (2.823)						
Trial 1436 Glimepiride add-on									
Lira 0.6	230	179.9 (43.2)	-13.0 (2.855)	-31.13	-42.6; -19.7	<.0001	2.85	-6.5; 12.2	0.8786
Lira 1.2	218	177.1	-28.3 (2.946)	-46.41	-58.0; -	<.0001	-12.44	-22.0; -2.9	0.0056

		(48.0)			34.9				
Lira 1.8	227	173.9 (43.7)	-28.7 (2.953)	-46.81	-58.3; -35.3	<.0001	-12.84	-22.3; -3.3	0.0036
Placebo	109	171.2 (36.9)	18.1 (4.042)						
Comparator	226	179.2 (44.9)	-15.8 (2.880)						
#Comparator in trial 1572 is glimepiride and in trial 1436 is rosiglitazone The 95% CI for the estimated differences are based on Dunnett's method *The change in mean FPG was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline value as covariate									
Source: Tables 14.2.68 and 14.2.72 trial 1572 report; Tables 14.2.65 and 14.2.65 trial 1436 report									

Reviewer's comment: the reduction in FPG for liraglutide + one OAD compared to one OAD + placebo appears consistent across the two trials in favor of liraglutide. The two highest doses of liraglutide appear virtually identical in their FPG lowering effect. Liraglutide at all doses was similar to glimepiride when added to metformin. Liraglutide at the two highest doses was better than rosiglitazone when added to glimepiride. The previously discussed caveat applies regarding the half maximal rosiglitazone comparator dose.

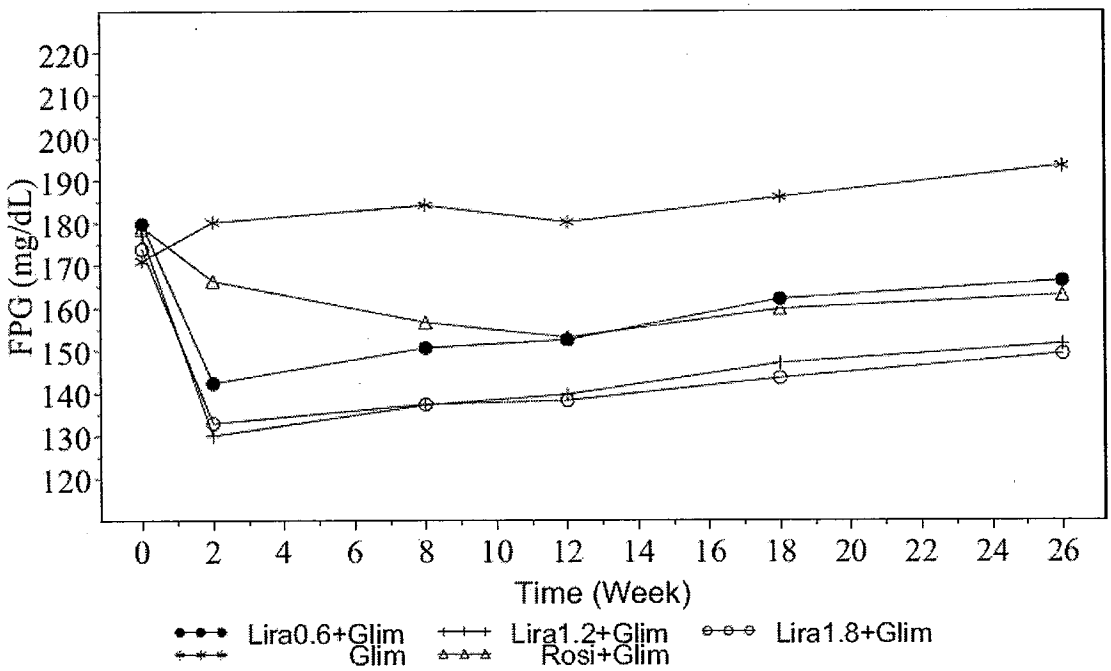
Plots of FPG values by treatment and week are shown for trial 1572 in Figure 6.12 and for trial 1436 in Figure 6.13. In summary, for trials 1572 and 1436, in the 3 liraglutide groups and in the active comparator treatment groups, FPG decreased within the first 2 weeks after randomization while an increase in FPG was seen in the placebo treatment groups. During the remaining 24 weeks of the trial, no change to a slight increase in FPG was demonstrated for all 3 liraglutide treatment groups and the active comparator treatment groups, although the end of treatment FPG values for these treatment groups were still below the baseline values.

Figure 6.12 – Trial 1572 - Plot of Mean Fasting Plasma Glucose by Treatment and Week (mg/dL)



Source: EOT Figure 14.2.67, Trial 1572 report

Figure 6.13 - Trial 1436 - Plot of Mean Fasting Plasma Glucose by Treatment and Week (mg/dL)



Source: EOT Figure 14.2.64

Reviewer's comment: **The proposed label states that** [redacted] b(4)

[redacted] **The lower value of** [redacted] **mg/dL appears to have come from trial 1436 at the liraglutide 0.6 mg dose. The upper value of** [redacted] **mg/dL derives from trial 1574. The plots over time for these two trials support the claim that the reduction in FPG occurs within 2 weeks of starting treatment. However, the type 1 error rate was not controlled and this was not prespecified as a key endpoint. Therefore, this information may not be appropriate for the product label.**

6.1.4.2.6.2 Post-Prandial Plasma Glucose

ANCOVA analyses for the change in mean postprandial glucose are presented in table 6.27.

Post-prandial glucose was patient-measured by glucometer 90 minutes after the start of each meal. The values measured at each of the three daily meals were averaged to obtain the mean post-prandial glucose value. In both trials, there was a dose-dependent reduction in estimated mean post-prandial plasma glucose across all 3 dose levels of liraglutide.

Liraglutide vs. placebo: In both trials, liraglutide at all doses was better than placebo when added to one OAD at reducing mean post-prandial glucose, although the decrease was smaller in the liraglutide 0.6 mg groups.

Liraglutide vs. comparator: For liraglutide in combination with metformin compared with glimepiride + metformin (trial 1572), the reduction in mean post-prandial plasma glucose did not differ from the active comparator for the higher doses of liraglutide. Liraglutide at 0.6 mg was worse than the active comparator arm. In trial 1436, the mean reduction in post-prandial plasma glucose values was significantly greater in the liraglutide 1.8 mg+glimepiride and liraglutide 1.2 mg+glimepiride treatment groups compared to those in the rosiglitazone+glimepiride treatment group. The liraglutide 0.6 mg+glimepiride group was comparable to the rosiglitazone+glimepiride group.

Table 6.27
ANCOVA of Change in Mean Postprandial (PostP) Glucose (mg/dL) (add-on therapy with one OAD trials)

				Placebo			#Comparator		
	N	Baseline PostP glucose un-adjusted mean	*Adjusted mean change in PostP glucose (SE)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value

		(SD)							
Trial 1572 Metformin add-on									
Lira 0.6	214	223.2 (54.9)	-30.24 (2.91)	-19.15	-30.77; -7.54	0.0003	14.06	4.81; 23.31	0.0008
Lira 1.2	207	214.2 (49.6)	-42.00 (3.02)	-30.91	-42.53; -19.29	<.0001	2.30	-6.97; 11.58	0.9368
Lira 1.8	205	220.3 (47.8)	-46.21 (2.97)	-35.12	-46.75; -23.49	<.0001	-1.91	-11.17; 7.36	0.9670
Placebo	90	220.9 (53.9)	-11.09 (4.26)						
Comparator	214	220.2 (52.9)	-44.30 (2.95)						
Trial 1436 Glimepiride add-on									
Lira 0.6	220	228.5 (57.6)	-33.35 (3.32)	-26.87	-40.57; -13.17	<.0001	-0.18	-11.28; 10.91	1.0000
Lira 1.2	208	231.9 (60.6)	-44.70 (3.43)	-38.21	-52.07; -24.36	<.0001	-11.53	-22.81; -0.25	0.0434
Lira 1.8	221	233.2 (60.0)	-48.89 (3.40)	-42.41	-56.15; -28.66	<.0001	-15.72	-26.89; -4.55	0.0022
Placebo	96	228.2 (56.0)	-6.49 (4.91)						
Comparator	209	234.2 (61.6)	-33.17 (3.41)						
#Comparator in trial 1572 is glimepiride and in trial 1436 is rosiglitazone The 95% CI for the estimated differences are based on Dunnett's method *The change in mean PostP glucose was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline value as covariate									
Source: [EOT Table 14.2.94, Trial report 1572], [EOT Table 14.2.98, Trial report 1436]									

Reviewer's comment: It is reported in the labeling that [redacted] The number — mg/dL appears to come from trial 1572 at the 0.6 mg dose. The number — mg/dL comes from trial 1436 at the 1.8 mg dose. The label does not indicate that this reduction is on top of background therapy. b(4)

Overall conclusions regarding "other" glycemic control parameters: Liraglutide at the two higher doses appears to reduce both FPG and post-prandial glucose significantly over placebo when added to one OAD.

6.1.4.2.6.3 Body weight

Estimated change in body weight and analyses of change in body weight after 26 weeks for trials 1572 and 1436 are shown in Table 6.28. Changes in body weight for all three liraglutide groups (favoring

weight loss) were shown to be superior to the active comparator in both trials. Liraglutide 1.2 mg + metformin and liraglutide 1.8 mg + metformin were shown to be superior to placebo + metformin in trial 1572. The liraglutide + glimepiride groups were not better than placebo + glimepiride in trial 1436.

Reviewer's comment: It appears that for both trials the possible reason the change in body weight for all three liraglutide groups were shown to be superior to the active comparator was because the active comparator groups experienced weight gain, although in trial 1572, the weight loss with liraglutide was greater than the weight gain with the comparator glimepiride. The weight difference between the liraglutide groups compared to the placebo groups in both trials was clinically trivial (although statistically significant for the two higher liraglutide doses in trial 1572). These results suggest that although liraglutide per se may not result in a clinically important weight loss, the relative weight decrease compared with the active comparators in these trials (glimepiride and rosiglitazone – both known to be associated with weight gain) may be clinically meaningful when choosing a particular drug therapy for an individual patient.

Table 6.28
ANCOVA of Change in Body Weight after 26 weeks (kg) (add-on therapy with one OAD trials)

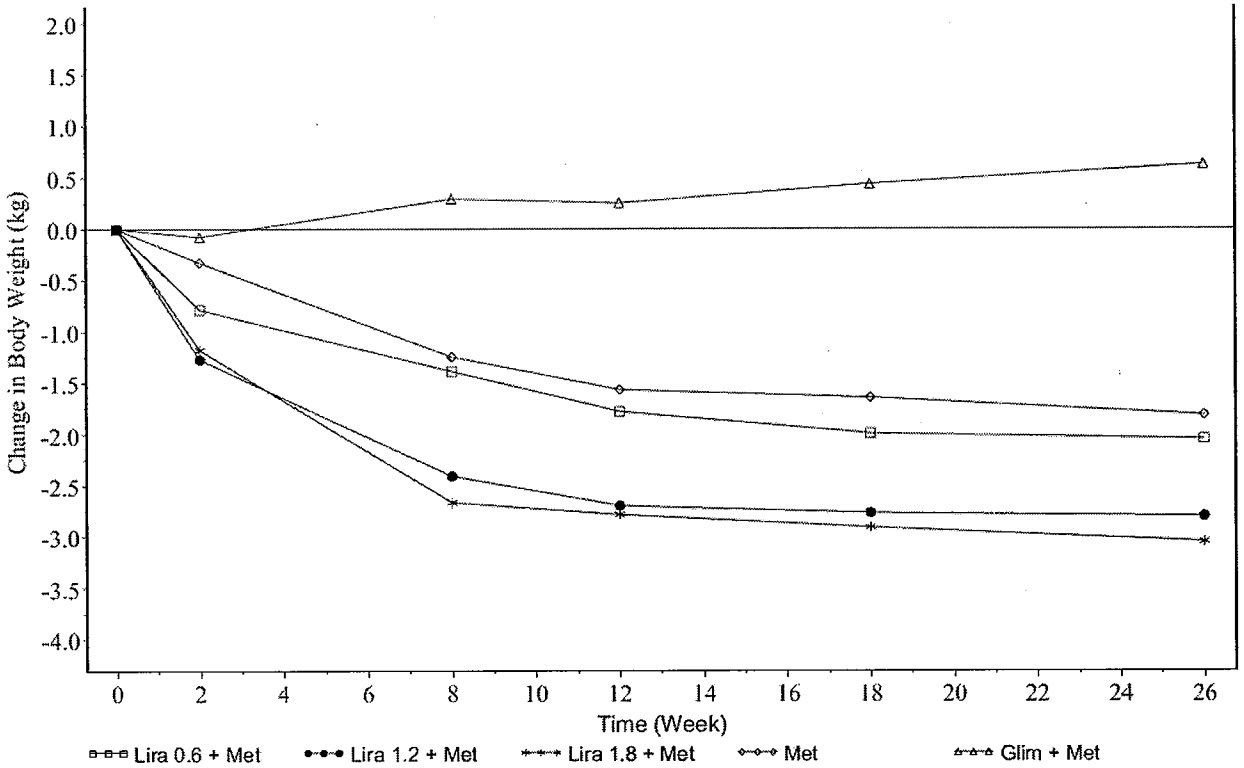
				Placebo			#Comparator		
	N	Baseline Body Weight un-adjusted mean (SD)	*Adjusted mean change in body weight (SE)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value
Trial 1572 Metformin add-on									
Lira 0.6	242	87.8 (17.1)	-1.78 (0.23)	-0.28	-1.15; 0.60	0.8198	-2.73	-3.47; 2.00	<.0001
Lira 1.2	236	88.5 (19.1)	-2.58 (0.24)	-1.07	-1.94; -0.19	0.0117	-3.53	-4.27; 2.79	<.0001
Lira 1.8	241	88.0 (16.3)	-2.79 (0.23)	-1.29	-2.16; 0.41	0.0016	-3.75	-4.48; 3.01	<.0001
Placebo	121	91.0 (17.0)	-1.51 (0.31)						
Comparator	237	89.0 (16.8)	0.95 (0.23)						
Trial 1436 Glimepiride add-on									
Lira 0.6	231	82.6 (17.7)	0.72 (0.20)	0.82	0.04; 1.60	0.0355	-1.38	-2.03; -0.74	<.0001
Lira 1.2	224	80.0 (17.1)	0.32 (0.20)	0.42	-0.37; 1.20	0.4546	-1.79	-2.44; -1.13	<.0001
Lira 1.8	232	83.0	-0.23 (0.20)	-0.14	-0.92; 0.64	0.9702	-2.34	-2.99; -	<.0001

		(18.1)						1.69	
Placebo	112	81.9 (17.1)	-0.10 (0.27)						
Comparator	229	80.6 (17.0)	2.11 (0.20)						
#Comparator in trial 1572 is glimepiride and in trial 1436 is rosiglitazone The 95% CI for the estimated differences are based on Dunnett's method *The change in body weight was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline value as covariate									
Source: Tables 11-4, 11-15 trial 1572 report; Tables 11-5 and 11-16 trial 1436 report									

Reviewer's comment: The reason for the differing findings in terms of body weight change vs. placebo in these two trials is unclear but likely has to do with the differing background therapy (metformin in trial 1574 and glimepiride in trial 1436). It may first appear to be due to the higher baseline weights in trial 1572. However, there was a higher proportion of men in trial 1572, and the baseline BMIs were similar between the two trials.

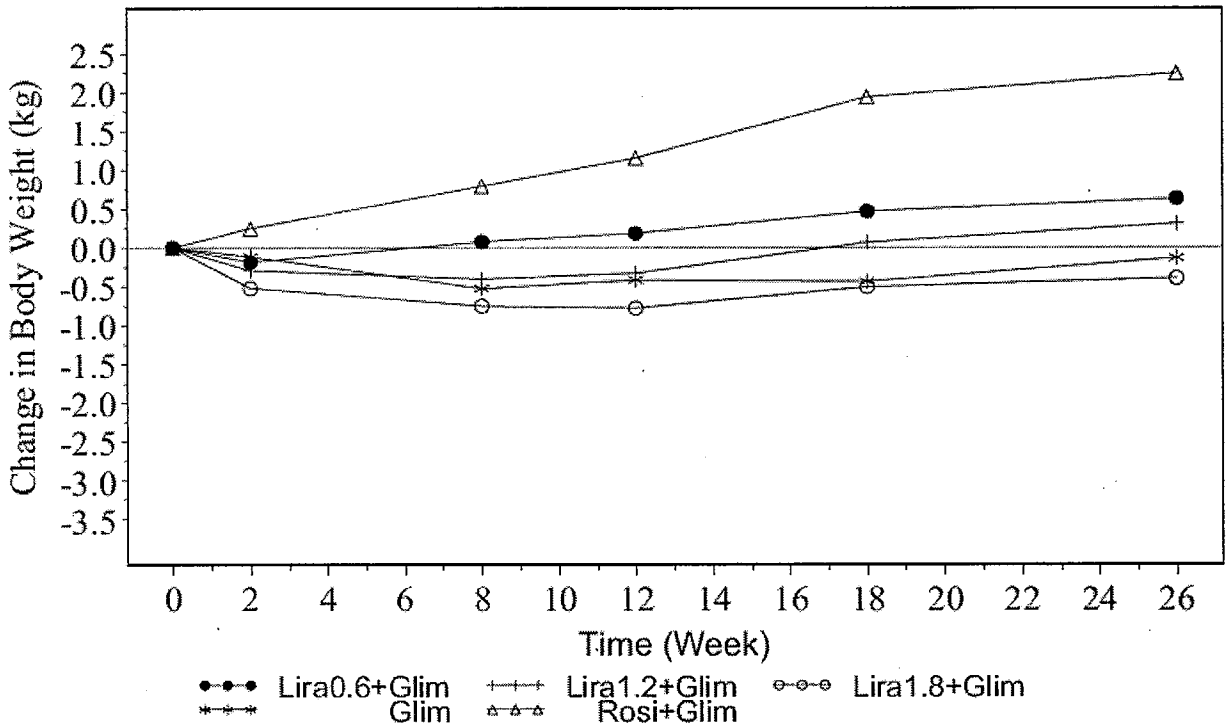
Figure 6.14 shows that for trial 1572, during the period from treatment start to Weeks 8-12, the 3 liraglutide+metformin groups and the placebo+metformin group appeared to show reductions in mean body weight, whereas the glimepiride+metformin group showed an increase in mean body weight. Figure 6.15 shows that for trial 1436 during the period from treatment start to Week 8, the two highest dose liraglutide+glimepiride groups and the glimepiride group appeared to show reductions in mean body weight, whereas the rosiglitazone+ glimepiride treatment group showed an increase in mean body weight. From Week 8 until end of treatment, the mean body weight appeared to increase slightly in the three liraglutide treatment groups and the glimepiride treatment group. Mean body weight in the rosiglitazone+ glimepiride treatment group increased steadily throughout the entire trial period.

Figure 6.14 – Trial 1572 - Mean Change in Body Weight (kg) by Treatment and Week



Source: Figure 11-3, trial 1572 report

Figure 6.15 – Trial 1436 - Mean Change in Body Weight (kg) by Treatment and Week



Source: Figure 11-2, trial 1436 report

Reviewer's comment: The early reductions in weight in the liraglutide groups were not maintained and at the end of 26 weeks. Even though there was a slight decrease in weight in the liraglutide 1.8 mg group, these weight changes are probably not clinically meaningful.

Further statistical analyses showed that differences between treatment groups with respect to change in body weight did not significantly depend on BMI group (non-significant treatment by BMI group interaction) for trial 1572, while the effect of baseline BMI on change in body weight was dependent on treatment group (p=0.0233) in trial 1436 with the greater BMI groups benefiting from the greatest weight loss. Also, because nausea was a common side effect of liraglutide, the change in body weight was evaluated for 6 different nausea subgroups; there was no consistent pattern with respect to the relation between nausea and change in body weight for either trial.

6.1.4.2.6.4 Measures of beta-cell function and insulin resistance

In the two trials some measures of beta-cell function significantly improved in the liraglutide groups relative to the comparators and placebo groups as follows:

In trial 1572 increases (by 20-26 percentage points) in HOMA-B from baseline to end of treatment were seen in the 3 liraglutide groups and in the glimepiride+metformin group, while no relevant change was seen in the metformin group. There were slight decreases in the pro-insulin to insulin ratio in the 3 liraglutide groups and in the glimepiride+metformin group, while no relevant change was seen in the metformin group. There were no significant differences between the 3 liraglutide groups and the glimepiride+metformin group with respect to change in HOMA-B or pro-insulin to insulin ratio. There was no difference in fasting insulin, fasting C-peptide or HOMA-IR between the liraglutide groups and the comparator or placebo group.

In trial 1436, measures of beta-cell function including fasting insulin, C-peptide, pro-insulin to insulin ratio, and HOMA-B showed significant improvement favoring liraglutide in some analyses although these changes were not always dose dependent. For HOMA-IR, no statistically significant differences were seen between liraglutide at any dose, in addition to glimepiride, and glimepiride alone or rosiglitazone+glimepiride treatments. Comparable results were obtained when the same analysis was performed without data imputation, except for a significantly reduced insulin resistance observed in the rosiglitazone+glimepiride treatment group versus the liraglutide 1.8 mg+glimepiride treatment group.

Reviewer's comment: The proposed label reports that liraglutide [redacted] but these data suggest this effect may not be consistent across trials as these two 26-week trials showed different results regarding HOMA-IR. However, it may not be appropriate to compare monotherapy to add-on therapy. b(4)

6.1.4.2.6.5 Blood Pressure

The results of analyses of systolic blood pressure (SBP) for trials 1572 and 1436 are summarized in Table 6.29. Reductions in SBP from baseline to week 26 were seen in all treatment groups except the active comparator group in trial 1572 which had a small mean increase.

In an ANCOVA model, there were no significant differences between the 3 liraglutide groups and the placebo groups with respect to change in SBP in either trial. When compared to the active comparator arms, there were no differences between the 3 liraglutide groups and the rosiglitazone+glimepiride group in trial 1436, but in trial 1574 the change in SBP was significantly different between the liraglutide 1.2 mg+metformin and liraglutide 1.8 mg+metformin groups which showed lowering from baseline and the glimepiride+metformin group which experienced a small increase from baseline. When sensitivity analyses were performed on the data set with no imputation, the same conclusions were reached except for the difference between the liraglutide 1.8 mg+metformin group and the glimepiride+metformin group in trial 1574, which was not statistically significant (data not shown).

There were no significant findings related to diastolic blood pressure for either trial.

Table 6.29
ANCOVA of Change in Systolic Blood Pressure (SBP) in mmHg after 26 weeks (add-on therapy with one OAD trials)

				Placebo			#Comparator		
	N	Baseline SBP un-adjusted mean (SD)	*Adjusted mean change in SBP (SE)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value
Trial 1572 Metformin add-on									
Lira 0.6	242	131.2	-0.58 (0.84)	1.18	-2.01; 4.38	0.7286	-0.98	-3.66; 1.70	0.7885
Lira 1.2	236	132.1	-2.81 (0.86)	-1.05	-4.25; 2.15	0.7987	-3.21	-5.90; -0.52	0.0128
Lira 1.8	241	131.3	-2.29 (0.83)	-0.53	-3.72; 2.66	0.9765	-2.69	-5.36; -0.03	0.0467
Placebo	121	134.9	-1.76 (1.14)						
Comparator	239	131.7	0.41 (0.85)						
Trial 1436 Glimepiride add-on									
Lira 0.6	232	130.9	-0.94 (0.84)	1.38	-1.93; 4.70	0.6453	-0.01	-2.76; 2.74	1.0000
Lira 1.2	224	133.1	-2.56 (0.85)	-0.24	-3.58; 3.11	0.9990	-1.63	-4.41; 1.15	0.4186
Lira 1.8	231	132.4	-2.81 (0.86)	-0.49	-3.82; 2.84	0.9841	-1.88	-4.65; 0.89	0.2842
Placebo	112	131.3	-2.32 (1.17)						
Comparator	229	132.5	-0.93 (0.84)						

#Comparator in trial 1572 is glimepiride and in trial 1436 is rosiglitazone
The 95% CI for the estimated differences are based on Dunnett's method
*The change in SBP was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline value as covariate

Source: [Table 11-33 trial 1572 report]; [Table 11-33 trial 1436 report]

Reviewer's comment: Neither trial showed a reduction in SBP compared with placebo at the end of 26 weeks. The statistically significant difference found between the active comparator and liraglutide in trial 1572 has as much to do with a SBP increase in the comparator group. While a reduction in blood pressure was seen, it was seen among placebo groups as well, suggesting that the blood pressure reduction was not related to liraglutide use per se. Alternative explanation are that subjects enrolled in clinical trials may have better monitoring and treatment of comorbidities such as blood pressure, or that subjects enrolled in clinical trials are more health conscious (i.e. diet and exercise) that may promote lower blood pressure. These studies do not support the claim in the label that b(4)

b(4)

6.1.4.2.6.6 Metabolic syndrome prevalence

In trial 1572, the proportion of subjects without metabolic syndrome at end of treatment was significantly higher in all 3 liraglutide groups compared with the metformin group (p=0.009 for liraglutide 1.8 mg). However, when the analysis was performed without data imputation, none of the comparisons were significant. In trial 1436, there were no significant differences between groups in the proportion of subjects without metabolic syndrome at the end of the trial.

Reviewer's comment: These data as a whole do not support the proposed labeling claim that ' ' Although some analyses from trial 1572 did suggest that liraglutide overall data across the liraglutide development program do not consistently support this labeling claim. Further, the concept of ' ' is problematic because of the several different definitions employed by researchers and clinicians. Therefore, this information has not been previously allowed into labeling by the Division. This reviewer does not see the data presented here (because of lack of consistent effect) as strong enough to change this position. b(4)

6.1.4.2.6.7 Liver to Spleen Attenuation Ratio – Trial 1572 only

Visceral and subcutaneous adipose tissue areas in the central region of the body as well as the liver/spleen attenuation ratio were measured using CT performed at baseline and at 26 weeks. Baseline levels of liver to spleen attenuation ratio were comparable in all 5 treatment groups. In the liraglutide 1.8 mg+metformin group, an increase in the liver to spleen attenuation ratio was observed (indicating a relief in hepatic steatosis) while no relevant changes were observed in the other 4 treatment group. The Sponsor concluded that hepatic steatosis was reduced following treatment with liraglutide 1.8 mg + metformin.

Reviewer's comment: The proposed label states that liraglutide . This reviewer has concerns about including this information in the product label because it was only shown with this technique with one liraglutide dose in one of the phase 3 studies. It is also unclear if this technique is validated for measuring . The Division of Metabolism and Endocrinologic Products has never put such language in diabetes drug labels. b(4)

6.1.4.3 Combination therapy population with two OADs (Trials 1574 and 1697)

Both Trials 1574 and 1697 evaluated 26 weeks of treatment with liraglutide in combination with two OADs. In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin. Trial 1574 assessed two liraglutide dose levels; 1.2 and 1.8 mg and compared these with placebo (the two OADs alone). Trial 1697 assessed the 1.8 mg liraglutide dose and compared this with placebo (the two OADs alone) and with insulin glargine (+ the two OADs).

6.1.4.3.1 Demographic features of the add-on with two OADs population

A summary of screening characteristics and demographics for trials 1574 and 1697 is presented in Table 6.30. In trial 1574, the baseline demographic parameters were similar between treatment groups except in the sex category where the three groups appeared slightly imbalanced. For trial 1697, the trial population in all 3 groups was well matched with only small differences in baseline characteristics, again most notably in the category of sex where the trial population had a somewhat higher representation of male subjects in the liraglutide 1.8 mg+OADs and glargine+OADs groups compared to the OADs alone group.

Reviewer's comment: There was not a significant sex by HbA1c interaction in analyses of the primary efficacy variable. See section 6.1.4.3.5.2

There were some notable differences between the two trials. Subjects in trial 1697 appear to be slightly older, have a mean duration of diabetes slightly longer, and a mean HbA1c slightly higher than trial subjects in trial 1574. Mean BMI was slightly higher in trial 1574. Also a higher percentage of subjects (94.3%) had been using OAD combination therapy prior to participation in the trial than used combination therapy in trial 1574. Racial distribution was also somewhat different between the trials with Black subjects representing a smaller proportion in trial 1697 with 15.7% of subjects categorized as Asian or Pacific Islanders.

Reviewer's comment: Within each trial randomization seems successful for the most part. Comparing between trials, overall, trial 1697 enrolled slightly older and more advanced diabetics. In trial 1697, there were a small number of African Americans which is unlike the U.S. diabetic population.

Table 6.30
Subject Baseline and Demographic Features of all Randomized Subjects – Add-On therapy with Two OADs^ Studies

	Trial 1574 – 26 weeks			Trial 1697 – 26 weeks		
	Lira 1.8 + OADs	**Lira 1.2 + OADs**	**OADs**	**Lira 1.8 + OADs**	**OADs**	**Glargine + OADs**
All randomized subjects (N)	178	178	177	232	115	234
Sex N (%)						
Male	87 (48.88)	102 (57.30)	109 (61.58)	132 (56.9)	56 (48.7)	140 (59.8)
Female	91 (51.12)	76 (42.70)	68 (38.42)	100 (43.1)	59 (51.3)	94 (40.2)
Age (years)						
Mean (SD)	55.1 (10.7)	55.2 (10.2)	54.9 (9.8)	57.6 (9.5)	57.5 (9.6)	57.5 (10.5)
***Race N (%)**						
White	148 (83.15)	144 (80.90)	149 (84.18)	176 (75.9)	89 (77.4)	171 (73.1)
Black	18 (10.11)	27 (15.17)	18 (10.17)	9 (3.9)	5 (4.3)	7 (3.0)
Asian/Pacific Islander				34 (14.7)	15 (13.0)	42 (17.9)
Asian	5 (2.81)	2 (1.12)	3 (1.69)			
Native Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)			
American Indian – Alaska Native	1 (0.56)	1 (0.56)	2 (1.13)	0 (0.0)	0 (0.0)	0 (0.0)
Other	6 (3.37)	4 (2.25)	5 (2.82)	2 (0.9)	1 (0.9)	2 (0.9)
Unknown				11 (4.7)	5 (4.3)	12 (5.1)
BMI (kg/m2)						
Mean (SD)	33.5 (5.0)	33.2 (5.4)	33.9 (5.2)	30.4 (5.3)	31.3 (5.0)	30.3 (5.3)
Duration of diabetes (years)						
Mean (SD)	9.1 (5.6)	8.9 (5.5)	8.9 (5.9)	9.2 (5.8)	9.4 (6.2)	9.7 (6.4)
Previous anti-diabetic treatment, N (%)						
Monotherapy	29 (16.29)	29 (16.29)	32 (18.08)	15 (6.5)	6 (5.2)	12 (5.1)
Combination therapy	149 (83.71)	149 (83.71)	145 (81.92)	217 (93.5)	109 (94.8)	222 (94.9)
HbA1c at screening (%)						
Mean (SD)	8.3 (0.9)	8.3 (0.9)	8.3 (1.1)	8.6 (0.8)	8.5 (0.8)	8.5 (0.8)

*Racial categorization differed between the trials
^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.
Source: [Table 11-1, Trial 1574 report]; [Table 11-2, Trial 1697 report]

The mean baseline values of selected efficacy parameters (HbA1c, FPG, and blood pressure) of the randomized population in the add-on with two OADs studies are summarized in Table 6.31. These values were comparable between all treatment arms within each study. Between the studies, it appears that in Trial 1697, HbA1c decreased slightly from screening, while in trial 1574 HbA1c increased

slightly from screening resulting in a slightly higher HbA1c at baseline for trial 1574. Blood pressure was overall slightly higher among 1697 trial participants.

Table 6.31
Selected Baseline Efficacy Parameters Subjects – Add-On therapy with Two OADs^ Studies

	Trial 1574 - 26 weeks			Trial 1697 - 26 weeks		
	Lira 1.8 + OADs	**Lira 1.2 + OADs**	**Pbo + OADs**	**Lira 1.8 + OADs**	**Pbo + OADs**	**Glargine + OADs**
All randomized subjects (N)	178	178	177	232	115	234
HbA1c (%)						
N	178	178	177	232	113	234
Mean (SD)	8.56 (1.22)	8.48 (1.23)	8.43 (1.16)	8.3 (0.9)	8.3 (0.9)	8.2 (0.9)
Fasting plasma glucose (mg/dL)						
N	174	177	169	231	112	232
Mean (SD)	184.9 (43.3)	181.1 (42.5)	179.6 (47.1)	163.8 (37.8)*	169.2 (36.0)*	163.8 (36.0)*
Diastolic BP (mmHg)						
N	178	178	177	232	115	234
Mean (SD)	75.2 (8.4)	75.8 (9.0)	76.2 (9.2)	80.8 (9.1)	80.4 (9.3)	80.5 (8.0)
Systolic BP (mmHg)						
N	178	178	177	232	115	234
Mean (SD)	126.0 (14.2)	128.7 (14.8)	128.2 (14.5)	135 (15.0)	133 (14.0)	133 (14.7)

^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.
* Mean and SD converted from mmol/L using formula mg/dL = mmol/L * 18

Source: [Table 11-2, Trial 1574 report]; [Table 11-3 Trial 1697 report]

6.1.4.3.2 Participation and withdrawals in the add-on therapy to two OADs population (disposition of subjects)

In trial 1574, 821 subjects were screened and 533 subjects were randomized. Three subjects (2 in the liraglutide 1.2 mg+OADs group and 1 in the OADs alone group) were randomized but did not receive trial drug (liraglutide or placebo). In trial 1697, 973 subjects were screened, 581 subjects were randomized to treatment, and 576 subjects were exposed to trial products after randomization; 5 subjects were randomized but not exposed to liraglutide active/placebo or insulin glargine.

Participation and withdrawals in the pivotal add-on with two OADs treatment groups are summarized in Table 6.32. For trial 1574 in both liraglutide treatment groups, most subjects that withdrew did so due to adverse events (AEs), and, in the OADs alone group, most subjects withdrew due to ineffective

therapy or "other" reasons. The number of withdrawals was highest during the first month, with a steady decrease throughout the trial for the liraglutide groups. Most of the withdrawals due to AEs in the liraglutide groups occurred in the first two months.

In trial 1697, the largest percentage of withdrawals occurred in the OADs alone group primarily due to ineffective therapy. The liraglutide 1.8 mg+OADs group had a withdrawal rate of 10.8% with the main reasons being adverse events and 'other reasons'. In the glargine+OADs group, the main reasons for withdrawal were adverse events and non-compliance with the protocol. Overall, 30.5% of the withdrawals occurred within the first month. There was an imbalance in the timing of the withdrawals, i.e. earlier withdrawals in the liraglutide group (44% of total withdrawals in the first month) and the glargine group (40% of total withdrawals in the first month) compared with only 5% of the total withdrawals in the OAD group.

Table 6.32 Subject Disposition of All Randomized Subjects – Add-on Therapy to Two OADs^ Trials

	Trial 1574 – 26 weeks			**Trial 1697 - 26 weeks**		
	Lira 1.8 + OADs	**Lira 1.2 + OADs**	**OADs**	**Lira 1.8 + OADs**	**OADs**	**Glargine + OADs**
Subjects	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Randomized	178 (100)	178 (100)	177 (100)	232 (100)	115 (100)	234 (100)
Exposed (ITT analysis set)	178 (100)	177 (99.4)	175 (98.9)	230 (99.1)	114 (99.1)	232 (99.1)
Withdrawals	45 (25.3)	25 (14.0)	56 (31.6)	25 (10.8)	19 (16.5)	15 (6.4)
Adverse Events	27 (15.2)	11 (6.2)	6 (3.4)	11 (4.7)	1 (0.9)	5 (2.1)
Ineffective therapy	3 (1.7)	3 (1.7)	29 (16.4)	2 (0.9)	13 (11.3)	1 (0.4)
Non-compliance with protocol	4 (2.2)	4 (2.2)	5 (2.8)	1 (0.4)	1 (0.9)	5 (2.1)
Other	11 (6.2)	7 (3.9)	16 (9.0)	11 (4.7)	4 (3.5)	4 (1.7)
Completers	133 (74.7)	153 (86.0)	121 (68.4)	207 (89.2)	96 (83.5)	219 (93.6)
PP analysis set	123 (69.1)	133 (74.7)	106 (59.9)	195 (84.1)	90 (78.3)	205 (87.6)

^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.

Source: [Table xx Trial 1574 report];[Table 14.2.1 Trial 1697 report]

Reviewer's comment: According to Dr. Derr's statistical review, support for the efficacy of liraglutide compared to a placebo control and compared to an active control comes from a consistent pattern of early withdrawals due to ineffective therapy in comparator arms, when observed across the studies. The completer rate is adequate.

6.1.4.3.3 Adequacy of comparator drug dosages used in the key add-on with two OADs studies

In Trial 1574 the background therapy OADs were metformin 1000 mg bid + rosiglitazone 4 mg bid, in Trial 1697 the OADs were glimepiride 2-4 mg/day + metformin 2000 mg/day.

Trial 1574 did not have an active comparator arm. In trial 1697 the active comparator was glargine. (Please see section 6.1.3.8.4 (Table 6.6) for details of the titration guidelines). Glargine was expected to be titrated to a FPG target. Therefore, adequacy of titration is important in determining adequacy of comparator dose. The percent of subjects reaching glargine targets is presented in Table 6.33.

Table 6.33
Percent of Subjects Reaching Glargine Targets in Trial 1697

	Glargine + OAD N (%)
ITT Analysis Set	232
Week 26 FPG ≤ 100 mg/dL	47 (20.26)
Week 26 FPG < 120 mg/dL	93 (40.09)

100 mg/dL = 5.5 mmol/L; 120 mg/dL = 6.7 mmol/L
Source: Table 11-5 Trial 1697 report

Reviewer's comment: The background therapy for both trials was adequate. As described in section 6.1.3.8.4 the glargine titration guidelines were adequate although they were entirely patient effort-dependent. The percentage of subjects reaching glargine titration targets was notably low. However, the Sponsor claims that this reflects real-world experience with insulin glargine.

