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LIRAGLUTIDE
April 2, 2009

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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

BACKGROUND INTRODUCTORY MEMORANDUM

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Forum: Endocrinologic and Metabolic Drugs Advisory Committee meeting

Topic: April 2, 2009: NDA 22-341 - Liraglutide (Novo Nordisk)

INTRODUCTION

On July 1 and 2, 2008, the Food and Drug Administration (FDA) convened a public advisory committee meeting to discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus. The advisory panel was populated by the Endocrinologic and Metabolic Drugs Advisory Committee, diabetologists, cardiologists, statisticians, and members of the Drug Safety and Risk Management Committee (DSARM). The committee was asked to vote on the following question:

> *"It should be assumed that an anti-diabetic therapy with a concerning CV [cardiovascular] safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial, or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk?"*

Fourteen panel members voted "yes" to this question and two voted "no". The transcript is available at http://www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic.

After considering the discussion at this meeting as well as other available data, FDA determined that cardiovascular safety of therapies developed for type 2 diabetes should be more thoroughly evaluated during drug development. Therefore, in December 2008, FDA issued a final guidance for industry titled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, a copy of which is included in this background package.

In this guidance, FDA reaffirmed that HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication for glycemic control. However, FDA acknowledged that diabetes is associated with an elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population. FDA stated that the absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical. However, for type 2 diabetes, FDA noted that the wider range of therapies available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type 2 diabetes.

Therefore, this guidance asks sponsors to demonstrate that new therapies for type 2 diabetes do not result in an unacceptable increase in cardiovascular risk. This guidance does not address cardiovascular assessment of already-approved treatments for type 2 diabetes, which will be addressed in a future guidance.

Specifically, this guidance asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

- Establish an independent cardiovascular endpoints committee to prospectively and blindly adjudicate major cardiovascular events (e.g., cardiovascular death, myocardial infarction, and stroke) during phase 2 and 3 clinical trials.
- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a pre-specified meta-analysis of major cardiovascular events can reliably be performed. The sponsor should provide a protocol describing the statistical methods for the proposed meta-analysis of all placebo-controlled trials, add-on trials, and active-comparator trials. The guidance states that it is likely that the controlled trials will need to last longer than the typical 3-6 months duration to obtain a sufficient number of events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies.
- To enroll patients at increased cardiovascular risk, such as elderly patients and those with renal impairment.

The guidance states that to support approvability from a cardiovascular standpoint, the sponsor should compare the incidence of major cardiovascular events with the investigational agent to the incidence of the same types of events occurring with the control group and show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally may not be necessary.

FDA has publically communicated that all new unapproved therapies for type 2 diabetes (even pending new drug applications submitted to FDA prior to issuance of the final diabetes cardiovascular guidance) will be held to the standards of this guidance.

LIRAGLUTIDE ADVISORY COMMITTEE MEETING

FDA has convened an advisory committee meeting on April 2, 2009, to discuss the pending new drug application for liraglutide, which is seeking an indication for the treatment of type 2 diabetes. The Phase 2 and 3 clinical trials for this application were designed and completed well in advance of the final guidance being issued. Despite not having a prospective plan for cardiovascular risk assessment, FDA and the applicant have strived to objectively characterize cardiovascular risks for this therapy. The goal of the advisory committee meeting is to discuss whether the liraglutide new drug application sufficiently meets the December 2008 diabetes cardiovascular guidance, with respect to meeting the upper bound of the two-sided 95% confidence interval of 1.8, to support approvability. An additional focus of the advisory committee meeting for liraglutide pertains to findings of benign and malignant thyroid c-cell tumors in rats and mice.

LIRAGLUTIDE: MECHANISM OF ACTION

Liraglutide is a glucagon-like peptide (GLP)-1-based pharmacologic therapy for type 2 diabetes. GLP-1 stimulates glucose-dependent insulin release, slows gastric emptying, inhibits inappropriate post-meal glucagon release, and reduces food intake. GLP-1 concentrations are reduced in patients with type 2 diabetes but cannot be supplemented by unmodified GLP-1 because of the short half-life (<2 minutes) due to rapid degradation by the dipeptidyl peptidase (DPP)-4 enzyme. Therefore, GLP-1-based therapies for type 2 diabetes either inhibit DPP-4 to slow the degradation of endogenous GLP-1 or involve administration of pharmacological doses of modified GLP-1 that is resistant to DPP-4 degradation.

Liraglutide is an injectable GLP-1 analog that is resistant to DPP-4 degradation. Currently, there is one FDA-approved GLP-1 analog known as Byetta (exenatide). Byetta is dosed twice daily whereas liraglutide is dosed once daily.

IMPORTANT CONSIDERATIONS

The liraglutide new drug application was received by FDA on May 23, 2008 prior to the July 2008 advisory committee meeting that was convened to discuss cardiovascular assessment for drugs and biologics developed for the treatment of type 2 diabetes. Therefore, the liraglutide program was not prospectively designed to assess cardiovascular risk. Instead, the sponsor and FDA performed post-hoc evaluation of cardiovascular events (see below). There were no pre-specified definitions or prospective adjudication of major cardiovascular events and, because of the retrospective nature of these analyses, some events have insufficient information to definitively determine whether a cardiovascular event of interest occurred.

POST-HOC ANALYSES OF CARDIOVASCULAR EVENTS

After submission of the liraglutide new drug application, the FDA requested that the sponsor perform similar post-hoc analyses of cardiovascular events. The analyses that were requested by FDA are described in more detail in the joint clinical and statistical review documents prepared by FDA reviewers. An overview is provided here.

FDA requested that the main cardiovascular analysis be conducted on the randomized, controlled periods for all completed phase 2 and phase 3 clinical trials. An additional analysis included data from unblinded (but controlled) treatment periods that extended beyond the timepoint of the primary efficacy endpoint for glycemic control.