6.1.4.3.4 Primary efficacy endpoint for the add-on with two OADs population

Analysis of the changes in HbA1c from baseline to the end of the trials for the ITT with LOCF populations is summarized in table 6.34. In trial 1574, the mean decrease in HbA1c from baseline to end of treatment was 1.48% in both liraglutide groups and 0.54% in the OADs alone group. Treatment with liraglutide at both the 1.8 and 1.2 mg dose was superior to treatment with OADs alone (both $p<0.0001$). Analyses of the PP population and the ITT population without imputation showed similar results.

In trial 1697, the estimated mean reduction in HbA1c from baseline to end of treatment was -1.33% for the liraglutide 1.8 mg+OADs group, -0.24% for the OADs alone group, and -1.09% for the glargine+OADs group. The results were similar for the PP population (-1.35% for the liraglutide 1.8 mg+OADs group, -0.35% for the OADs alone group, and -1.10% for the glargine+OADs group). The ANCOVA analysis demonstrated that treatment with liraglutide was superior to treatment with placebo when added to metformin and glimepiride (upper CI limit below 0%). Subsequently it was demonstrated that treatment with liraglutide was non-inferior to treatment with glargine and that treatment with

liraglutide was superior to treatment with glargine (upper CI limit below 0%). The analysis performed without using LOCF supported these results as did the analysis performed on the PP analysis set. Finally, therapy with glargine was demonstrated to be superior to the placebo treatment (the OADs alone group).

Table 6.34
Analysis of HbA1c (%) Change from Baseline at 26 weeks (add-on therapy with two OADs trials)

				Placebo			#Comparator		
	N	Baseline HbA1c un-adjusted mean (SD)	*Adjusted mean change in HbA1c (SEM)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value
Trial 1574									
Lira 1.2+OADs	174	8.5 (1.2)	-1.482 (0.078)	-0.94	-1.12; -0.76	<.0001			
Lira 1.8+OADs	177	8.6 (1.2)	-1.487 (0.075)	-0.94	-1.12; -0.75	<.0001			
Placebo+OADs	167	8.4 (1.2)	-0.541 (0.080)						
Trial 1697									
Lira 1.8+OADs	224	8.3 (0.9)	-1.33	-1.09	-1.28; -0.90	<.0001	-0.24	-0.39; -0.08	0.0029
Placebo+OADs	110	8.3 (0.9)	-0.24						
Glargine+OADs	225	8.1 (0.9)	-1.09						

^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.
The p-values correspond to a two-sided test for superiority on a 5% significant level (statistical significance for p <0.05).
*The change in HbA1c was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline HbA1c as covariate
Test for non-inferiority with switch to superiority if non-inferiority is shown.
Non-inferiority is concluded if the upper limit of the 95% confidence interval for the treatment difference is below 0.4% i.e. non-inferiority to comparator is shown for all liraglutide groups.
There was no comparator in Trial 1574; the comparator in Trial 1697 was glargine+OADs
A hierarchical testing procedure is used.

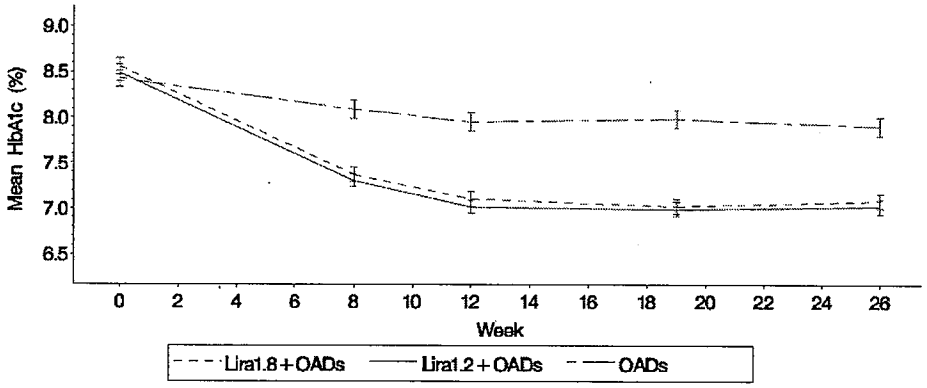
Source: Tables 3-2, 3-3 Summary of Clinical Efficacy

Reviewer's comments: In trial 1574 liraglutide 1.2 mg and 1.8 mg show almost identical efficacy.

It is not clear that comparing the efficacy of liraglutide to glargine in this particular trial is a useful comparison because the efficacy of glargine is dependent on the dose which was not optimized in all subjects, and subjects who failed to meet titration criteria were not excluded from the PP analysis set (making the PP analysis set not useful for sensitivity analysis). However, this comparison may be useful for predicting "real world" efficaciousness.

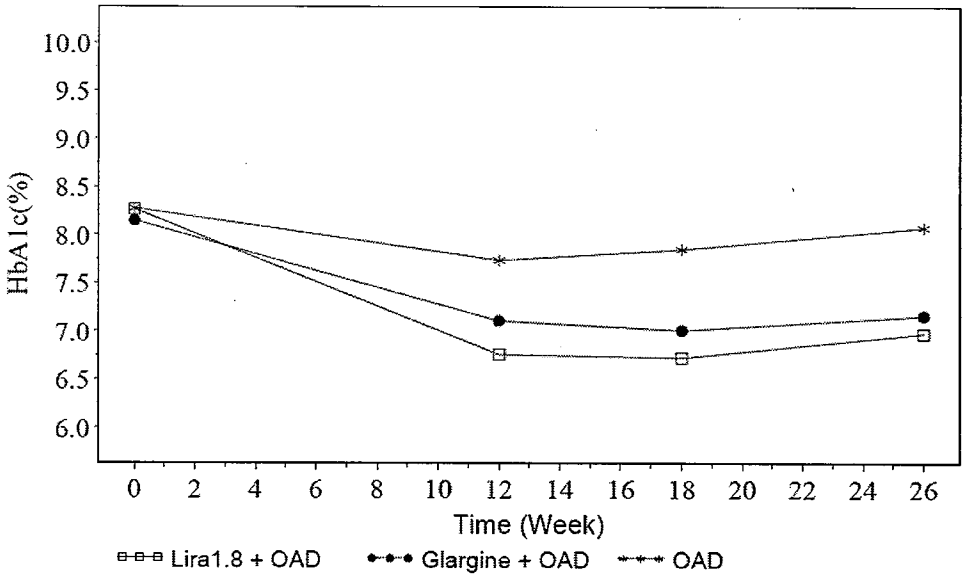
A plot of the mean HbA1c values over time by treatment in trial 1574 is presented in Figure 6.16 and for trial 1697 in Figure 6.17. The PP and completer populations showed similar results (data not shown).

Figure 6.16 – Trial 1574 – Mean HbA1c (%) Over Time by Treatment



Source: Figure 11-1, Trial 1574 report

Figure 6.17 – Trial 1697 - Mean HbA1c (%) Over Time by Treatment



Source: Figure 11-1, Trial 1697 report

Both trials show that the majority of the response to therapy was seen in the first 12 weeks which was then followed by a leveling off of HbA1c or a slight increase as was seen in trial 1697.

Reviewer's comment: These figures generally support the sustainability of liraglutide's effect on HbA1c up to 26 weeks although there may be a slight loss of efficacy after 18 weeks when added to glimepiride and metformin in (data from trial 1697).

6.1.4.3.5 Supplementary Analyses of the Primary Endpoint HbA1c

6.1.4.3.5.1 Percentage of Subjects Achieving HbA1c targets

The percentages of subjects reaching the pre-defined HbA1c targets (ADA target < 7% and AACE target ≤ 6.5%) at Week 26 are summarized in Table 6.35 and Table 6.36, respectively.

For trial 1574, statistical analysis by logistic regression showed that the percentages of subjects achieving ADA and AACE targets were significantly greater in the liraglutide+OADs groups as compared to the OADs alone group. Similarly, for trial 1697, the likelihood of achieving ADA and AACE targets was statistically significantly higher in the liraglutide 1.8 mg+OADs group as compared to the glargine+OADs and the OADS alone groups.

Table 6.35
Percentage of Subjects Reaching ADA Target (HbA1c < 7%) at 26 weeks (add-on therapy with two OADs^ trials)
Logistic Regression

			Placebo			Comparator		
	N	% of Subjects Reaching Target	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Trial 1574								
Lira 1.2+OADs	174	57.5	5.91	3.41 – 10.24	<.0001			
Lira 1.8+OADs	177	53.7	4.78	2.81 – 8.12	<.0001			
Placebo+OADs	167	28.1						
Trial 1697								
Lira 1.8+OADs	230	53.1	9.03	4.73 – 17.23	<.0001	1.71	1.12 – 2.64	0.0139
Placebo+OADs	114	15.3						
Glargine+OADs	232	45.8						

^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.
There was no comparator in Trial 1574; the comparator in Trial 1697 was glargine+OADs
N=number of subjects in ITT analysis set
The estimates are obtained from a logistic regression with treatment as fixed effect and baseline HbA1c value as a covariate.
Source: [Table 11-6, Trial 1574 report] [Table 11-14, Trial 1697 report]

Table 6.36
Percentage of Subjects Reaching AACE Target (HbA1c ≤ 6.5%) at 26 weeks (add-on therapy with two OADs^ trials) Logistic Regression

			Placebo			Comparator		
	N	% of Subjects Reaching Target	Odds Ratio	95% CI	p value	Odds Ratio	95% CI	p value
Trial 1574								
Lira 1.2+OADs	174	37.3	4.84	2.64 – 8.86	<.0001			
Lira 1.8+OADs	177	36.2	5.62	3.08 – 10.26	<.0001			
Placebo+OADs	167	14.4						
Trial 1697								
Lira 1.8+OADs	230	37.1	5.83	2.88 – 11.78	<.0001	2.52	1.59 – 4.00	<.0001
Placebo+OADs	114	10.8						
Glargine+OADs	232	23.6						

^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.
There was no comparator in Trial 1574; the comparator in Trial 1697 was glargine+OADs
N=number of subjects in ITT analysis set
The estimates are obtained from a logistic regression with treatment as fixed effect and baseline HbA1c value as a covariate.
Source: [Table 11-7, Trial 1574 report] [Table 11-15, Trial 1697 report]

Reviewer's comments: Both doses of liraglutide when combined with these two OADs were superior to the two OADs alone for the efficacy endpoint of dichotomous HbA1c treatment goals. Similar to the primary efficacy variable of percent HbA1c reduction, there does not seem to be a dose dependent effect in trial 1574 for the efficacy endpoint of HbA1c dichotomous treatment goals (only one dose of liraglutide was tested in trial 1697).

6.1.4.3.5.2 Treatment effect on selected subgroups

All analyses were performed using the ITT population with LOCF to test for significant interactions.

For both trials, previous antidiabetic treatment, country, gender, BMI, and age did not have a significant effect on efficacy (i.e. analyses for interaction between these variables and treatment group were not significant). For trial 1574, there was no effect of race/ethnicity on efficacy. For trial 1697, an analysis of race by treatment interaction effect showed a p value of 0.0407. A summary of the changes in HbA1c showed that both liraglutide and glargine reduced HbA1c in all racial groups as follows [mean HbA1c change from baseline (SD)]: Caucasian (n=176): -1.4 (0.9), Black (n=9): -1.5 (0.9), Asian/Pacific Islander (n=32): -1.0 (1.0), and Other (n=2): -0.3 (0.0). The Sponsor states that while, there was a

statistically significant treatment by race interaction effect across all therapies, the number of subjects in particular in the 'Black' and the 'Other' group are too small to draw any conclusions.

Reviewer's comments: The statistical reviewer concluded that across the five Phase 3 studies, the average HbA1c response to liraglutide was not consistently affected by race or ethnicity. Most of the p-values of the interactions of race/ethnicity with treatment group were greater than 0.1. In the opinion of the statistical reviewer, the few p-values that were less than 0.1 (such as in this case) were not consistent across studies and do not indicate an important effect of race on the efficacy of liraglutide.

6.1.4.3.5.3 Selected Exploratory Analyses

Renal and hepatic impairment: For trial 1574 the relationship between change in HbA1c and renal and hepatic impairment (baseline creatinine, ALT and AST by baseline quartiles) was stated as a pre-specified analysis but data were not presented. For trial 1697, summaries of changes in HbA1c by renal impairment (by baseline quartiles of creatinine values) and hepatic impairment (by baseline quartiles of AST and ALT values) did not indicate an effect of renal or hepatic impairment by creatinine, AST, or ALT on the changes in HbA1c.

Reviewer's comment: See section 6.1.4.2.5.3 for a discussion of renal and hepatic impairment markers.

6.1.4.3.6 Secondary efficacy variables for the add-on with two OADs population

6.1.4.3.6.1 Glycemic control parameters

Secondary glycemic control parameters were changes in fasting plasma glucose and post-prandial plasma glucose.

Fasting Plasma Glucose (FPG)

Table 6.35 summarizes the mean changes in FPG for the add-on to two OADs studies.

Liraglutide vs. placebo: In trial 1574 all groups had a mean decrease in FPG, with the greatest mean decrease occurring in the liraglutide 1.8 mg+OADs group (44 mg/dL). The liraglutide 1.2 mg+OADs group had a decrease of 40 mg/dL, and the placebo+OADs group had the smallest decrease (8 mg/dL). The liraglutide groups were significantly better than the placebo+OADs group. In trial 1697, the

liraglutide 1.8 mg group was significantly better than the placebo+OADs group (-27.9 vs. 9.6 mg/dL, p<0.0001).

Analysis of the number of subjects achieving target FPG values (90-130 mg/dL) demonstrated that subjects treated with liraglutide+OADs were significantly more likely to achieve these FPG goals than the subjects treated with placebo+OADs. In trial 1574, approximately 47% of subjects in the liraglutide+OADs treatment groups reached the FPG target compared to 24% in the placebo+OADs treatment group, and in trial 1697 43% of subjects reached the FPG goal in the liraglutide+OADs group, while only 14% reached the goal in the placebo+OADs group (data not shown).

Liraglutide vs. active comparator: In trial 1697 reduction in FPG in the liraglutide 1.8 mg+OADs group was not statistically significantly different from the reduction seen in the glargine+OADs group (Table 6.35).

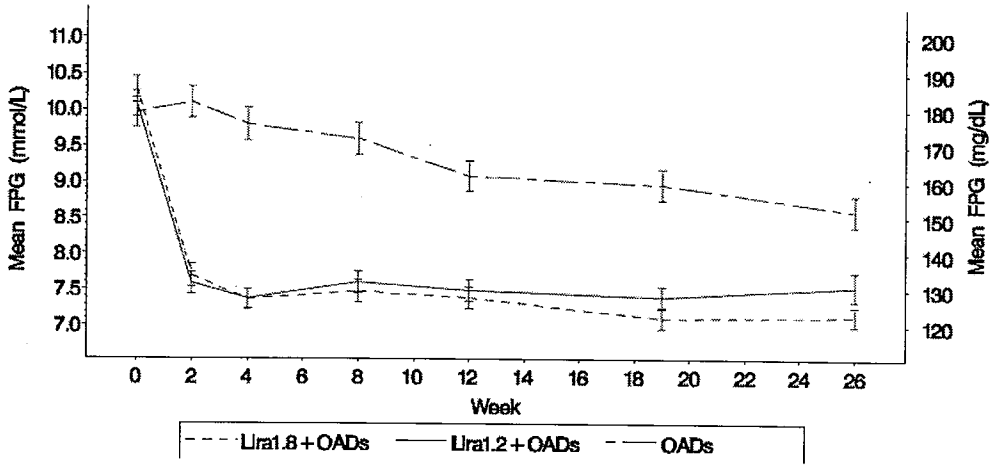
Table 6.35
Analysis of FPG (mg/dL) Change from Baseline at 26 weeks (add-on therapy with two OADs trials)

				Placebo			#Comparator		
	N	Baseline FPG un-adjusted mean (SD)	*Adjusted mean change in FPG (SEM)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value
Trial 1574									
Lira 1.2+OADs	175	181.3 (42.49)	-39.96 (3.74)	-35.56	-44.40; -26.71	<0.0001			
Lira 1.8+OADs	174	184.9 (43.35)	-43.58 (3.62)	-31.94	-40.70; -23.19	<0.0001			
Placebo+OADs	164	179.2 (47.25)	-8.02 (3.86)						
Trial 1697									
Lira 1.8+OADs	225	164.6 (37.6)	-27.92 (3.70)	-37.48	-45.47; -29.48	<.0001	4.24	-2.25; 10.73	0.2002
Placebo+OADs	111	169.6 (36.4)	-32.16 (3.75)						
Glargine+OADs	226	164.1 (35.4)	9.56 (4.43)						

^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.
The p-values correspond to a two-sided test for superiority on a 5% significant level (statistical significance for p <0.05).
*The change in FPG was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline value as covariate
There was no comparator in Trial 1574; the comparator in Trial 1697 was glargine+OADs
Source: [Tables 11-14, 11-15, trial 1574 report] [Tables 11-23, 11-24, trial 1697 report]

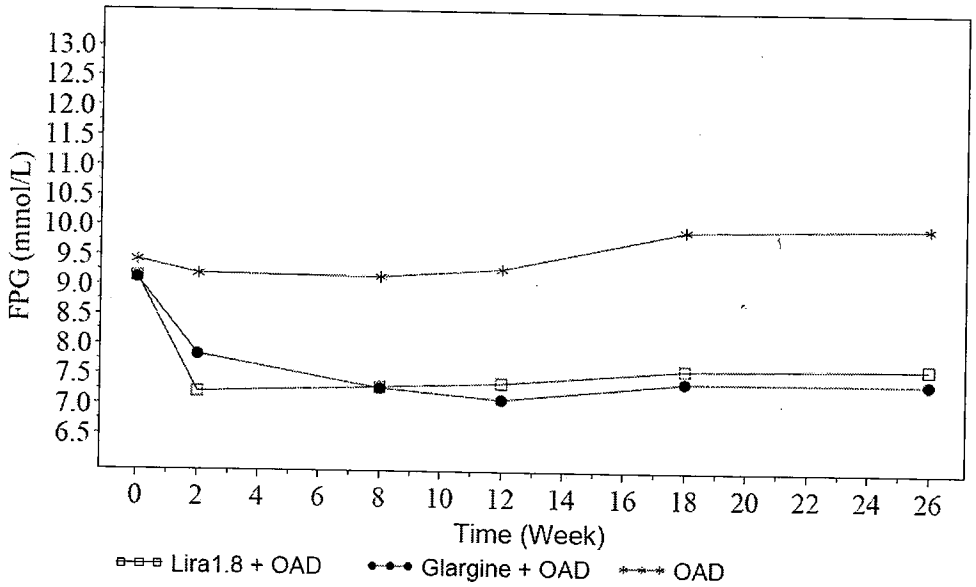
Plots of FPG values by treatment and week are shown for trial 1574 in figure 6.18 and for trial 1697 in figure 6.19. In trial 1574, mean FPG appeared to decrease in the liraglutide+OADs groups within the first 2 weeks after randomization. The placebo+OADs group had a modest downward trend in FPG starting at Week 4. The liraglutide 1.8 mg+OADs and placebo+OADs groups showed sustained FPG reduction through the trial while the liraglutide 1.2 mg+OADs group's mean FPG seemed to increase slightly by the end of the trial. In trial 1697, mean FPG values decreased within the first 2 weeks after randomization for all 3 groups and in the last period of the trial, a slight increase in mean FPG was observed for all 3 treatment groups.

Figure 6.18 – Trial 1574 – Plots of Mean FPG over Time by Treatment – ITT Population



Source: Figure 11-2, trial 1574 report

Figure 6.19 – Trial 1697 – Plots of Mean FPG over Time by Treatment – ITT Population



Source: Figure 11-3, trial 1697 report

b(4)

Reviewer's comment: The proposed label states that [redacted] The upper value of [redacted] mmol/L appears to have come from trial 1574 (the lower value came from trial 1436). Similar to the add-on to one OAD trials, here the FPG also appears to drop within two weeks of starting treatment as the proposed label states. However, the type 1 error rate was not controlled and this was not prespecified as a key endpoint. Therefore, this information may not be appropriate for the product label.

Post-prandial Plasma Glucose

Post-prandial glucose was patient-measured by glucometer 90 minutes after the start of each meal. The values measured at each of the three daily meals were averaged to obtain the mean post-prandial glucose value.

Trial 1574-The decreases in mean post-prandial glucose in the liraglutide+OADs groups were significantly greater than the decrease seen in the placebo+OADs group (both $p<0.0001$). The reductions were -47.97 mg/dL and -46.35 mg/dL for the liraglutide 1.8 mg+OADs and 1.2 mg+OADs groups, respectively. The mean difference between the liraglutide 1.8 mg+OADs group and the placebo+OADs group was -33.47 mg/dL and between the liraglutide 1.2 mg+OADs group and the placebo+OADs group was -31.85 mg/dL.

Trial 1697-The estimated mean reduction in post-prandial plasma glucose in the liraglutide 1.8 mg+OADs group (-32.67 mg/dL) was not statistically significantly different from the reduction seen in the glargine+OADs group (-29.00 mg/dL) (p=0.3364, 95% CI -11.15 – 3.82 mg/dL) but statistically significantly greater than the very slight increase in the placebo+OADs group (0.57 mg/dL, p<0.0001, 95% CI -42.47 – (-24.00) mg/dL).

Reviewer's comment: the label states [redacted] **. The number — mg/dL appears to come from trial 1572 at the 0.6 mg dose. These values were generated from the add-on with one OAD trials but are generally consistent with the add-on to two OADs trials reviewed in this section. The number — mg/dL comes from trial 1436 at the 1.8 mg dose (See section 6.1.4.2.6.2). The label does not indicate that this reduction is on top of background therapy.** b(4)

6.1.4.3.6.2 Body Weight

Estimated change in body weight from baseline to end of treatment and analyses of change in body weight after 26 weeks for trials 1574 and 1697 are shown in Table 6.36. In both trials, change in weight for the liraglutide+OADs treatment groups was significantly different from the placebo+OADs groups in favor of liraglutide. Treatment with liraglutide 1.8mg+OADs was significantly better than treatment with glargine+OADs for weight reduction (although the glargine+OADs group experienced a mean weight gain).

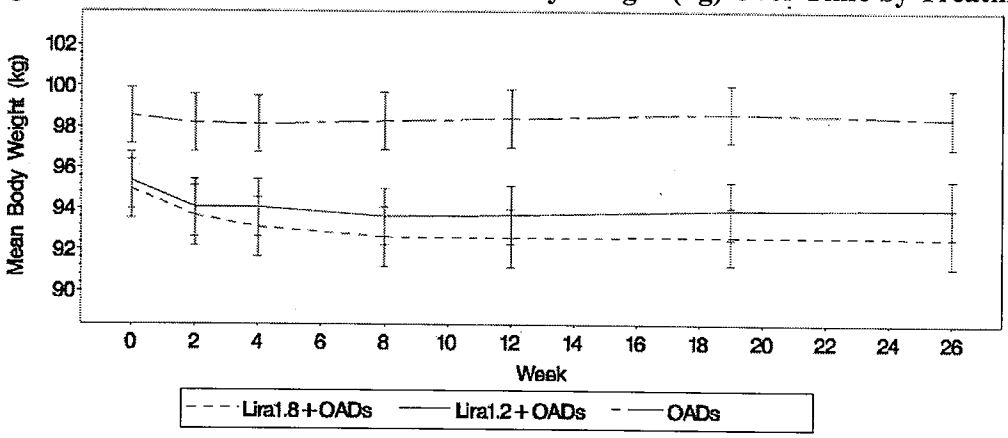
Table 6.36
Analysis of Body Weight (kg) Change from Baseline at 26 weeks (add-on therapy with two OADs trials)

				Placebo			#Comparator		
	N	Baseline body weight un-adjusted mean (SD)	*Adjusted mean change in body weight (SEM)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value
Trial 1574									
Lira 1.2+OADs	176	95.3 (18.3)	-1.02 (0.33)	-1.62	-2.39; -0.85	<.0001			
Lira 1.8+OADs	178	94.9 (19.2)	-2.02 (0.32)	-2.62	-3.39; -1.89	<.0001			
Placebo+OADs	173	98.5 (18.2)	0.60 (0.34)						
Trial 1697									

Lira 1.8+OADs	227	85.8 (19.3)	-1.81 (0.33)	-1.39	-2.10; -0.69	0.0001	-3.43	-4.00; -2.86	<.0001
Placebo+OADs	113	85.4 (16.3)	-0.42 (0.39)						
Glargine+OADs	227	85.2 (17.9)	1.62 (0.33)						
^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin. The p-values correspond to a two-sided test for superiority on a 5% significant level (statistical significance for p <0.05). *The change in body weight was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline value as covariate There was no comparator in Trial 1574; the comparator in Trial 1697 was glargine+OADs									
Source: [Tables 11-8, 11-9, trial 1574 report] [Tables 11-16, 11-17, trial 1697 report]									

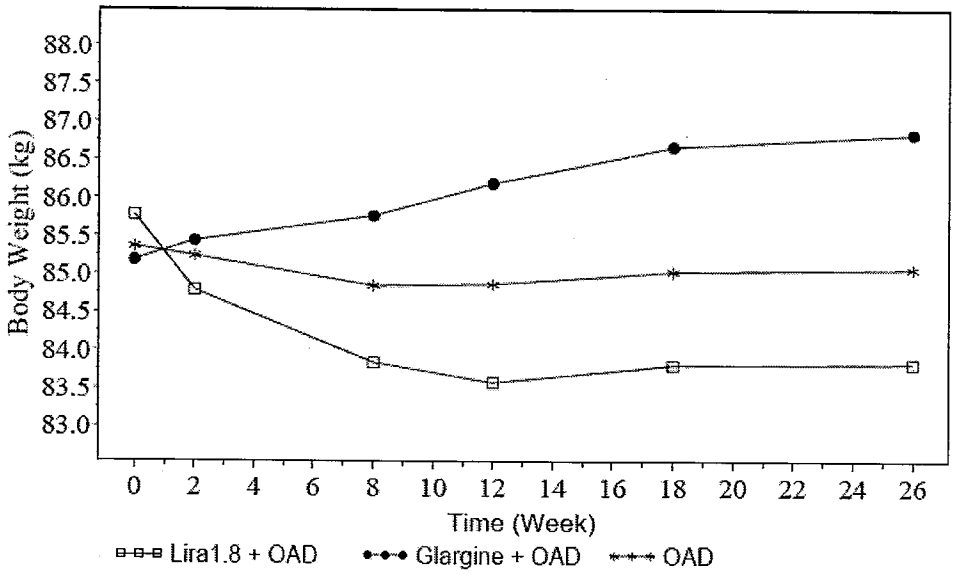
Plots of mean body weight over time by treatment in the ITT population with LOCF are presented in figure 6.20 for trial 1574 and in figure 6.21 for trial 1697.

Figure 6.20 – Trial 1574 – Plot of Mean Body Weight (kg) Over Time by Treatment



Source: Table 14.2-6-20, trial 1574 report

Figure 6.21 – Trial 1697 – Plot of Mean Body Weight (kg) Over Time by Treatment



Source: Figure 11-2, trial 1697 report

However, it should be noted that the duration of the studies was relatively short (only 6 months in duration).
The figures above show that placebo+OADs groups show either mean weight maintenance or weight gain over time, and the liraglutide+OADs groups show mean body weight reduction early on in the trials with most of the weight lost by week 8 to week 12 and with weight maintenance to a slight increase in the latter part of the trial. The plots for completers (not shown) were similar.

Reviewer's comment: This reviewer agrees with the proposed wording in the label b(4)

6.1.4.3.6.3 Blood Pressure

The mean changes after 26 weeks and results of analyses of systolic blood pressure (SBP) for trials 1574 and 1697 are summarized in Table 6.37.

Table 6.37
Analysis of Systolic Blood Pressure (SBP) in mmHg - Change from Baseline at 26 weeks (add-on therapy with two OADs trials)

				Placebo			#Comparator		
	N	Baseline SBP un-adjusted mean (SD)	*Adjusted mean change in SBP (SEM)	Mean difference from com-parator	95% CI	p value	Mean difference from com-parator	95% CI	p value
Trial 1574									
Lira 1.2+OADs	176	128.8 (14.8)	-6.7 (1.1)	-5.6	-8.2; -2.9	<.0001			
Lira 1.8+OADs	178	126.0 (14.2)	-5.6 (1.1)	-4.5	-7.2; -1.9	0.0009			
Placebo+OADs	173	128.2 (14.5)	-1.1 (1.2)						
Trial 1697									
Lira 1.8+OADs	227	134.9 (14.9)	-4.0 (1.3)	-2.5	-5.4; 0.3	0.0791	-4.5	-6.8; -2.2	0.0001
Placebo+OADs	114	133.4 (14.1)	-1.4 (1.6)						
Glargine+OADs	228	133.0 (14.7)	0.5 (1.3)						

^In Trial 1574 the OADs were metformin + rosiglitazone, in Trial 1697 glimepiride + metformin.
The p-values correspond to a two-sided test for superiority on a 5% significant level (statistical significance for $p < 0.05$).
*The change in SBP was estimated using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline value as covariate
There was no comparator in Trial 1574; the comparator in Trial 1697 was glargine+OADs
Source: [Table 11-28, trial 1574 report] [EOT Table 14.2.123, trial 1697 report]

In trial 1574 systolic blood pressure decreased in the liraglutide treatment groups (-6.7 mmHg in the liraglutide 1.2 mg+OADs group and -5.6 mmHg in the liraglutide 1.8 mg+OADs group) from baseline to end of treatment, and decreased only slightly in the placebo+OADs group (-1.1 mmHg). ANCOVA analysis of the estimated mean changes demonstrated that the difference between the liraglutide+OADs groups and the placebo+OADs group was statistically significant. However, there was no difference between the two liraglutide groups. Similar results were obtained when analyzing only completers (data not shown).

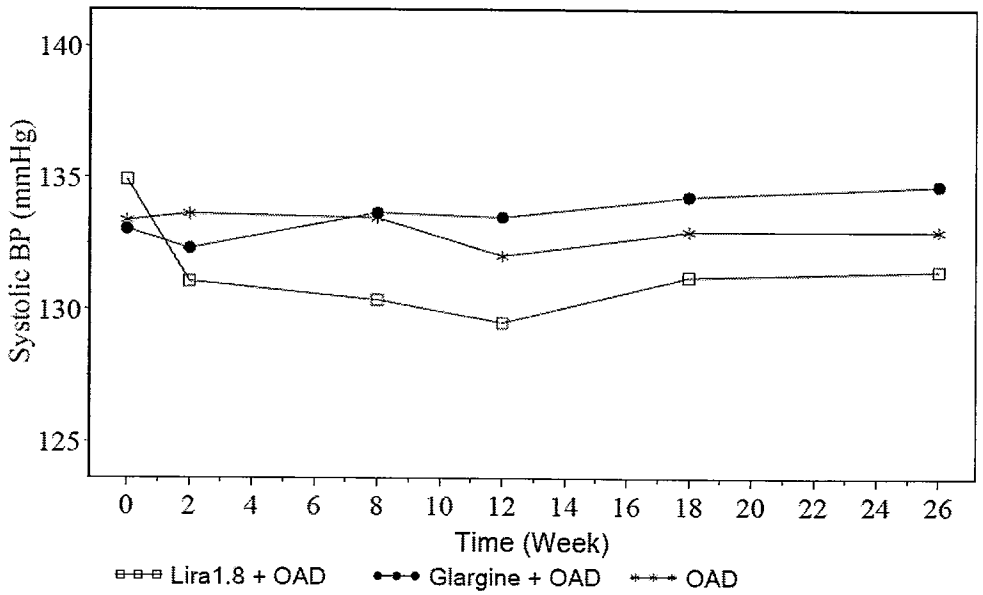
In trial 1697, The liraglutide 1.8 mg+OADs group had an estimated mean reduction in systolic blood pressure of -4.0 mmHg, the placebo+OADs group a mean reduction of -1.4 mmHg and the glargine+OADs group a mean increase of +0.5 mmHg. There was a statistically significant difference between the reduction in the liraglutide 1.8 mg+OADs and the increase in the glargine+OADs group but

not between the reduction in the liraglutide 1.8 mg+OADs and the reduction in the placebo+OADs group. This was also the result when the analysis was performed without LOCF (data not shown).

Reviewer's comment: There seems to be clinically relevant systolic blood pressure reduction in the liraglutide + two OADs groups. Unlike the add-on to one OAD trials, which showed no decrease in SBP compared with the placebo groups, here trial 1574 does show a reduction in SBP compared to placebo. However, these reductions are not dose dependent in trial 1574, and there was only one dose of liraglutide tested in trial 1697 making an assessment of dose-dependency impossible. It is unclear why there is an inconsistency in the blood pressure results across the Phase 3 trials. Also, as mentioned in previous sections, it is unclear if there is confounding by blood pressure medications that may have been given in the trials.

A plot of SBP by treatment and week in the ITT population with LOCF was not presented for trial 1574. For trial 1697, a plot of mean SBP during the trial is presented in Figure 6.22.

Figure 6.22 – Trial 1697 – Plot of SBP (mmHg) by Treatment and Week – ITT with LOCF



Source: Figure 11-5, trial 1697 report

Reviewer's comment: This plot illustrates [redacted] b(4)

6.1.4.3.6.4 Proportion of Subjects Having Metabolic Syndrome

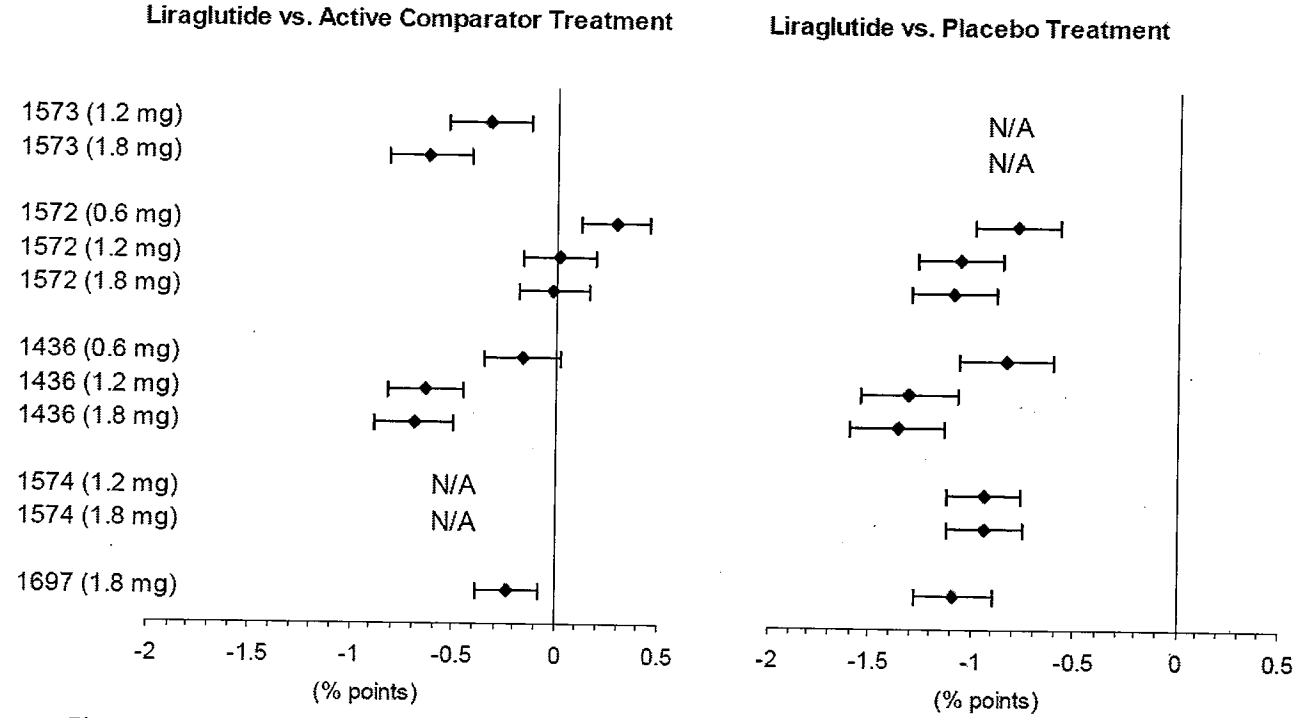
In trial 1574 the proportion of subjects with metabolic syndrome at the end of treatment in the liraglutide 1.2 mg+OADs group was significantly lower than the placebo+OADs group, but the liraglutide 1.8 mg+OADs group did not reach a statistically significant difference from the placebo+OADs group. Similar results were observed by analysis performed with completer values. In trial 1697 there was no statistical difference between the liraglutide 1.8 mg+OADs group and the two other arms of the trial in the proportion of subjects with metabolic syndrome.

Reviewer's comment: The findings in the add-on to two OADs trials related to metabolic syndrome do not support the labeling claim '

Note that the add-on to one OAD trials also did not show a consistent effect. Further, as mentioned previously the concept of "metabolic syndrome" is problematic because of the several different definitions employed by researchers and clinicians. Therefore, this information has not been previously allowed into labeling by the Division. b(4)

6.1.4.4 Efficacy Results Regarding Liraglutide Dose

This figure from the Sponsor's summary of clinical efficacy compares the estimated mean treatment differences for the primary efficacy variable HbA1c change from baseline (± 95% CI) for the five pivotal phase 3 studies. The figure demonstrates clearly that only in trial 1573 was there a notable difference in efficacy between the 1.2 mg and 1.8 mg doses of liraglutide for HbA1c lowering. The reason for this finding is unclear but could be that trial 1573 is a one-year trial whereas the others are 6-month trials. However, at the 6-month timepoint for trial 1573 there appears to be a statistically significant difference between the 1.2 mg and 1.8 mg doses (see Figure 6.7) albeit a smaller absolute difference than at 52 weeks.