The cardiovascular endpoints requested by FDA are based on "MedDRA" and "Standardised MedDRA Queries" (SMQs). A brief description of these methodologies is presented here as background. MedDRA, which stands for "Medical Dictionary for Regulatory Activities", was developed by the International Conference on Harmonisation (ICH) and is used by regulatory authorities and sponsors to code adverse events reported in clinical trials and postmarketing databases. Because investigators can report the same adverse event in many different ways, it would be difficult to rely only on these verbatim investigator-reported terms for tabulating the incidence of various adverse events. Coders who are trained in the use of MedDRA review the verbatim terms reported by investigators and match these verbatim terms to one of over 65,000 "Lowest Level Terms (LLTs)". Each LLT is linked to a single "Preferred Term" (PT). For example, LLTs of "arrhythmia", "dysrhythmias", and "arrhythmia not otherwise specified" would all be linked to the single PT of "arrhythmia". Analyses of adverse events are then performed using PTs, which represent single medical entities.

The size and complexity of MedDRA terminology may result in different users selecting different sets of PTs when trying to retrieve cases related to a particular safety issue. SMQs for a wide variety of medical conditions of interest have been developed in an attempt to standardize the sets of PTs that should be included when evaluating a particular safety issue. An SMQ is a grouping of PTs that are potentially related to a defined medical condition of interest. For example, in MedDRA version 11.1, the "Myocardial Infarction" SMQ contains 30 preferred terms (e.g., "acute coronary syndrome", "coronary artery occlusion", "silent myocardial infarction", "blood creatine phosphokinase increased"). Therefore, patients who were reported to have experienced any of these 30 preferred terms would be counted as having had a myocardial infarction in this SMQ. Although some of these preferred terms could be consistent with myocardial infarction, there may be an alternate explanation in some patients. For example, "blood creatine phosphokinase increased" could be related to exercise, muscle trauma, medications, or a variety of other causes. Therefore, the SMQ analyses will detect all patients with reported PTs that could be consistent with, but not necessarily diagnostic of, the condition of interest.

FDA requested that the sponsor use two endpoints for the cardiovascular analyses. The first endpoint, called "SMQ MACE", was defined as a composite endpoint of cardiovascular death and all preferred terms in the Standardised MedDRA Queries (SMQs) for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents." A

second endpoint, called “Custom MACE”, was also analyzed. The “Custom MACE” endpoint is a subset of “SMQ MACE” and is considered to be more specific than “SMQ MACE” for the reasons explained above.

The “Custom MACE” was created as follows. Without considering which events had actually occurred, a panel of 3 FDA clinical reviewers independently reviewed the list of all PTs included in the “SMQ MACE” with the following 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?” The goal was to select only those PTs that seemed highly likely to represent true events of myocardial infarction or stroke with a mechanism of atherosclerotic plaque development followed by plaque rupture or thrombosis (as opposed to events with non-atherosclerotic mechanisms, such as rupture of a congenital aneurysm). The lists generated by the 3 clinical reviewers were compared and any PTs for which there was not unanimous agreement to include or exclude were open for discussion. Consensus was reached regarding inclusion or exclusion for all PTs. FDA acknowledges that this post-hoc approach is imperfect – some events have insufficient information to definitively assess whether an endpoint of interest occurred and other reasonable physicians may have chosen a different set of PTs for the “Custom MACE” endpoint. A listing of the PTs included in the “SMQ MACE” and “Custom MACE” endpoints as well as the results of the requested cardiovascular analyses are shown in FDA’s clinical/statistical review of liraglutide.

The cardiovascular risk analyses, based on both “SMQ MACE” and “Custom MACE”, are presented in the FDA background materials. Because both analyses are *post hoc*, there is no conclusion that one set of preferred terms is superior to the other. Rather, FDA reviews attempt to explain how use of certain preferred terms may contribute to differences in point estimates for cardiovascular risk and the accompanying confidence intervals or to highlight how different analyses might still yield consistent findings.

CONTENTS OF THE FDA BACKGROUND PACKAGE

This FDA background package contains:

- This introductory document
- Non-clinical pharmacology/toxicology review of thyroid c-cell tumors in animals
- Joint clinical/statistical review of major cardiovascular events and thyroid tumors in the liraglutide phase 2/3 program
- The cardiovascular analyses requested by FDA that formed the basis for the joint clinical/statistical review of major cardiovascular events
- Statistical review of liraglutide’s efficacy
- The February 2007 draft guidance for industry entitled *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*
- The December 2008 final guidance for industry entitled *Diabetes Mellitus -- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*

CONCLUSIONS

Type 2 diabetes affects millions of people in the United States, causing considerable morbidity and mortality. Cardiovascular disease accounts for most deaths among people with diabetes. Therefore, the question of cardiovascular safety for new drugs developed for the treatment of type 2 diabetes, such as liraglutide, is of high public health importance. We look forward to a thorough and reasoned discussion of this topic as well as a discussion of the clinical relevance of animal findings of thyroid c-cell tumors in animals treated with liraglutide. Thank you in advance for your recommendations and for the vital public health contribution you are making through your participation in this important meeting.

Advisory Committee Nonclinical Briefing Document
NDA 22-341

Drug: Victoza® (liraglutide, NNC 90-1170)
Drug Class: GLP-1 receptor agonist
Chemical Class: lipidated peptide
Clinical Indication: Type 2 diabetes (daily subcutaneous injection)

Reviewer: Anthony Parola, PhD
Pharmacologist, Division of Metabolism and Endocrinology Products

Introduction

Glucagon-like peptide-1 (GLP-1) is a 30- or 31-amino acid peptide secreted from epithelial L-cells in the distal small intestine and colon in response to ingesting food. The 30-amino acid amidated form and the 31-amino acid glycine extended form of GLP-1 are equipotent, but in humans, GLP-1(7-36)amide is the predominant circulating active GLP-1. GLP-1 improves glycemic control by stimulating glucose-dependent insulin secretion (incretin effect), increasing insulin synthesis, inhibiting glucagon secretion, slowing gastric emptying and acid secretion, and decreasing food consumption and body weight gain. The effects of GLP-1 are mediated by a single family B G-protein coupled receptor, the GLP-1 receptor, that is widely distributed throughout the body; in the pancreas (alpha, delta, and beta cells), peripheral and central nervous systems, heart, kidney, lung, stomach (parietal cells), and at other sites in the GI tract. Systemic activity of GLP-1 is limited because dipeptidyl peptidase IV (DPP-IV or CD26), a widely expressed enzyme with membrane bound and soluble forms that cleaves off the first 2 N-terminal amino acids, rapidly metabolizes it. The resulting metabolite, GLP-1(9-36)amide, has weak insulinotropic effects, but it potently and directly inhibits hepatic glucose production. Drugs which effect control of hyperglycemia via an incretin mechanism by reducing the clearance of endogenous GLP-1 (DPP-IV inhibitors, such as sitagliptin) or GLP-1 receptor peptide agonists resistant to inactivation (such as exenatide) are currently approved for the treatment of type 2 diabetes. Several GLP-1 receptor peptide agonists are in various stages of clinical development in the U.S, and one, exenatide, is marketed.

Liraglutide (NN2211 or NNC 90-1170) is a lipidated GLP-1 analog with prolonged pharmacologic activity after subcutaneous administration (Figure 1). Its prolonged activity is due to delayed absorption resulting from self association of the attached lipid and because liraglutide is highly plasma protein bound in systemic circulation, it is resistant to inactivation by DPP-IV. Liraglutide is pharmacologically active at cloned GLP-1 receptors from mice, rats, and monkeys *in vitro* and *in vivo*, in animal models of type 2 diabetes and obesity. Liraglutide improves glycemic control in diabetic ob/ob mice, db/db mice, ZDF rats, high fat fed obese SD rats, obese sand rats, and streptozocin-induced diabetic minipigs. Liraglutide didn't cause hypoglycemia in hyperglycemic or normoglycemic animals. Liraglutide was well tolerated in chronic repeat dose toxicity studies in rats and monkeys, and it didn't affect survival in 2-year carcinogenicity bioassays in mice and rats. In rodent carcinogenicity studies, liraglutide caused benign and malignant thyroid c-cell tumors in rats at low multiples of human exposure and in mice at somewhat higher exposures. Liraglutide is the only marketed or investigational drug known to cause c-cell tumors in both rats and mice (based on available data).

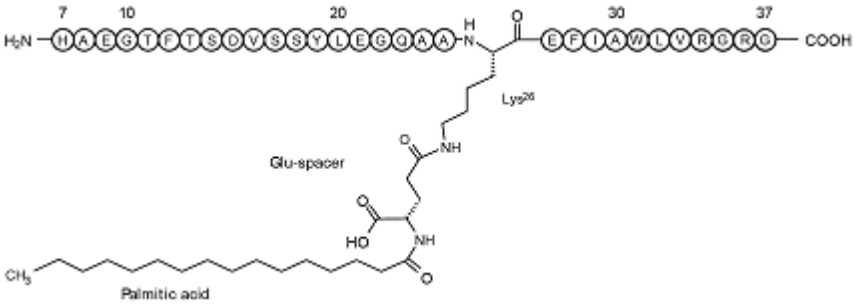


Figure 1. Chemical stucture of liraglutide

The effects of GLP-1 on thyroid function are not well characterized. GLP-1 receptors are found in the thyroid of rats, mice, and humans with a similar receptor tissue density across species, but specific thyroid cell types expressing the receptor have not been identified. Although [^{125}I]GLP-1(7-36)amide binding to thyroid tissue samples occurred in 100% of rats tested, only 60% of mice and 5% of humans had GLP-1 receptor positive thyroid tissue samples (Table 4) (Korner 2007). When GLP-1 receptors are expressed in thyroid, there is indirect evidence the receptor is localized to c-cells. For example, in the same autoradiography ligand binding study (Korner 2007), 28% of human medullary thyroid carcinomas (MTCs) were GLP-1 receptor positive, so compared to normal human thyroid, GLP-1 receptor expression occurs more frequently in thyroid c-cell tumors. In mice, GLP-1 regulates bone resorption through a calcitonin-dependent mechanism and it regulates calcitonin transcript levels in thyroid c-cells (Yamada 2008). In perfused rat thyroid, GLP-1 induces calcium-dependent calcitonin secretion (Crespel 1996). Although functional GLP-1 receptors coupled to adenylyl cyclase activation and calcitonin secretion were identified in a rat c-cell line, calcium-dependent calcitonin secretion may be altered (Lamari 1996).

Rodent Carcinogenicity

In 2-year life-time exposure studies in rats and mice treated by once-a-day bolus subcutaneous injection, liraglutide caused thyroid c-cell tumors in rats and mice and fibrosarcomas on the dorsal surface in male mice, the body surface used for drug administration. Liraglutide was not genotoxic in a standard battery of tests.

C-cell proliferation occurs along a continuum ranging from diffuse hyperplasia, focal hyperplasia, adenomas to carcinomas (Greaves 2007). Diffuse hyperplasia is considered a physiologic response with cells more uniformly distributed in the parafollicular areas while focal hyperplasia is considered preneoplastic because these cells are often slightly larger with pale eosinophilic cytoplasm and a round to oval nucleus. Nodular aggregates showing displacement of the surrounding gland without invasion are considered adenomas. Focal c-cell hyperplasia and adenomas are only differentiated by size with a focus of c-cells > 5 average-sized contiguous follicles considered adenomas. However, whether or not these adenomas are autonomous neoplastic growths is unknown. C-cell carcinoma, also called thyroid medullary carcinoma (MTC), occurs when c-cell nodules or cords develop stromal or vascular invasion.