Source: Figure 3-2, Summary of Clinical Efficacy

This finding (i.e. that only in trial 1573 was there a notable difference in efficacy between the 1.2 mg and 1.8 mg) was also shown by ANCOVA analysis as shown in the following table (6.38):

Table 6.38 - Comparing Liraglutide Dose Levels

	Comparison after 26 weeks of treatment		
Treatment/comparison	LS Means/Estimated Treatment Difference	95% CI	p value
Trial 1573			
Liraglutide 1.8 mg	-1.11		
Liraglutide 1.2 mg	-0.81		
Liraglutide 1.8 vs. 1.2	-0.29	-0.50; -0.09	0.0046
Trial 1572			
Liraglutide 1.8 mg	-1.01		
Liraglutide 1.2 mg	-0.97		
Liraglutide 0.6 mg	-0.70		
Liraglutide 1.8 vs. 1.2	-0.04	-0.21; 0.13	0.6484
Liraglutide 1.2 vs. 0.6	-0.27	-0.44; -0.10	0.0021
Trial 1436			
Liraglutide 1.8 mg	-1.11		
Liraglutide 1.2 mg	-1.07		
Liraglutide 0.6 mg	-0.63		
Liraglutide 1.8 vs. 1.2	-0.04	-0.23; 0.15	0.6785
Liraglutide 1.2 vs. 0.6	-0.44	-0.63; -0.25	<0.0001

Trial 1574				
Liraglutide 1.8 mg	-1.52			
Liraglutide 1.2 mg	-1.54			
Liraglutide 1.8 vs. 1.2	0.02	-0.16; 0.20	0.8106	
Explanatory variables are Previous Treatment (Monotherapy/Combination), Randomized Treatment and baseline HbA1c value as a covariate. Source: Sponsor's Table 3-4				

When analyzing liraglutide treatment with regard to the number of subjects reaching HbA1c targets, the small difference between liraglutide 1.2 mg and 1.8 mg can be distinguished. The table below (6.39) of percent reaching targets shows better why 1.8 should be considered for the maximal approved dose depending on the risk:benefit profile determined based on the safety review.

Table 6.39 - Comparing Liraglutide Treatment Arms with Regard to Number of Subjects Reaching HbA1c <7%

	Comparison after 26 weeks of treatment					
Treatment/comparison	N	n	n/N	Odds/Odds Ratio	95% CI	p value
Trial 1573						
Liraglutide 1.8 mg	234	119	0.51	1.22		
Liraglutide 1.2 mg	236	101	0.43	0.82		
Liraglutide 1.8 vs. 1.2				1.50	1.00 – 2.25	0.0484
Trial 1572						
Liraglutide 1.8 mg	236	100	0.42	0.79		
Liraglutide 1.2 mg	232	82	0.35	0.48		
Liraglutide 0.6 mg	239	67	0.28	0.34		
Liraglutide 1.8 vs. 1.2				1.64	1.06 – 2.53	0.0265
Liraglutide 1.2 vs. 0.6				1.44	0.92 – 2.27	0.1121
Trial 1436						
Liraglutide 1.8 mg	226	94	0.42	0.91		
Liraglutide 1.2 mg	223	77	0.35	0.53		
Liraglutide 0.6 mg	224	54	0.24	0.27		
Liraglutide 1.8 vs. 1.2				1.71	1.10 – 2.68	0.0182
Liraglutide 1.2 vs. 0.6				2.00	1.24 – 3.22	0.0044
Trial 1574						
Liraglutide 1.8 mg	177	95	0.54	1.51		
Liraglutide 1.2 mg	174	100	0.57	1.86		
Liraglutide 1.8 vs. 1.2				0.81	0.49 – 1.35	0.4160
Explanatory variables are Previous Treatment (monotherapy/combination), Randomized Treatment and baseline HbA1c value as a covariate Source: Sponsor's Table 3-8						

6.1.4.5 Data presented at the June 1, 2009 Type A meeting between the Division and the Sponsor

Currently, exenatide is the only approved GLP-1 agonist and is marketed as Byetta®. For the Type A meeting between the Division and the Sponsor held on June 1, 2009, the Sponsor submitted a summary of the results of trial 1797 which compared liraglutide to exenatide In this randomized, open-label, parallel group study, subjects who were on metformin, sulfonylurea, or both were randomized in a 1:1

ratio to either liraglutide or exenatide. From week 0 to 26 weeks (ITT with LOCF) the reduction in HbA1c was -1.12% for liraglutide and -0.79% for exenatide, which resulted in a statistically significant treatment difference of -0.33% in favor of liraglutide (95% CI, -0.47 – -0.18%, p <0.0001). A 14 week extension was also conducted for this trial in which subjects in the exenatide group were switched to liraglutide at week 26 and continued on therapy until week 40. From week 26 to week 40 (LOCF), the mean decreases in HbA_{1c} were -0.32% for the exenatide→liraglutide group (p <0.0001) and -0.06% for the liraglutide→liraglutide group (p =0.12). From week 0 to week 40 (LOCF), the mean decreases in HbA_{1c} were 1.17% for the exenatide→liraglutide group and 1.29% for the liraglutide→liraglutide group (p <0.0001 for both groups). 86% of subjects (N=202/235) treated with liraglutide and 81% of subjects (N=187/232) treated with exenatide completed the 26-week, head-to-head phase of the trial. 99% of randomized subjects (N=199/202) who entered the extension in the liraglutide→liraglutide group and 95% of subjects (N=177/187) who entered the extension in the exenatide→liraglutide group completed the 14-week extension. The sponsor also noted that antibody development and nausea were less frequent with liraglutide than with exenatide. In this head-to-head trial, 58% of patients treated with exenatide were positive for antibodies while only 1.5% of patients treated with liraglutide had antibodies.

6.1.4.6 Efficacy Conclusions

The key phase 3 studies fulfill the criteria for "adequate and well-controlled" because

- the study objectives and statistical plans were stated *a priori*
- the study designs used valid control groups given adequate doses of comparator drugs in most cases (see important considerations and limitations)
- the inclusion and exclusion criteria assured selection of patients with type 2 diabetes (HbA1c inclusion criteria)
- bias was limited by randomization, blinding, and objective, standardized endpoints

Liraglutide's major efficacy findings (1-year monotherapy)

- Liraglutide lowered HbA1c from baseline by -0.84% to -1.14%, on average (not placebo-adjusted)
- Liraglutide lowered HbA1c by -0.34% to -0.62% relative to glimepiride
- Maximal HbA1c reduction occured by 12 weeks and was maintained through week 52
- Liraglutide 1.8 mg and liraglutide 1.2 mg were both superior to glimepiride for HbA1c lowering
- Liraglutide 1.8 mg was superior to liraglutide 1.2 mg for HbA1c lowering
- The percentage of subjects achieving ADA and AACE targets was significantly greater in the liraglutide groups as compared to the glimepiride group
- There was no reported notable effect on change in HbA1c due to country, gender, race, ethnicity, age, and BMI.
- Liraglutide (and glimepiride) was more effective among patients with higher baseline HbA1c, which may reflect regression to the mean

Liraglutide's major efficacy findings (6-month add-on therapy with one OAD)

- Liraglutide add-on to metformin 2000 mg/day lowered HbA1c by -0.78% (0.6 mg qd) and -1.06% (1.2 mg qd) to -1.09% (1.8 mg qd) relative to placebo add-on to metformin; liraglutide add-on to metformin was superior to placebo add-on to metformin
- Liraglutide add-on to metformin 2000 mg/day was non-inferior to glimepiride add-on to metformin
- Liraglutide add-on to glimepiride 2 - 4 mg a day reduced HbA1c by -0.83% (0.6 mg qd) and -1.31% (1.2 mg qd) to -1.36% (1.8 mg qd) relative to placebo add-on to glimepiride
- Liraglutide add-on to glimepiride 2 - 4 mg a day was superior to rosiglitazone 4 mg add-on to glimepiride
- Liraglutide 1.2 mg and 1.8 mg qd showed similar efficacy when added to one other OAD
- Liraglutide add-on therapy with one OAD resulted in near-maximal HbA1c reduction by week 12
- Liraglutide add-on to one OAD maintained HbA1c reduction through week 26, although with a slight increase at the end of the trials

Liraglutide's major efficacy findings (6-month add-on therapy with two OADs)

- Liraglutide add-on to metformin and rosiglitazone lowered HbA1c by -0.94% at both doses of liraglutide relative to placebo add-on to those same OADs; liraglutide was superior to placebo plus OADs
- Liraglutide 1.8 mg add-on to glimepiride and metformin lowered HbA1c by -1.09% relative to placebo plus glimepiride and metformin
- Liraglutide 1.8 mg add-on to glimepiride and metformin lowered HbA1c by -0.24% relative to glargine plus glimepiride and metformin
- Liraglutide 1.8 mg add-on to glimepiride and metformin was superior to placebo add-on to the two OADs and glargine add-on to the two OADs
- Liraglutide add-on therapy with two OADs resulted in near-maximal HbA1c reduction by week 12
- Liraglutide add-on to two OADs maintained HbA1c reduction through week 26, although with a slight increase at the end of one trial

Other efficacy findings

A summary report submitted by the Sponsor and data presented at the Type A meeting between the Division and the Sponsor on June 1, 2009, suggests that liraglutide may have greater efficacy than exenatide, the only other approved member of the GLP-1 analogue class (section 6.1.1.5). These data have not yet been fully reviewed by the Division and therefore, these data were not used by this reviewer in the decision to recommend approval. However, these data may be considered by signatory authorities for regulatory action because they provide some information about the potential role of liraglutide in the anti-diabetes drug armamentarium.

Important considerations and limitations

One limitation of some of the phase 3 pivotal studies is the low enrollment of non-Caucasians, particularly blacks and Asians. These minority populations will likely make up a sizable segment of the real world population treated with liraglutide because they are at higher risk for diabetes than

Caucasians. The Sponsor should increase enrollment of minorities in ongoing liraglutide studies to obtain a better assessment of efficacy in these populations.

Given the similar efficacy between liraglutide 1.2 mg and 1.8 mg qd, it remains to be seen whether the small benefit of 1.8 mg over 1.2 mg is worth any extra risk incurred by the higher dose. This decision will be made taking the safety review into account.

Rosiglitazone 8 mg qd is the maximal FDA approved dose. In trial 1436, the highest proposed doses of liraglutide are being compared to the half maximal dose of rosiglitazone (4 mg qd). Therefore, caution is warranted in concluding that liraglutide is superior to rosiglitazone given at the maximal FDA approved dose of 8 mg.

In trial 1697, the rate of attainment of fasting plasma glucose goals for the glargine comparator group was notably low. Therefore, caution is also warranted in making conclusions regarding the efficacy of liraglutide added to two OADs to the efficacy of glargine added to those same OADs.

6.1.5 Clinical Microbiology

Not applicable to this NDA

6.1.6 Efficacy Conclusions

See section 6.1.4.6

7 INTEGRATED REVIEW OF SAFETY

The entirety of section 7 was completed by Dr. Mahoney in her Clinical Safety Review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor's proposed dosing regimen is as follows:
For all patients liraglutide treatment should be initiated with a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on tolerability and/or clinical response and after at least one week at 1.2 mg, the dose can be increased to 1.8 mg to achieve maximum efficacy. The dose can be given any time of day and does not need to be given in relation to meals.

This reviewer has full confidence that the doses and regimen have been studied adequately. Please see section 5.3 for a discussion of exposure – response relationships. The findings discussed in that section suggest that the 1.2 mg and 1.8 mg doses will have similar efficacy in long-term trials and in fact, the efficacy review identified very little difference between the 1.2 mg and 1.8 mg dose in terms of the primary efficacy endpoint – HbA1c (see section 6). The question is then raised whether 1.2 mg would be the appropriate maximal dose if liraglutide were to be approved. One consideration is the dose-toxicity relationship and the differential rate of adverse events between the 1.2 mg and 1.8 mg dose (if one exists); if the rate of adverse events were significantly higher with the 1.8 mg dose one might consider only approving up to 1.2 mg daily. (See section 7.4.2.1 in Dr. Mahoney's safety review for explorations for dose dependency of adverse reactions).

From an efficacy standpoint, this reviewer agrees with the sponsor's dosing recommendations because in three of the four of the phase 3 efficacy trials that evaluated both the 1.2 mg and 1.8 mg doses (trials 1573, 1572, 1436) there was a greater proportion of subjects reaching glycemic targets of $< 7\%$ and/or $\leq 6.5\%$ with 1.8 mg. (In trial 1574 the proportions meeting targets were similar between the doses). However, if the Clinical Safety Review reveals significant adverse events with the 1.8 mg dose compared with the 1.2 mg dose, this reviewer believes that the 1.2 mg dose would be sufficient.

8.2 Drug-Drug Interactions

See Dr. Mahoney's safety review.

8.3 Special Populations

Special dosing considerations based on demographics

There are no special dosing considerations based on demographics and diabetes disease characteristics except that liraglutide has not been tested in the pediatric population and therefore, cannot be recommended for use in children at this time. See section 5.1 for a discussion of the pharmacokinetic investigations in demographic subgroups which suggest that special dosing considerations are not warranted. Comparison of the clinical efficacy of liraglutide in sub-populations was assessed through statistical testing of interaction between treatment effect and demographic and other intrinsic factors, based on data from the five phase 3 trials 1573, 1572, 1436, 1574 and 1697. These analyses were performed in order to evaluate whether there were any subsets of the population that demonstrated differences with respect to the effectiveness, as measured by HbA1c, among treatments. Both data from the individual trials as well as pooled data from the four 26-weeks combination trials (Trials 1572, 1436, 1574 and 1697) were assessed. Pooled analyses using all of the phase 3 studies took into account factors of demographic differences between groups of subjects (gender, age, race, ethnicity, BMI and body weight), and disease (baseline HbA1c, duration of diabetes, previous anti-diabetic treatment (diet, oral antidiabetic drug monotherapy, or oral antidiabetic drug combination therapy). From an efficacy standpoint, there were no meaningful differences in efficacy across these variables that would affect this product's use.

Special dosing considerations based on renal and hepatic impairment

Based on clinical pharmacology data no dose adjustment is proposed for renal and hepatic impairment subjects (see section 5.1). The clinical efficacy review of the phase 3 program supports this conclusion to some extent (see caveat below). In order to assess whether disease-related factors influence the clinical efficacy of treatment with liraglutide, statistical tests were performed for interactions among treatment and disease factors either related to diabetes or resulting from comorbidities. Results from the test for interaction among treatment and disease-related factors on glycemic control as measured by HbA1c by the end of 26 weeks of treatment (Trials 1572, 1436, 1574, 1697) and 52 weeks of treatment (Trial 1573) on the individual data and on the pooled data from the four 26-weeks combination therapy trials displayed no clinically relevant effect on any of the selected disease factors: serum albumin, creatinine or ALT. One caveat, however, is that although the clinical pharmacology program evaluated severe renal and hepatic impairment, the phase 3 clinical program excluded those patients. Exclusion criteria for the phase 3 studies included impaired renal function, defined as serum creatinine ≥125 µmol/L (≥1.4 mg/dL) for males and ≥110 µmol/L (≥1.24 mg/dL) for females (although renal function based on CrCl or eGFR (e.g., Cockcroft-Gault or MDRD) often reveals that there are some patients with mild renal impairment in the studies) and impaired liver function, defined as alanine aminotransferase or aspartate aminotransferase ≥2.5 times upper limit of normal. The only therapeutic experience in patients with moderate renal impairment (creatinine clearance of 30-59 ml/min) and severe renal impairment (creatinine clearance below 30 ml/min) comes from one clinical pharmacology study. In addition, the therapeutic experience in patients with all degrees of hepatic impairment is currently limited again stemming from one clinical pharmacology study.

Special dosing considerations in pregnancy

There are insufficient data for the use of liraglutide in pregnant and nursing women, and therefore, efficacy in pregnant and nursing women is unknown. However, there is no known reason why the efficacy in pregnancy would be different. The use of liraglutide in pregnancy is primarily a safety issue.

8.4 Pediatrics

The Sponsor has studied liraglutide in patients aged 18 years and older. In the United States, the prevalence of type 2 diabetes has been increasing substantially over the past decade in parallel with the obesity epidemic. Although originally considered a disease of middle- and older-aged people, type 2 diabetes is being increasingly diagnosed in obese children. Therefore, liraglutide needs to undergo testing in children to comply with the Pediatric Research Equity Act (PREA). With the original NDA the sponsor submitted a partial pediatric waiver for children below 10 years of age because pediatric studies in this age group are impossible or highly impractical, and requested a deferral for older children. At the May 4, 2004 end-of-phase 2 meeting conducted under IND 61,040 between the sponsor and the Agency, the Division agreed that the sponsor's plan to seek a waiver for subjects below — years of age and a deferral for older children was acceptable, provided regulations did not change by the time the initial NDA was submitted. At the pre-NDA meeting on February 5, 2008, the sponsor proposed to b(4)

revise the age range for the pediatric development plan to include a deferral for children of age 10 and older, effectively changing the age cut-off for the proposed waiver population.

The proposed pediatric development plan includes a pharmacodynamics/pharmacokinetics study (NN2211-1800) and an efficacy and safety study (NN2211-3659). These studies have not yet been formally reviewed by DMEP clinical reviewers or by PeRC (Pediatric Review Committee) at the time of this review. Please see Dr. Mahoney's review for more information regarding pediatric studies.

8.5 Advisory Committee Meeting

See Dr. Mahoney's safety review for discussion of the Advisory Committee Meeting held Apr 2009. Please see also Dr. Mahoney's review for a discussion of the CDER Regulatory Briefing held June 26, 2009.

8.6 Literature Review

Published literature used in this review is referenced throughout the review (references are listed at the end of the document).

8.7 Postmarketing Risk Management Plan

See Dr. Mahoney's safety review.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy conclusions are discussed in section 6.1.4.5.

9.2 Recommendation on Regulatory Action

The recommendation on regulatory action is discussed in section 1.1.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

See Dr. Mahoney's safety review.

9.3.2 Required Phase 4 Commitments

See Dr. Mahoney's safety review.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

Comments regarding labeling related to efficacy data are included throughout section 6.

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Reports

Details of phase 2 studies

Dose Selection/Dose Regimen Trials (Phase 2 trials relevant for efficacy)

Trial 1571
This is the phase 2 study cited by the Sponsor as the study that determined the doses for the phase 3 study.
Design: 14 week, multicenter, four-arm, double-blind, randomized (1:1:1:1), parallel group, placebo-controlled trial with three doses of liraglutide (fixed doses of 0.65 (n=40), 1.25 (n=42) or 1.90 (n=41) mg/day liraglutide, once daily with forced titration during 1-2 weeks for the two higher doses) vs. placebo (n=40) in patients with type 2 diabetes either on diet/exercise therapy or drug monotherapy (baseline HbA1c 6.4 – 10.0%). *Efficacy Results:* Liraglutide dose-dependently reduced HbA1c levels in all active groups compared with placebo ($p<0.0001$). The estimated difference of change in HbA1c from baseline to end of treatment between the 1.90 mg dose and placebo was -1.74%, and between the 1.25 mg dose and placebo was -1.69%, with 46% of subjects from both groups achieving an HbA1c level <7.0% (placebo group: 5%). The estimated difference of change in HbA1c from baseline to end of treatment between the 0.65 mg dose and placebo was -1.27%

Reviewer's comment: The 1.25 and 1.90 mg doses appear equally effective in this trial with the 0.65 mg dose effective compared with placebo as well. The minimally effective dose was not established by this phase 2 study. The maximally effective dose seems to be close to 1.90 mg.

Trial 1310
Primary Objectives: to establish the dose-response relationship on glycemic control of five dose levels of liraglutide and placebo. Design: A 12-week, multi-center, multi-national, seven-arm parallel-group trial with five doses of liraglutide (0.045, 0.225, 0.45, 0.60 or 0.75 mg/day, s.c., double-blind) versus placebo (s.c., double-blind) or glimepiride (1 or 2 mg, p.o., open-label) in subjects with type 2 diabetes mellitus. *Efficacy Results:* The effect of liraglutide on HbA1c increased with increasing dose; the estimated maximal effect, Emax, was a 1.74 percent unit decrease, while the estimated dose for half-maximal effect, ED50, was 0.76 mg. As the estimated ED50 was similar to the highest dose investigated, this indicates that only the lower part of the dose-response curve has been established in this trial. A dose-response relationship was found for glycemic control. After 12 weeks of treatment, HbA1c had decreased in all but the lowest liraglutide dose group. Mean HbA1c (% [95%CI]) decreased by -0.70 [-1.1;-0.3] at 0.60 mg and -0.75 [-1.1;-0.4] at 0.75 mg and the difference was significant as compared to placebo ($p=0.0002$ and $p<0.0001$, respectively).

Reviewer's comment: This trial establishes that the ED50 is 0.76 mg. Therefore, the selection of 0.6 mg as the starting dose in the phase 3 program is appropriate.

Trial 1333
Primary Objectives: To evaluate the effect of liraglutide in obese subjects with type 2 diabetes mellitus on weight. Design: An 8-week, single-centre, double-blind, parallel-group mechanism of action trial with one dose of liraglutide (0.60 mg/day, s.c.) versus placebo in subjects with type 2 diabetes mellitus. Glycemic control was not the primary endpoint of this study, however treatment with liraglutide improved glycemic control as measured by a reduction in HbA1c (liraglutide: -0.33%; placebo: 0.47%, p=0.028) as compared with placebo. The placebo subtracted change in HbA1c was 0.8%.

Reviewer's comment: The HbA1c reduction in this trial is consistent with the results of trial 1310 for the 0.6 mg dose.

Trial 2072
Primary Objectives: to determine the dose-response relationship between body weight and five escalating doses of liraglutide in subjects with type 2 diabetes mellitus.
Design: A 12-week multi-center, double-blind, parallel-group, double-dummy trial with 5 doses of liraglutide (0.045, 0.225, 0.45, 0.60 or 0.75 mg/day, s.c. q.d.) versus metformin (1000 mg, p.o. b.i.d.) in obese subjects with type 2 diabetes mellitus. HbA1c was a secondary endpoint in this trial. *Efficacy results*: The primary efficacy endpoint in this trial was body weight, but HbA1c was obtained as a secondary efficacy endpoint. Results showed that the subjects were well controlled at baseline with a mean HbA1c ranging from 6.76 to 7.38 %. Mean HbA1c changes (all increases) from baseline for 0.045, 0.225, 0.45, 0.60, 0.75 mg liraglutide and metformin were 1.28, 0.86, 0.22, 0.16, 0.30 and 0.09 %, respectively. No significant differences in HbA1c were found between liraglutide and metformin groups at the three highest liraglutide dose levels (0.45, 0.6 and 0.75 mg). The two lowest liraglutide doses (0.045 and 0.225 mg) were not able to maintain HbA1c values comparable to metformin.

Trial 1499
Primary Objectives: to assess the effect on glycemic control of individual maximum effective dose of liraglutide as add-on therapy to metformin, and to compare this to the effect of maximum effective dose of metformin given as monotherapy, assessed by serum glucose. Design: A 5-week, multi-centre, multi-national, double-blind, double-dummy, randomized, parallel, individual dose titration trial with 0.5–2.0 mg/day liraglutide as add-on to metformin (1000 mg, p.o., b.i.d.) versus liraglutide + placebo, metformin + placebo, or metformin + glimepiride (2–4 mg, adjusted according to glycemic control). *Efficacy Results:* Liraglutide in combination with metformin produced significant improvement in glycemic control, as assessed by fasting serum glucose, compared to metformin monotherapy, by -3.90% (95% CI [-4.95;-2.85], p<0.0001 and compared to metformin + glimepiride treatment, by -1.25% (95% CI [-2.25;-0.25], p=0.0146. Likewise, liraglutide as monotherapy significantly improved glycemic control compared to metformin monotherapy, by -1.37% (95% CI [-2.43;-0.32], p=0.0109. The dose-response curve (and thus the maximum effect) for liraglutide + metformin was established within the tested dose range with ED_{50} = 0.51 mg and ED_{90} = 0.80 mg.

Reviewer's comment: This trial suggests a slightly lower dose might be effective compared to the minimally effective dose shown in the other phase 2 studies. However, the primary efficacy endpoint in this trial was not HbA1c.

Trial 1334 (Exploratory Japanese Trial)
Primary Objectives: to evaluate the dose-response relationship on glycemic control as assessed by HbA1c of four doses of liraglutide and placebo in Japanese subjects with type 2 diabetes mellitus. Design: A 14-week multi-centre, double-blind, randomized (1:1:1:1:1), parallel, placebo-controlled Japanese trial with four doses of liraglutide (0.1, 0.3, 0.6 and 0.9 mg/day, s.c., q.d.) versus placebo in Japanese subjects with type 2 diabetes mellitus. *Efficacy Results:* HbA1c decreased dose-dependently in all treatment groups compared to placebo from a baseline value of 8.3% by -0.8%, -1.2%, -1.6% and -1.9%, respectively ($p<0.0001$). HbA1c <7.0 % was achieved by 22, 43, 62 and 75% of the subjects in the liraglutide groups compared to 9% in the placebo group.

Reviewer's comments: **In summary the selected doses for the phase 3 studies appear justified by the phase 2 data.**

10.2 Line-by-Line Labeling Review

Not performed

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Welchol Prescribing Information, revised January, 2008

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22341	ORIG 1		VICTOZA (LIRAGLUTIDE)

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

/s/

LISA B YANOFF
08/13/2009

HYLTON V JOFFE
08/13/2009
Please see CDTL memorandum.

CLINICAL REVIEW

Application Type	NDA
Submission Number	22341
Submission Code	N
Letter Date	23 May 2008
Stamp Date	23 May 2008
PDUFA Goal Date	23 Mar 2009 (Division Action Goal Date 26 Aug 2009)
Reviewer Name	Karen Murry Mahoney, MD, FACE
Review Completion Date	22 Jul 2009
Established Name	Liraglutide injection
(Proposed) Trade Name	Victoza®
Therapeutic Class	Glucagon-like-peptide-1 analogue
Applicant	Novo Nordisk®
Priority Designation	S
Formulation	Subcutaneous injection
Dosing Regimen	0.6-1.8 mg SQ q day
Indication	Improve glycemic control in patients with type 2 diabetes mellitus
Intended Population	Adults with type 2 diabetes mellitus

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical safety reviewer does not recommend approval of liraglutide at this time, for two reasons:

- A strong signal in animals of C-cell tumors of the thyroid gland, with inadequate duration of controlled study in humans to adequately assess the human risk, and
- Inadequate data to assess the risk of major adverse cardiovascular events in humans.

In the United States, there are already 11 classes of drugs approved for glycemic control in type 2 diabetes, and one other in this class. The need for new therapies for type 2 diabetes is not so urgent that one must tolerate a significant degree of uncertainty regarding serious risk concerns.

Other safety concerns exist for liraglutide, but are not part of the basis for this recommendation.

It should be noted that this reviewer conducted only the clinical safety review, and that this recommendation is made solely on the basis of safety information. The clinical efficacy review of liraglutide is ongoing by Dr. Lisa Yanoff. It is possible that signatory authorities, after having considered efficacy information and all other available data regarding liraglutide, may reasonably decide that the drug has an acceptable risk:benefit ratio.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Not applicable, as approval is not recommended. However, the applicant's proposed risk management activities are discussed in Section 8.7.

1.2.2 Required Phase 4 Commitments

Not applicable, as approval is not recommended. However, the applicant's proposed Phase 4 activities are discussed in Section 8.7.

1.2.3 Other Phase 4 Requests

Not applicable, as approval is not recommended. However, the applicant's proposed Phase 4 activities are discussed in Section 8.7.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Liraglutide injection (Victoza®) is an analogue of human glucagon-like-peptide-1, intended for the treatment of type 2 diabetes mellitus. Native glucagon-like-peptide-1 is a gut incretin hormone which causes glucose-dependent secretion of insulin. The native hormone has a very short half-life, due to rapid degradation by dipeptidyl-peptidase-4. Liraglutide's altered structure renders it less susceptible to degradation, and thus prolongs its half-life. It is intended for once daily subcutaneous injection.

At the time of NDA submission, there had been 38 completed trials of liraglutide. At the time of the 120-day safety update, liraglutide had been administered to 4430 patients for a total of 2434 patient-years. Of these patients, 2412 had received liraglutide for ≥24 weeks, and 840 had received it for ≥50 weeks.

1.3.2 Efficacy

Please see Dr. Yanoff's clinical efficacy review.

1.3.3 Safety

Up to the time of the safety update, there were 4 deaths among patients who had received liraglutide, and 3 deaths among patients who had received comparator. There was no evidence of an association between liraglutide and overall mortality or cause-specific mortality.

Withdrawals due to adverse events were more common among liraglutide-treated patients than among comparator-treated patients. This difference was primarily due to withdrawals due to gastrointestinal adverse events. These withdrawals were primarily in the two higher dose groups (1.2 and 1.8 mg). The most common reason for withdrawal from the 0.6 mg dose group was ineffectiveness of therapy. All withdrawals due to injection site reactions (n=8) and all withdrawals due to hepatobiliary adverse events (n=5) were among liraglutide-treated patients.

For the clinical safety reviewer, there were two major safety concerns that affected approvability; inadequate data to assess the human risk of medullary thyroid carcinoma, and inadequate data to assess the risk of major adverse cardiovascular events.

Medullary thyroid carcinoma and C-cell tumors are discussed in Sections 7.1.3.3.2 and 9.1.1. In lifetime carcinogenicity studies in rats and mice, liraglutide caused C-cell tumors in both species, in both genders, at clinically relevant exposures. In rats, adenomas and carcinomas occurred in both genders at clinically relevant exposures. In mice, adenomas occurred at clinically relevant exposures, but carcinomas were seen only in females at high exposures. However, in rodents, C-cell adenomas are considered to be a precancerous lesion. There was a long latent period between initial exposure and development of C-cell tumors. A similar signal is being noted in interim carcinogenicity data for other long-acting glucagon-like-peptide-1 analogues. In rodents,

calcitonin may not have been a reliable biomarker for development of these tumors; in humans, serum calcitonin has historically served as a clinical marker for medullary thyroid carcinoma, the human form of C-cell carcinoma. Calcitonin physiology differs somewhat between rodents and humans, and rodent thyroids may be more likely to contain glucagon-like-peptide-1 receptors. The applicability of these rodent findings to the risk of human medullary thyroid carcinoma is uncertain. In a meeting of the Endocrine and Metabolic Drugs Advisory Committee, the Committee voted 12 to 1 that the applicant had not established that the rodent C-cell tumor risk was not relevant to humans.

Medullary thyroid carcinoma is ordinarily a rare tumor, which occurs in sporadic and familial forms. No drug-induced forms have been described in humans. The described sporadic and familial forms are usually, although not always, indolent in terms of rate of growth. Although usually indolent in terms of rate of growth, the tumor can be aggressively invasive if not discovered in time for complete resection, and medullary thyroid carcinoma is considered to be a more serious form of thyroid cancer than the more common differentiated thyroid cancers. Early complete surgical resection is currently the only curative option. Those who undergo complete resection usually survive, and go on to die of something other than medullary thyroid cancer. However, the outcome for nonresectable cases is much worse, with a median survival of 3.2 years, and with medullary thyroid cancer as the usual cause of death. In these patients, local neck invasion, with asphyxia or other catastrophic local invasive process, is often the cause of death.

In the liraglutide program, there were no treatment-emergent cases of medullary thyroid carcinoma, but one might not expect to see this relatively indolent tumor over the duration of the typical drug development program.

A total of five liraglutide-treated patients and one comparator-treated patient had C-cell hyperplasia. These represent approximate rates per 1000 patient-years of 1.7 (5 cases/2882 PY) and 0.7 (1 case/1486 PY), respectively. There is controversy in the medical literature regarding whether C-cell hyperplasia is a preneoplastic lesion in humans, and C-cell hyperplasia has been noted at autopsy in some people who had no known thyroid disease prior to death.

Calcitonin is a peptide hormone which is synthesized primarily by the C-cells of the thyroid. There are multiple stimuli for release, including calcium, several gut hormones, proton pump inhibitors, and several disease states such as renal impairment. Historically, it was used as a screening test for medullary thyroid cancer in relatives of patients with known medullary thyroid cancer; this use has largely been replaced by assays for specific genetic mutations known to occur in the familial forms. Most patients with medullary thyroid cancer have marked elevations of calcitonin, to over 50 ng/L, while the upper limit of normal is 5 ng/L for women and 8.4 ng/L for men. Serum calcitonin was measured in the major Phase 3 trials of liraglutide.

In general, liraglutide did not cause marked changes in calcitonin levels. In the blinded controlled portions of trials (6 months in 4 trials and 1 year in 1 trial), mean calcitonin values remained near the lower limit of quantitation. In voluntary unblinded extension studies out to two years, mean calcitonin levels remained near the lower limit of quantitation, but dropout rates were high and somewhat different between treatment groups. Patients who began study with

calcitonin elevations did not tend to develop progressive further increases in calcitonin over time. Among patients who began study with calcitonin values <50 ng/L, two liraglutide-treated patients and one comparator-treated patient developed calcitonin levels >50 ng/L (ratio 1:1).

However, liraglutide may have had some effect on calcitonin levels. From baseline to 26 weeks (the end of the blinded controlled portion of the trials), there was a dose-dependent trend for women to shift from below the lower limit of quantitation to within the range of quantitation. Also, from baseline to 26 weeks, the percentage of patients who had any upward category shift in calcitonin levels was highest, in both genders, for patients treated with the highest proposed liraglutide dose, 1.8 mg. At Week 12, for comparisons of all doses of liraglutide to active control, and to placebo, mean percent changes in calcitonin values were statistically significantly higher for liraglutide. At 26 weeks, this remained true for comparisons of liraglutide to placebo, and a dose dependent trend was noted for comparisons to both active control and placebo. However, mean values in these analyses were near the lower limit of quantitation. The incidence of new elevations of calcitonin to >20 ng/L was numerically higher for liraglutide (0.88%) than for comparator (0.57%), and there appeared to be a dose-related trend. The highest percentage of patients who developed a new elevation of calcitonin to >20 ng/L was among patients in the liraglutide 1.8 mg group (1.39%). The clinical significance of small changes in calcitonin in this setting is uncertain.

When asked whether the available data on thyroid C-cell tumors permit marketing of liraglutide, the Advisory Committee vote was 6 "no", 6 "yes", and 1 "abstain".

Most trials of liraglutide were 6 months or less in duration. Calcitonin data from voluntary unblinded extensions of two trials are available for up to two years for approximately 500 liraglutide-treated patients. In the clinical safety reviewer's opinion, this duration of observation is not adequate to assess the human risk of this tumor, which may be relatively indolent in terms of expected rate of growth, but which can have very poor outcomes in unresectable cases. The applicant's proposed labeling does not provide for monitoring with calcitonin, thyroid ultrasound, or thyroid physical examination.

Besides calcitonin, there are other potential biomarkers for medullary thyroid carcinoma, including procalcitonin and carcinoembryonic antigen.

Drugs for the treatment of type 2 diabetes have the potential to be prescribed for millions of patients, and inadequately assessed safety problems can have significant public health consequences. To address the deficiency related to inadequate assessment of human medullary thyroid cancer risk for liraglutide, the clinical safety reviewer recommends a longer duration randomized, controlled, blinded trial, that would include monitoring not only of calcitonin, but of these other biomarkers, with measurements at baseline and every three to six months. The applicant has already proposed a large cardiovascular outcomes trial which would include approximately 9000 patients. The clinical safety reviewer recommends that, in that trial, the applicant measure these biomarkers as outlined, and perform an interim analysis of calcitonin, procalcitonin and carcinoembryonic antigen levels at three years of study in this trial (i.e. when the last enrolled patient has three years of follow-up). At three years of study, one would not expect to see actual cases of medullary thyroid carcinoma, but the proposed analyses of multiple

biomarkers could provide a reasonable assessment of whether any degree of C-cell activation is going on. Three years is recommended because currently, there are limited data for calcitonin (and no data for other biomarkers) from voluntary unblinded extensions out to two years. These extensions had high dropout rates that differed between treatment groups. At the Advisory Committee meeting, at which the applicant discussed calcitonin data out to two years, Dr. Burman (the Chairman of the Committee, and one of the two thyroid cancer experts on the Committee) recommended a longer period of observation, and measurement of additional biomarkers. If there is no evidence of C-cell activation, even over three years of study, this could provide some level of comfort that the likelihood of induction of an aggressive form of medullary thyroid cancer by liraglutide would be small. With this information in hand, the public health consequences related to medullary thyroid cancer risk for liraglutide could reasonably be expected to be relatively low.

The second safety concern which, in the clinical safety reviewer's opinion, affects approvability of liraglutide, is that of inadequate data to assess the risk of major adverse cardiovascular events. In a recent Guidance, the Agency outlined requirements for sponsors of new diabetes drugs to rule out unacceptably increased risk of cardiovascular events. There are multiple elements to the Guidance, but two relevant elements are inclusion in the development program of patients at high risk for cardiovascular events (which permits accrual of sufficient events for analysis), and premarket exclusion of a certain level of increased cardiovascular risk. Events of interest include a composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. The liraglutide NDA had already been submitted at the time of finalization of the Guidance, but the Agency has stated that it and other applications in the same circumstance must also meet the requirements of the Guidance.

The liraglutide trials excluded patients with known cardiovascular disease, and event rates were very low. In a composite of event terms deemed likely to represent true events of cardiovascular death, myocardial infarction or stroke, there were only 26 total events (liraglutide and comparator combined) during the controlled, blinded portions of the trials, and only 23 of these events met the definition of a serious adverse event. In general, stratified analyses of liraglutide versus total comparator (active control plus placebo) did have point estimates which favored liraglutide, and upper bounds of the 95% confidence interval of <1.8, which was the prespecified upper boundary that could permit approval of a diabetes drug with a requirement for a large postmarketing cardiovascular outcomes trial. The Guidance does not require applicants to meet specified confidence interval boundaries for subgroup analyses. However, subgroups were analyzed for consistency of the findings. Analyses of liraglutide versus active comparator were qualitatively similar to those versus total comparator. Analyses of liraglutide versus placebo, however, were sensitive to analysis method, and sometimes had point estimates >1, not favoring liraglutide, and upper bounds of 95% confidence intervals which exceeded 1.8. The finding of upper bounds that sometimes exceeded 1.8 can be attributed in large part, to very low event rates. The finding of point estimates that sometimes exceeded 1 cannot be attributed to lower cardiovascular risk among placebo-treated patients, as these analyses were stratified by study, and baseline risk was similar between treatment arms in each of the included studies. Analyses by baseline duration of diabetes (<10 years or ≥10 years) also showed point estimates >1, and upper bounds >1.8, for comparisons of liraglutide versus placebo, particularly when one considered patients who had had diabetes for <10 years at baseline. This was not an expected

finding, as the risk of cardiovascular events is generally thought to be higher in patients with diabetes of longer duration, but very low event rates limited interpretability.