Mechanistic studies aimed at determining a mode of action for liraglutide-induced thyroid tumors and their relevance to humans were performed using thyroid tissue, rat and human c-cell lines, and *in vivo* in mice, rats, and monkeys. The weight of evidence from rodent carcinogenicity studies, mechanistic studies, and clinical data is not sufficient to conclude liraglutide-induced thyroid-cell tumors are rodent-specific.

Rats

Thyroid c-cell tumors occurred at all doses tested in males and females in a 104-week repeat subcutaneous dose study of 0.075, 0.25, or 0.75 mg/kg/day liraglutide in Sprague Dawley rats (Table 1), but survival was unaffected by treatment. The No Observed Adverse Effect Level (NOAEL) for thyroid c-cell tumors was < 0.075 mg/kg/day liraglutide, below the lowest dose tested. Tumors occurred at therapeutic exposure in humans based on plasma AUC_{0-24} comparison across species. Thyroid c-cell adenomas are common tumors in 2 year studies in Sprague Dawley rats (historical control group incidence > 1%), but c-cell carcinomas are rare (historical control group incidence < 1%). Benign c-cell adenomas dose-dependently increased at ≥ 0.25 mg/kg in males and at ≥ 0.075 mg/kg in females. Malignant c-cell carcinomas increased with dose in males at 0.75 mg/kg and the incidence was above the historical control group range at ≥ 0.075 mg/kg in males and at ≥ 0.75 mg/kg in females. Combined c-cell carcinomas and adenomas increased dose-dependently at ≥ 0.25 mg/kg in males and at ≥ 0.075 mg/kg in females. The incidence of diffuse thyroid c-cell hyperplasia was not increased by treatment, but in the absence of identifying c-cells in thyroid tissue sections by calcitonin immunoreactivity, diffuse c-cell hyperplasia was not adequately assessed (data not shown). Focal c-cell hyperplasia, a preneoplastic lesion, increased above concurrent control groups and above the historical control group range at ≥ 0.075 mg/kg liraglutide in males and at ≥ 0.25 mg/kg in females.

Table 1. Incidence of Proliferative Thyroid C-cell Findings in 104-Week Carcinogenicity Study of Subcutaneously Injected Liraglutide in Rats

Sex		Male					Female				
Liraglutide Dose (mg/kg/day)		0	0.075	0.25	0.75	Trend	0	0.075	0.25	0.75	Trend
Proliferative Thyroid C-cell Findings	N	50	49	50	50		50	49	49	50	
Hyperplasia	focal	11	14	20	24*		14	14	27**	24	
Tumors	adenoma (B)	6	8	21**	23***	0.000	5	13*	16**	28***	0.000
	carcinoma (M)	1	4	3	7**	0.020	0	0	2	3	0.028
	carcinoma (M) + adenoma (B)	7	11	21***	28***	0.000	5	13*	18***	29***	0.000
Human Exposure Multiple[1]		-	0.5	2.2	7.6		-	0.5	2.2	7.6	

B = benign, M = malignant

Statistically significantly different from control by Peto analysis: *p< 0.05, **p< 0.01, ***p < 0.001.

Underlined values were statistically significant by trend analysis based on p-values for rare (p < 0.025) or common (p < 0.005) tumors. For pairwise comparison, underlined values were significantly different from controls based on p-values for rare (p < 0.05) or common (p < 0.01) tumors. C-cell adenomas in rats are common (incidence > 1%) and carcinomas are rare (incidence < 1%).

Shaded values (yellow) were outside concurrent and historical control group range for c-cell focal hyperplasia (0 – 14.3% in males, 0 – 20% in females), adenomas (4 – 21.1% in males, 1.3 – 16% in females) and carcinomas (0 – 2.1% in males, 0 – 4% in females).

[1]Based on plasma liraglutide AUC_{0-24} ratio using week 104 toxicokinetic data from rats and steady state plasma pharmacokinetic data from humans at the maximum proposed clinical dose of 1.8 mg/day (AUC_{0-24} 816 nM.hr).

Mice

A 104-week lifetime-exposure carcinogenicity study of 0.03, 0.2, 1, or 3 mg/kg/day liraglutide injected subcutaneously once a day in CD-1 mice included a main study group and a 78-week interim sacrifice group. Although mortality was unaffected by liraglutide treatment, due to reduced survival in main study control group females, the 78-week interim sacrifice was canceled with dosing continued to week 104 (week 78/104 group). Tumor analysis combined

results from both main study and week 78/104 groups (Tables 2 and 3). The NOAEL for thyroid c-cell tumors in mice was 0.2 mg/kg/day liraglutide (1.8x human exposure) and the NOAEL for fibrosarcomas on the dorsal skin and subcutis was 1 mg/kg/day (10x human exposure). Benign c-cell adenomas dose-dependently increased compared to concurrent controls and above the historical control group range at ≥ 1 mg/kg liraglutide in males and females. Malignant c-cell carcinoma occurred in 2 high dose females, and the incidence of combined c-cell carcinoma and adenomas dose-dependently increased at ≥ 1 mg/kg in females. C-cell hyperplasia dose-dependently increased above concurrent controls and above the historical control group range at ≥ 0.2 mg/kg liraglutide in males and females. Based on historical control group data from CD-1 mice, proliferative thyroid c-cell lesions, including focal hyperplasia, adenomas, and carcinomas are rare (incidence < 1%). These data are consistent with dose-related progression of focal hyperplasia to adenomas in males and females with further progression to carcinomas in high dose females.

Table 2. Incidence of Proliferative Thyroid C-cell Findings in 104-Week Carcinogenicity Study of Subcutaneously Injected Liraglutide in Mice

	Sex	**Males**						**Females**					
	Liraglutide Dose (mg/kg/day)	**0**	**0.03**	**0.2**	**1**	**3**	Trend	**0**	**0.03**	**0.2**	**1**	**3**	Trend
Proliferative Thyroid C-cell Findings	**N**	79	66	65	67	79		75	66	67	66	76	
Hyperplasia	focal	**0**	0	1	11***	30***		0	0	7**	10***	22***	
Tumors	adenoma (B)	0	0	0	9***	15***	0.000	0	0	0	4*	15***	0.000
	carcinoma (M)	0	0	0	0	0	-	0	0	0	0	2	0.043
	carcinoma (M) + adenoma (B)	-	-	-	-	-	-	0	0	0	4*	17***	0.000
Human Exposure Multiple[1]		-	0.2	1.8	10.0	45.0	-	-	0.2	1.8	10.0	45.0	-

B = benign, M = malignant

Statistically significantly different from control by Peto analysis: *p< 0.05, **p< 0.01, ***p < 0.001.

Underlined values were statistically significant by trend analysis based on p-values for rare tumors (p < 0.025) . For pairwise comparison, underlined values were significantly different from controls based on p-values for rare tumors (p < 0.05). Based on historical control data, C-cell hyperplasia, adenomas, and carcinomas in mice are rare (incidence < 1%).

Shaded values (yellow) are outside the historical control group range for c-cell hyperplasia (0% in males, 0 - 0.9% in females), adenomas (0% in males and females) and carcinomas (0 % in males and females).

[1]Based on plasma liraglutide AUC_{0-24} ratio using week 104 toxicokinetic data from mice and steady state plasma pharmacokinetic data from humans at the maximum proposed clinical dose of 1.8 mg/day (AUC_{0-24} 816 nM.hr).

Fibrosarcomas in the dorsal skin and subcutis of male mice, the body surface used for drug administration, dose-dependently increased above concurrent control and historical control group ranges at 3 mg/kg liraglutide (Table 3). Based on historical control group data, spontaneous fibrosarcomas in the skin and subcutis are common in mice (incidence > 1 %). Fibrosarcomas at the subcutaneous injection site are rare (< 1%) based on the background incidence in subcutaneously injected control group mice in 4 previous 2-year carcinogenicity studies performed at the same facility (incidence of 0%).

Table 3. Incidence of Dorsal Surface Tumors in 104-Week Carcinogenicity Study of Subcutaneously Injected Liraglutide in Mice

Sex		Males						Females					
Liraglutide Dose (mg/kg/day)		0	0.03	0.2	1	3	Trend	0	0.03	0.2	1	3	Trend
Dorsal SurfaceTumors	N	79	67	67	67	79		79	67	67	67	79	
Skin & subcutis	fibrosarcoma (M)	0	2	1	2	7**	0.001	1	1	1	0	2	0.31
Skin & subcutis	sarcoma (not otherwise specified) (M)	1	0	0	0	1	0.37	1	0	1	0	5	0.007
Injection site	fibrosarcoma (M)	0	1	1	0	4	0.013	1	0	0	0	2	0.14
Human Exposure Multiple[1]		-	0.2	1.8	10.0	45.0	-	-	0.2	1.8	10.0	45.0	-

B = benign, M = malignant

Statistically significantly different from control by Peto analysis: *p< 0.05, **p< 0.01, ***p < 0.001

Underlined values were statistically significant by trend analysis based on p-values for common tumors (p < 0.005). For pairwise comparison, underlined values were significantly different from controls based on p-values for common tumors (p < 0.01).

Shaded values (yellow) were outside concurrent and historical control group ranges (0 - 7.5% in males, 0 – 10.0% in females) .

[1]Based on plasma liraglutide AUC_{0-24} ratio using week 104 toxicokinetic data from mice and steady state plasma pharmacokinetic data from humans at the maximum proposed clinical dose of 1.8 mg/day (AUC_{0-24} 816 nM.hr).

Proposed Mode of Action for Liraglutide-Induced Rodent Thyroid C-cell Tumors

To determine the human relevance of liraglutide-induced thyroid c-cell tumors in rodents, the applicant proposed a novel GLP-1 receptor-dependent mode of action, then performed mechanistic studies to evaluate it. The proposed mode of action is:

1. GLP-1 receptor agonists activate thyroid c-cell GLP-1 receptors.
2. C-cell GLP-1 receptor activation stimulates calcitonin secretion (calcitonin is a 'prehyperplasia' biomarker).
3. C-cell GLP-1 receptor activation increases calcitonin synthesis.
4. Persistent calcitonin secretion and increased calcitonin synthesis causes c-cell hyperplasia.
5. C-cell hyperplasia progresses to c-cell tumors, including progression of benign adenomas to carcinomas.

The proposed mode of action implies diffuse c-cell hyperplasia, a physiologic response, precedes focal c-cell hyperplasia, a preneoplastic lesion, and that liraglutide causes c-cell proliferation. Drug-induced persistent calcitonin secretion leading to thyroid c-cell tumors is a novel mode of action that has not been previously demonstrated for any approved drug causing thyroid c-cell tumors in rats (Table 6). As a result of the counter-regulatory effects of calcitonin-induced hypocalcemia, it's not clear that GLP-1receptor –mediated persistent calcitonin secretion can occur, at least in rats. Cinacalcet, a calcitonin secretagogue in rats, only transiently increases plasma calcitonin due to the counter-regulatory effects of calcitonin-induced hypocalcemia.

Carcinogenicity of Drugs Known to Increase Calcitonin Secretion

Cinacalcet is a type II calcium sensing receptor (CaSR) agonist used to treat secondary hyperparathyroidism in chronic renal failure patients. In rats, cinacalcet increases the sensitivity of calcitonin secretion to extracellular calcium resulting in transiently elevated plasma calcitonin and lower blood calcium. Cinacalcet dose-dependently decreased the incidence of thyroid c-cell adenomas in 2-year carcinogenicity studies in rats and did not cause c-cell tumors in mice (Kuipers 2004). At least for cinacalcet, increased calcitonin secretion by itself is not sufficient to induce tumors. The mechanism of CaSR agonist lowering proliferative C-cell lesions is possibly

due to activating counter-regulatory mechanisms in response to transient hypercalcitoninemia, persistent hypocalcemia, or calcitonin directly inhibiting c-cell growth (Kuijpers 2004, Kakudo 1989).