In the Advisory Committee meeting, data regarding major adverse cardiovascular events were presented to the panel, which included two cardiologists and a biostatistician, in addition to endocrinologists, an epidemiologist, a patient representative and a consumer representative. The panel's overall vote was 8 "yes" and 5 "no" regarding whether the applicant had ruled out an unacceptable increase in cardiovascular risk. However, both cardiologists and the biostatistician voted "no", citing concerns about small numbers of events, low cardiovascular risk of the studied population, and the difference in results for analyses versus placebo. Other panel members, including some who voted "yes", also expressed concerns about the adequacy of the data.

There are several other safety concerns for liraglutide, but, in the clinical safety reviewer's opinion, these other issues, while potentially important, can be addressed through labeling and/or future studies, and do not rise to the level of approvability issues. They include:

- A numerical imbalance in cases of papillary thyroid cancer, not favoring liraglutide (6 cases versus 1; ratio 3:1). Almost all of these cancers were <1 cm, and were discovered at surgery that was prompted by routine protocol-specified calcitonin or ultrasound screening. They are likely incidental papillary microcarcinomata, which are common in the general population. However, ascertainment issues cannot fully explain the imbalance, because screening occurred for both liraglutide and comparator groups, and one would expect a similar rate of incidental papillary cancers if this observation was entirely related to increased screening.
- Gastrointestinal adverse events, especially nausea, vomiting and diarrhea. Rates of withdrawals due to gastrointestinal adverse events were higher for liraglutide-treated patients.
- Pancreatitis. There were 8 events of pancreatitis among liraglutide-treated patients, and 1 among comparator-treated patients (ratio 4:1). One liraglutide-treated case was fatal, although there were confounding elements to this case. The comparator group patient, and four of the liraglutide group patients, had risk factors for pancreatitis. Pancreatitis may be a class effect for glucagon-like-peptide-1 analogues, given recent postmarketing reports for exenatide, for which final labeling discussions are ongoing.
- Serious neoplasm events. In the original New Drug Application, serious neoplasm events occurred at rates of 8.9 versus 5.3 events per 1000 patient-years for liraglutide versus total comparator. After the 120-day safety update, these rates were 12.3 versus 8.1. After removal of serious but nonmalignant neoplasms, and papillary thyroid cancers, these rates were 10.3 versus 8.1 events per 1000 patient years. No particular cancer cell type predominated. There have been recent concerns, based on epidemiologic data (some of which are conflicting), of a possible association between insulin and increased risk of malignancy. Liraglutide causes an increase in insulin levels. This risk should be further assessed in future trials of liraglutide.
- Serious hypoglycemic events. In the major Phase 3 trials submitted with the NDA, all serious hypoglycemic events (defined as events requiring the assistance of another person) occurred among liraglutide-treated patients, with none among comparator-treated patients. Six of these 9 events occurred among patients concomitantly administered a sulfonylurea. The risk for this may be similar between liraglutide and exenatide; in recent preliminary results of a comparative trial, two exenatide-treated patients and one liraglutide-treated patient had serious hypoglycemic events.

- Injection site reactions were more common among liraglutide-treated patients than among comparator-treated patients, and liraglutide dose-dependency was noted.
- Antibodies to liraglutide developed in approximately 10% of liraglutide-treated patients, and antibodies which cross-reacted with native glucagon-like-peptide-1 developed in about 5% of patients. About 1-2% of liraglutide-treated patients developed antibodies which had a neutralizing effect on liraglutide in an *in vitro* assay. Efficacy as measured by mean hemoglobin A1c was not affected by antibody formation. The three liraglutide-treated patients with the highest antibody titres had almost no change in hemoglobin A1c over time, suggesting that those patients with the highest anti-liraglutide antibody titres may have some diminution in efficacy, but these three patients are too few upon which to base a conclusion. Antibody-positive patients were more likely to have events related to infections; most of these were nonserious nasopharyngeal or upper respiratory infections. Antibody-positive patients also had more events of musculoskeletal pain and of certain injection site adverse reactions.
- Immunogenicity events from standardized queries using the Medical Dictionary for Regulatory Activities were more common among liraglutide-treated patients than among comparator-treated patients. About 40% of immunogenicity-related events were urticaria events.
- Slowing of gastric emptying, with effects on the pharmacokinetics of other drugs. The clinical significance of this effect is under discussion with the Clinical Pharmacology team.
- Overall thyroid neoplasms (19 versus 4 for liraglutide versus comparator; ratio 2.4:1). These were mostly thyroid nodules discovered after protocol-specified screening.
- Hepatobiliary adverse events. Overall rates of hepatobiliary adverse events were similar for liraglutide and comparator, but all withdrawals due to hepatobiliary adverse events (n=5) occurred among liraglutide-treated patients. A higher numerical percentage of liraglutide-treated patients had bilirubin levels above the upper limit of normal. There was no difference between liraglutide and comparator for transaminase elevations. No patients met the criteria for Hy's law.
- A small increase in heart rate of 2-3 beats per minute, and a numerical imbalance in adverse events related to increased heart rate, not favoring liraglutide. A "thorough QT study" did not show evidence of a liraglutide-associated risk of QT prolongation.
- Risk of medication errors due to design and labeling of the pen injector for the 0.6 and 1.2 mg doses. The applicant is submitting a new pen device to address these concerns, and reviews by the Chemistry, Manufacturing and Controls reviewer and the Devices reviewer are ongoing.
- Potential for off-label use/abuse for weight loss. Liraglutide was associated with a small amount of weight loss in clinical trials. Potential exists for off-label use in a non-diabetic population that would not benefit from liraglutide's glucose-lowering effects, but could still be at risk for all its adverse effects.
- Animal fetal anomalies at exposures at or below that expected for the human clinical dose. Pregnancy Category C is recommended.
- Nonserious adverse events of dizziness and fatigue.

During the review cycle, there were some issues with data quality regarding laboratory reporting for serum calcitonin, bilirubin and creatinine. There was a discrepancy regarding missing calcitonin values, which the applicant attributed to programming errors. Two sets of errata were submitted. During the review of bilirubin and creatinine data, the clinical safety reviewer noted

that the applicant's analyses had omitted some patients who had elevated values. The applicant attributed the bilirubin data omissions to a programming error, and submitted errata. A response from the applicant regarding the creatinine elevation reporting discrepancy is pending.

1.3.4 Dosing Regimen and Administration

Please see Dr. Yanoff's clinical efficacy review.

1.3.5 Drug-Drug Interactions

Liraglutide had little effect on the metabolism of other drugs by multiple cytochrome P450 isoforms. It is metabolized by dipeptidyl-peptidase-4, and by other peptidases.

Liraglutide slows gastric emptying, and thus may prolong Tmax, and lower Cmax of orally administered drugs. Liraglutide delayed Tmax and lowered Cmax for atorvastatin, lisinopril, paracetamol and digoxin. For griseofulvin, however, Cmax was 37% higher at liraglutide steady state conditions when compared to placebo. The clinical significance of these effects is under discussion with the Clinical Pharmacology team.

No drug-drug interaction study with warfarin was performed. There have been postmarketing reports of possible warfarin interactions with exenatide. The Clinical Pharmacology team is discussing whether a warfarin interaction study would be advisable for liraglutide.

1.3.6 Special Populations

Dosage adjustment does not appear necessary for patients with hepatic or renal impairment. There were too few patients age 75 years or older to make conclusions regarding dosing in this population; the 1.8 mg dose may be associated with more gastrointestinal and nervous system adverse events in this age group than in younger patients. No dosage adjustment appears necessary by race or ethnicity.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Victoza® (liraglutide injection, hereafter often referred to as LGT) is a human glucagon-like-peptide-1 (GLP-1) analogue, intended for the treatment of type 2 diabetes mellitus. Native GLP-1 is a gut incretin hormone which causes glucose-dependent secretion of insulin. Therefore, a medication which mimics GLP-1 would be expected to have the potential to lower blood glucose only when glucose is high, and not when it is normal or low. This is in contrast to some other oral antidiabetic drugs, such as sulfonylureas, which stimulate insulin secretion independently of blood glucose levels, and are therefore associated with a risk of hypoglycemia. A lower risk for hypoglycemia is a potential advantage of this drug class. However, native GLP-1 has a very short half-life, due to almost instantaneous degradation via the enzyme dipeptidyl-peptidase-4 (DPP4). Approaches to the development of drugs which act via GLP-1 have focused on either altering the structure of GLP-1 to make it resistant to degradation, or on inhibition of DPP4 activity. Liraglutide is an analogue of GLP-1, with a prolonged pharmacokinetic (PK) profile intended for once daily subcutaneous (SQ) injection. The applicant states that liraglutide has an elimination half-life of 13 hours, and a duration of action of 24 hours.

The proposed indication is: "Liraglutide, a human GLP-1 analogue, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus."

Initiation at a dose of 0.6 mg SQ once daily is proposed, with titration to 1.2 mg SQ once daily after at least one week. Uptitration to 1.8 mg SQ once daily is possible after at least one week at 1.2 mg/day.

2.2 Currently Available Treatment for Indications

Please see Dr. Yanoff's clinical efficacy review.

2.3 Availability of Proposed Active Ingredient in the United States

Please see Dr. Yanoff's clinical efficacy review.

2.4 Important Issues With Pharmacologically Related Products

There is one approved GLP-1 analogue, exenatide (Byetta®). Clinical safety issues with exenatide include:

- gastrointestinal adverse events such as nausea, vomiting and diarrhea
- formation of anti-exenatide antibodies, some of which are neutralizing and may result in reduction in glycemic control response
- hypoglycemia, particularly when coadministered with a sulfonylurea
- altered renal function, such as increased serum creatinine and adverse events of renal impairment

- a recent concern regarding pancreatitis; some postmarketing cases have been severe

2.5 Presubmission Regulatory Activity

Please see Dr. Yanoff's clinical efficacy review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There are 2 reviews by the Chemistry, Manufacturing and Controls (CMC) reviewer, Dr. Leginus (Division File System Archive [DFS] 29 Dec 2008 and 17 Apr 2009). He recommends approval and does not have significant concerns regarding CMC issues.

The device reviewer, Dr. Syed, had some concerns in his review memorandum, which was attached to Dr. Riley's second review (DFS 17 Apr 2009). Novo had used their own ——— b(4) device, which they have used for insulin products, and modified it to be used with liraglutide.

- The applicant had not provided the 510K number or an NDA number for their predicate device ——— which was modified to produce the liraglutide pen device.
- He felt that the color and marking changes on the device could confuse the user, and that a proper Human Factors study needed to be conducted to support the reasoning behind these changes, and their effectiveness.

Dr. Riley, the Microbiology reviewer, did not note Microbiology issues that would preclude approvability. The drug product is sterile ——— b(4) and contains an ——— Dr. Riley's review is in DFS (10 Mar 2009).

3.2 Animal Pharmacology/Toxicology

In his review (DFS 8 Jul 2009), Dr. Parola, the Pharmacology/Toxicology reviewer states that the application is not approvable from a Pharmacology/Toxicology standpoint because there is insufficient nonclinical information about liraglutide to determine if it is safe for chronic use. His primary concern is the finding in 2-year lifetime exposure carcinogenicity studies in mice and rats that liraglutide caused thyroid C-cell tumors in both species, in both genders, at clinically relevant exposures. In rats, C-cell carcinomas occurred at clinically relevant exposures. In mice, only females developed carcinomas, and only at high multiples of expected human exposure. However, in rodents, C-cell adenomas are considered to be a precarcinomatous lesion. A similar animal signal is being noted in interim carcinogenicity data for some other long-acting (q day and longer) GLP-1 analogues in development. In animal studies of liraglutide, calcitonin (which has been used historically as a biomarker for medullary thyroid cancer in humans) may not have been a reliable biomarker for C-cell tumor risk. Dr. Parola stated that the mechanistic studies performed by the applicant did not mitigate this risk. Dr. Parola recommends that the applicant determine the mode of action for liraglutide-induced rodent C-cell tumors. Determination of the mode of action could provide important information to evaluate the potential human relevance of these rodent C-cell adenomas and carcinomas. Dr.

Parola suggests some possible animal studies which could provide further mode of action information.

Dr. Parola was also concerned that local toxicity after repeat subcutaneous injection had not been adequately assessed in nonclinical studies. In chronic repeat dose toxicity studies, liraglutide caused irreversible injection site reactions in monkeys, using drug formulations that were at least 3 times more dilute than the clinical formulation. Liraglutide also caused fibrosarcomas in the dorsal skin and subcutis in mice in the high dose group in the 2-year carcinogenicity study. Dr. Parola states that these fibrosarcomas were attributable to local toxicity due to high drug concentration at or near the injection site. The concentration of liraglutide in the high dose formulation in the mouse study was 0.6 mg/mL, which is $1/10^{th}$ the concentration of the clinical formulation (6 mg/mL).

An additional concern was that some liraglutide impurities were not qualified in genetic toxicity studies. Dr. Parola recommends evaluation of the *in vitro* genetic toxicity of liraglutide impurities at impurity levels consistent with drug substance and drug product acceptance criteria.

Dr. Parola recommends Pregnancy Category C. Liraglutide cause abnormalities in fetal rats at maternal systemic exposures that were 0.8 times the expected human exposure from the 1.8 mg liraglutide dose. Liraglutide also caused major fetal malformations in rabbits at 0.2x human dose.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

As of the date of submission of the NDA (23 May 2008), the liraglutide development program consisted of 38 completed clinical trials (data cutoff date 31 Jan 2008) and 2 ongoing controlled open-label extension trials (data cutoff date 21 Feb 2008).

The clinical safety review included review of pooled data from these trials, from a safety update submitted by the applicant on 23 Sep 2008, from multiple other submissions containing liraglutide-related safety information, from the only approved GLP-1 analogue (Byetta®, exenatide injection), and from the medical literature.

After submission of the original NDA, the applicant has forwarded 41 additional submissions to the NDA. These submissions are discussed in Section 7.2.9.

Throughout the NDA review period, the applicant continued to submit individual safety reports to the IND (61040), which were also incorporated into the review.

4.2 Tables of Clinical Studies

The following table lists all studies included in the original NDA submission.

Table 4.2.1: Clinical Studies in Liraglutide Development Program at Time of NDA Submission

Trial ID[2]	Country	Type of Study	Design and Control	Study Drugs	N	Pop	Duration	Status[1]
NN2211-1331	DE	Bioequiv	SC, R, SB, XO	SD SQ, 1 mg LGT formulations 2 and 3	22	Healthy	SD	Complete
NN2211-1636	AU	Bioequiv	SC, R, DB, XO	SD SQ, 0.75 mg LGT formulation 3 at pHs 7.7, 7.9 and 8.15	24	Healthy	SD	Complete
NN2211-1692	SE	Bioequiv	SC, R, DB, XO	SD SQ, 0.72 mg LGT formulation 4 and formulation 4 with final manufacturing process for drug substance	21	Healthy	SD	Complete
NN2211-1693	SE	Bioequiv	SC, R, DB, XO	SD SQ, 0.71 mg LGT formulations 3 and 4	22	Healthy	SD	Complete
NN2211-1745	DE	PK and BA	SC, R, OL, XO	SD SQ 0.6 mg LGT, in abd, thigh and upper arm	21	Healthy	SD	Complete
NN2211-1149	GB	PK, PD and BA	SC, R, DB, PC, parallel-grp, dose escalation	Eight single SQ doses (1.25, 2.5, 5, 10, 12.5, 15, 17.5 or 20 mcg/kg) or one single IV dose 5 mcg/kg	72 (54 LGT, 18 PBO)	Healthy	SD	Complete
NN2211-1699	NL	PK	SC, OL	SD SQ 0.75 mg radiolabeled LGT	7	Healthy	SD	Complete
NN2211-1189	GB	PK and PD	SC, R, DB, PC, parallel grp, dose escalation	Initial SD SQ, followed by QD escalating doses of 1.25, 5, 7.5, 10 and 12.5 mcg/kg	Healthy: 20 LGT, 10 PBO DM2: 2 LGT, 2 PBO	Healthy and DM2	SD followed by 7 days	Complete
NN2211-1327	DE	PK	SC, OL, parallel grp	SD SQ 1 mg	16 elderly, 16 non-elderly	Healthy elderly and non-elderly	SD	Complete
NN2211-1329	NZ	PK	SC, OL, parallel grp	SD SQ 0.75 mg	Nondiabetic: 27 DM2: 3 (All divided into 5 grps by renal fxn)	Nondiabetic and DM2 with normal or impaired renal fxn	SD	Complete
NN2211-1328	PL	PK	SC, OL, parallel grp	SD SQ 0.75 mg	Nondiabetic: 24 DM2: 5 (All divided into 4 grps by hepatic fxn)	Nondiabetic and DM2 with normal or impaired hepatic fxn	SD	Complete

Table 4.2.1: Clinical Studies in Liraglutide Development Program at Time of NDA Submission

Trial ID[2]	Country	Type of Study	Design and Control	Study Drugs	N	Pop	Duration	Status[1]
NN2211-1330	SE	DDI	SC, R, DB, PC, XO	QD SQ, titrated from 0.6-1.8 mg and SD by mouth OCP	21	Healthy postmenopausal women	3 wks LGT and SD OCP	Complete
NN2211-1608	SE	DDI	2C, R, DB, PC, 2-way XO trial in 2 parts	LGT SQ, titrated from 0.6-1.8 mg. Part A: SD by mouth 40 mg atorva and 20 mg lisinopril Part B: SD by mouth 500 mg griseofulvin and 1 mg digoxin	Part A: 42 Part B: 28	Healthy	4 wks LGT and SD drug for DDI	Complete
NN2211-1644	US	QT	SC, R, DB, PC XO followed by OL moxi	LGT, titrated from 0.6-1.8 mg SQ, then moxi SD 400 mg by mouth	58	Healthy	7 wks	Complete
NN2211-1698	DE	PD and DDI	SC, R, DB, PC, XO	LGT, titrated from 0.6-1.8 mg SQ, and paracetamol SD 1 gm by mouth	18	DM2	3 wks	Complete
NN2211-1589	AU, DE	PD	2C, R, DB, balanced incomplete Latin square. PBO and glimepiride controls	LGT: titrated from 0.6-1.8 mg. Glimepiride: 1-4 mg by mouth QD Paracetamol: SD 1 gm by mouth	46	DM2	4 wks	Complete
NN2211-1332	DK	PK, PD	SC, R, DB, PC, XO	LGT 0.6 mg SQ QD x 9-10 days	13	DM2	9-10 days	Complete
NN2211-1219	DK	PK, PD	SC, R, DB, PC, SD, XO	SD LGT 10 mcg/kg SQ	11	DM2	SD	Complete
NN2211-2063	US	PK, PD	SC, R, DB, PC, XO	SD LGT 7.5 mcg/kg SQ	Healthy: 10 DM2: 10	Healthy and DM2	SD	Complete
NN2211-1224	DE	PK, PD	2C, R, DB, PC, XO	SD LGT 7.5 mcg/kg SQ	19	DM2	SD	Complete
NN2211-1571[2]	DK, FR, NL, SK	Efficacy, safety	MC, R, DB, PC, parallel grp	LGT QD SQ (0.65, 1.25 or 1.9 mg) x 14 wks	Healthy: 12 (not dosed) DM2: 163 (LGT 0.65 mg: 40 LGT 1.25 mg: 42 LGT 1.9 mg: 41 PBO: 40)	DM2	14 wks	Complete

Table 4.2.1: Clinical Studies in Liraglutide Development Program at Time of NDA Submission

Trial ID[2]	Country	Type of Study	Design and Control	Study Drugs	N	Pop	Duration	Status[1]
NN2211-1310[2]	DK, NO, SE, GB	Efficacy, safety	MC, R, DB (LGT vs. PBO) parallel grp, with AC OL glimepiride	LGT QD SQ (0.045, 0.225, 0.45, 0.6 or 0.75 mg) Glimepiride 1-4 mg by mouth QD	190 total LGT 0.045 mg: 26 LGT 0.225 mg: 24 LGT 0.45 mg: 27 LGT 0.6 mg: 30 LGT 0.75 mg: 28 GLIM: 26 PBO: 29	DM2	12 wks	Complete
NN2211-1499[2]	AT, AU, CZ, DK, FR, DE, PL, GB	Efficacy, safety	MC, R, DB (LGT vs. PBO), parallel grp, with AC OL MET and GLIM	LGT QD SQ, titrated from 0.5-2 mg. MET 1 gm by mouth BID GLIM, 2-4 mg by mouth QD	144 total LGT: 36 LGT + MET: 36 MET: 36 MET + GLIM: 36	DM2	5 wks	Complete
NN2211-1573[2]	US, MX	Efficacy, safety, pop PK	MC, R, DB, AC, parallel group	LGT QD SQ, titrated from 0.6 to 1.2 or 1.8 mg GLIM, 8 mg by mouth QD	745 total LGT 1.2: 251 LGT 1.8: 246 GLIM: 248	DM2	52 wks	Complete
NN2211-1573 EXT 1[2]	US, MX	Efficacy, safety	MC, R, OL, parallel grp, AC, extension	LGT QD SQ, 1.2 or 1.8 mg GLIM, 8 mg by mouth QD	440 total LGT 1.2: 149 LGT 1.8: 154 GLIM: 137	DM2	approx 18 mo	Ongoing
NN2211-1572[2]	AR, AU, BE, BG, DE, DK, ES, GB, HR, HU, IE, IN, IT, NL, NO. NZ, RO, RU, SE, SK, ZA	Efficacy, safety	MC, R, DB, parallel grp, PBO and AC	LGT QD SQ, 0.6 or 1.2 or 1.8 mg, titrated from 0.6 mg, in combo with MET MET 1 gm by mouth BID + PBO GLIM 4 mg by mouth QD + MET	1087 total LGT 0.6 + MET: 242 LGT 1.2 + MET: 240 LGT 1.8 + MET: 242 MET + PBO: 121 GLIM + MET: 242	DM2	26 wks	Complete
NN2211-1572 EXT 1[2]	AR, AU, BE, BG, DE, DK, ES, HR, HU, IE, IN, IT, NL, NO. NZ, RO, RU, SE, SK, ZA	Efficacy, safety	MC, R, OL, parallel grp, AC and PBO, extension	LGT QD SQ, 0.6 or 1.2 or 1.8 mg, titrated from 0.6 mg, in combo with MET MET 1 gm by mouth BID + PBO GLIM 4 mg by mouth QD + MET	780 total LGT 0.6 + MET: 184 LGT 1.2 + MET: 178 LGT 1.8 + MET: 174 MET + PBO: 61 GLIM + MET: 183	DM2	approx 18 mo	Ongoing

Table 4.2.1: Clinical Studies in Liraglutide Development Program at Time of NDA Submission

Trial ID[2]	Country	Type of Study	Design and Control	Study Drugs	N	Pop	Duration	Status[1]
NN2211-1436[2]	AR, AU, BG, HR, CZ, FI, FR, HK, IN, IL, IT, KR, MY, PH, PL, RO, ZA, CH, TW, TH, TR	Efficacy, safety	MC, R, DB, parallel grp, AC and PBO	LGT QD SQ, 0.6 or 1.2 or 1.8 mg, titrated from 0.6 mg, in combo with GLIM GLIM 4 mg by mouth QD + PBO RSG 4 mg by mouth QD + GLIM	1040 total LGT 0.6 + GLIM: 233 LGT 1.2 + GLIM: 228 LGT 1.8 + GLIM: 234 GLIM + PBO: 114 RSG + GLIM: 231	DM2	26 wks	Complete
NN2211-1574[2]	US, CA	Efficacy, safety	MC, R, DB, parallel grp, PBO	LGT QD SQ, 1.2 or 1.8 mg, titrated from 0.6 mg, in combo with MET and RSG MET 1 gm by mouth BID RSG 4 mg by mouth BID	530 total LGT 1.2 + MET + RSG: 177 LGT 1.8 + MET + RSG: 178 PBO + MET + RSG: 175	DM2	26 wks	Complete
NN2211-1697[2]	AR, AT, DK, ES, FI, FR, GB, IN, IT, ME, NL, NO, PH, PL, RS, RU, SK, ZA	Efficacy, safety	MC, R, DB, parallel grp, PBO and AC	LGT QD SQ, 1.8 mg, titrated from 0.6 mg, in combo with GLIM and MET GLIM 4 mg by mouth QD MET, 1 gm by mouth QD Glargine QD SQ, titrated	576 total LGT + GLIM + MET: 230 PBO + GLIM + MET: 114 Glargine + GLIM + MET: 232	DM2	26 wks	Complete
NN2211-1694	JP	PK, PD	R, DB, PC, dose escalation	LGT QD SQ, 15, 20 or 25 mcg/kg, titrated in weekly steps of 5 mcg/kg	24 total LGT: 18 PBO: 6	Healthy	5 wks	Complete
NN2211-1551	JP	PK, PD	R, DB, PC, dose escalation	LGT QD SQ, 5, 10 or 15 mcg/kg, titrated in weekly steps of 5 mcg/kg	24 total LGT: 18 PBO: 6	Healthy	3 wks	Complete
NN2211-1326	JP	PK, PD	R, DB, PC, parallel grp	LGT SD SQ, 2.5, 5, 10 or 15 mcg/kg	32 total LGT: 24 PBO: 8	Healthy	SD	Complete
NN2211-1591	JP	PK, PD	R, DB, PC, parallel grp	LGT SQ QD, 5 or 10 mcg	15 total LGT: 11 PBO: 4	DM2	14 d	Complete
NN2211-1334[2]	JP	Efficacy, safety	MC, R, DB, PC, parallel grp	LGT SQ QD, 0.1, 0.3, 0.6, or 0.9 mg	226 total LGT: 180 PBO: 46	DM2	14 wks	Complete

Table 4.2.1: Clinical Studies in Liraglutide Development Program at Time of NDA Submission

Trial ID[2]	Country	Type of Study	Design and Control	Study Drugs	N	Pop	Duration	Status[1]
NN2211-2072[2]	US	Efficacy, safety	MC, R, DB, AC, parallel grp	LGT SQ QD, 0.045, 0.225, 0.45, 0.6 or 0.75 mg MET 1 gm by mouth BID	210 total LGT 0.045: 37 LGT 0.225: 35 LGT 0.45: 33 LGT 0.6: 34 LGT 0.75: 37 MET: 34	Obese DM2	12 wks	Complete
NN2211-1333[2]	DK	Efficacy, safety	R, DB, PC, parallel grp	LGT SQ QD, 0.6 mg	33 total LGT: 21 PBO: 12	Obese DM2	8 wks	Complete
NN2211-1464	GB	BA (pulmonary)	R, XO	LGT single inhalation, 6, 12 or 24 mcg/kg LGT SQ, 6 mcg/kg	32 total LGT: 30 PBO: 2	Healthy	SD	Complete
NN8022-1807	DK, SE, FI, GB, NL, BE, ES, CZ	Efficacy, safety	MC, R, DB (orlistat OL), PC and AC	LGT SQ QD 1.2, 1.8, 2.4 or 3 mg, titrated from 0.6 Orlistat: 120 mg by mouth TID	564 total LGT 1.2: 95 LGT 1.8: 90 LGT 2.4: 93 LGT 3.0: 93 Orlistat: 95	Obese healthy	20 wks	Complete
NN9233-1898	US	BA (intranasal)	R, DB, PC	LGT single intranasal dose, 2.5, 5 or 10 mg LGT SQ, 0.6 mg	12 total LGT: 9 PBO: 3	Healthy	SD	Complete

Source: Applicant's Tabular Listing, Module 5.2, pages 4-11
1 Status at time of NDA submission (23 May 2008)
2 Denotes Phase 2 and Phase 3 trials which were included in analyses of major adverse cardiovascular events (MACE). The MACE analyses also included 3 trials for which data were submitted after the original NDA submission (Studies 1700, 1701 and 1797).
Abbreviations: 2C = two center, abd = abdomen, AC = active control, approx = approximately, AR = Argentina, AT = Austria, atorva = atorvastatin, AU = Australia, BA = bioavailability, BE = Belgium, BG = Bulgaria, BID = 2 times per day, Bioequiv = bioequivalence, CA = Canada, CH = Switzerland, contr = controlled, CZ = Czech Republic, d = days, DB = double blind, DDI = drug-drug interaction, DE = Germany, DM2 = type 2 diabetes mellitus, ES = Spain, FI = Finland, FR = France, fxn = function, GB = United Kingdom, GLIM = glimepiride, grp = group, HK = Hong Kong, HR = Croatia, HU = Hungary, IE = Ireland, IL = Israel, IN = India, IT = Italy, IV = intravenous, JP = Japan, KR = Korea, LGT = liraglutide, MC = multicenter, ME = Montenegro, MET = metformin, moxi = moxifloxacin, MX = Mexico, MY = Malaysia, moxi = moxifloxacin, NL = The Netherlands, NO = Norway, NZ = New Zealand, OCP = oral contraceptive pill (Neovletta®, 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel), OL = open label, PC = placebo-controlled, PD = pharmacodynamics, PH = Philippines, PK = pharmacokinetics, PL = Poland, pop = population, QD = each day, R = randomized, RO = Romania, RS = Serbia, RSG = rosiglitazone, RU = Russia, SB = single-blind, SC = single center, SD = single dose, SE = Sweden, SK = Slovakia, SQ = subcutaneously, TH = Thailand, TID = three times per day, TW = Taiwan, US = United States, wk = week, XO = crossover, ZA = South Africa

The applicant submitted data from 38 completed clinical trials. One trial (NN8022-1807) was a Phase 2 dose-finding trial for the treatment of obesity in nondiabetic subjects. Two Phase 1 trials explored alternate routes of administration; intranasal in NN9233-1898 and pulmonary in NN2211-1464. The other trials were conducted in healthy volunteers or patients with diabetes for the diabetes indication. Seven trials were conducted exclusively in Japanese subjects. At the time of NDA submission, there were also six ongoing trials.

The following table, by Dr. Janice Derr of FDA Biometrics, provides additional summary information regarding the designs, rescue criteria, and extensions of the five major Phase 3 trials.

Table 4.2.2: Summary of Design, Rescue and Extension for Phase 3 Studies

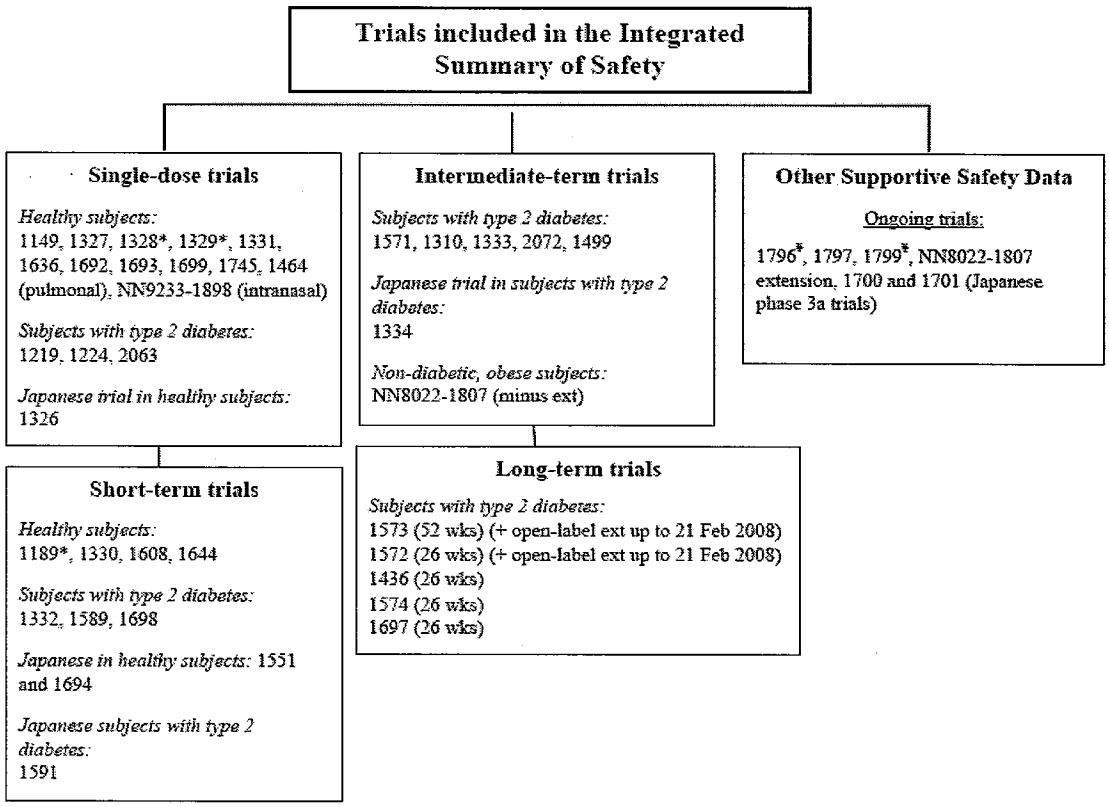
Study #	Randomized, controlled, double blind period from randomization to 1^0 HbA1c endpoint			Rescue		Extension study		
	Groups / # Pts exposed (Safety database)	# weeks	Pt-YR exposure	Rescue criteria	What happened to rescued pts	Extension study?	Describe: treatments / blinded / duration	Number enrolled / arm
1436	Total: 1040 1. Lira 0.6 mg + glimepiride: 233 2. Lira 1.2 mg + glimepiride: 228 3. Lira 1.8 mg + glimepiride: 234 4. Placebo + Glimepiride: 114 5. Rosi + glimepiride: 231	26 weeks	1. 109.2 2. 102.9 3. 110.1 4. 47.1 5. 104.6	Wks 8-26: FPG > 239 mg/dL	Removed from study	No	N/A	N/A
1572	Total: 1087 1. Lira 0.6 mg + metformin: 242 2. Lira 1.2 mg + metformin: 240 3. Lira 1.8 mg + metformin: 242 4. Placebo + Metformin: 121 5. Glimepiride + metformin: 242	26 weeks	1. 110.8 2. 106.2 3. 103.9 4. 46.8 5. 110.8	Dbl-blind period: Wks 8-26: FPG > 239 mg/dL Extension period Wks 26-52: FPG > 220 mg/dL Wks 52-105: FPG > 200 mg/dL	Removed from study	Yes, Trial 1572-ES	Open label, subjects stayed on randomized treatment assignments, weeks 26-105	Total: 780 1. 184 2. 178 3. 174 4. 61 5. 183
1573	Total: 745 1. Liraglutide 1.2 mg: 251 2. Liraglutide 1.8 mg: 246 3. Glimepiride: 248	52 weeks	1. 192.2 2. 194.8 3. 185.9	Dbl-blind period: Wks 8-28: FPG > 240 mg/dL Wks 28-52: FPG > 220 mg/dL Extension period: Wks 52-104: FPG > 220 mg/dL	Removed from study	Yes, Trial 1573-ES	Open label, subjects stayed on randomized treatment assignments, weeks 52-104	Total: 440 1. 154 2. 149 3. 137
1574	Total: 530 1. Lira 1.2 mg + metf + rosi: 177 2. Lira 1.8 mg + metf + rosi: 178 3. Placebo + Metf + rosi: 175	26 weeks	1. 81.1 2. 73.3 3. 71.8	Wks 8-26: FPG > 240 mg/dL	Removed from study	No	N/A	N/A
1697	Total: 576 1. Lira 1.8 mg + metf + glim: 230 2. Placebo + Metf + glim: 114 3. Insulin gl + metf + glim: 232	26 weeks	1. 107.3 2. 52.9 3. 111.9	Wks 8-26: FPG > 239 mg/dL	Removed from study	No	N/A	N/A

Source: Table by Dr. Derr, FDA Biometrics

Of note from the above table is the fact that patients who met criteria for glycemic control rescue were removed from study, and therefore were not available to experience further adverse events. Rescue withdrawals were more common among patients treated with add-on placebo than with liraglutide or active control.

The following figure displays the clinical trials grouped by duration:

Figure 4.2: Liraglutide Clinical Trials Grouped by Duration



Total: 38 trials + 2 open-label extensions, 6 ongoing trials
*included 5, 3 and 4 subjects with type 2 diabetes, respectively
* did not contribute subject exposure in this document

Source: Applicant's Figure 1-1, pg 23, ISS

The primary source of data for the safety review was the set of all patients who received at least one dose of study medication from the set of all completed trials at time of NDA submission. For some safety descriptions, other data were used, such as the set of the five major Phase 3 studies (referred to as "long-term" studies in the above figure), or the set of all extension data out to certain time periods. In each section of the review, the safety population under consideration is described.

4.3 Review Strategy

The clinical safety review was conducted by Dr. Karen Murry Mahoney. The clinical efficacy review is being conducted to Dr. Lisa Yanoff, and will be provided in a separate document.

Within this clinical safety review document, those sections which ordinarily would include only efficacy data are marked, and the reader is referred to Dr. Yanoff's review.

4.4 Data Quality and Integrity

In general, the data were of sufficient quality to permit safety review. A full listing of adverse events had not been provided in the original NDA, but the applicant complied with a request to submit a complete list. An inquiry from the Agency regarding missing calcitonin data led the applicant to submit corrected calcitonin analyses on 25 Jun 2009 and 8 Jul 2009; the applicant reported that there had been a programming error in the calcitonin analyses. Two inquiries from the Agency regarding bilirubin data led the applicant to submit corrected analyses on 17 Jul 2009; the applicant reported that there had been a programming error in the bilirubin analyses. An inquiry from the Agency regarding serum creatinine values raised a question regarding whether the applicant had appropriately captured elevated values. The Agency is awaiting clarification of this discrepancy from the applicant.