Extracellular free calcium is the major stimulus for calcitonin secretion from thyroid, and its effects are mediated by the G-protein coupled CaSR on thyroid c-cells. Calcitonin secretion is increased at high extracellular calcium concentrations. In rats, increased calcitonin decreases extracellular calcium, primarily by inhibiting osteoclast-mediated bone resorption, and as calcium levels drop, calcitonin secretion diminishes. Because of calcitonin's counter-regulatory hypocalcemic effect, CaSR agonists only transiently increase plasma calcitonin, but hypocalcemia persists (Fox 1999). Drugs causing persistent calcitonin secretion should uncoupled calcitonin secretion from extracellular calcium and/or abrogate the counter-regulatory effects of calcitonin-induced hypocalcemia as part of their mode of action.

Evaluation of the Proposed Mode of Action

GLP-1 Receptor Coupling to Calcitonin Secretion.

There is no direct evidence of thyroid c-cell GLP-1 receptors. Autoradiography using [^{125}I]GLP-1(7–36)amide in thyroid tissue showed GLP-1 receptors occurred in thyroid from 6% of humans, compared to 60% of thyroids from mice and 100% of thyroids from rats (Table 4) (Körner 2007). GLP-1 receptors are expressed in thyroid of all rats, but only in subpopulations of mice and humans. Specific thyroid cell types binding [^{125}I]GLP-1(7–36)amide were not identified.

Table 4

GLP-1 Receptor (GLP-1 R) Expression in Lung and Thyroid Gland of Rat, Mouse, and Human: Comparison of Receptor Incidence and Density

Organ	GLP-1 R	Rat*	Mouse*	Human*
Lung	Incidence	3/3 (100)	6/6 (100)	11/28 (39)
	Density†	3,477 ± 1,539	1,677 ± 439	636 ± 164
Thyroid	Incidence	12/12 (100)	3/5 (60)	1/18 (6)
gland	Density†	2,289 ± 282	1,982 ± 470	1,193

*Values in parentheses are percentages.
†Mean ± SEM of receptor-positive cases (dpm/mg tissue).

(From Körner 2007)

The applicant evaluated GLP-1 receptor expression in c-cells in thyroid tissue sections from mice, rats, monkeys, and humans, but immunohistochemical and in situ hybridization studies were equivocal. Immunohistochemical studies did not conclusively show colocalization of calcitonin and GLP-1 receptor immunoreactivities because specificity of the rabbit polyclonal human anti-GLP-1 receptor antibody was not demonstrated. In situ hybridization studies using radiolabeled riboprobes aimed at colocalizing GLP-1 receptor mRNA in calcitonin immunoreactive cells in thyroid tissue were also considered equivocal because of the low signal to noise ratio for GLP-1 receptor mRNA.

Evidence for GLP-1 receptor mediated calcitonin release in rats comes from a published study by Crespel using perfused thyroid glands (Crespel 1996). In the presence of low calcium (1 mM), 10 nM GLP-1 (7-36)amide did not stimulate calcitonin secretion, but in the presence of high calcium (3 mM), 1 and 10 nM GLP-1 (7-36)amide dose-dependently increased calcitonin secretion above levels elicited by 3 mM calcium alone.

GLP-1 receptors in pancreatic beta cells and in rat thyroid c-cell lines are coupled to adenylyl cyclase via the stimulatory heterotrimeric G-protein, Gs. Increased intracellular cAMP

activates protein kinase A (PKA) and cAMP-regulated exchange factor II (cAMP-GEFII). Activated PKA and cAMP-GEFII increase insulin secretion by increasing intracellular calcium (activating L-type calcium channels and ryanodine receptor-dependent and IP_3 receptor-dependent intracellular calcium release) and inhibiting efflux of intracellular potassium through K_{ATP} channels and Kv channels. GLP-1 receptor agonists increase glucose-dependent insulin release from pancreas beta cells, but not glucose-independent insulin release. In rat c-cell lines (MTC 6-23 and CA77), GLP-1 receptor agonist increased intracellular cAMP and calcitonin secretion, but calcitonin secretion occurs even at low extracellular calcium levels, so calcitonin secretion may not be tightly coupled to calcium in c-cell lines (NDA 22-341, Lamari 1996). Glucagon, a calcitonin secretogogue in rat CA-77 cells, didn't elicit calcitonin secretion from rat MTC 6-23 cells (Vertongen 1994), another c-cell line, further demonstrating that receptor-mediated calcitonin secretion from c-cell lines may not be relevant to calcitonin secretion *in vivo*. The absence of GLP-1 receptor-mediated calcitonin secretion from a human thyroid c-cell line, TT cells, was not sufficient evidence to conclude GLP-1 agonists do not elicit calcitonin secretion in humans *in vivo* (NDA 22-341).

There was no evidence of adverse effects due to hypercalcitoninemia in liraglutide-treated rats or mice. Chronic administration of exenatide or liraglutide to mice or rats had no persistent hypocalcemic effect or any effects on bone detectable by standard necropsy and histopathology procedures. However, GLP-1 receptors in mice are linked to bone resorption by a calcitonin-dependent pathway. Osteoclasts and bone resorption were increased and thyroid calcitonin mRNA was decreased in GLP-1 receptor knockout mice, and treatment with eel calcitonin suppressed bone resorption (Yamada 2008). Exenatide had no direct affect on osteoblasts or osteoclasts.