The Division of Scientific Investigations performed multiple inspections of Novo facilities and investigative sites related to this application. Inspections were performed of clinical and analytic facilities in Plainsboro, New Jersey; Copenhagen, Denmark; and Lund, Sweden. The Plainsboro, New Jersey site inspection revealed some minor procedural deficiencies; the applicant submitted a corrective plan which the inspector concluded was adequate. The applicant also submitted responses to deficiencies noted at the Copenhagen and Lund sites; as of 21 Jul 2009, evaluation of the adequacy of the applicant's responses by the Division of Scientific Investigations is pending. In addition, individual study sites were inspected in Des Moines, Iowa; Las Lomas, Puerto Rico; and Los Angeles, California. Inspection of the site in Puerto Rico revealed some minor regulatory violations which the investigator at the site agreed to correct. At all sites, the conclusion was that the data generated from the sites could be used in support of the application.

4.5 Compliance with Good Clinical Practices

Please see Dr. Yanoff's clinical efficacy review.

4.6 Financial Disclosures

Please see Dr. Yanoff's clinical efficacy review.

5 CLINICAL PHARMACOLOGY

Please see Dr. Khurana's Clinical Pharmacology review and Dr. Yanoff's clinical efficacy review. Drug-drug interactions are discussed in Section 8.2. Dr. Khurana found the clinical pharmacology evaluation acceptable, and does not have recommendations for postmarketing commitments related to clinical pharmacology issues.

No dose adjustment is proposed for renal or hepatic impairment. In a renal study, AUC 0-inf was 19-35% lower in renally impaired patients than in patients with normal renal function.

Severe hepatic impairment was associated with a 2-fold increase in clearance and a 42% mean lower AUC 0-inf for liraglutide.

Liraglutide's effect on metabolism by multiple cytochrome P450 isoforms was investigated, and liraglutide had little effect. It is metabolized by DPP4, and by other peptidases.

Liraglutide slows gastric emptying, and thus may prolong Tmax, and lower Cmax of orally administered drugs. Liraglutide delayed Tmax and lowered Cmax for atorvastatin, lisinopril, paracetamol and digoxin. For griseofulvin, however, Cmax was 37% higher at liraglutide steady state conditions when compared to placebo. The clinical significance of this effect is under discussion with the Clinical Pharmacology team. Liraglutide lowered the Cmax of ethinylestradiol and levonorgestrel by 12 and 13%, respectively, and delayed Tmax by 1.5 hrs; these effects are unlikely to affect the contraceptive efficacy of these drugs.

6 INTEGRATED REVIEW OF EFFICACY

Please see Dr. Yanoff's clinical efficacy review.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

At the time of submission of the NDA, the applicant reported a total of 8 deaths in the liraglutide development program. Three deaths occurred among liraglutide-treated patients, three occurred among active-comparator-treated patients, and two occurred in patients who had not yet been randomized to a study drug. The applicant states that they have reported all deaths of which they have knowledge, even those which occurred after study drug discontinuation. Deaths which occurred post-randomization are listed in the following table.

Table 7.1.1: Postrandomization Deaths Listing

Treatment	Trial	Ctr	Pt ID	Age (Yrs)	Gender	Dose (mg)	Pt-Time (Days)	Applicant's Listed Cause of Death	Clinical Safety Reviewer's Assessment of Cause of Death
Liraglutide	1697	698	698004	47	M	1.8	117	Renal cell carcinoma stage IV	Same
Liraglutide	1572	225	225011	63	M	1.2	160	Liver cirrhosis and hepatocellular carcinoma	Same
Liraglutide	1700	09	9025	63	F	0.9	34	Gastroenteritis	Cardiorespiratory arrest, possibly due to aspiration of vomitus
Glimepiride + metformin	1697	689	689012	67	F	n/a	78	Acute myocardial infarction	Acute myocardial infarction during hospitalization for pulmonary embolism
Glargine + glimepiride + metformin	1697	827	827005	54	M	n/a	117	Acute myocardial infarction	Same
Glimepiride	1573	504	504036	56	F	n/a	194	Road traffic accident	Same

Source: Applicant's Table 2-6, pg 79, Summary of Clinical Safety, Narratives beg pg 3930 ISS
Abbreviations: ctr = center, ID = identification, n/a = not applicable, pt = patient

Brief narratives follow for each of these deaths.

Patient 698004 was a 48 year old man with a past medical history of hypertension and dyslipidemia. Approximately 4 months after beginning liraglutide, the patient began to have "left-sided discomfort", but did not report it to a physician. The patient completed 117 days of liraglutide treatment per protocol; he also received metformin (MET) and glimepiride (GLIM) during the study. Approximately two weeks after routine per-protocol discontinuation of liraglutide, the patient felt a lump in his left side, and three weeks later saw a physician. At that time, ultrasound revealed a 15 cm renal mass, and chest computerized tomography (CT) showed a suspicious node in the left mediastinum. One week after initial presentation, the patient underwent a left radical nephrectomy for a Fuhrman Grade IV renal cell carcinoma. On an unknown date, a CT of the thorax and abdomen showed extensive hepatic, pulmonary and skeletal metastases. The patient's postoperative course is not otherwise mentioned in the narrative, but he died 7 months postoperatively from his renal cancer. His last liraglutide exposure had been approximately 8.5 months prior to his death.

Patient 225011 was a 63 year old man with a prior history of "hypersensitive bronchial tubes". The narrative states that he had not had alcohol for seven years prior to study entry, but does not

discuss whether he had a significant prior alcohol history. Approximately four months after beginning liraglutide, he presented with bronchitis and hyperglycemia; four days later, he was hospitalized. Six days after hospitalization, he was diagnosed with liver cirrhosis and hepatocellular carcinoma. His presenting signs and/or symptoms were not mentioned in the narrative, but during the hospitalization, he was found to have elevated transaminases and ferritin. Five days after diagnosis of his liver cancer, liraglutide was discontinued. He had also been taking concomitant metformin. He was discharged from the hospital; treatment for this hepatocellular carcinoma is not mentioned. He died approximately 10 months after diagnosis.

Patient 9025 was a 63 year old woman with a prior medical history of hypertension and hyperlipidemia. Approximately 5 weeks after starting liraglutide, the patient experienced abdominal enlargement, malaise and headache. The next day, vomiting and diarrhea began. One day later, the patient was admitted to the hospital with a diagnosis of acute gastroenteritis. The patient was febrile and had an elevated white blood cell count, C-reactive protein, blood urea nitrogen, creatinine and creatine phosphokinase. Troponin and ECG were normal. Meropenem trihydrate was initiated. The next morning, the patient was found in cardiorespiratory arrest. Resuscitation was attempted for two hours, but the patient did not respond. The investigator stated that "the direct cause of death was airway obstruction as a result of vomiting". An autopsy was not done. In the clinical safety reviewer's opinion, the cause of death was more likely due to aspiration of vomitus with resultant respiratory and cardiac arrest, rather than to gastroenteritis per se. Had the patient not aspirated, recovery would have been likely (as in the vast majority of cases of acute gastroenteritis), although the clinical course described for this patient was particularly severe (fever, leukocytosis and renal dysfunction at presentation). The possibility of another explanation for the patient's presentation exists, also, such as bowel infarction, which might have been expected to have a much more severe course, sometimes resulting in sepsis and/or hypotension with cardiovascular collapse and death. However, the paucity of data does not permit a determination of whether a different diagnosis was possible.

Patient 689012 was a 67 year old woman with a prior medical history of hypertension, hyperlipidemia and nephrolithiasis. Approximately 2.5 months after starting control medications (glimepiride and metformin), the patient was admitted to the intensive care unit (ICU) with a pulmonary embolism; presenting symptoms were not mentioned in the narrative. Five days after presentation, a stent was placed in the left anterior descending coronary artery; the reason for stent placement was not mentioned. The patient was hemodynamically unstable; stent occlusion was suspected. Thrombolytic was administered and two more stents were placed. The patient never regained hemodynamic stability, and remained hospitalized. Twelve days later, the patient suffered an acute myocardial infarction with cardiorespiratory arrest and died. Autopsy was not performed.

Patient 827005 was a 54 year old man with a prior medical history of hypertension and dyslipidemia. After approximately 3.5 months on control medications (glargine, glimepiride and metformin), the patient awoke at 0245 with chest pain, shortness of breath and sweating. An ambulance arrived within 5 minutes, but the patient died during transport to the hospital. Electrocardiogram during transport showed flat line. Cause of death was listed as acute myocardial infarction; autopsy was not performed.

Patient 504036 was a 57 year old woman with no prior medical history mentioned other than diabetes mellitus. She received control medication (glimepiride) for 194 days. A relative notified the principal investigator that the patient had died in an automobile accident; the narrative states that hypoglycemia was not suspected.

Overall, deaths occurred at a low rate, and occurred with equal frequency among liraglutide- and comparator-treated patients. There was no evidence of an association between liraglutide and overall mortality or cause-specific mortality.

In the 120-day safety update, an additional death was reported, with the cause of death being acute pancreatitis. Patient 117006 was a 64 year old woman who received liraglutide 1.8 mg for 668 days. She had no known history of alcohol consumption. Approximately 5 weeks prior to her death, she had undergone a colonoscopy which revealed a dysplastic colonic polyp, which was suspicious for adenocarcinoma. Three days prior to her death, she underwent a repeat colonoscopy, in order to "re-biopsy the area and to determine the extent and need for invasive surgery". No perforation appeared to occur, and endoscopic retrograde cholangiopancreatography was not performed. After the colonoscopy, the patient reported abdominal pain, but two days later, she was reported to be active. The next day, she rapidly deteriorated and died. Autopsy was reportedly consistent with acute and chronic pancreatitis. Macroscopic evaluation revealed mottled white, tan and dark red to black areas, "with most of the lighter areas about the periphery". Microscopic analysis revealed fatty change and autolysis. Autolysis was seen "in a range of organs beyond the pancreas". Gallbladder stones were present; biliary obstruction was not mentioned. The presence of dark red to black areas raised the question of whether this patient had necrotizing pancreatitis, and further information was requested from the applicant. On 29 Jun 2009, in an email to Dr. Parks (Division of Metabolism and Endocrinology Products [DMEP] Division Director), Dr. Thompson of Novo submitted a report of a pathology consultation that was performed at Dartmouth by Dr. Daniel Longnecker. He had received 3 slides from the original autopsy, which had been performed in Florida. Novo Nordisk had requested the consultation from Dr. Longnecker. In his blinded review of the slides, which he performed prior to knowledge of the original autopsy findings, he did not identify pancreatic tissue. Some of the tissues on the slides were unidentifiable, with advanced autolysis. After examining the slides, he received the autopsy report. He concurred with the diagnosis of acute pancreatitis based on the macroscopic description. He also stated "The fact that pancreatic tissue was not identified in the blinded review of the autopsy slides is not surprising inasmuch as necrosis is an expected finding in acute pancreatitis. In addition, the pancreas is known to undergo autolysis more rapidly than many other tissues because of its high content of hydrolytic digestive enzymes. One can assume that one or more of the unidentified tissues in the slides came from the pancreas and was unidentifiable because of the combined effects of antemortem necrosis and post mortem autolysis."

7.1.2 Other Serious Adverse Events

In general, serious adverse events occurred with similar frequency among liraglutide-treated and non-liraglutide-treated patients across the development program. The following table summarizes serious adverse events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term.

Table 7.1.2.1: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
Any	Any	160	3.8	86.6	90	4.0	97.5
Cardiac	Any	37	0.9	17.4	18	0.8	16.7
	Angina pectoris	7	0.2	3.1	3	0.1	2.6
	Acute myocardial infarction	5	0.1	2.2	4	0.2	3.5
	Myocardial infarction	5	0.1	2.2	5	0.2	4.4
	Coronary artery disease	4	0.1	1.8	1	<0.1	0.9
	Atrial fibrillation	2	<0.1	0.9	1	<0.1	0.9
	Cardiac failure congestive	2	<0.1	0.9	0	0	0
	Myocardial ischemia	2	<0.1	0.9	0	0	0
	Supraventricular tachycardia	2	<0.1	0.9	0	0	0
	Acute coronary syndrome	1	<0.1	0.4	0	0	0
	Angina unstable	1	<0.1	0.4	0	0	0
	Atrial flutter	1	<0.1	0.4	1	<0.1	0.9
	Cardiac arrest	1	<0.1	0.4	0	0	0
	Cardiac failure	1	<0.1	0.4	0	0	0
	Congestive cardiomyopathy	1	<0.1	0.4	0	0	0
	Coronary artery occlusion	1	<0.1	0.4	0	0	0
	Right ventricular failure	1	<0.1	0.4	0	0	0
	Tachycardia	1	<0.1	0.4	1	<0.1	0.9
	Tachycardia paroxysmal	1	<0.1	0.4	0	0	0
	Coronary artery stenosis	0	0	0	1	<0.1	0.9
	Ischemic cardiomyopathy	0	0	0	1	<0.1	0.9
	Ventricular tachycardia	0	0	0	1	<0.1	0.9
Gastrointestinal disorders	Any	20	0.5	10.7	9	0.4	10.5
	Appendicitis perforated	2	<0.1	0.9	0	0	0
	Gastritis	2	<0.1	0.9	0	0	0
	Inguinal hernia	2	<0.1	0.9	1	<0.1	0.9
	Pancreatitis	2	<0.1	0.9	0	0	0
	Vomiting	2	<0.1	0.9	1	<0.1	0.9
	Abdominal distension	1	<0.1	0.4	1	<0.1	0.9
	Abdominal pain upper	1	<0.1	0.4	0	0	0
	Crohn's disease	1	<0.1	0.4	0	0	0
	Diarrhea	1	<0.1	0.4	1	<0.1	0.9
	Duodenal ulcer	1	<0.1	0.4	0	0	0
	Femoral hernia, obstructive	1	<0.1	0.4	0	0	0
	Gastrointestinal hemorrhage	1	<0.1	0.4	0	0	0
	Gastroesophageal reflux disease	1	<0.1	0.4	0	0	0
	Hemorrhoids	1	<0.1	0.4	0	0	0
	Hiatus hernia	1	<0.1	0.4	0	0	0
	Mallory-Weiss syndrome	1	<0.1	0.4	0	0	0

Table 7.1.2.1: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
	Edematous pancreatitis	1	<0.1	0.4	0	0	0
	Pancreatitis chronic	1	<0.1	0.4	0	0	0
	Umbilical hernia	1	<0.1	0.4	0	0	0
	Abdominal pain	0	0	0	1	<0.1	0.9
	Constipation	0	0	0	1	<0.1	0.9
	Diverticulum	0	0	0	1	<0.1	0.9
	Diverticulum esophageal	0	0	0	1	<0.1	0.9
	Gastrointestinal pain	0	0	0	1	<0.1	0.9
	Ileus	0	0	0	1	<0.1	0.9
	Intestinal obstruction	0	0	0	1	<0.1	0.9
	Pancreatitis acute	0	0	0	1	<0.1	0.9
Infections and infestations	Any	20	0.5	9.8	10	0.4	10.5
	Upper respiratory tract infection	3	0.1	1.3	0	0	0
	Appendicitis	2	<0.1	0.9	1	<0.1	0.9
	Bronchitis	2	<0.1	0.9	0	0	0
	Gastroenteritis	2	<0.1	0.9	1	<0.1	0.9
	Osteomyelitis	2	<0.1	0.9	0	0	0
	Abscess sweat gland	1	<0.1	0.4	0	0	0
	Clostridial infection	1	<0.1	0.4	0	0	0
	Diabetic foot infection	1	<0.1	0.4	0	0	0
	Erysipelas	1	<0.1	0.4	0	0	0
	Herpes zoster	1	<0.1	0.4	0	0	0
	Infected skin ulcer	1	<0.1	0.4	1	<0.1	0.9
	Influenza	1	<0.1	0.4	0	0	0
	Pyelonephritis	1	<0.1	0.4	0	0	0
	Sinusitis	1	<0.1	0.4	0	0	0
	Spermatic cord funiculitis	1	<0.1	0.4	0	0	0
	Abscess limb	0	0	0	1	<0.1	0.9
	Breast abscess	0	0	0	1	<0.1	0.9
	Cellulitis	0	0	0	1	<0.1	0.9
	Ear infection	0	0	0	1	<0.1	0.9
	Localized infection	0	0	0	1	<0.1	0.9
	Parapharyngeal abscess	0	0	0	1	<0.1	0.9
	Viral infection	0	0	0	1	<0.1	0.9
	Wound sepsis	0	0	0	1	<0.1	0.9
Neoplasms benign, malignant and unspecified	Any	19	0.5	8.9	6	0.3	5.3
	Papillary thyroid cancer	4	0.1	1.8	1	<0.1	0.9
	Prostate cancer	4	0.1	1.8	1	<0.1	0.9
	Breast cancer	2	<0.1	0.9	1	<0.1	0.9
	B-cell lymphoma	1	<0.1	0.4	0	0	0
	Benign neoplasm of thyroid gland	1	<0.1	0.4	0	0	0

Table 7.1.2.1: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
	Colon adenoma	1	<0.1	0.4	0	0	0
	Gastrointestinal carcinoma	1	<0.1	0.4	0	0	0
	Hepatic neoplasm malignant	1	<0.1	0.4	0	0	0
	Lung carcinoma cell type unspecified recurrent	1	<0.1	0.4	0	0	0
	Malignant lymphoma unclassifiable high grade	1	<0.1	0.4	0	0	0
	Nasopharyngeal cancer	1	<0.1	0.4	0	0	0
	Renal cell carcinoma stage unspecified	1	<0.1	0.4	1	<0.1	0.9
	Uterine leiomyoma	1	<0.1	0.4	0	0	0
	Colon cancer	0	0	0	1	<0.1	0.9
	Glioblastoma multiforme	0	0	0	1	<0.1	0.9
Nervous system disorders	Any	18	0.4	8.0	7	0.3	6.1
	Cerebrovascular accident	3	0.1	1.3	0	0	0
	Syncope	2	<0.1	0.9	0	0	0
	Cerebral hemorrhage	1	<0.1	0.4	0	0	0
	Cerebrovascular disorder	1	<0.1	0.4	1	<0.1	0.9
	Diabetic neuropathy	1	<0.1	0.4	0	0	0
	Dizziness	1	<0.1	0.4	0	0	0
	Hemorrhage intracranial	1	<0.1	0.4	0	0	0
	Headache	1	<0.1	0.4	0	0	0
	Hypoaesthesia	1	<0.1	0.4	0	0	0
	Loss of consciousness	1	<0.1	0.4	0	0	0
	Nerve compression	1	<0.1	0.4	0	0	0
	Radial nerve palsy	1	<0.1	0.4	0	0	0
	Sciatica	1	<0.1	0.4	0	0	0
	Subarachnoid hemorrhage	1	<0.1	0.4	0	0	0
	Transient ischemia attack	1	<0.1	0.4	1	<0.1	0.9
	Carotid artery stenosis	0	0	0	2	0.1	1.8
	Grand mal convulsion	0	0	0	1	<0.1	0.9
	Ischemic stroke	0	0	0	1	<0.1	0.9
	Presyncope	0	0	0	1	<0.1	0.9
Musculoskeletal and connective tissue disorders	Any	14	0.3	6.2	7	0.3	6.1
	Intervertebral disc protrusion	2	<0.1	0.9	0	0	0
	Osteoarthritis	2	<0.1	0.9	3	0.1	2.6
	Collagen disorder	1	<0.1	0.4	0	0	0
	Intervertebral disc degeneration	1	<0.1	0.4	0	0	0
	Intervertebral disc disorder	1	<0.1	0.4	1	<0.1	0.9
	Lumbar spinal stenosis	1	<0.1	0.4	0	0	0
	Muscle spasms	1	<0.1	0.4	0	0	0

Table 7.1.2.1: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
	Myositis	1	<0.1	0.4	0	0	0
	Osteolysis	1	<0.1	0.4	0	0	0
	Patellofemoral pain syndrome	1	<0.1	0.4	0	0	0
	Rheumatoid arthritis	1	<0.1	0.4	0	0	0
	Tendon disorder	1	<0.1	0.4	0	0	0
	Arthralgia	0	0	0	1	<0.1	0.9
	Back pain	0	0	0	1	<0.1	0.9
	Spinal column stenosis	0	0	0	1	<0.1	0.9
Injury, poisoning and procedural complications	Any	11	0.3	6.2	12	0.5	11.4
	Fall	4	0.1	1.8	3	0.1	2.6
	Brain contusion	1	<0.1	0.4	0	0	0
	Concussion	1	<0.1	0.4	0	0	0
	Hip fracture	1	<0.1	0.4	1	<0.1	0.9
	Humerus fracture	1	<0.1	0.4	1	<0.1	0.9
	Joint injury	1	<0.1	0.4	0	0	0
	Limb injury	1	<0.1	0.4	0	0	0
	Lower limb fracture	1	<0.1	0.4	0	0	0
	Road traffic accident	1	<0.1	0.4	1	<0.1	0.9
	Sympathetic nerve injury	1	<0.1	0.4	0	0	0
	Wound	1	<0.1	0.4	0	0	0
	Ankle fracture	0	0	0	1	<0.1	0.9
	Femur fracture	0	0	0	1	<0.1	0.9
	Joint dislocation	0	0	0	1	<0.1	0.9
	Open fracture	0	0	0	1	<0.1	0.9
	Patella fracture	0	0	0	1	<0.1	0.9
	Pelvic fracture	0	0	0	1	<0.1	0.9
	Tibia fracture	0	0	0	1	<0.1	0.9
General disorders and administration site conditions	Any	8	0.2	3.6	6	0.3	5.3
	Chest pain	5	0.1	2.2	4	0.2	3.5
	Hernia	1	<0.1	0.4	0	0	0
	Noncardiac chest pain	1	<0.1	0.4	1	<0.1	0.9
	Pyrexia	1	<0.1	0.4	0	0	0
	Malaise	0	0	0	1	<0.1	0.9
Endocrine disorders	Any	6	0.1	2.7	0	0	0
	Goitre	3	0.1	1.3	0	0	0
	Adrenocortical insufficiency acute	2	<0.1	0.9	0	0	0
	Thyroid disorder	1	<0.1	0.4	0	0	0
Metabolism and nutrition disorders	Any	5	0.1	2.2	5	0.2	4.4

Table 7.1.2.1: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
	Hypoglycemia	3	0.1	1.3	0	0	0
	Hyperglycemia	1	<0.1	0.4	3	0.1	2.6
	Hypokalemia	1	<0.1	0.4	0	0	0
	Dehydration	0	0	0	1	<0.1	0.9
	Hyponatremia	0	0	0	1	<0.1	0.9
Respiratory, thoracic and mediastinal disorders	Any	5	0.1	2.2	4	0.2	3.5
	Pulmonary embolism	2	<0.1	0.9	1	<0.1	0.9
	Asthma	1	<0.1	0.4	0	0	0
	Cryptogenic organizing pneumonia	1	<0.1	0.4	0	0	0
	Snoring	1	<0.1	0.4	0	0	0
	Bronchitis chronic	0	0	0	1	<0.1	0.9
	Pulmonary edema	0	0	0	1	<0.1	0.9
	Sleep apnea syndrome	0	0	0	1	<0.1	0.9
Hepatobiliary disorders	Any	4	0.1	1.8	2	0.1	1.8
	Cholecystitis	1	<0.1	0.4	1	<0.1	0.9
	Cholecystitis acute	1	<0.1	0.4	0	0	0
	Cholelithiasis	1	<0.1	0.4	0	0	0
	Hepatic cirrhosis	1	<0.1	0.4	0	0	0
	Biliary colic	0	0	0	1	<0.1	0.9
Reproductive system and breast disorders	Any	3	0.1	1.3	1	<0.1	0.9
	Menorrhagia	1	<0.1	0.4	0	0	0
	Ovarian cyst	1	<0.1	0.4	0	0	0
	Testicular pain	1	<0.1	0.4	0	0	0
	Benign prostatic hypertrophy	0	0	0	1	<0.1	0.9
Vascular disorders	Any	3	0.1	1.3	4	0.2	3.5
	Arteriosclerosis	1	<0.1	0.4	0	0	0
	Orthostatic hypotension	1	<0.1	0.4	0	0	0
	Peripheral vascular disorder	1	<0.1[a]	0.4	0	0	0
	Aortic aneurysm	0	0	0	1	<0.1	0.9
	Arterial stenosis limb	0	0	0	1	<0.1	0.9
	Arteriosclerosis obliterans	0	0	0	1	<0.1	0.9
	Hypertension	0	0	0	1	<0.1	0.9
Eye disorders	Any	2	<0.1	0.9	2	0.1	1.8
	Retinal detachment	1	<0.1	0.4	1	<0.1	0.9
	Uveitis	1	<0.1	0.4	0	0	0
	Glaucoma	0	0	0	1	<0.1	0.9
Investigations	Any	2	<0.1	0.9	1	<0.1	0.9
	Blood calcitonin increased	1	<0.1	0.4	0	0	0
	Heart rate increased	1	<0.1	0.4	0	0	0

Table 7.1.2.1: Serious Adverse Events by MedDRA System Organ Class and Preferred Term, All Completed Trials at Time of NDA Submission

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
	Electrocardiogram abnormal	0	0	0	1	<0.1	0.9
Renal and urinary disorders	Any	2	<0.1	0.9	5	0.2	4.4
	Hematuria	1	<0.1	0.4	0	0	0
	Renal pain	1	<0.1	0.4	0	0	0
	Nephrolithiasis	0	0	0	1	<0.1	0.9
	Renal colic	0	0	0	1	<0.1	0.9
	Renal failure acute	0	0	0	1	<0.1	0.9
	Renal tubular acidosis	0	0	0	1	<0.1	0.9
	Urethral stenosis	0	0	0	1	<0.1	0.9
Skin and subcutaneous tissue disorders	Any	2	<0.1	0.9	2	0.1	1.8
	Angioedema	1	<0.1	0.4	0	0	0
	Penile ulceration	1	<0.1	0.4	0	0	0
	Skin ulcer	0	0	0	2	0.1	1.8
Psychiatric disorders	Any	1	<0.1	0.4	0	0	0
	Suicidal ideation	1	<0.1	0.4	0	0	0
Blood and lymphatic system disorders	Any	0	0	0	1	<0.1	0.9
	Anemia	0	0	0	1	<0.1	0.9
Congenital, familial and genetic disorders	Any	0	0	0	1	<0.1	0.9
	Urachal abnormality	0	0	0	1	<0.1	0.9
Ear and labyrinth disorders	Any	0	0	0	1	<0.1	0.9
	Vertigo	0	0	0	1	<0.1	0.9

Source: Applicant's Table 72, beg pg 1123 ISS
Abbreviations: LGT = liraglutide; PY = patient-years

Most serious adverse events occurred with approximately equal frequency among LGT-treated and non-LGT-treated patients. Types of events which occurred with somewhat greater numeric frequency among LGT-treated patients than among non-LGT-treated patients included pancreatitis, thyroid cancer, thyroid disorders in general, events of immune etiology, stroke or cerebral hemorrhage events, angina events, and malignancies overall. Serious adverse events of fractures, which have been events of particular recent interest for diabetes drugs, did not appear to have occurred more frequently among liraglutide-treated patients.

Thyroid disorders, pancreatitis and cardiovascular adverse events are discussed further in Section 7.1.3.3. The observed imbalance in the incidence of serious adverse events (SAEs) of malignancies is discussed in Section 7.1.11. Serious events of immune etiology are further discussed below.

The following table summarizes events which may have been immune in nature.

Table 7.1.2.2: Serious Adverse Events of Possible Immune Etiology

System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
Gastrointestinal disorders	Crohn's disease	1	<0.1	0.4	0	0	0
Musculoskeletal and connective tissue disorders	Collagen disorder	1	<0.1	0.4	0	0	0
	Myositis	1	<0.1	0.4	0	0	0
	Rheumatoid arthritis	1	<0.1	0.4	0	0	0
Endocrine disorders	Adrenocortical insufficiency acute	2	<0.1	0.9	0	0	0
Respiratory, thoracic and mediastinal disorders	Cryptogenic organizing pneumonia	1	<0.1	0.4	0	0	0
Eye disorders	Uveitis	1	<0.1	0.4	0	0	0
Skin and subcutaneous tissue disorders	Angioedema	1	<0.1	0.4	0	0	0

Source: Applicant's Table 72, beg pg 1123 ISS

A total of nine serious potential immune-related events occurred among 4211 liraglutide-treated patients. Narratives for these cases follow:

Patient 175012 had an event of uveitis. This was a 71 year old Spanish woman who presented with blurred vision and "vision of black dots" after 297 days of LGT 1.8 mg/day. She had a prior history of glaucoma and hypertension. She was admitted. Ophthalmoscopy showed pale optic papillae and atrophic retinal lesions. Intraocular pressure was 45 mmHg. "Hypertensive uveitis" was diagnosed. She was treated with dexamethasone, atropine, and cusimolol. Angiography was not performed. Serology (not specified) showed "nothing abnormal". She was discharged one day later, and one month later was considered recovered.

Patient 180014 had an event of Crohn's disease. This was a 52 year old American woman who presented with "regional enteritis" after 462 days of liraglutide 1.8 mg/day. The narrative states only that the patient was admitted to the hospital and discharged two days later. No details of how the diagnosis of Crohn's disease was made, or what treatment was administered, were provided.

Patient 188004 had an event of acute adrenocortical insufficiency. This was a 47 year old American woman with a prior history of adrenogenital syndrome, hirsutism, polycystic ovaries, vitamin D deficiency, dyslipidemia and depression. She presented with "adrenal crisis" after 226 days of liraglutide 1.2 mg/day. At presentation, her potassium was 6.6 mEq/L. The narrative states that the patient was discontinued from study at this time, but discontinuation was due to alcohol abuse. The narrative does not specifically state that the patient was admitted to the hospital at that time. It does state that she was admitted seven days later due to hyperkalemia, with a serum potassium of 7.0 mEq/L. She also had bronchitis. Aldactone was discontinued, and she received intravenous fluids and Kayexalate. Intravenous hydrocortisone and an intravenous insulin drip were administered. Doxycycline was also administered. She was discharged three days later. She did not resume study, and began subcutaneous insulin for treatment of her diabetes. The narrative states that she resumed physiologic steroid replacement.

Patient 375005 had an event of angioedema. This was a 60 year old Russian woman who presented with difficulty swallowing, facial and eyelid swelling, and a "suffocation attack" after administration of Bioparox (fusafungine) for acute laryngopharyngitis. Fusafungine appears to be an agent with local antibacterial action that is used for treatment of upper respiratory infections in some countries outside the United States. She had been taking liraglutide 1.2 mg for 211 days prior to onset of the angioedema. She was hospitalized and treated with intravenous glucocorticoids and recovered. She was discharged from the hospital 9 days later; LGT was never discontinued.

Patient 471040 was a 51 year old Finnish man who had an event of cryptogenic organizing pneumonia (COP). He presented with prolonged flu-like symptoms and fatigue after 48 days of LGT 0.6 mg/day. About two months prior to starting LGT, he had had a pneumonia. At the time of presentation (Study Day 48), he had a left lung infiltrate on chest X-ray, and was admitted to hospital. Computerized tomography and bronchoscopy confirmed an organizing pneumonia of unknown etiology. He was discharged the next day. It appears that two weeks later, he had a high-resolution CT which showed a 4 cm diameter left lung infiltrate; bronchoscopy showed "a mild inflammation". One month later, LGT was discontinued due to "ineffective therapy", and the patient was withdrawn from study. About two months later, prednisone was initiated. Two months later, he underwent mediastinoscopy which revealed only mildly enlarged lymph nodes. At that time, he was considered to be "recovering".

Patient 504010 had an event of acute adrenocortical insufficiency. This was a 48 year old Mexican woman with a prior history of Cushing's syndrome and bilateral adrenalectomy. She presented with malaise, fever, abdominal pain, nausea and vomiting after 213 days of liraglutide 1.2 mg/day. She was hypotensive on presentation, and was treated with intravenous hydrocortisone, followed by oral prednisone. She also received ciprofloxacin. She was discharged two days later. Liraglutide was discontinued during the hospitalization, but was resumed on discharge.

Patient 516007 had an event of rheumatoid arthritis. This was a 62 year old Australian woman with a prior diagnosis of rheumatoid arthritis, who presented with worsening knee pain after 103 days of liraglutide 0.6 mg/day. She was admitted, underwent knee arthroscopy to determine if knee replacement was warranted, and was discharged 1 day later. Four days after the arthroscopy, she developed a knee infection, which was treated with cephalexin, and resolved after 7 days of treatment. The narrative states that knee replacement will be required at some point in the future.

Patient 526011 had an event of myositis. This was a 45 year old South African woman who presented with severe left thigh pain after 229 days of liraglutide 1.8 mg/day. Eighteen days after presentation with thigh pain, she was admitted to the hospital. Magnetic resonance imaging revealed "increased signaling" of muscles in the anterior upper thigh. The narrative does not mention whether she had measurements of creatine phosphokinase (CPK) or inflammatory markers. She was treated with antibiotics, vitamin B12, iron supplements, amitriptyline, ciprofloxacin, diclofenac and "anti-inflammatory medication". She had a history of chronic iron deficiency anemia. The narrative states that doctors felt that the pain might be due to diabetic

microvascular disease. After three days in hospital, the patient was discharged. After about one more month, the pain resolved.

Patient 762012 had an event of collagen disorder. This was a 59 year old Polish man who presented with fever, weakness, abdominal pain and hyperglycemia after 123 days of liraglutide 1.8 mg/day. He was diagnosed with "collagenosis" and "spermatitis". He was treated with Novomix® (mixed insulin aspart and protamine-crystallized insulin aspart) and ciprofloxacin. Study medication was discontinued. He was discharged after 17 days in the hospital. The narrative does not include details of how the diagnosis of collagen disorder was assigned. "Collagenosis" is an alternative term for collagen-vascular disease, and is defined as "any of a group of diseases affecting connective tissue and often characterized by fibrinoid necrosis or vasculitis and including such diseases as lupus erythematosus, progressive systemic sclerosis, rheumatoid arthritis, rheumatic fever, polyarteritis nodosa and dermatomyositis".

Although there was an apparent imbalance in serious immune system events based on event terms, review of narratives revealed that several of the events were exacerbations of pre-existing conditions, and others had inadequate information to assign causality. Patients 188004 and 504010 had pre-existing chronic adrenal insufficiency, and presented with acute adrenal insufficiency at the time of infections, a common scenario in patients with chronic adrenal insufficiency. Patient 516007 presented with an exacerbation of pre-existing rheumatoid arthritis. Patient 175012's uveitis, Patient 526011's myositis, and Patient 471040's COP were not clearly immune in etiology. Patient 375005's angioedema appeared temporally related to antibiotic therapy rather than LGT therapy. There were too few details of Patient 180014's Crohn's disease and Patient 762012's collagen disorder to assign causality. Overall, it appears unlikely that LGT was associated with causality for new immune disorders. If another large study of LGT is initiated, e.g. for cardiovascular (CV) outcomes, systematic collection of immune system event data would be useful.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Across the development program, the highest rate of withdrawal occurred among placebo-treated patients, for whom the most common reason for withdrawal was ineffectiveness of therapy. Withdrawals due to adverse events were more common among LGT-treated patients than among comparator-treated patients, with gastrointestinal events contributing to the excess withdrawal rate. This excess withdrawal rate was seen primarily for the 1.2 and 1.8 mg/day dose groups; the most common reason for withdrawal from the 0.6 mg/day dose group was ineffectiveness of therapy.

The following table summarizes disposition for the five major Phase 3 trials.

Table 7.1.3.1.1: Disposition in the Five Major Phase 3 Trials

		LGT 0.6 mg	LGT 1.2 mg	LGT 1.8 mg	LGT Total	PBO	Active Comp	Total Comp
Randomized (N)		475	898	1133	2506	528	958	1486
Exposed (N)		475	896	1130	2501	524	953	1477
Withdrawals during controlled portion of trial	**Any reason [n (%)]**	59 (12.4)	188 (21.0)	213 (18.9)	460 (18.4)	150 (28.6)	178 (18.7)	328 (22.2)
	AE [n (%)]	16 (3.4)	69 (7.7)	93 (8.2)	178 (7.1)	15 (2.9)	35 (3.7)	50 (3.4)
	Noncompliance with protocol [n (%)]	5 (1.1)	24 (2.7)	22 (2.0)	51 (2.0)	11 (2.1)	19 (2.0)	30 (2.0)
	Ineffective therapy [n (%)]	31 (6.5)	34 (3.8)	34 (3.0)	99 (4.0)	91 (17.4)	50 (5.3)	141 (10.0)
	Other [n (%)]	7 (1.5)	61 (6.8)	64 (5.7)	132 (5.3)	33 (6.3)	74 (7.8)	107 (7.2)
Completers of controlled portion of trial [n (%)]		416 (87.6)	708 (79.0)	917 (81.2)	2041 (81.6)	374 (71.4)	775 (81.3)	1149 (77.8)
Entered extension [n (% of original randomized)]		184 (38.7)	327 (36.5)	328 (29.0)	839 (33.6)	61 (11.6)	320 (33.6)	381 (25.8)
Withdrawals during open-label extension portion of trial	**Any reason [n (%)]**	40 (21.7)	46 (14.1)	54 (16.5)	140 (16.7)	25 (41.0)	70 (21.9)	95 (24.9)
	AE [n (%)]	5 (2.7)	7 (2.1)	6 (1.8)	18 (2.2)	1 (1.6)	5 (1.6)	6 (1.6)
	Noncompliance with protocol [n (%)]	5 (2.7)	6 (1.8)	4 (1.2)	15 (1.8)	0	5 (1.6)	5 (1.3)
	Ineffective therapy [n (%)]	22 (12.0)	25 (7.7)	25 (7.6)	72 (8.6)	19 (31.2)	43 (13.4)	62 (16.3)
	Other [n (%)]	8 (4.4)	8 (2.5)	19 (5.8)	35 (4.2)	5 (8.2)	17 (5.3)	22 (5.8)
Total 12 month completers [n (%)]		171 (92.9)	330 (76.9)	337 (80.2)	838 (81.1)	48 (78.7)	318 (73.8)	366 (74.4)
Total 18 month completers [n (%)]		110 (59.8)	200 (61.2)	187 (57.0)	497 (59.2)	29 (47.5)	168 (52.5)	197 (51.7)

Source: Applicant's Table 14, pg 542, ISS
Abbreviations: comp = comparator, LGT = liraglutide, PBO = placebo

The following table summarizes disposition by trial, for the five major Phase 3 trials.

Table 7.1.3.1.2: Disposition by Trial, Five Major Phase 3 Trials

Trial	Pt Status	Reason for W/D, if Applicable	LGT 0.6	LGT 1.2	LGT 1.8	PBO	AC	Total
1436	Rand N		233	228	234	114	232	1041
	Expos N		233	228	234	114	231 (RSG)	1040
	Compl %		89.3	86.0	91.0	72.8	83.6	85.9
	W/D %		10.7	14.0	9.0	27.2	16.4	14.1
		Ineff therapy %	5.2	3.5	3.0	17.5	6.9	6.1
		AE %	2.1	4.8	3.8	5.3	3.0	3.7
		Non-compliance %	1.3	2.2	1.3	1.8	2.6	1.8
		Other %	2.1	3.5	0.9	2.6	3.9	2.6
1572	Rand N		242	241	242	122	244	1091
	Expos N		242	240	242	121	242 (GLIM)	1087
	Compl %		86.0	81.7	78.9	60.7	86.1	80.7
	W/D %		14.0	18.3	21.1	39.3	13.9	19.3
		Ineff therapy %	7.9	3.3	5.4	23.8	3.7	7.1
		AE %	4.5	9.5	12.0	1.6	3.3	6.7
		Non-compliance %	0.8	1.7	1.7	3.3	2.0	1.7
		Other	0.8	3.7	2.1	10.7	4.9	3.8
1573	Rand N			247	251		248	746
	Expos N			246	251		248 (GLIM)	745
	Compl %			70.0	64.5		61.3	65.3
	W/D %			30.0	35.5		38.7	34.7
		Ineff therapy %		3.6	6.0		10.1	6.6
		AE %		7.3	10.0		6.0	7.8
		Non-compliance %		4.5	4.4		2.0	3.6
		Other %		14.6	15.1		20.6	16.8
1574	Rand N			178	178	177		533
	Expos N			178	177	175		530
	Compl %			74.7	86.0	68.4		76.4
	W/D %			25.3	14.0	31.6		23.6
		Ineff therapy %		1.7	1.7	16.4		6.6
		AE %		15.2	6.2	3.4		8.3
		Non-compliance %		2.2	2.2	2.8		2.4
		Other %		6.2	3.9	9.0		6.4
1697	Rand N				232	115	234	581
	Expos N				230	114	232 (GLAR)	576
	Compl %				89.2	83.5	93.6	89.8
	W/D %				10.8	16.5	6.4	10.2
		Ineff therapy %			0.9	11.3	0.4	2.8
		AE %			4.7	0.9	2.1	2.9
		Non-compliance %			0.4	0.9	2.1	1.2
		Other %			4.7	3.5	1.7	3.3

Table 7.1.3.1.2: Disposition by Trial, Five Major Phase 3 Trials								
Trial	Pt Status	Reason for W/D, if Applicable	LGT 0.6	LGT 1.2	LGT 1.8	PBO	AC	Total
Source: Table 5, beg pg 23, Statistical Review by Dr. Derr								

In studies which had a placebo arm, patients in the placebo arm were more likely to withdraw early due to ineffective therapy. In the studies which had an active comparator arm, patients in the liraglutide and active control arms were approximately equally likely to withdraw early due to ineffective therapy.

7.1.3.2 Adverse events associated with dropouts

The following adverse events were associated with dropouts.

Table 7.1.3.2: Adverse Events Associated with Dropouts, All Completed Trials at Time of NDA Submission

SOC	Preferred Term	LGT N=4211 n (%)	Non-LGT N=2272 n (%)
Any	Any	250 (5.9)	69 (3.0)
Gastrointestinal disorders	Any	155 (3.7)	16 (0.7)
	Nausea	81 (1.9)	2 (0.1)
	Vomiting	46 (1.1)	1 (<0.1)
	Diarrhea	31 (0.7)	4 (0.2)
	Dyspepsia	14 (0.3)	0
	Constipation	12 (0.3)	2 (0.1)
	Abdominal distension	9 (0.2)	2 (0.1)
	Abdominal pain upper	7 (0.2)	0
	Abdominal pain	6 (0.1)	3 (0.1)
	Gastritis	5 (0.1)	0
	Abdominal discomfort	4 (0.1)	2 (0.1)
	Dry mouth	4 (0.1)	0
	Eructation	4 (0.1)	0
	Gastrointestinal discomfort	4 (0.1)	0
	Gastroesophageal reflux disease	4 (0.1)	1 (<0.1)
	Flatulence	3 (0.1)	0
	Abdominal tenderness	2 (<0.1)	0
	Diverticulum	1 (<0.1)	1 (<0.1)
	Dysphagia	1 (<0.1)	0
	Hemorrhoids	1 (<0.1)	0
	Infrequent bowel movements	1 (<0.1)	0
	Lip swelling	1 (<0.1)	0
	Edematous pancreatitis	1 (<0.1)	0
	Pancreatitis	1 (<0.1)	0
	Stomach discomfort	1 (<0.1)	0
	Umbilical hernia	1 (<0.1)	0
	Diverticulum esophagus	0	1 (<0.1)

Table 7.1.3.2: Adverse Events Associated with Dropouts, All Completed Trials at Time of NDA Submission

SOC	Preferred Term	LGT N=4211 n (%)	Non-LGT N=2272 n (%)
	Intestinal obstruction	0	1 (<0.1)
	Pancreatitis acute	0	1 (<0.1)
Metabolism and nutrition disorders	Any	41 (1.0)	9 (0.4)
	Anorexia	20 (0.5)	2 (0.1)
	Decreased appetite	10 (0.2)	0
	Hyperglycemia	7 (0.2)	7 (0.3)
	Hypoglycemia	2 (<0.1)	0
	Polydipsia	2 (<0.1)	0
	Fluid retention	1 (<0.1)	0
	Hypertriglyceridemia	1 (<0.1)	0
Nervous system disorders	Any	35 (0.8)	6 (0.3)
	Headache	13 (0.3)	1 (<0.1)
	Dizziness	9 (0.2)	2 (0.1)
	Lethargy	4 (0.1)	1 (<0.1)
	Burning sensation	2 (<0.1)	0
	Paresthesia	2 (<0.1)	0
	Ageusia	1 (<0.1)	0
	Cerebrovascular accident	1 (<0.1)	0
	Cerebrovascular disorder	1 (<0.1)	1 (<0.1)
	Dysgeusia	1 (<0.1)	0
	Facial palsy	1 (<0.1)	0
	Hemorrhage intracranial	1 (<0.1)	0
	Hypoaesthesia	1 (<0.1)	0
	Somnolence	1 (<0.1)	0
	Tunnel vision	1 (<0.1)	0
	Ischemic stroke	0	1 (<0.1)
General disorders and administration site conditions	Any	34 (0.8)	6 (0.3)
	Fatigue	9 (0.2)	0
	Aesthenia	6 (0.1)	2 (0.1)
	Malaise	4 (0.1)	0
	Pyrexia	3 (0.1)	0
	Chest discomfort	2 (<0.1)	0
	Injection site bruising	2 (<0.1)	0
	Injection site rash	2 (<0.1)	0
	Edema peripheral	2 (<0.1)	1 (<0.1)
	Chest pain	1 (<0.1)	1 (<0.1)
	Injection site discomfort	1 (<0.1)	0
	Injection site erythema	1 (<0.1)	0
	Injection site irritation	1 (<0.1)	0
	Injection site nodule	1 (<0.1)	0
	Gait disturbance	0	1 (<0.1)
	Pain	0	1 (<0.1)
Investigations	Any	22 (0.5)	13 (0.6)
	Weight decreased	6 (0.1)	0

Table 7.1.3.2: Adverse Events Associated with Dropouts, All Completed Trials at Time of NDA Submission

SOC	Preferred Term	LGT N=4211 n (%)	Non-LGT N=2272 n (%)
	Weight increased	3 (0.1)	4 (0.2)
	Blood calcitonin increased	2 (<0.1)	1 (<0.1)
	Blood creatine phosphokinase increased	2 (<0.1)	0
	Blood creatinine increased	2 (<0.1)	2 (0.1)
	Heart rate increased	2 (<0.1)	0
	Aspartate aminotransferase increased	1 (<0.1)	0
	Blood glucose increased	1 (<0.1)	3 (0.1)
	Blood pressure increased	1 (<0.1)	0
	Electrocardiogram abnormal	1 (<0.1)	0
	Hepatic enzyme increased	1 (<0.1)	1 (<0.1)
	Liver function test abnormal	0	1 (<0.1)
	Transaminases increased	0	1 (<0.1)
Infections and infestations	Any	13 (0.3)	4 (0.2)
	Gastroenteritis	2 (<0.1)	0
	Tonsillitis	2 (<0.1)	0
	Diabetic foot infection	1 (<0.1)	0
	Ear infection	1 (<0.1)	0
	Erysipelas	1 (<0.1)	0
	Gastroenteritis viral	1 (<0.1)	0
	Herpes Zoster	1 (<0.1)	0
	Oral fungal infection	1 (<0.1)	0
	Pharyngitis	1 (<0.1)	0
	Sinusitis	1 (<0.1)	0
	Spermatic cord funiculitis	1 (<0.1)	0
	Upper respiratory tract infection	1 (<0.1)	0
	Vulvovaginal mycotic infection	1 (<0.1)	0
	Infected skin ulcer	0	1 (<0.1)
	Nasopharyngitis	0	1 (<0.1)
	Viral infection	0	1 (<0.1)
Cardiac disorders	Any	12 (0.3)	7 (0.3)
	Myocardial infarction	3 (0.1)	3 (0.1)
	Acute myocardial infarction	2 (<0.1)	3 (0.1)
	Angina pectoris	1 (<0.1)	0
	Atrioventricular block first degree	1 (<0.1)	0
	Cardiac arrest	1 (<0.1)	0
	Cardiac failure congestive	1 (<0.1)	0
	Coronary artery disease	1 (<0.1)	0
	Myocardial ischemia	1 (<0.1)	0
	Palpitations	1 (<0.1)	0
	Atrial fibrillation	0	1 (<0.1)
	Tachycardia	0	1 (<0.1)
Skin and subcutaneous tissue disorders	Any	12 (0.3)	6 (0.3)
	Rash	3 (0.1)	3 (0.1)
	Erythema	2 (<0.1)	0

Table 7.1.3.2: Adverse Events Associated with Dropouts, All Completed Trials at Time of NDA Submission

SOC	Preferred Term	LGT N=4211 n (%)	Non-LGT N=2272 n (%)
	Hyperhidrosis	2 (<0.1)	0
	Pruritus	2 (<0.1)	0
	Hyperkeratosis	1 (<0.1)	0
	Rash papular	1 (<0.1)	0
	Urticaria	1 (<0.1)	0
	Skin ulcer	0	3 (0.1)
Psychiatric disorders	Any	10 (0.2)	3 (0.1)
	Food aversion	2 (<0.1)	0
	Insomnia	2 (<0.1)	1 (<0.1)
	Aggression	1 (<0.1)	0
	Alcohol abuse	1 (<0.1)	0
	Depressed mood	1 (<0.1)	0
	Depression	1 (<0.1)	0
	Mood swings	1 (<0.1)	0
	Sleep disorder	1 (<0.1)	0
	Anxiety	0	2 (0.1)
Musculoskeletal and connective tissue disorders	Any	9 (0.2)	1 (<0.1)
	Myalgia	2 (<0.1)	1 (<0.1)
	Pain in extremity	2 (<0.1)	0
	Back pain	1 (<0.1)	1 (<0.1)
	Collagen disorder	1 (<0.1)	0
	Intervertebral disc protrusion	1 (<0.1)	0
	Muscle spasms	1 (<0.1)	1 (<0.1)
	Musculoskeletal chest pain	1 (<0.1)	0
Neoplasms	Any	8 (0.2)	3 (0.1)
	Breast cancer	2 (<0.1)	1 (<0.1)
	Prostate cancer	2 (<0.1)	0
	Gastrointestinal carcinoma	1 (<0.1)	0
	Hepatic neoplasm malignant	1 (<0.1)	0
	Lung carcinoma cell type unspecified recurrent	1 (<0.1)	0
	Malignant lymphoma unclassifiable high grade	1 (<0.1)	0
	Papillary thyroid cancer	0	1 (<0.1)
	Renal cell carcinoma stage unspecified	0	1 (<0.1)
Hepatobiliary disorders	Any	5 (0.1)	0
	Cholelithiasis	2 (<0.1)	0
	Cholecystitis	1 (<0.1)	0
	Hepatic cirrhosis	1 (<0.1)	0
	Hepatic function abnormal	1 (<0.1)	0
Vascular disorders	Any	5 (0.1)	2 (0.1)
	Hypertension	2 (<0.1)	1 (<0.1)
	Aneurysm	1 (<0.1)	0
	Flushing	1 (<0.1)	0

Table 7.1.3.2: Adverse Events Associated with Dropouts, All Completed Trials at Time of NDA Submission

SOC	Preferred Term	LGT N=4211 n (%)	Non-LGT N=2272 n (%)
	Hypotension	1 (<0.1)	0
	Arterial stenosis limb	0	1 (<0.1)
Eye disorders	Any	4 (0.1)	1 (<0.1)
	Eye pain	1 (<0.1)	0
	Macular edema	1 (<0.1)	0
	Vision blurred	1 (<0.1)	0
	Visual acuity reduced	1 (<0.1)	0
	Diplopia	0	1 (<0.1)
Renal and urinary disorders	Any	4 (0.1)	2 (0.1)
	Polyuria	2 (<0.1)	0
	Nephrolithiasis	1 (<0.1)	0
	Nocturia	1 (<0.1)	0
	Renal colic	1 (<0.1)	0
	Urinary retention	1 (<0.1)	0
	Renal failure acute	0	1 (<0.1)
	Renal tubular necrosis	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	Any	4 (0.1)	1 (<0.1)
	Dyspnea	2 (<0.1)	0
	Hiccups	1 (<0.1)	0
	Pleural effusion	1 (<0.1)	0
	Tachypnea	1 (<0.1)	0
	Pulmonary edema	0	1 (<0.1)
Ear and labyrinth disorders	Any	3 (0.1)	0
	Vertigo	3 (0.1)	0
Immune system disorders	Any	3 (0.1)	0
	Allergy to metals	1 (<0.1)	0
	Drug hypersensitivity	1 (<0.1)	0
	Hypersensitivity	1 (<0.1)	0
Injury, poisoning and procedural complications	Any	3 (0.1)	4 (0.2)
	Arthropod bite	1 (<0.1)	0
	Carbon monoxide poisoning	1 (<0.1)	0
	Fall	1 (<0.1)	0
	Femur fracture	0	1 (<0.1)
	Pelvic fracture	0	1 (<0.1)
	Road traffic accident	0	1 (<0.1)
	Wrist fracture	0	1 (<0.1)
Blood and lymphatic system disorders	Any	1 (<0.1)	4 (0.2)
	Thrombocytopenia	1 (<0.1)	1 (<0.1)
	Anemia	0	2 (0.1)
	Granulocytopenia	0	1 (<0.1)
Endocrine disorders	Any	1 (<0.1)	0
	Goitre	1 (<0.1)	0
Reproductive system and breast	Any	1 (<0.1)	1 (<0.1)

Table 7.1.3.2: Adverse Events Associated with Dropouts, All Completed Trials at Time of NDA Submission

SOC	Preferred Term	LGT N=4211 n (%)	Non-LGT N=2272 n (%)
disorders			
	Vulvovaginal pruritus	1 (<0.1)	0
	Erectile dysfunction	0	1 (<0.1)

Source: Applicant's Table 108, beginning pg 1262, ISS

Across all completed trials of liraglutide at the time of NDA submission, withdrawals due to adverse events occurred in 5.9% of liraglutide-treated patients and in 3.0% of non-liraglutide-treated patients. This difference was largely accounted for by more withdrawals for gastrointestinal (GI) events among liraglutide-treated patients, especially events of nausea, vomiting and diarrhea.

All withdrawals due to injection site events (8 versus 0), and all withdrawals due to hepatobiliary disorders (5 versus 0), occurred among liraglutide-treated patients.

The event of "hepatic enzyme increased" in a liraglutide-treated patient occurred in a 42 year old man (ID 267005) who had a maximum elevation of alanine aminotransferase of 85 U/L (ULN 43 U/L), but who was withdrawn from study due to the event.

The event of "aspartate aminotransferase (AST) increased" occurred in a 57 year old man (ID 499003), who had a baseline elevation of AST to 129 U/L (ULN 43 U/L). After 3 months of liraglutide treatment, he had an AST of 174 U/L, and LGT was discontinued. After 42 days off liraglutide, he was considered "recovered", but follow-up AST values were not reported.

Two liraglutide-treated patients were withdrawn from study due to events of elevated creatine phosphokinase (CPK). Patient 124003 was a 39 year old man who had a CPK of 361 U/L (ULN 179 U/L) after 6 months of liraglutide therapy. Liraglutide was withdrawn; a brief narrative states that 6 days after withdrawal, the patient was recovering, but follow-up CPK was not reported. Patient 273015 was a 57 year old man who had a CPK of 207 U/L after 9 months of liraglutide. He also had a mild elevation of aspartate aminotransferase of 58 U/L (ULN 43 U/L). He was withdrawn from study; follow-up CPK values are not mentioned. These elevations of CPK are relatively mild, and do not represent rhabdomyolysis.

The events of hypersensitivity were both reported as nonserious events, but resulted in withdrawal from study. Patient 185006 was a 65 year old woman who developed "delayed hypersensitivity reaction" after 28 days of LGT treatment. The event was not further characterized. Liraglutide was discontinued and she was reported as recovered 6 days after the event. Patient 502007 was a 42 year old woman who had an event of "drug hypersensitivity" that was not further characterized. She had been on liraglutide for 28 days. She recovered 3 days after discontinuation of liraglutide.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Major Adverse Cardiovascular Events

7.1.3.3.1.1 Introduction to the Review of Major Adverse Cardiovascular Events

There has been a great deal of interest in the cardiovascular safety of drugs for the treatment of diabetes. This interest has resulted in two recent Advisory Committee meetings in July 2007 and July 2008. In the 2008 Advisory Committee meeting, the panel (populated by members of the Endocrine and Metabolic Drugs Advisory Committee, members of the Drug Safety and Risk Management Advisory Committee, and other diabetologists, cardiologists and statisticians) was asked to discuss whether cardiovascular outcomes trials (or equivalent evidence of cardiovascular safety) were needed for new drugs for the treatment of type 2 diabetes mellitus. This panel recommended, by a vote of 14:2, that more extensive cardiovascular safety assessment should be required. After that meeting, the Division of Metabolism and Endocrinology Products issued a Guidance for Industry regarding the evaluation of cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Please refer to that Guidance for further details. In the Guidance, prospective planning of an overall development program is recommended, in order that the eventual marketing application will contain adequate information for evaluation of cardiovascular risk. Some important elements of the guidance include:

- All Phase 2 and Phase 3 trials should have prospective independent blinded adjudication of major adverse cardiovascular events. The events should include cardiovascular mortality, myocardial infarction, and stroke, but could possibly include other major adverse cardiovascular events.
- All Phase 2 and Phase 3 trials should be designed so that a meta-analysis can be performed on the overall Phase 2/3 trial population.
- Patients at higher risk of cardiovascular events should be included in clinical trials.
- Prior to submission of a New Drug Application, the applicant must demonstrate that the drug is unlikely to carry a significantly increased risk of cardiovascular events. This may be done by a meta-analysis of the overall Phase 2/3 development program, or by the addition of a large single cardiovascular outcomes trial to the Phase 2/3 development program. In either instance, when the overall study drug is compared to the overall control population, the upper bound of the 95% confidence interval for the risk ratio of the chosen composite of major adverse cardiovascular events should be less than 1.8, prior to submission of the New Drug Application.
- If the upper bound of the 95% confidence interval is between 1.3 and 1.8, and the remainder of the overall risk-benefit analysis supports approval, a postmarketing cardiovascular outcomes trial will generally be required, this time with an upper bound of the 95% confidence interval of less than 1.3.
- If the premarketing upper bound of the 95% confidence interval is less than 1.3, and the remainder of the overall risk-benefit analysis supports approval, a postmarketing cardiovascular outcomes trial might not be needed.

This Guidance is important, but it is intended for drugs that are currently in development. At the time that the Guidance was issued, Novo Nordisk had already submitted its New Drug

Application for liraglutide, and thus would not have been able to prospectively design its development program in the fashion described in the Guidance. However, evaluation of the cardiovascular risk of liraglutide is still necessary prior to approval, and the Agency has stated that drugs with pending applications would still be expected to meet the standards of the guidance for reassurance regarding a lack of an overall increase in cardiovascular risk. To the extent possible, the clinical review of cardiovascular safety attempts to present data consistent with the requirements of the Guidance. However, for liraglutide, it was not possible to follow the Guidance entirely for several reasons, including:

- Cardiovascular events were not prospectively adjudicated in the development program, and there were inadequate data to perform *post hoc* adjudication.
- A specific effort had not been made in the liraglutide development program to include patients at high risk of cardiovascular events; in fact, patients with significant cardiovascular disease were generally excluded.
- The overall Phase 2/3 development program was not designed to be combined into a meta-analysis. Trials were of varying durations, and the blinded and open-label extension periods differed among major Phase 3 trials.
- Few major adverse cardiovascular events occurred.

Therefore, the approach to evaluation of the cardiovascular risk of liraglutide had to be adapted to the available data, which presented challenges.

7.1.3.3.1.2 Description of Types of Analyses and Summaries for Major Adverse Cardiovascular Events

Initially, the Agency requested that Novo Nordisk, and the applicants for two other recent New Drug Applications, submit analyses of an endpoint of myocardial infarction, stroke and cardiovascular death. The applicants were allowed discretion in which MedDRA (Medical Dictionary for Regulatory Activities) Preferred Terms were included in their endpoints. The analyses for liraglutide are presented in Section 7.1.3.3.1.4 below. However, upon comparison, it was noted that the component terms chosen by the applicants were quite different for the three products. The types of data presentations also differed considerably. While realizing that the development programs were quite different from one another, and that cross-comparisons should not be made between drugs, the Division felt that it would be useful for the Advisory Committee and signatory authorities to see a similar type of information for each of the three drugs. Therefore, the Division made a "uniform" information request of each of the applicants. A precisely identical format for data presentation is not possible for the three products, because the development programs differed in several ways, and cross-development-program comparisons would not be appropriate. However, the endpoints are uniform, and to the extent possible, similar analyses were presented for each product. The intention for each of the endpoints was still to provide an assessment of the incidence of the composite of cardiovascular death, myocardial infarction or stroke. Results of the "uniform" analyses are presented in Section 7.1.3.3.1.3 below, and are likely the most useful for evaluation of the cardiovascular risk of liraglutide. In the interest of completeness, Section 7.1.3.3.1.5 also presents data on all cardiovascular adverse events by MedDRA System Organ Class and Preferred Term. This provides the reader with information on cardiovascular events other than myocardial infarction, stroke and cardiovascular death. Total mortality data are also presented in Section 7.1.1.

For clarity, the following table presents the terms included in the endpoints which were analyzed, and the sections in which each endpoint's analyses may be found. For "Broad MACE SMQ", "FDA Custom MACE", and "Narrow MACE SMQ", all possible terms for the endpoint are included. That is, the listed terms are not limited to events which actually occurred, but rather are all the Preferred Terms for which the applicant was asked to query their database. The endpoint "Prior Novo MACE" is from an earlier analysis submitted by the applicant, and is composed entirely of event terms for events which actually occurred in the database.

Table 7.1.3.3.1.2: MedDRA Preferred Terms Included in Endpoints[1] Presented for Evaluation of Myocardial Infarction and Stroke for Liraglutide (All Terms Included in Database Queries, but Actual Events Did Not Occur for Every Term)

	"Broad MACE SMQ"	"FDA Custom MACE"	"Narrow MACE SMQ"	Prior Novo MACE[2]
Location of Analyses in Review	7.1.3.3.1.3	7.1.3.3.1.3	7.1.3.3.1.3	7.1.3.3.1.4
Myocardial Infarction Terms				
Acute coronary syndrome	x		x	
Acute myocardial infarction	x	x	x	x
Blood creatine phosphokinase abnormal	x			
Blood creatine phosphokinase increased	x			
Blood creatine phosphokinase MB abnormal	x			
Blood creatine phosphokinase MB increased	x			
Cardiac arrest				x
Cardiac enzymes increased	x			
Circulatory collapse				x
Coronary artery embolism	x		x	
Coronary artery occlusion	x		x	x
Coronary artery reocclusion	x			
Coronary artery thrombosis	x	x	x	
Coronary bypass thrombosis	x			
Electrocardiogram Q wave abnormal	x			
Electrocardiogram ST segment abnormal	x			
Electrocardiogram ST segment elevation	x			
Electrocardiogram ST-T segment elevation	x			
Infarction	x			
Myocardial infarction	x	x	x	x
Myocardial reperfusion injury	x			
Papillary muscle infarction	x	x	x	
Postinfarction angina	x		x	

Table 7.1.3.3.1.2: MedDRA Preferred Terms Included in Endpoints[1] Presented for Evaluation of Myocardial Infarction and Stroke for Liraglutide (All Terms Included in Database Queries, but Actual Events Did Not Occur for Every Term)

	"Broad MACE SMQ"	"FDA Custom MACE"	"Narrow MACE SMQ"	Prior Novo MACE[2]
Postprocedural myocardial infarction	x	x	x	
Scan myocardial perfusion abnormal	x			
Silent myocardial infarction	x	x	x	
Troponin I increased	x			
Troponin increased	x			
Troponin T increased	x			
Vascular graft occlusion	x			
Stroke Terms				
Agnosia	x			
Amaurosis fugax	x			
Angiogram cerebral abnormal	x			
Aphasia	x			
Balint's syndrome	x			
Basal ganglia hemorrhage	x		x	
Basilar artery occlusion	x		x	
Basilar artery stenosis	x		x	
Basilar artery thrombosis	x	x	x	
Brain stem hemorrhage	x		x	
Brain stem infarction	x	x	x	x
Brain stem ischemia	x		x	
Brain stem stroke	x	x	x	
Brain stem thrombosis	x	x	x	
Capsular warning syndrome	x		x	
Carotid aneurysm rupture	x		x	
Carotid arterial embolus	x	x	x	
Carotid arteriosclerosis	x		x	
Carotid artery aneurysm	x			
Carotid artery bypass	x		x	
Carotid artery disease	x		x	
Carotid artery dissection	x			
Carotid artery insufficiency	x		x	
Carotid artery occlusion	x		x	
Carotid artery stenosis	x		x	
Carotid artery stent insertion	x		x	
Carotid artery thrombosis	x	x	x	
Carotid endarterectomy	x		x	
Central pain syndrome	x			
Cerebellar artery occlusion	x		x	
Cerebellar artery thrombosis	x		x	
Cerebellar embolism	x		x	
Cerebellar hematoma	x		x	
Cerebellar hemorrhage	x		x	
Cerebellar infarction	x	x	x	x

Table 7.1.3.3.1.2: MedDRA Preferred Terms Included in Endpoints[1] Presented for Evaluation of Myocardial Infarction and Stroke for Liraglutide (All Terms Included in Database Queries, but Actual Events Did Not Occur for Every Term)

	"Broad MACE SMQ"	"FDA Custom MACE"	"Narrow MACE SMQ"	Prior Novo MACE[2]
Cerebellar ischemia	x		x	
Cerebral aneurysm ruptured syphilitic	x			
Cerebral arteriosclerosis	x		x	
Cerebral arteriovenous malformation hemorrhagic	x		x	
Cerebral artery embolism	x	x	x	
Cerebral artery occlusion	x		x	
Cerebral artery stenosis	x		x	
Cerebral artery thrombosis	x	x	x	
Cerebral hematoma	x		x	
Cerebral hemorrhage	x		x	x
Cerebral hemorrhage fetal	x		x	
Cerebral hemorrhage neonatal	x		x	
Cerebral infarction	x	x	x	x
Cerebral infarction fetal	x		x	
Cerebral ischemia	x		x	
Cerebral thrombosis	x	x	x	
Cerebral vasoconstriction	x		x	
Cerebral venous thrombosis	x		x	
Cerebrovascular accident	x	x	x	x
Cerebrovascular accident prophylaxis	x			
Cerebrovascular disorder	x		x	
Cerebrovascular insufficiency	x		x	
Cerebrovascular spasm	x		x	
Cerebrovascular stenosis	x		x	
Charcot-Bouchard microaneurysms	x			
Cranial nerve palsies multiple				x
Diplegia	x			
Dysarthria	x			
Embolic cerebral infarction	x	x	x	
Embolic stroke	x	x	x	
Facial palsy				x
Hematomyelia	x		x	
Hemiparesis	x			x
Hemiplegia	x			
Hemorrhage intracranial	x		x	x
Hemorrhagic cerebral infarction	x	x	x	
Hemorrhagic stroke	x	x	x	
Hemorrhagic transformation stroke	x	x	x	
Intracerebral aneurysm operation	x			

Table 7.1.3.3.1.2: MedDRA Preferred Terms Included in Endpoints[1] Presented for Evaluation of Myocardial Infarction and Stroke for Liraglutide (All Terms Included in Database Queries, but Actual Events Did Not Occur for Every Term)

	"Broad MACE SMQ"	"FDA Custom MACE"	"Narrow MACE SMQ"	Prior Novo MACE[2]
Intracerebral hematoma evacuation	x		x	
Intracranial aneurysm	x			
Intracranial hematoma	x		x	
Intraventricular hemorrhage	x		x	
Intraventricular hemorrhage neonatal	x		x	
Ischemic cerebral infarction	x	x	x	
Ischemic stroke	x	x	x	x
Lacunar infarction	x	x	x	x
Lateral medullary syndrome	x	x	x	
Meningorrhagia	x		x	
Millard-Gubler syndrome	x		x	
Monoparesis	x			
Monoplegia	x			
Moyamoya disease	x	x	x	
Paralysis	x			x
Paralysis flaccid	x			
Paraparesis	x			
Paraplegia	x			
Paresis	x			x
Postprocedural stroke	x	x	x	
Precerebral artery occlusion	x		x	
Putamen hemorrhage	x		x	
Quadriparesis	x			
Quadriplegia	x			
Red blood cells cerebrospinal fluid positive	x			
Reversible ischemic neurologic deficit	x		x	
Ruptured cerebral aneurysm	x		x	
Spastic paralysis	x			
Spastic paraplegia	x			
Spinal artery embolism	x		x	
Spinal cord hemorrhage	x		x	
Spinal epidural hemorrhage	x		x	
Spinal hematoma	x		x	
Stroke in evolution	x	x	x	
Subarachnoid hemorrhage	x		x	x
Subarachnoid hemorrhage neonatal	x		x	
Subdural hemorrhage	x		x	
Subdural hemorrhage neonatal	x		x	
Thalamic infarction	x	x	x	
Thalamus hemorrhage	x		x	
Thrombotic cerebral infarction	x	x	x	
Thrombotic stroke	x	x	x	

Table 7.1.3.3.1.2: MedDRA Preferred Terms Included in Endpoints[1] Presented for Evaluation of Myocardial Infarction and Stroke for Liraglutide (All Terms Included in Database Queries, but Actual Events Did Not Occur for Every Term)

	"Broad MACE SMQ"	"FDA Custom MACE"	"Narrow MACE SMQ"	Prior Novo MACE[2]
Transient ischemic attack	x		x	
Vascular encephalopathy	x		x	
Vertebral artery occlusion	x		x	
Vertebral artery stenosis	x		x	
Vertebral artery thrombosis	x		x	
Vertebrobasilar insufficiency	x		x	
Visual midline shift syndrome	x			
Wallenberg syndrome	x	x	x	

1 All endpoints also included cardiovascular death
2 Source: NDA 22341-000, EDR 7 Oct 2008, pg 6. Terms in this endpoint were selected from events which actually occurred, rather than from a MedDRA SMQ

7.1.3.3.1.3: "Uniform MACE Analyses"

Please refer to the Information Request (DFS 11 Jan 2009) which was sent to each of the applicants for the three products which had pending applications at the time of the diabetes cardiovascular evaluation Guidance. The information request details what was requested for these "uniform" analyses.

As mentioned earlier, when comparing MACE analyses initially submitted by different applicants, it was noted that the component Preferred Terms chosen by the applicants differed considerably, as did the analysis methods. Therefore, a group of three FDA Clinical Reviewers collaborated to attempt to devise uniform endpoints for evaluation. This was not a simple task; there are many possible Preferred Terms which might be assigned when a patient has had a myocardial infarction or stroke. *Post hoc* adjudication of all events was not possible due to inadequate information. Therefore, a collection of MedDRA Preferred Terms for myocardial infarction and stroke, as originally coded, with the addition of cardiovascular deaths, seemed the best approach. Two endpoints were chosen, one intended to broadly capture all possible strokes and myocardial infarctions; and one intended to include those terms which seemed likely to be chosen as the term to describe an event that truly was a myocardial infarction or a stroke. The broad endpoint used was the combination of the Broad MedDRA Standard Queries for myocardial infarction and central nervous system hemorrhages and cerebrovascular accidents; and cardiovascular deaths (see Section 7.1.1). This is referred to as the "Broad MACE SMQ". The more specific endpoint, referred to as the "FDA Custom MACE", is a subset of the "Broad MACE SMQ". Without considering which events had actually occurred for a given product, each clinical reviewer independently reviewed the list of all possible terms included in the "Broad MACE SMQ". The clinical reviewer then considered each term, with this question in mind: "If I had a patient who actually had a myocardial infarction or a stroke, is this a Preferred Term that I might actually have chosen for such an event?", with the goal of selecting only those Preferred Terms that seemed highly likely to represent events that would truly be a myocardial infarction or a stroke. The interest was also that these events likely represent acute events with a mechanism of atherosclerotic plaque development followed by plaque rupture/thrombosis (as

opposed to events with nonatherosclerotic mechanisms, e.g. rupture of congenital aneurysma). The three reviewers' lists were compared, and any terms for which there was not unanimous agreement to include or exclude were open for discussion. Consensus was reached on which terms were included. The clinical safety reviewer acknowledges that this is an imperfect process; other reasonable physicians may have chosen a different set of terms. Also, although the MedDRA SMQs are broad, they may not be all-inclusive. For example, the MedDRA Broad Myocardial Infarction SMQ does not contain the terms "cardiac arrest" or "circulatory collapse"; "cardiac arrest" was a Preferred Term assigned for one patient exposed to LGT, and "circulatory collapse" was assigned for one patient each in the placebo and active comparator groups. However, the overall goal was to have a uniform, fairly specific endpoint for use with each of the agents, in order that the Advisory Committee and signatory authorities could see data that were as similar as possible for each product. It should be noted that this endpoint is not a standard FDA endpoint and should not be presumed to be the Agency's choice for future evaluations of cardiovascular events. Please see Table 7.1.3.3.1.2 for an exact list of terms included in the "Broad MACE SMQ" and the "FDA Custom MACE" endpoints.

In addition to the above two endpoints requested by the FDA, the applicant also included an endpoint composed of cardiovascular death and the Narrow Standard MedDRA Queries for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents". This is a subset of the aforementioned "Broad MACE SMQ". This endpoint is referred to as "Narrow MACE SMQ", and the included Preferred Terms are also listed in Table 7.1.3.3.1.2.

These analyses include all data from all Phase 2 and Phase 3 trials, up to the 120-day safety update submitted during the review cycle. The applicant included data both from their diabetes development program, and from their obesity development program. For pooled analyses, the applicant obtained estimates and 95% confidence intervals using a Cochran Mantel-Haenszel estimation with stratification by trial. Only the first MACE for each patient was counted in the analyses.

Summary tables follow which display these estimates, and the numbers of events which actually occurred, for liraglutide versus comparator. In these tables, there are two time period populations. Population A includes the randomized, controlled periods for all completed Phase 2 and Phase 3 trials of LGT, up to collection of the primary efficacy endpoint. The Division considers Population A the primary population of interest. Population B adds the controlled, but unblinded, voluntary extension periods (after collection of the primary endpoint) of Trials 1572 and 1573. Exposure for these populations is as follows:

Table 7.1.3.3.1.3.1: Exposure in Trials Included in Time Period Populations A and B in the "Broad MACE SMQ", "FDA Custom MACE", and "Narrow MACE SMQ" Analyses

	Pop A[1]	Pop B[2]
Total number of patients included	6638	6638
Total patient-years of exposure	2926	4368
Total number of patients exposed to LGT	4257	4257
Total patient-years of liraglutide exposure	1880	2882

Source: Applicant's Table 1, pg 10, NDA 22341 subm 21 Jan 2009
1 Population A includes the randomized, controlled portions of all Phase 2 and Phase 3 trials, up to collection of the primary endpoint
2 Population B includes all of Population A, plus the controlled, but unblinded, voluntary extension periods (after collection of the primary endpoint) of Trials 1572 and 1573.
Abbreviations: MACE = major adverse cardiovascular events, Pop = time period population, SMQ = Standard MedDRA Query

The majority of the patients and the patient-year exposure came from the Phase 3 diabetes trials. These trials included 3978 patients, or 60% of all patients included in the analyses, and 2501 LGT-exposed patients (59% of all LGT-exposed patients in the analyses). Patient-year exposure in the randomized, controlled portions of the Phase 3 DM trials (up to collection of the primary endpoint) was 2024 total patient-years, with 1291 patient-years of LGT exposure, representing 69% of total patient exposure, and 69% of LGT exposure, for time period "Population A".