Any effect of liraglutide to increase plasma calcitonin in Sprague Dawley rats was variable, transient, and minor compared to age-related increases that normally accompany proliferative c-cell changes. In repeat-dose mechanistic studies of liraglutide in rats, calcitonin was not a reliable biomarker for liraglutide pharmacodynamic effects or for liraglutide-induced proliferative c-cell lesions. Calcitonin may be a biomarker in mice. Liraglutide dose-dependently increased plasma calcitonin in CD-1 mice, but in nearly all dose groups in studies up to 9 weeks, some mice were resistant to liraglutide's hypercalcitoninemic effect, even though they developed focal c-cell hyperplasia. In mice treated with liraglutide for 9 weeks followed by 6- or 15-week recovery periods, elevated plasma calcitonin was largely reversed, even when c-cell hyperplasia persisted in recovery.

A Forest plot of pooled results from weeks 26/28 of long term clinical trials of liraglutide showed significant, dose-dependent increased plasma calcitonin compared to placebo at all liraglutide doses, but no significant difference between liraglutide and active comparator at any dose (Figure 2). At week 52, calcitonin was significantly higher than placebo at both 1.2 or 1.8 mg/day liraglutide, and calcitonin was significantly higher than active comparator at 1.8 mg/day (data from clinical trial 1573.) A calcium-stimulation test performed in a subset of subjects from long-term clinical studies 1573 (90 subjects) and 1574 (54 subjects) showed there were no significant differences in calcium-stimulated calcitonin secretion between comparator or liraglutide groups (1.2 or 1.8 mg/day) prior to initiating treatment or after 52 weeks of treatment. Please refer to Dr. Mahoney's briefing document for details of clinical effects of liraglutide on hypercalcitoninemia and thyroid cancer.

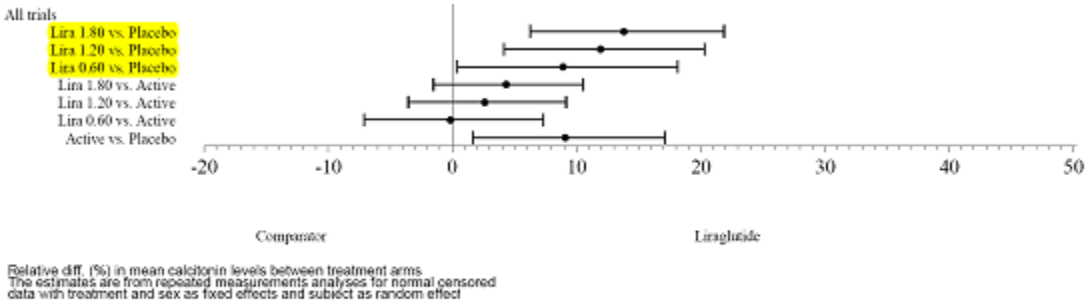


Figure 2 Forest plot of Calcitonin Continous Analysis – Week 26/28 – All Long-term Trials - Safety analysis set Figure edited, removed results from individual clinical trials.
[N000 Module 2.5 P192]

GLP-1 Receptor Mediated Effects on Thyroid Calcitonin mRNA

Thyroid calcitonin mRNA was upregulated by GLP-1 agonists in mice, but not in rats. Liraglutide had no consistent effect on calcitonin mRNA in rats. Single doses of liraglutide decreased thyroid calcitonin peptide and mRNA levels in normal rats, but increase levels of both in calcium-loaded rats. Four weeks of treatment with 0.75 mg/kg/day liraglutide had no effect on calcitonin transcript levels in male rats. In mice, GLP-1 receptors are coupled to thyroid calcitonin mRNA regulation. Single subcutaneous injections of exenatide increase thyroid calcitonin mRNA in wild-type mice and calcitonin transcript levels are significantly reduced in GLP-1 receptor knockout mice (Yamada 2008). Calcitonin transcript levels were significantly increased after 9 weeks of treatment with 5 mg/kg/day liraglutide in CD-1 mice, and dose-dependently increased by 0.083, 0.33, or 1.67 mg/kg/injection exenatide administered 3 times a day for 2 weeks.

Progression of Proliferative Thyroid C-cell Lesions in Liraglutide Treated Rodents

Mechanistic studies of subcutaneously injected liraglutide in rats and mice and exenatide in mice showed both GLP-1 receptor agonists caused focal c-cell hyperplasia, a preneoplastic lesion, without causing diffuse hyperplasia, a physiologic response. GLP-1 receptors can couple to signaling pathways regulating cell survival and growth. In CHO cells, heterologously expressed human GLP-1 receptors were coupled to mitogen-activated protein kinase (MAPK) signaling by inhibitory G-proteins G(i1, 2). In hair follicles and in cultured skin-derived cells from mice, GLP-1 receptors were coupled to MAPK/ERK signaling, but not to adenylyl cyclase (List 2006).

Liraglutide was not a c-cell mitogen in mice, rats, or monkeys. There was no evidence of liraglutide-induced thyroid c-cell proliferation because it didn't occur in mice treated for 2 weeks with 5 mg/kg/day (quantitative assessment of calcitonin immunoreactive cells), rats treated for 6 weeks with 0.75 mg/kg/day (BrdU labeling calcitonin immunoreactive cells), rats treated for 26 weeks with 1 mg/kg/day (colocalization of PCNA and calcitonin immunoreactivity), or monkeys treated for 52 weeks with 1 mg/kg/day (colocalization of PCNA and calcitonin immunoreactivity).

Rats

A time course for the development of focal c-cell hyperplasia, adenomas, and carcinomas in male Sprague Dawley rats approximately 2 months old at the start of treatment ("young" rats) with vehicle or high dose liraglutide ($\geq$ 0.75 mg/kg) was constructed using data from 4-week (0.75 mg/kg high dose [HD]), 13-week (1 mg/kg HD), and 26-week (1 mg/kg HD) repeat dose toxicity studies, mechanistic studies examining thyroid histopathology after treatment for 4, 30, 43, 56, and 69 weeks, and a 104-week carcinogenicity study (Figure 3). For rats treated for $\geq$ 30

weeks, the high dose was 0.75 mg/kg/day liraglutide. The incidence of C-cell adenomas, but not focal hyperplasia, increased in young male rats treated with 0.75 mg/kg/day liraglutide for 7 months (9 months old). Liraglutide accelerated the onset of c-cell adenomas, but without increasing focal hyperplasia, and more importantly, without accelerating its onset. After 10 months of treatment (12 month old rats), liraglutide increased the incidence of both focal hyperplasia and adenomas. At 24 months (26 month old rats), liraglutide increased the incidence of carcinomas. Liraglutide did not cause diffuse c-cell hyperplasia.

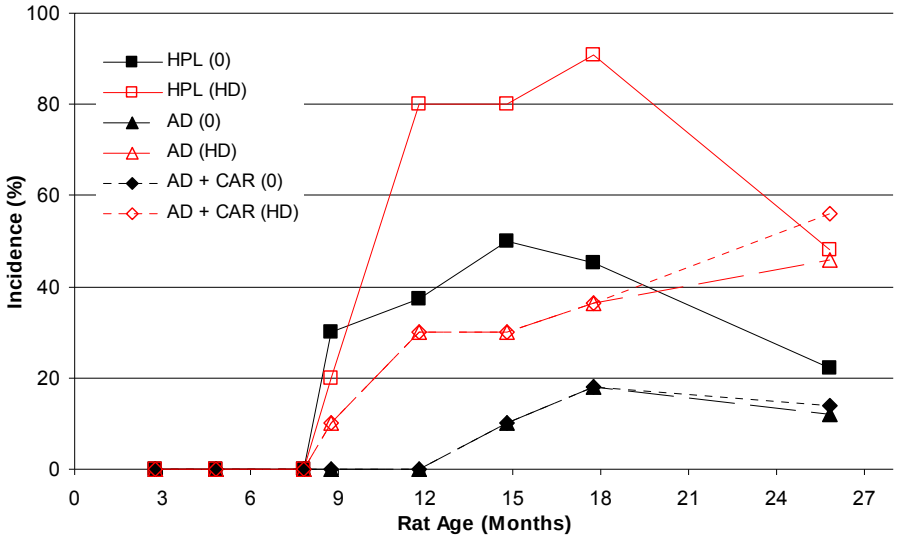


Figure 3. Incidence of Focal C-cell Hyperplasia (HPL), Adenomas (AD), and Combined Adenomas and Carcinomas (AD + CAR) in Young Male Rats* Treated with Vehicle (0) or High Dose Liraglutide (HD, ≥ 0.75 mg/kg/day).

*Rats were ~2 months old when treatment started.

A pivotal mechanistic study evaluated the effect of liraglutide on age-related increased thyroid C-cell proliferative lesions and plasma calcitonin using 2 month old male rats ("young" rats) treated for 30 to 69 weeks (7 to 16 months) or 8 month old male rats ("aged" rats) treated for 4 to 43 weeks (1 to 10 months).

Plasma calcitonin increased with age, but it was not affected by liraglutide dose (Figure 4) or the incidence of proliferative c-cell lesions. Young rats treated for 302 days (43 weeks, ~ 362 days old) and aged rats treated for 119 days (17 weeks, ~ 359 days old) were the same age at the end of treatment and they had similar plasma calcitonin levels.

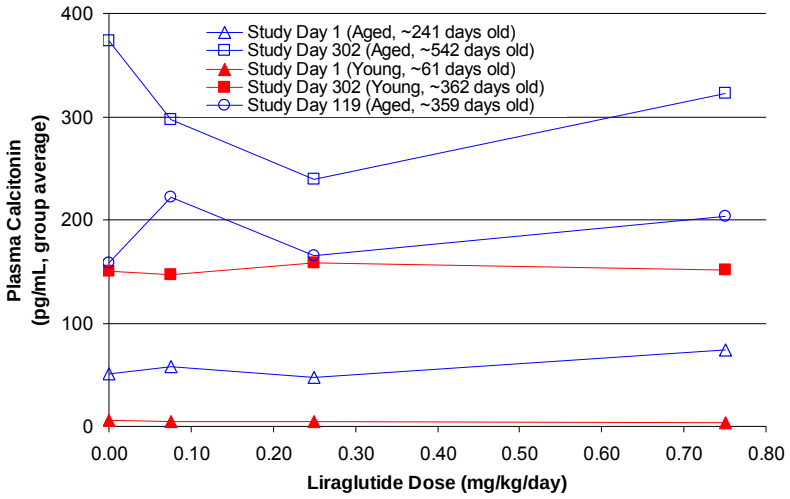


Figure 4. Effect of Liraglutide on Plasma Calcitonin in Young and Aged Male Rats

Liraglutide had no effect on the incidence of focal c-cell hyperplasia in young male rats treated for up to 6 months with up to 1 mg/kg liraglutide (see Figure 3). In the mechanistic study comparing thyroid c-cell parameters in young and aged male rats, adenomas didn't occur at all in the control group for aged rats (up to 18 months old) and in control young rats, adenomas didn't occur until they were at least 15 months old (13 months of treatment in young rats). In young rats, liraglutide (0.75 mg/kg/day) increased the incidence of C-cell adenomas after 7 months of treatment, but without increasing the incidence of focal C-cell hyperplasia (Figure 5). At 12 months in young rats, liraglutide increased the incidence of both focal c-cell hyperplasia and adenomas, and this increase persisted up to the end of the study when rats were 18 months old. In aged rats, 0.75 mg/kg/day liraglutide increased the incidence of focal c-cell hyperplasia after only 1 month of dosing, but only increased the incidence of adenomas after 7 months (Figure 5). These results show liraglutide-induced c-cell adenomas were treatment-duration dependent in both young and aged rats.