Serious adverse events were defined using a commonly used regulatory definition. Specifically, a serious adverse event was defined as an experience that at any dose results in any of the following:

- Death
- A life-threatening experience (refers to an event in which the subject was at risk of death at the time of the event; does not refer to an event which hypothetically might have caused death if it was more severe)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect

Additionally, the applicant stated the following: "Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious adverse events (SAEs) when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition." (Source: NDA 22341-000, received 23 May 2008, Module 2.7.4, pg 45)

Statistical Methods for the Analysis of Major Adverse Cardiovascular Events (Point Estimates and 95% Confidence Intervals)

The focus in this document is on the incidence ratio, calculated from the proportion of patients in the liraglutide dose arms with a MACE event (all dose levels combined) divided by the proportion of patients in the comparator arms with a MACE event. The point estimate and 95% confidence interval (CI) were calculated using several statistical methods. The intention in using several methods was to explore the sensitivity of the results, in particular the upper 95% CI bound, to the estimation method. Each method has advantages and disadvantages with respect to estimating this upper bound in the context of the MACE analysis for the liraglutide studies. The primary source of difficulty is the relative rarity of the MACE events, such that, depending on

the specific MACE endpoint, some studies had 0 MACE events in one or both groups that were being compared. In this context, Dr. Derr, the FDA Biostatistician, did not identify one specific method of estimation that was preferable to others. For this reason, she evaluated the sensitivity of the upper 95% CI bound estimate across a selection of methods. An estimated upper 95% CI bound that varied greatly from method to method would suggest that there is an insufficient number of MACE events, or other inconsistencies among studies, to provide a stable estimate of the upper 95% CI bound.

The methods that Novo and Dr. Derr used are the following, presented with a brief description of the advantages and disadvantages of each method in the context of the MACE analysis in the liraglutide studies:

- Novo used an asymptotic, stratified, Cochran Mantel-Haenszel analysis (CMH). While this method is well-established for the analysis of incidence ratios, a limitation is that studies with 0 MACE events in the comparator group are omitted from the estimate. The asymptotic method relies on the assumption that the variance of the estimated ratio is approximately normally distributed. This assumption may not apply well in circumstances where the events are rare.
- Dr. Derr conducted an exact, stratified analysis, and obtained the estimates from StatXact7™ software. This method uses a different approach to estimation than the asymptotic approach used in the CMH analysis. The exact method tends to be conservative, resulting in upper 95% CI bounds that may be wider than they need to be. Another limitation is that studies with 0 MACE events in the comparator group are omitted from the estimate.
- Dr. Derr also conducted a stratified fixed-effects Mantel-Haenszel meta-analysis with a continuity correction of 0.5 applied to studies with 0 events in one or both groups. This approach permits studies with 0 events to be included in the estimate. However, in circumstances where the events are rare, the continuity correction can be quite influential in estimating the 95% CI bounds. In addition, Dr. Derr constructed forest plots to depict the study-by-study estimates as well as the overall estimate.

Dr. Derr notes that all three methods are stratified, reflecting her preference for this approach in the context of the analysis of MACE events from the liraglutide studies. The primary reason for this preference is the variety of designs in the Phase 2 and 3 studies, with different allocation ratios of liraglutide to comparator and somewhat different study populations. Dr. Derr believes that use of a stratified analysis in this context results in a more accurate point estimate for the incidence ratio than does use of an unstratified analysis.

Dr. Derr notes further that other estimation methods are available, and that this is not intended as a comprehensive list of all available methods. In addition, Dr. Derr notes that other forms of the summary statistic are available, such as the incidence difference and the incidence rate ratio (the incidence divided by the patient-years of exposure, expressed as a ratio between liraglutide and the comparator). Novo also provided estimates for these summary statistics. However, the focus in this document is on the incidence ratio and the three methods Dr. Derr selected for evaluating sensitivity.

Results From the Statistical Analysis of Major Adverse Cardiovascular Events

The analyses that Novo conducted produced 12 point estimates with associated 95% confidence intervals (CI). These 12 point estimates were obtained from the combination of three MACE endpoints (FDA Custom, SMQ Broad and SMQ Narrow), two types of events (all treatment-emergent adverse events [TEAE] and serious TEAE), both analysis populations A and B, and one estimation method. The analyses that Dr. Derr conducted produced 8 point estimates with 95% CIs. These 8 point estimates were obtained from a combination of two MACE endpoints (FDA Custom and SMQ Broad), one type of event (TEAE), both analysis populations A and B, and two estimation methods.

As these are presented, there are three important values to keep in mind. The point estimate of the risk for liraglutide versus comparator will be considered. Also presented is how the upper bound of the 95% confidence interval for that point estimate falls with respect to the aforementioned boundary of 1.8, which is the boundary above which the cardiovascular risk evaluation guidance states that further study of cardiovascular events would be needed *prior* to approval. Also considered is how the upper bound of the 95% confidence interval falls with respect to 1.3. In the guidance, products that have values >1.3 and <1.8 could be considered for approval, but would require *postmarketing* study to provide further reassurance of cardiovascular safety.

Liraglutide versus Total Comparator (Placebo and Active Controls)

The stratified analyses that Dr. Derr and Novo conducted were based on 15 studies, because all 15 studies had either a placebo arm, an active comparator arm or both arms. Based on Novo's analyses, all 12 point estimates for the incidence ratio of LGT versus total comparator were <1.0 and 12 of the 12 of the estimated upper 95% CI bounds were <1.8, with 1 being <1.3. This finding is consistent with the estimates calculated by FDA using two other estimation procedures (Tables 7.1.3.3.1.3.9, 7.1.3.3.1.3.10, 7.1.3.3.1.3.11 and 7.1.3.3.1.3.12 for FDA Custom Mace and SMQ broad MACE, all TEAE and analysis populations A and B). All 8 of the FDA point estimates were < 1.0 and all 8 estimated upper 95% CI bounds were < 1.8, with 3 being < 1.3. Results were similar for different endpoints, time period populations, event seriousness groupings, and statistical analysis methods. For this reason Dr. Derr concluded that the estimates for liraglutide versus total comparator were not very sensitive to the choice of estimation methodology.

The number of actual events for the liraglutide and pooled comparator groups is summarized in Table 7.1.3.3.1.3.3. Of note is the small number of relevant events that occurred in the overall development program. For the FDA Custom MACE endpoint (all treatment-emergent events, Pop A), there were only 26 events, only 23 of which met the regulatory definition of a serious adverse event. For the analysis with the most events (Broad SMQ MACE, all TEAE, Pop B), there were 114 events, of which 44 were serious adverse events (SAEs).

Liraglutide versus Placebo Control

The cardiovascular risk guidance does not require that applicants meet the specified boundaries for subgroups. However, subgroups were examined, as an assessment of consistency of the results for the overall comparison. When considering comparator subgroups (active control or placebo), results for comparisons of liraglutide to placebo differed somewhat from those that had been seen with comparisons of liraglutide to total comparator.

The stratified analyses that Dr. Derr and Novo conducted were based on the 12 studies which had a placebo comparator group. Based on Novo's analyses, 7 of the 12 point estimates for the incidence ratio of LGT versus placebo control were >1.0. The upper 95% CI bound of all of the 95% CIs was >1.8 for all 12 estimates. Two of the 6 point estimates from time period Population A exceeded 1.0; the Division considers time period Population A to be the primary time period population of interest. Based on the FDA analysis, the upper 95% CI bound estimates were sensitive to the choice of estimation methodology, displaying a range from 1.25 to 4.76, on both sides of the critical boundary of 1.8 (Tables 7.1.3.3.1.3.9, 7.1.3.3.1.3.10, 7.1.3.3.1.3.11 and 7.1.3.3.1.3.12). One estimate of the upper 95% CI bound was <1.3, 3 were between 1.3 and 1.8, and 4 were >1.8. Six of the 8 point estimates were <1.0. The Agency believes that the sensitivity and the wide confidence intervals are due in part to the low event rates in the placebo arms (Tables 7.1.3.3.1.3.9-7.1.3.3.1.3.12).

The number of actual events for the liraglutide and placebo control groups is summarized in Table 7.1.3.3.1.3.5. This summary illustrates that the event rates in placebo arms were low. For example, in analyses for the FDA Custom MACE endpoint, all TEAE, Pop A, there were only 3 events in the combined placebo arms. In the analysis with the most placebo arm events (Broad SMQ, all TEAE, Pop B), there were only 13 events, of which only 3 were SAEs.

The reason why some point estimates were greater than 1 for subgroup analyses of liraglutide versus placebo is not clear. Because Dr. Derr and Novo conducted stratified analyses on the 12 studies that had placebo groups, the clinical safety reviewer expects the distribution of baseline cardiovascular risk factors to be relatively similar among the randomized arms within each study. For this reason, the clinical safety reviewer does not expect an imbalance in baseline cardiovascular risk factors to contribute appreciably to an imbalance in the incidence of MACE events between the liraglutide and placebo groups. As stated earlier, more placebo-treated patients were withdrawn from study for inadequate glycemic control and therefore, fewer of them may have been available to experience adverse cardiovascular events. The applicant conducted some analyses which took patient-year exposure into account, and these analyses had somewhat lower point estimated for liraglutide versus placebo (Tables 7.1.3.3.1.3.9-7.1.3.3.1.3.12). Low event rates may have contributed to unstable point estimates.

Liraglutide versus Active Control

The stratified analyses that Dr. Derr and Novo conducted were based on the nine studies that had an active control comparator. Based on Novo's analyses, all 12 point estimates for the incidence ratio of LGT versus active control were <1.0. All of the upper 95% CI bounds were <1.8, with one being <1.3. (Table 7.1.3.3.1.3.6). The findings from the FDA using two other estimation

procedures were somewhat more variable, with a wider range in the estimated 95% CI bounds. All 8 point estimates were <1.0. Seven of the 8 upper 95% CI bounds were <1.8, with 2 being <1.3 (Tables 7.1.3.3.1.3.9-7.1.3.3.1.3.12). For this reason Dr. Derr concluded that the estimates for the liraglutide versus active control were somewhat sensitive to the choice of estimation methodology.

The number of actual events for the liraglutide and active control groups is summarized in Table 7.1.3.3.1.3.7. The number of events was small in most analyses.

As mentioned earlier, time period Population A (in the Tables 7.1.3.3.1.3.2 through 7.1.3.3.1.3.7) includes all data from the randomized, controlled portions of the trials, out to measurement of the primary endpoint. The "Uniform" MACE analysis request had specifically requested data from the randomized, double-blind, controlled portions of the trials, out to measurement of the primary endpoint. However, in four of the Phase 2/3 trials of liraglutide, a comparator arm was open-label prior to the primary endpoint. These arms were not excluded from the above analyses, and that was the intent of the FDA request. Novo did comply completely with the request, and performed additional analyses excluding these open-label arms, and submitted the analyses on 13 Feb 2009. However, the Agency considers these analyses less useful than those which include all arms up to measurement of the primary endpoint.

A series of tables follows, which presents the data and analyses described above for the MACE analyses.

Table 7.1.3.3.1.3.2: Incidence Ratio, Liraglutide versus Pooled Comparator (Placebo + Active Comparator), Novo Stratified Asymptotic CMH Analysis

MACE Endpoint			Type of Events		Pop		Point Estimate (95% CI)
FDA Custom	Broad SMQ	Narrow SMQ	All TEAE	Serious Only	A	B	
x			x		x		0.72 (0.32, 1.61)
	x		x		x		0.87 (0.57, 1.34)
		x	x		x		0.87 (0.45, 1.69)
x				x	x		0.69 (0.29, 1.62)
	x			x	x		0.67 (0.32, 1.41)
		x		x	x		0.64 (0.30, 1.34)
x			x			x	0.79 (0.41, 1.54)
	x		x			x	0.88 (0.61, 1.28)
		x	x			x	0.89 (0.52, 1.52)
x				x		x	0.76 (0.37, 1.57)
	x			x		x	0.83 (0.44, 1.56)
		x		x		x	0.80 (0.42, 1.51)

Source: Applicant's Table 3, pg 23, NDA 22341 subm stamp date 13 Feb 2009
Abbreviations: CI = confidence interval, Pop = time period population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events; CMH = Cochran Mantel-Haenszel

Table 7.1.3.3.1.3.3: Number of Major Adverse Cardiovascular Events for Liraglutide versus Pooled Comparator (Placebo + Active Comparator)

Agent	MACE Endpoint			Type of Events		Time Period Population LGT N= 4257 Comp N=2381		n	%
	FDA Custom	Broad SMQ	Narrow SMQ	All TEAE	Serious Only	Pop A LGT PY=1880 Comp PY=1046	Pop B LGT PY=2882 Comp PY=1486		
LGT	x			x		x		13	0.31
Pooled Comp	x			x		x		13	0.55
LGT		x		x		x		51	1.20
Pooled Comp		x		x		x		35	1.47
LGT			x	x		x		22	0.52
Pooled Comp			x	x		x		17	0.71
LGT	x				x	x		11	0.26
Pooled Comp	x				x	x		12	0.50
LGT		x			x	x		16	0.38
Pooled Comp		x			x	x		16	0.67
LGT			x		x	x		15	0.35
Pooled Comp			x		x	x		16	0.67
LGT	x			x			x	21	0.49
Pooled Comp	x			x			x	17	0.71
LGT		x		x			x	69	1.62
Pooled Comp		x		x			x	45	1.89
LGT			x	x			x	35	0.82
Pooled Comp			x	x			x	24	1.01
LGT	x				x		x	17	0.40
Pooled Comp	x				x		x	15	0.63
LGT		x			x		x	25	0.59
Pooled Comp		x			x		x	19	0.80
LGT			x		x		x	24	0.56
Pooled Comp			x		x		x	19	0.80

Source: Applicant's Tables 16, 20, 24 and 28; pgs 66, 80, 94 and 108, NDA 22341 subm stamp date 21 Jan 2009. Also, Applicant's Tables 29, 33, 37 and 41; pgs 111, 125, 139, and 153, subm stamp date 13 Feb 2009 (updated from 21 Jan 2009 submission with addition of one event to active control for Custom FDA endpoint)
Abbreviations: CI = confidence interval, Pop = time period population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events

Table 7.1.3.3.1.3.4: Incidence Ratio, Liraglutide versus Placebo, Novo Stratified Asymptotic CMH Analysis

MACE Endpoint			Type of Events		Pop		Point Estimate (95% CI)
FDA Custom	Broad SMQ	Narrow SMQ	All TEAE	Serious Only	A	B	
x			x		x		0.80 (0.23, 2.83)
	x		x		x		1.04 (0.50, 2.16)
		x	x		x		1.06 (0.37, 3.02)
x				x	x		0.94 (0.19, 4.58)
	x			x	x		0.90 (0.25, 3.22)
		x		x	x		0.90 (0.25, 3.22)
x			x			x	0.92 (0.30, 2.83)
	x		x			x	1.02 (0.54, 1.92)
		x	x			x	1.11 (0.45, 2.74)
x				x		x	1.32 (0.28, 6.20)
	x			x		x	1.33 (0.38, 4.60)
		x		x		x	1.33 (0.38, 4.60)

Source: Applicant's Tables 16, 20, 24 and 28; pgs 66, 80, 94 and 108, NDA 22341 subm stamp date 21 Jan 2009
Abbreviations: CI = confidence interval, Pop = time period population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events; CMH = Cochran Mantel-Haenszel

Table 7.1.3.3.1.3.5: Number of Major Adverse Cardiovascular Events for Liraglutide versus Placebo

Agent	MACE Endpoint			Type of Events		Time Period Population LGT N=4257 PBO N=907		n	%
	FDA Custom	Broad SMQ	Narrow SMQ	All TEAE	Serious Only	Pop A LGT PY=1880 PBO PY=328	Pop B LGT PY=2882 PBO PY=449		
LGT	x			x		x		13	0.31
PBO	x			x		x		3	0.33
LGT		x		x		x		51	1.20
PBO		x		x		x		9	0.99
LGT			x	x		x		22	0.52
PBO			x	x		x		4	0.44
LGT	x				x	x		11	0.26
PBO	x				x	x		2	0.22
LGT		x			x	x		16	0.38
PBO		x			x	x		3	0.33
LGT			x		x	x		15	0.35
PBO			x		x	x		3	0.33
LGT	x			x			x	21	0.49
PBO	x			x			x	4	0.44
LGT		x		x			x	69	1.62
PBO		x		x			x	13	1.43
LGT			x	x			x	35	0.82
PBO			x	x			x	6	0.66
LGT	x				x		x	17	0.40
PBO	x				x		x	2	0.22
LGT		x			x		x	25	0.59
PBO		x			x		x	3	0.33
LGT			x		x		x	24	0.56
PBO			x		x		x	3	0.33

Source: Applicant's Tables 16, 20, 24 and 28; pgs 66, 80, 94 and 108, NDA 22341 subm stamp date 21 Jan 2009
Abbreviations: CI = confidence interval, Pop = time period population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events

Table 7.1.3.3.1.3.6: Incidence Ratio, Liraglutide versus Active Comparator, Novo Stratified Asymptotic CMH Analysis

MACE Endpoint			Type of Events		Pop		Point Estimate (95% CI)
FDA Custom	Broad SMQ	Narrow SMQ	All TEAE	Serious Only	A	B	
x			x		x		0.68 (0.28, 1.66)
	x		x		x		0.82 (0.51, 1.32)
		x	x		x		0.79 (0.37, 1.69)
x				x	x		0.63 (0.26, 1.57)
	x			x	x		0.61 (0.27, 1.38)
		x		x	x		0.57 (0.25, 1.30)
x			x			x	0.76 (0.36, 1.61)
	x		x			x	0.85 (0.55, 1.29)
		x	x			x	0.82 (0.44, 1.52)
x				x		x	0.68 (0.32, 1.47)
	x			x		x	0.74 (0.37, 1.47)
		x		x		x	0.70 (0.35, 1.41)

Source: Applicant's Tables 16, 20, 24 and 28; pgs 66, 80, 94 and 108, NDA 22341 subm stamp date 21 Jan 2009. Also, Applicant's Tables 29, 33, 37 and 41; pgs 111, 125, 139, and 153, subm stamp date 13 Feb 2009 (updated from 21 Jan 2009 submission with addition of one event to active control for Custom FDA endpoint)
Abbreviations: CI = confidence interval, Pop = time period population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events; CMH = Cochran Mantel-Haenszel

Table 7.1.3.3.1.3.7: Number of Events for Liraglutide versus Active Comparator

Agent	MACE Endpoint			Type of Events		Time Period Population LGT N= 4257 AC N=1474		n	%
	FDA Custom	Broad SMQ	Narrow SMQ	All TEAE	Serious Only	Pop A LGT PY=1880 AC PY=718	Pop B LGT PY=2882 AC PY=1038		
LGT	x			x		x		13	0.31
AC	x			x		x		10	0.68
LGT		x		x		x		51	1.20
AC		x		x		x		26	1.76
LGT			x	x		x		22	0.52
AC			x	x		x		13	0.88
LGT	x				x	x		11	0.26
AC	x				x	x		10	0.68
LGT		x			x	x		16	0.38
AC		x			x	x		13	0.88
LGT			x		x	x		15	0.35
AC			x		x	x		13	0.88
LGT	x			x			x	21	0.49
AC	x			x			x	13	0.88
LGT		x		x			x	69	1.62
AC		x		x			x	32	2.17
LGT			x	x			x	35	0.82
AC			x	x			x	18	1.22
LGT	x				x		x	17	0.40
AC	x				x		x	13	0.88
LGT		x			x		x	25	0.59
AC		x			x		x	16	1.09
LGT			x		x		x	24	0.56
AC			x		x		x	16	1.09

Source: Applicant's Tables 16, 20, 24 and 28; pgs 66, 80, 94 and 108, NDA 22341 subm stamp date 21 Jan 2009. Also, Applicant's Tables 29, 33, 37 and 41; pgs 111, 125, 139, and 153, subm stamp date 13 Feb 2009 (updated from 21 Jan 2009 submission with addition of one event to active control for Custom FDA endpoint)
Abbreviations: CI = confidence interval, Pop = time period population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events

As evidenced by the above tables of event numbers, the number of events included in an analysis could be quite different, depending on the analysis scenario. The following table displays a few examples of analysis scenarios and the numbers of events included in those analyses, with an explanation for the decrease in number of events from scenario to scenario. This table helps to illustrate the major factors which resulted in very few events for certain analysis scenarios, and in more (but less specific) events, in other scenarios.

Table 7.1.3.3.1.3.8: Examples of Raw Numbers of Patients with Events, and Effect of Changes in Analysis Scenario

Endpoint	Analysis Scenario	Change to Scenario	LGT N=4257 n (%)	Total Comp N=2381 n (%)	PBO N=907 n (%)	Reason for Decrease in # of Events from Row Above?
Broad SMQ	Broad, All MACE, Pop B*	n/a	69 (1.62)	45 (1.89)	13 (1.43)	n/a
	Broad, All MACE, Pop A	Pop B to Pop A	51 (1.20)	35 (1.47)	9 (0.99)	does not include extension data
	Broad, Serious MACE, Pop A	All MACE to Serious MACE	16 (0.38)	16 (0.67)	3 (0.33)	does not include nonserious CPK events
FDA Custom	Custom, All MACE, Pop B	n/a	21 (0.49)	17 (0.71)	4 (0.44)	CPK events not in Custom
	Custom, All MACE, Pop A	Pop B to Pop A	13 (0.31)	13 (0.55)	3 (0.33)	does not include extension data
	Custom, Serious MACE, Pop A**	All MACE to Serious MACE	11 (0.26)	12 (0.50)	2 (0.22)	does not include nonserious non-CPK events

* Scenario with largest numbers of patients with events
** Scenario with smallest numbers of patients with events

In this table, the top row contains the analysis scenario with the largest number of events of any scenario (Broad SMQ, serious + nonserious MACE, Pop B), and the number of events goes down as one moves down the table. One should not compare the percentages in the various cells; they are only raw numbers used to illustrate event rates, and do not reflect stratification by trial. As an example of event rates, one can look at the middle (green-shaded) column for liraglutide group events. Even in the top row, with the highest number of events, one can see that the event rates were low, with only 69, or 1.6%, of liraglutide-treated patients experiencing an event. As one moves down to the next LGT cell (change from Pop B to Pop A), event rates drop further, due to omission of extension data. The clinical safety and statistical reviewers consider Pop A to be more interpretable than Pop B, but less observation time results in fewer events (69 to 51). Moving down to the next LGT cell, there is a large drop (from 51 to 16 events), as this cell no longer includes nonserious events, but only those that were characterized as serious. This is because about half the events in the Broad SMQ were events of increased CPK, and the vast majority were nonserious events. The bottom 3 rows of the table include event numbers contributing to the FDA Custom endpoint, rather than to the Broad MACE endpoint. The FDA Custom endpoint tended to be more specific, and therefore to have fewer events (all other scenario elements being equal), than did the Broad MACE endpoint. For example, the scenario of Custom MACE, serious + nonserious events, Pop B, had 21 events, while there were 69 events in the corresponding Broad MACE scenario. Taking out extension data dropped the number of liraglutide FDA Custom events from 21 to 13. Taking out

nonserious events didn't change the numbers for liraglutide group events much for the FDA Custom endpoint, going from 13 to 11. This is because the FDA Custom endpoint didn't include CPK events, as well as some other mostly nonserious event terms. The primary message of this table is that event numbers were low, especially when one tried to include the most clinically relevant events, and the most interpretable time period. Low event rates presented a challenge to the review of major cardiovascular events for liraglutide.

Table 7.1.3.3.1.3.9: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-Analysis Method with Continuity Correction, All Treatment-Emergent MACE, Time Period Population A, FDA Custom Endpoint

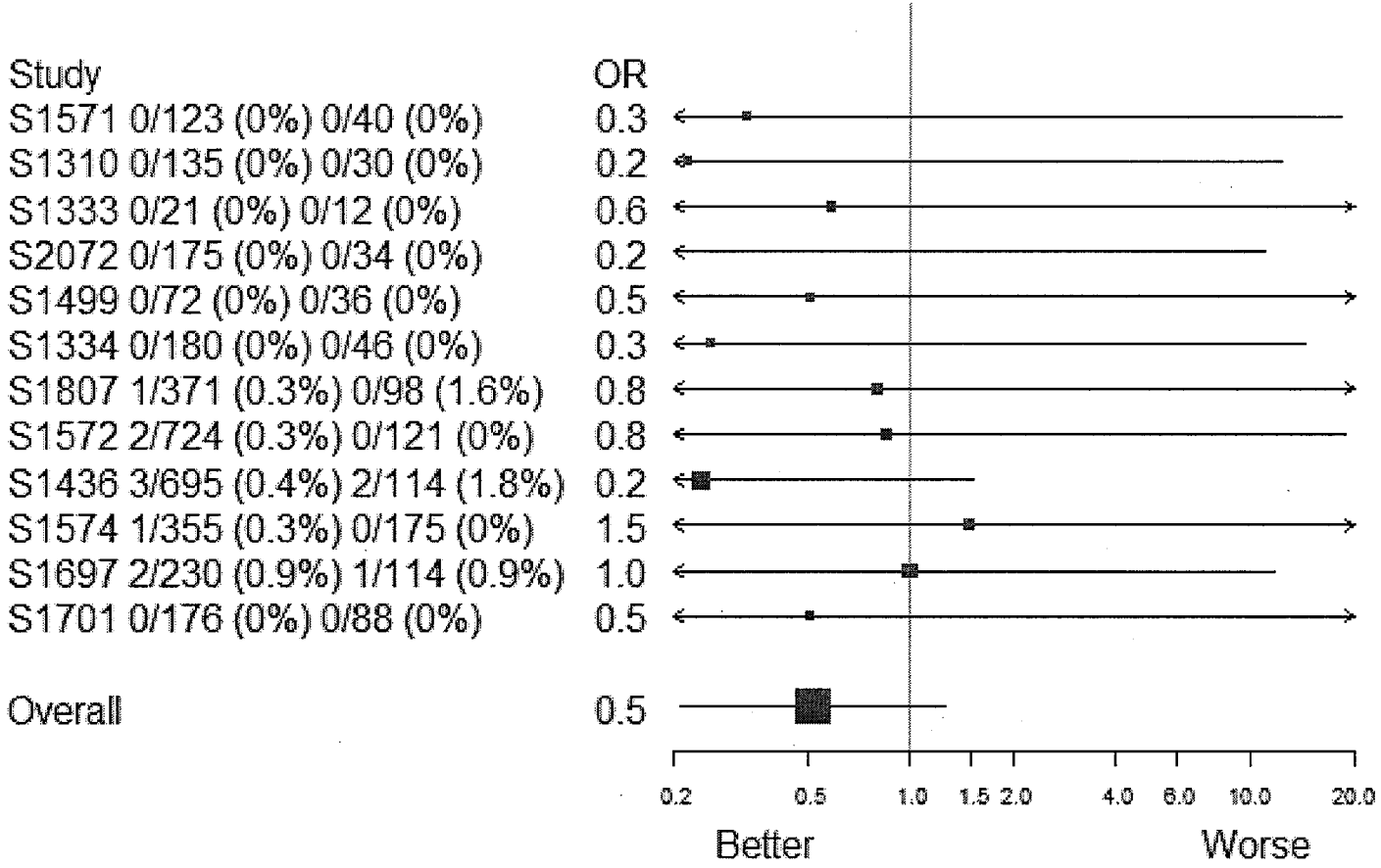
Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 1000 pt-yrs
Liraglutide	4257	1880	13	0.31%	6.92
Placebo	907	328	3	0.33%	9.14
Active Comparator	1474	718	10	0.68%	13.94
Total Comparators	2381	1046	13	0.55%	12.43

	# of studies included in the analysis (with at least 1 event in the comparator group)	Incidence Ratio (95% CI) *Stratified, asymptotic (MH)*[3]	% of cases excluded from analysis (studies with 0 events in the comparator group)	Incidence Rate Ratio (95% CI) *Stratified, asymptotic (MH)*[3]	% of pt-yrs excluded from analysis (studies with 0 events)
Liraglutide vs. Placebo	5 of 12	0.80 (0.23, 2.83)	25.6%	0.76 (0.22, 2.64)	14.0%
Liraglutide vs. Active	7 of 9	0.68 (0.28, 1.66)	1.9%	0.71 (0.28, 1.66)	0.4%
Liraglutide vs. Total Comparator	8 of 15	0.72 (0.32, 1.61)	18.1%	0.71 (0.32, 1.57)	10.7%
		Stratified, exact[4]		*Stratified, exact*[5]	
Liraglutide vs. Placebo	5 of 12	0.78 (0.19, 4.76)	25.6%	---[6]	---
Liraglutide vs. Active	7 of 9	0.68 (0.26, 1.83)	1.9%	---	---
Liraglutide vs. Total Comparator	8 of 15	0.72 (0.30, 1.74)	18.1%	0.75 (0.31, 1.84)	10.7%
		Stratified, fixed effects MH meta-analysis with a continuity correction[7]			
Liraglutide vs. Placebo	12 of 12	0.52 (0.21, 1.25)	0%		
Liraglutide vs. Active	9 of 9	0.60 (0.27, 1.31)	0%		
Liraglutide vs. Total Comparator	15 of 15	0.63 (0.32, 1.24)	0%		

[1] Novo, submitted in response to FDA request for information 1/11/2009, Appendix B, Table 15 and Table 16
[2] Novo provided differences scaled as incidence events/N and incidence rates/pt yr (Appendix B, Table 15). The results are not reported in this table.
[3] Test conducted by Novo, MH = Mantel-Haenszel
[4] Test conducted by Dr. Derr; p-values for homogeneity across studies: Liraglutide vs. Placebo p=0.649; Liraglutide vs. Active p= 0.713; Liraglutide vs. Total Comparator, p=0.937
[5] Test conducted by Dr. Derr; p-values for homogeneity across studies: Liraglutide vs. Total Comparator, p=0.788
[6] The exact procedure did not provide an estimate.
[7] Test conducted by Dr. Derr; forest plots provided, with continuity correction of 0.5 for arms with zero MACE events (Figures 7.1.3.3.1.3.1, 7.1.3.3.1.3.2 and 7.1.3.3.1.3.3)

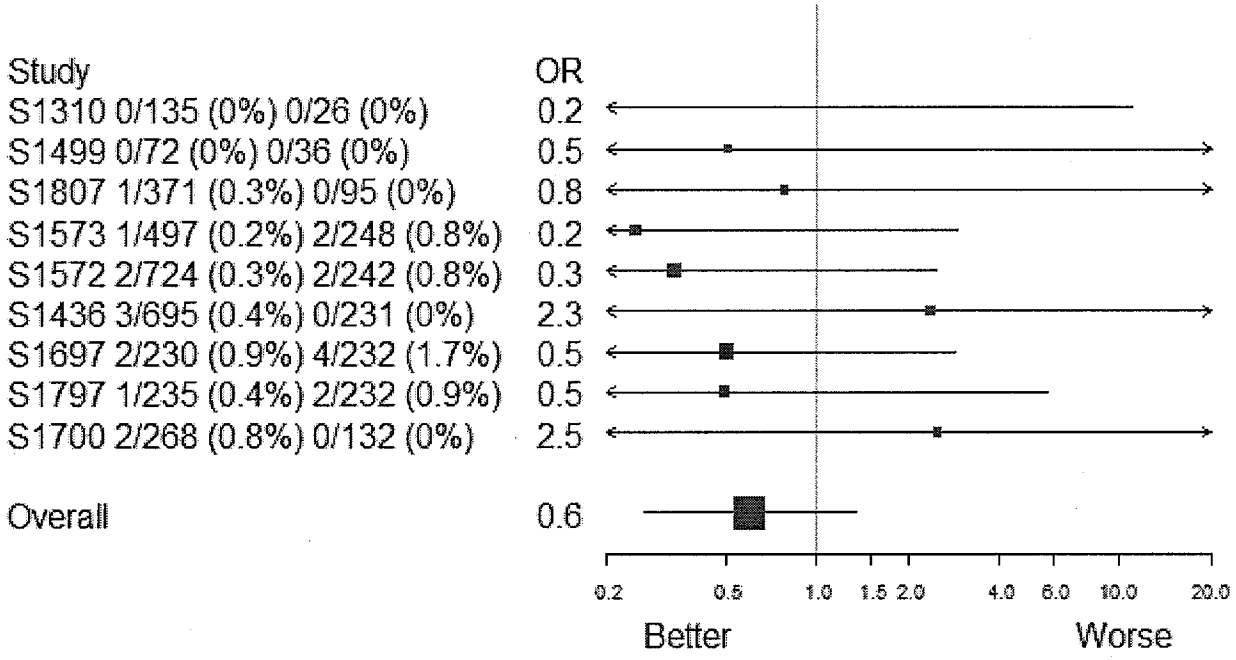
The following forest plots depict the odds ratio and 95% confidence intervals for each study and for the combined estimate from the stratified, fixed effects Mantel-Haenszel meta-analysis, with a continuity correction of +0.5 applied to studies with zero events in either arm or both arms. Studies with more precise results were given more weight in the computation of the common odds ratio. The size of the symbol is proportionate to the weight (the inverse variance). Some studies had estimates with low precision and the symbol was not visible in the figure.

Figure 7.1.3.3.1.3.1: Forest Plot for FDA Custom Endpoint, Liraglutide versus Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population A. Values to the left of 1.0 favor liraglutide.



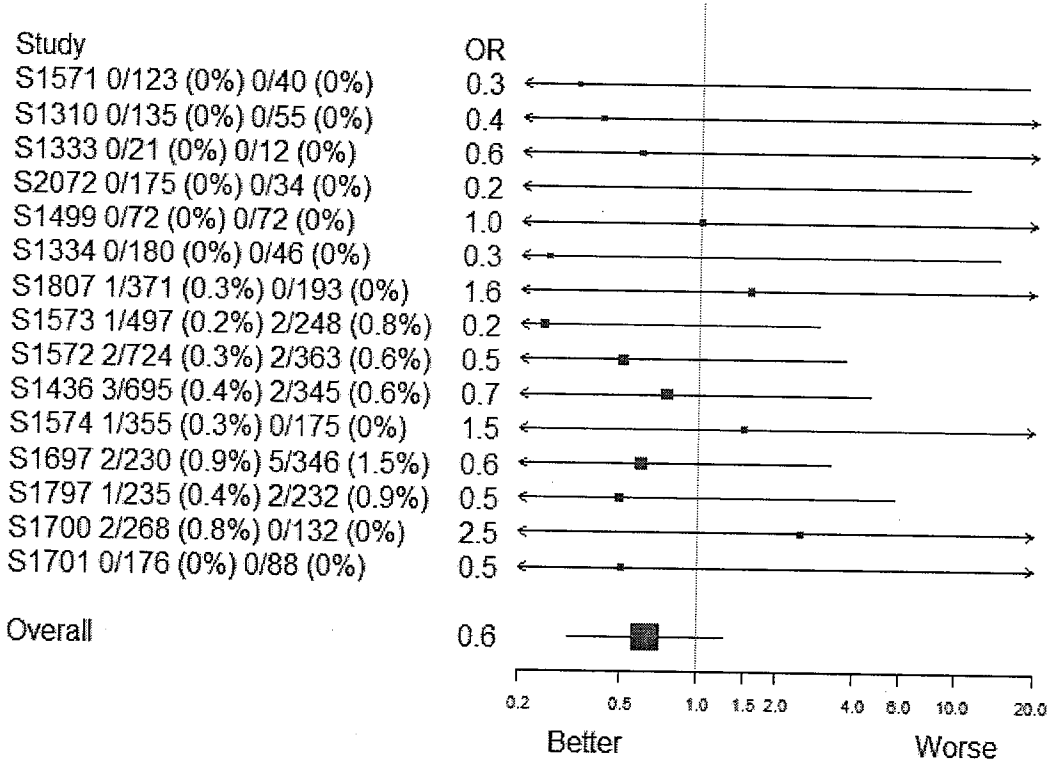
Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.2: Forest Plot for FDA Custom Endpoint, Liraglutide versus Active Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population A. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.3: Forest Plot for FDA Custom Endpoint, Liraglutide versus Total Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population A. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Table 7.1.3.3.1.3.10: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All Treatment-Emergent MACE, Time Period Population A, Broad SMQ Endpoint

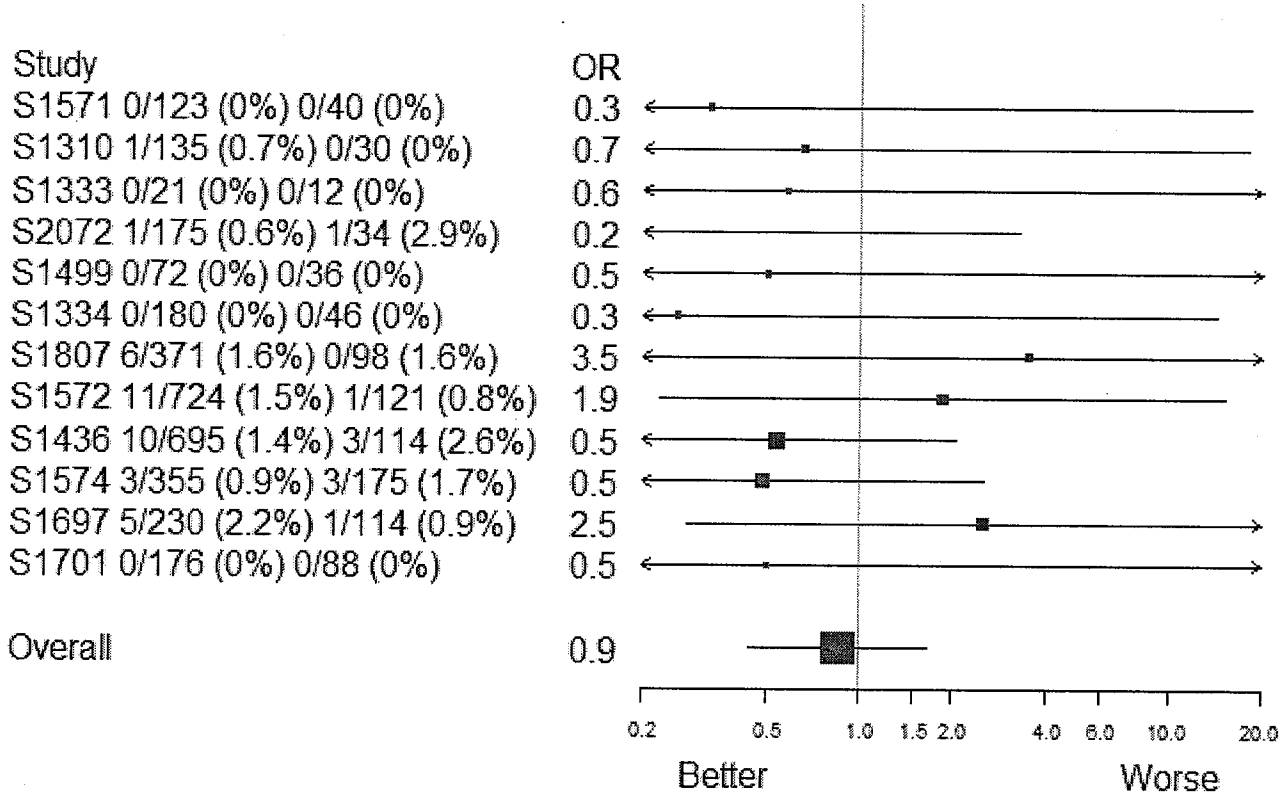
Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 1000 pt-yrs
Liraglutide	4257	1880	51	1.20%	27.13
Placebo	907	328	9	0.99%	27.43
Active Comparator	1474	718	26	1.76%	36.23
Total Comparators	2381	1046	35	1.47%	33.47

		Incidence Ratio (95% CI)		Incidence Rate Ratio (95% CI)	
	# of studies included in the analysis (with at least 1 event in the comparator group)	***Stratified, asymptotic (MH)***[3]	**% of cases excluded from analysis (studies with 0 events in the comparator group)**	***Stratified, asymptotic (MH)***[3]	**% of pt-yrs excluded from analysis (studies with 0 events)**
Liraglutide vs. Placebo	7 of 12	1.04 (0.50, 2.16)	15.4%	0.98 (0.47, 2.02)	10.3%
Liraglutide vs. Active	8 of 9	0.82 (0.51, 1.32)	1.9%	0.82 (0.51, 1.32)	0.4%
Liraglutide vs. Total Comparator	10 of 15	0.87 (0.57, 1.34)	12.5%	0.86 (0.56, 1.31)	3.5%
		Stratified, exact[4]		***Stratified, exact***[5]	
Liraglutide vs. Placebo	7 of 12	1.04 (0.48, 2.17)	15.4%	---[6]	
Liraglutide vs. Active	8 of 9	0.82 (0.48, 1.33)	1.9%	---	
Liraglutide vs. Total Comparator	10 of 15	0.86 (0.55, 1.41)	12.5%	0.85 (0.54, 1.87)	3.5%
	Stratified, fixed effects MH meta-analysis with a continuity correction[7]				
Liraglutide vs. Placebo	12 of 12	0.86 (0.45, 1.65)	0%		
Liraglutide vs. Active	9 of 9	0.79 (0.49, 1.28)	0%		
Liraglutide vs. Total Comparator	15 of 15	0.83 (0.55, 1.27)	0%		

Notes:
[1] Novo, submitted in response to FDA request for information 1/11/2009, Appendix B, Table 14 and Table 16
[2] Novo provided differences scaled as incidence events/N and incidence rates/pt yr (Appendix B, Table 14). The results are not reported in this table.
[3] Test conducted by Novo, MH = Mantel-Haenszel
[4] Test conducted by Dr. Derr; p-values for homogeneity across studies: Liraglutide vs. Placebo p=0.378; Liraglutide vs. Active p= 0.718; Liraglutide vs. Total Comparator, p=0.755
[5] Test conducted by Dr. Derr; p-values for homogeneity across studies: Liraglutide vs. Total Comparator, p=0.759
[6] The exact procedure did not provide an estimate.
[7] Test conducted by Dr. Derr, forest plots provided, with continuity correction of 0.5 for arms with 0 MACE events (Figures 7.1.3.3.1.3.4, 7.1.3.3.1.3.5, and 7.1.3.3.1.3.6)

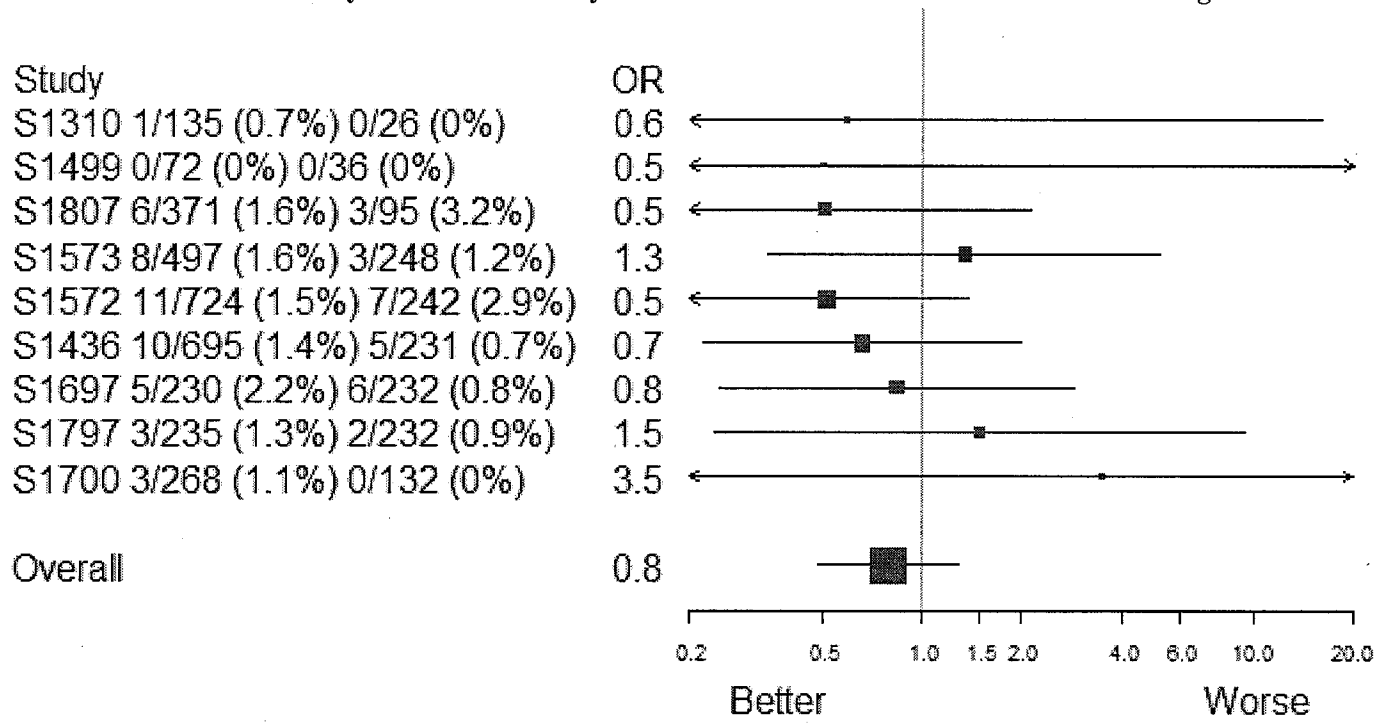
The following forest plots for the Broad SMQ endpoint display point estimates and 95% confidence intervals by study, and for the overall estimate, for Dr. Derr's analyses utilizing a stratified Mantel-Haenszel method with continuity correction applied.

Figure 7.1.3.3.1.3.4: Forest Plot for Broad SMQ Endpoint, Liraglutide versus Placebo, Time Period Population A, Stratified Mantel-Haenszel Analysis with Continuity Correction. Values to the left of 1.0 favor liraglutide.



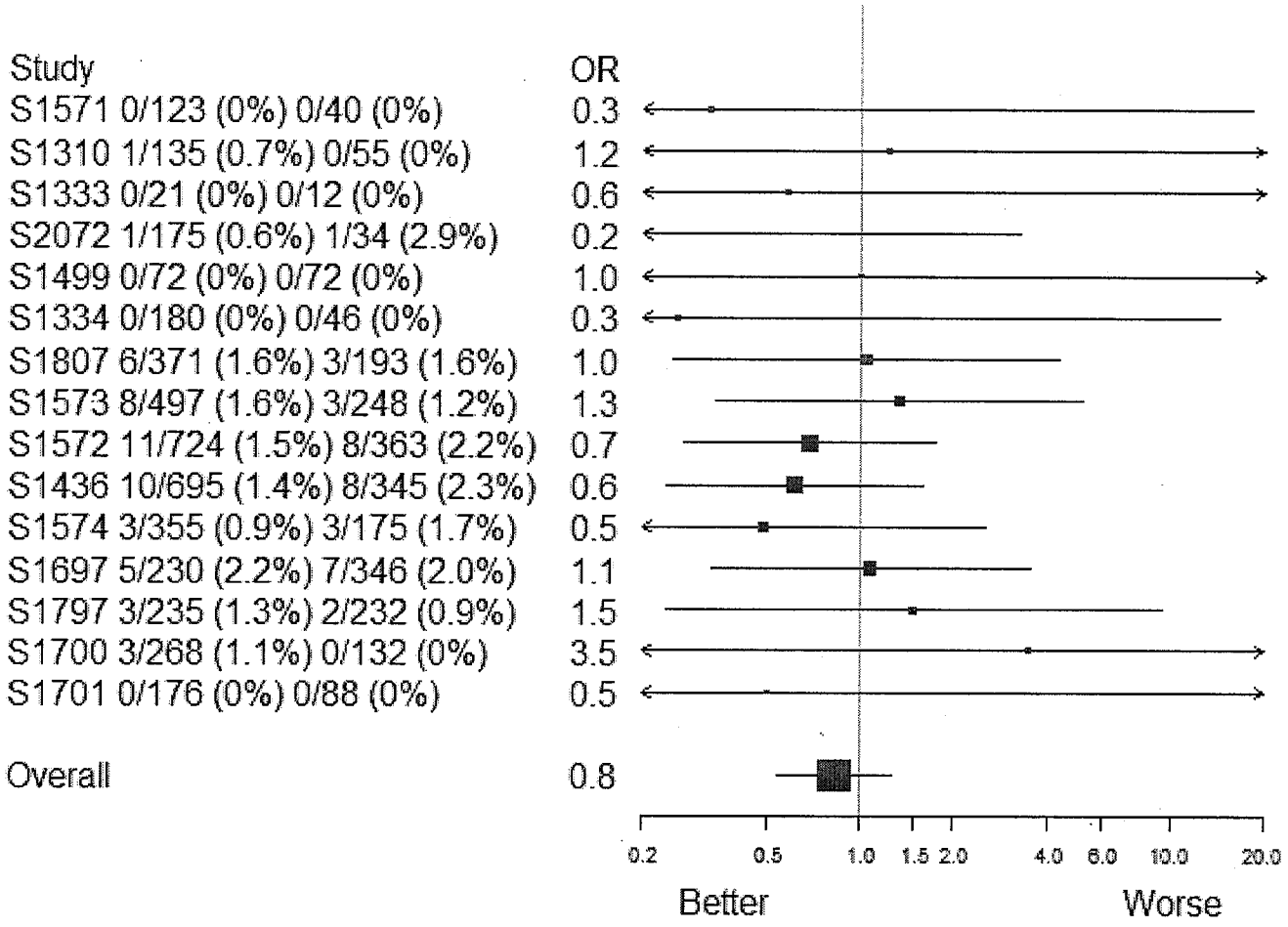
Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.5: Forest Plot for Broad SMQ Endpoint, Liraglutide versus Active Comparator, Time Period Population A, Stratified Mantel-Haenszel Analysis with Continuity Correction. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.6: Forest Plot for Broad SMQ Endpoint, Liraglutide versus Total Comparator, Time Period Population A, Stratified Mantel-Haenszel Analysis with Continuity Correction. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

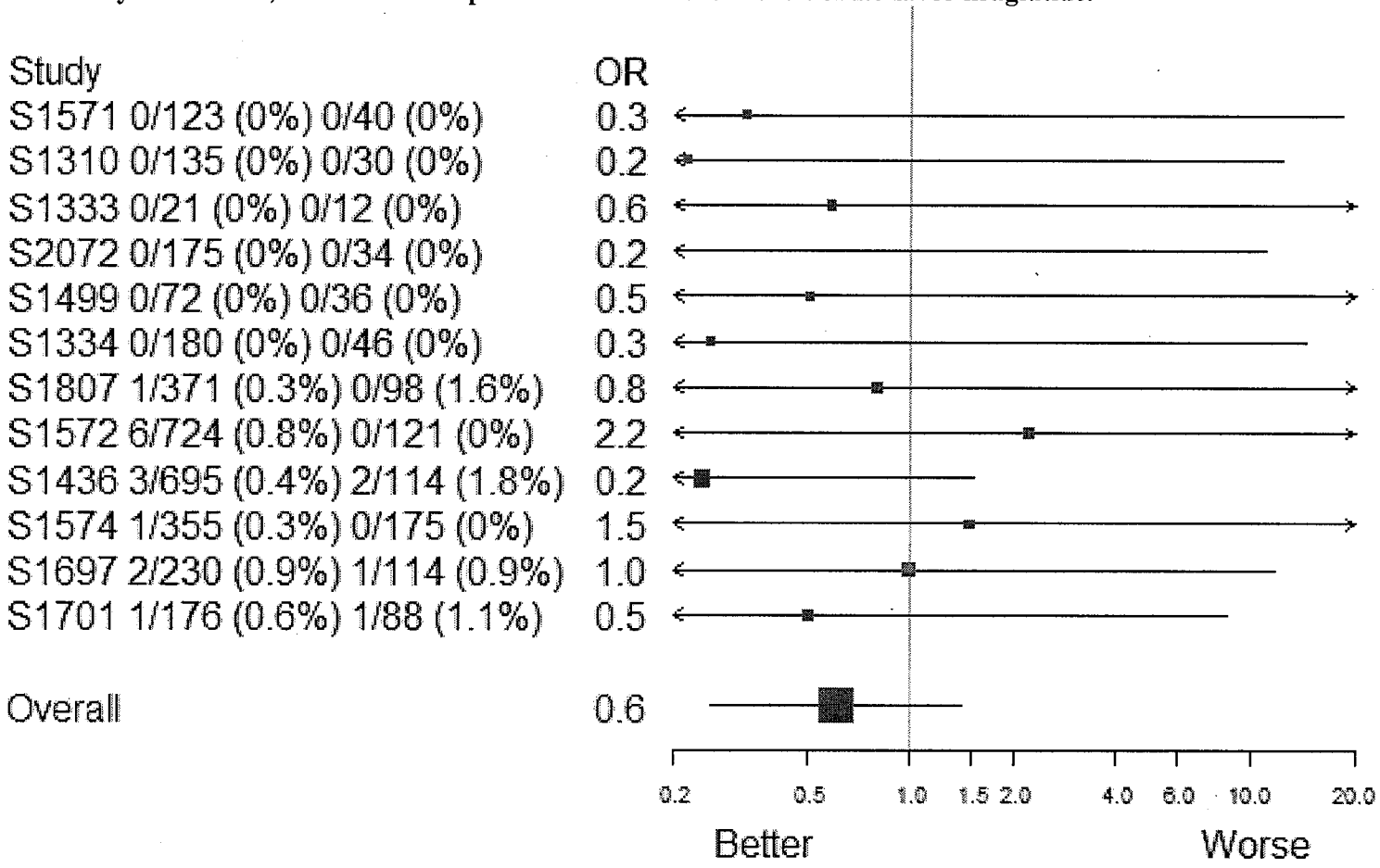
Table 7.1.3.3.1.3.11: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All Treatment-Emergent MACE, Time Period Population B, FDA Custom Endpoint

Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 1000 pt-yrs
Liraglutide	4257	2882	21	0.49%	7.29
Placebo	907	449	4	0.44%	8.91
Active Comparator	1474	1038	13	0.88%	12.53
Total Comparators	2381	1486	17	0.71%	11.44

		Incidence Ratio (95% CI)		Incidence Rate Ratio (95% CI)	
	# of studies included in the analysis (with at least 1 event in the comparator group)	*Stratified, asymptotic (MH)*[3]	% of cases excluded from analysis (studies with 0 events in the comparator group)	*Stratified, asymptotic (MH)*[3]	% of pt-yrs excluded from analysis (studies with 0 events)
Liraglutide vs. Placebo	6 of 12	0.92 (0.30, 2.83)	17.5%	0.80 (0.26, 2.47)	5.8%
Liraglutide vs. Active	7 of 9	0.76 (0.36, 1.61)	1.9%	0.75 (0.36, 1.59)	0.3%
Liraglutide vs. Total Comparator	9 of 15	0.79 (0.41, 1.54)	14.1%	0.76 (0.39, 1.48)	4.7%
		Stratified, exact[4]		*Stratified, exact*[5]	
Liraglutide vs. Placebo	6 of 12	0.92 (0.28, 3.97)	17.5%	---[6]	5.8%
Liraglutide vs. Active	7 of 9	0.76 (0.35, 1.72)	1.9%	---	0.3%
Liraglutide vs. Total Comparator	9 of 15	0.80 (0.39, 1.64)	14.1%	0.82 (0.40, 1.70)	4.7%
		Stratified, fixed effects MH meta-analysis with a continuity correction[7]			
Liraglutide vs. Placebo	12 of 12	0.60 (0.26, 1.39)	0%		
Liraglutide vs. Active	9 of 9	0.68 (0.34, 1.37)	0%		
Liraglutide vs. Total Comparator	15 of 15	0.71 (0.39, 1.30)	0%		

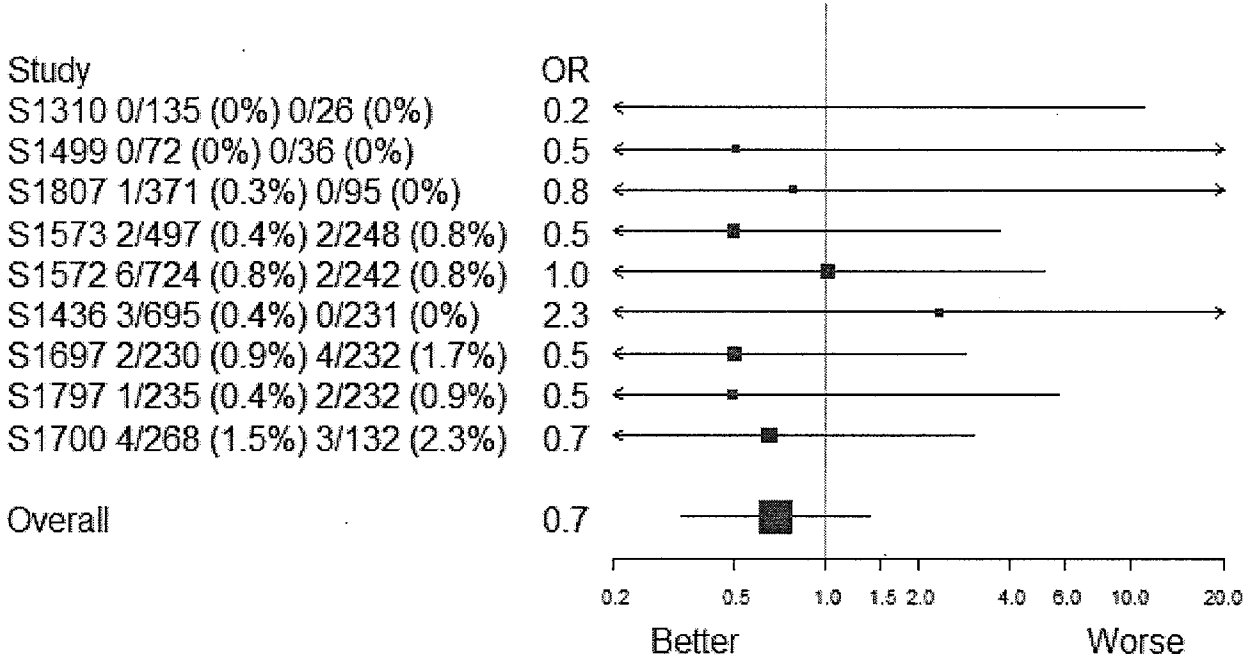
* *Since the date of this analysis, one more MACE event was added to custom MACE, populations A and B*
[1] Novo, submitted in response to FDA request for information 1/11/2009, Appendix B, Table 23 and Table 24
[2] Novo provided differences scaled as incidence events/N and incidence rates/pt yr (Appendix B, Table 14). The results are not reported in this table.
[3] Test conducted by Novo, MH = Mantel-Haenszel
[4] Test conducted by Dr. Derr; the tests for homogeneity across studies could not be calculated on StatXact™ 7.0
[5] Test conducted by Dr. Derr; p-values for homogeneity across studies: Liraglutide vs. Total Comparator, p=0.990
[6] The exact procedure did not provide an estimate.
[7] Test conducted by Dr. Derr, forest plots provided, with continuity correction of 0.5 for arms with 0 MACE events (Figures 7.1.3.3.1.3.7, 7.1.3.3.1.3.8, and 7.1.3.3.1.3.9)

Figure 7.1.3.3.1.3.7: Forest Plot for FDA Custom Endpoint, Liraglutide versus Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population B. Values to the left of 1.0 favor liraglutide.



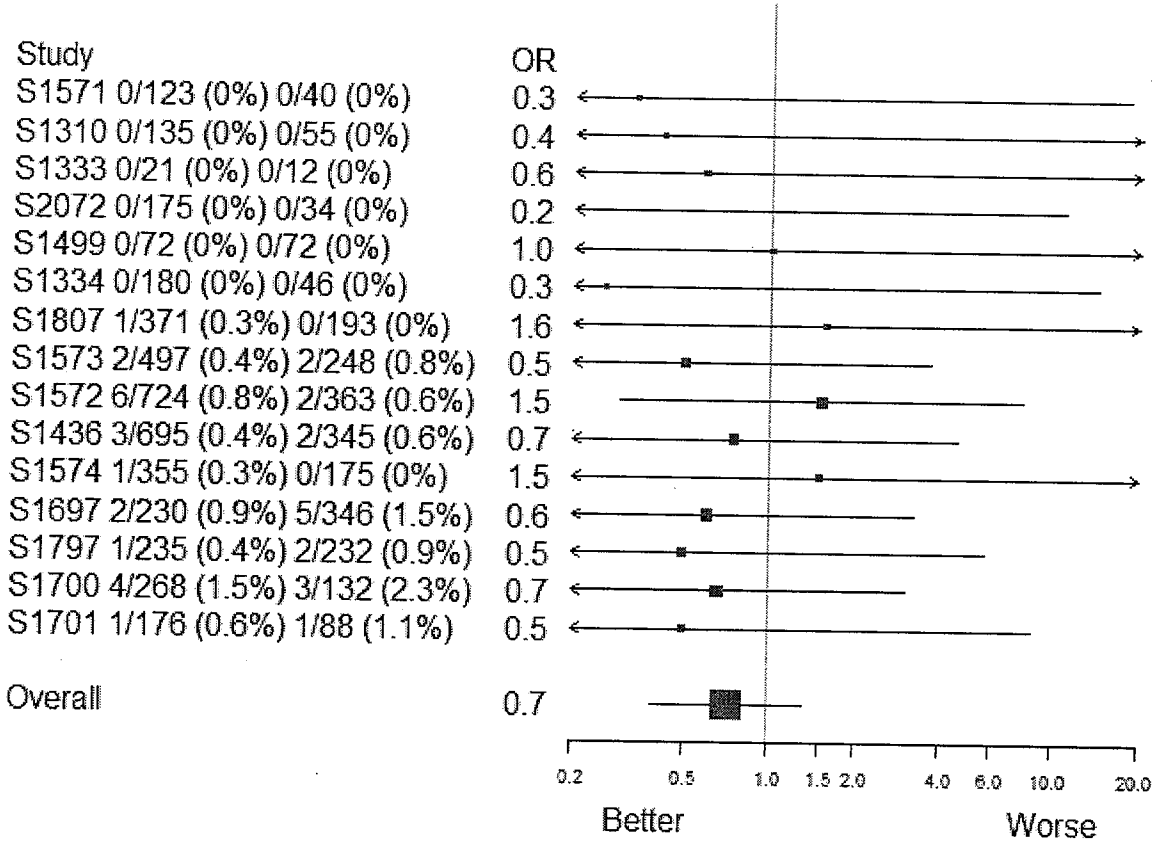
Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.8: Forest Plot for FDA Custom Endpoint, Liraglutide versus Active Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.9: Forest Plot for FDA Custom Endpoint, Liraglutide versus Total Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

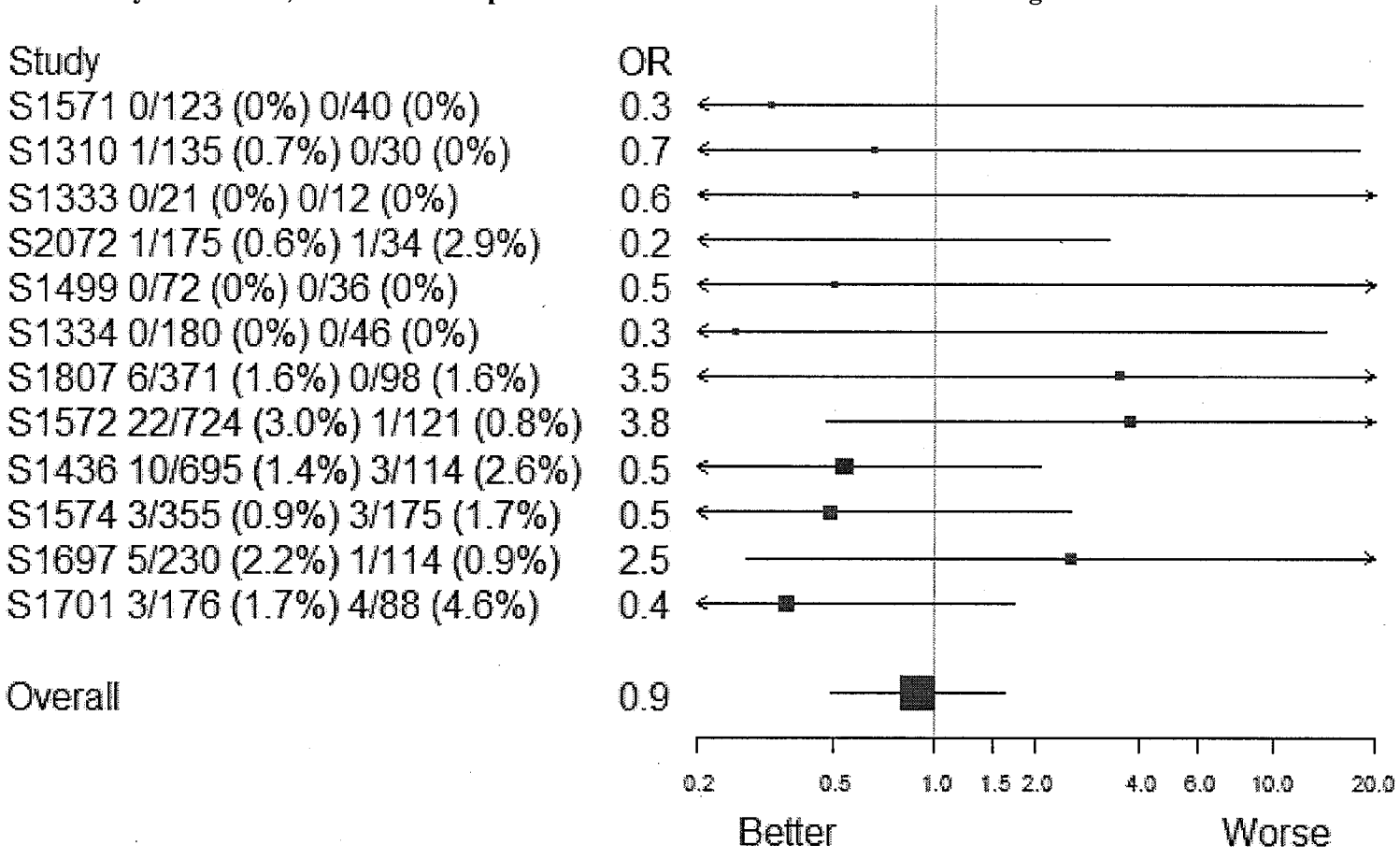
Table 7.1.3.3.1.3.12: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All Treatment-Emergent MACE, Time Period Population B, Broad SMQ Endpoint

Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 1000 pt-yrs
Liraglutide	4257	2882	69	1.62%	23.94
Placebo	907	449	13	1.43%	28.96
Active Comparator	1474	1038	32	2.17%	30.84
Total Comparators	2381	1486	45	1.89%	30.27

		Incidence Ratio (95% CI)		Incidence Rate Ratio (95% CI)	
	# of studies included in the analysis (with at least 1 event in the comparator group)	*Stratified, asymptotic (MH)*[3]	% of cases excluded from analysis (studies with 0 events in the comparator group)	*Stratified, asymptotic (MH)*[3]	% of pt-yrs excluded from analysis (studies with 0 events)
Liraglutide vs. Placebo	7 of 12	1.02 (0.54, 1.92)	10.3%	0.88 (0.47, 1.66)	1.6%
Liraglutide vs. Active	8 of 9	0.85 (0.55, 1.29)	1.9%	0.83 (0.55, 1.27)	0.3%
Liraglutide vs. Total Comparator	10 of 15	0.88 (0.61, 1.28)	9.6%	0.83 (0.57, 1.21)	1.5%
		Stratified, exact[4]		*Stratified, exact*[5]	
Liraglutide vs. Placebo	7 of 12	1.10 (0.56, 2.31)	10.3%	---[6]	1.6%
Liraglutide vs. Active	8 of 9	0.84 (0.53, 1.35)	1.9%	---	0.3%
Liraglutide vs. Total Comparator	10 of 15	0.90 (0.60, 1.36)	9.6%	0.86 (0.58, 1.29)	1.5%
		Stratified, fixed effects MH meta-analysis with a continuity correction[7]			
Liraglutide vs. Placebo	12 of 12	0.89 (0.50, 1.60)	0%		
Liraglutide vs. Active	9 of 9	0.83 (0.54, 1.27)	0%		
Liraglutide vs. Total Comparator	15 of 15	0.86 (0.59, 1.24)	0%		

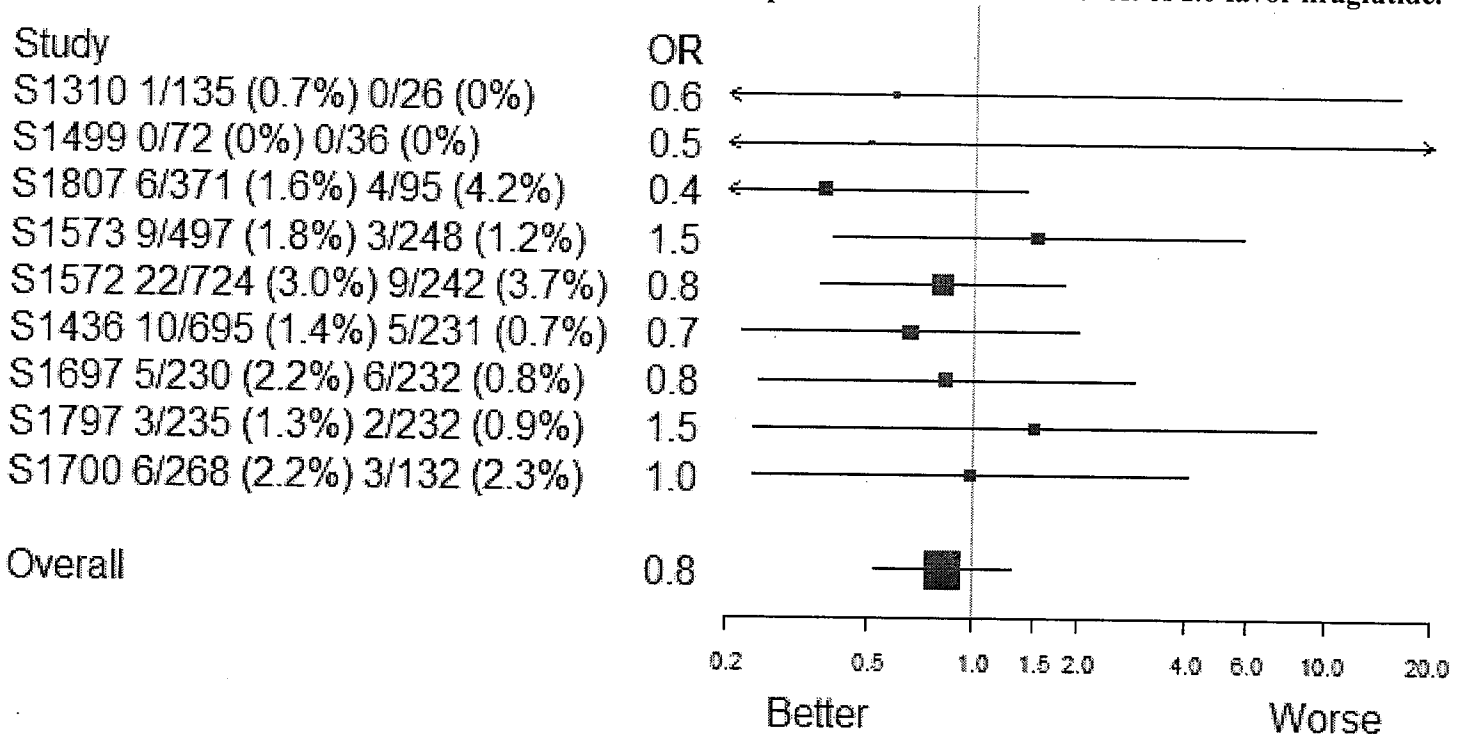
[1] Novo, submitted in response to FDA request for information 1/11/2009, Appendix B, Table 22 and Table 24
[2] Novo provided differences scaled as incidence events/N and incidence rates/pt yr (Appendix B, Table 14). The results are not reported in this table.
[3] Test conducted by Novo, MH = Mantel-Haenszel
[4] Test conducted by Dr. Derr; the tests for homogeneity across studies could not be calculated on StatXact™ 7.0
[5] Test conducted by Dr. Derr; p-values for homogeneity across studies: Liraglutide vs. Total Comparator, p=0.780
[6] The exact procedure did not provide an estimate.
[7] Test conducted by Dr. Derr, forest plots provided, with continuity correction of 0.5 for arms with 0 MACE events (Figures 7.1.3.3.1.3. 10, 7.1.3.3.1.3.11 and 7.1.3.3.1.3.12)

Figure 7.1.3.3.1.3.10: Forest Plot for Broad SMQ Endpoint, Liraglutide versus Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population B. Values to the left of 1.0 favor liraglutide.



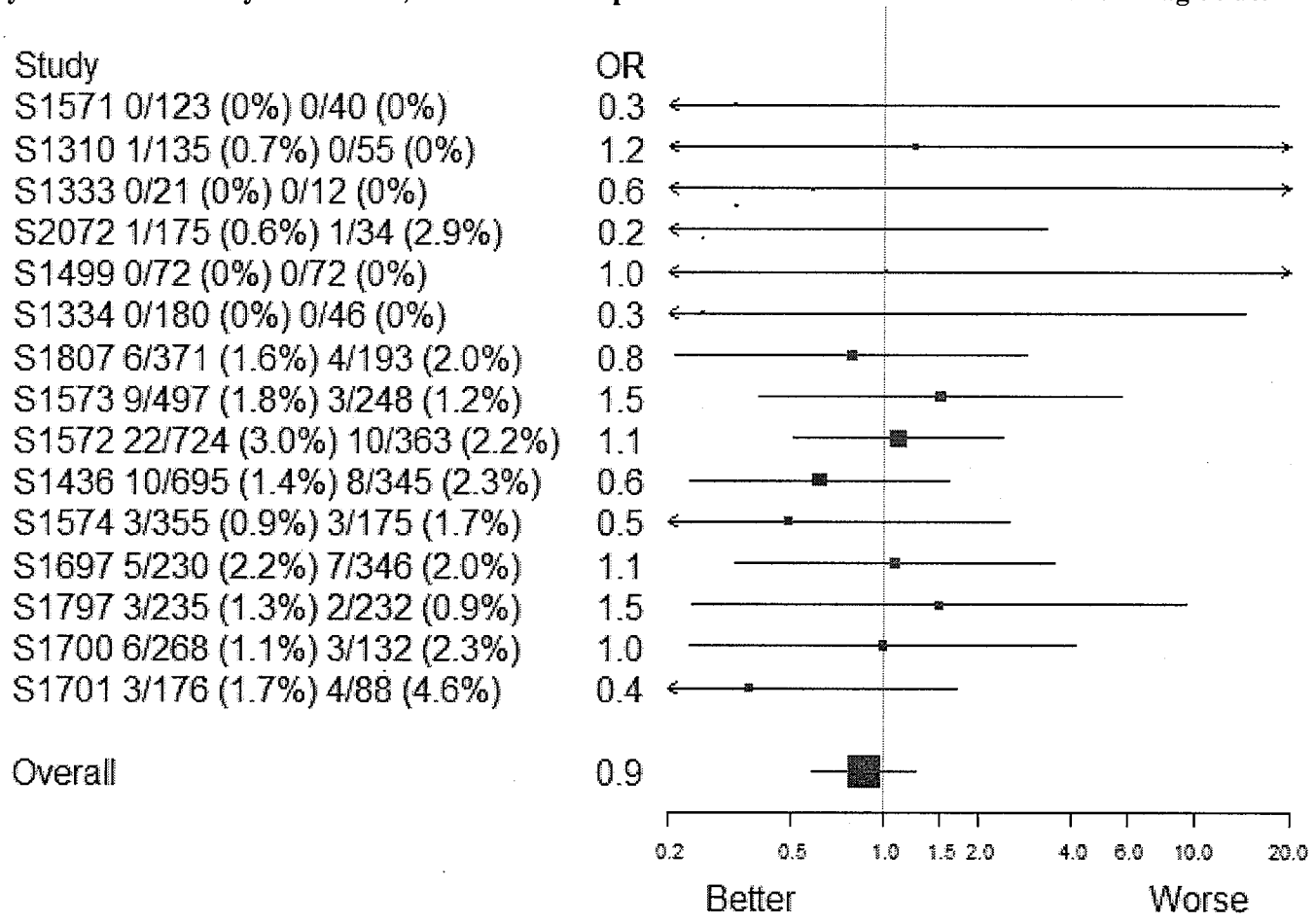
Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.11: Forest Plot for Broad SMQ Endpoint, Liraglutide versus Active Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure 7.1.3.3.1.3.12: Forest Plot for Broad SMQ Endpoint, Liraglutide versus Total Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Time Period Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics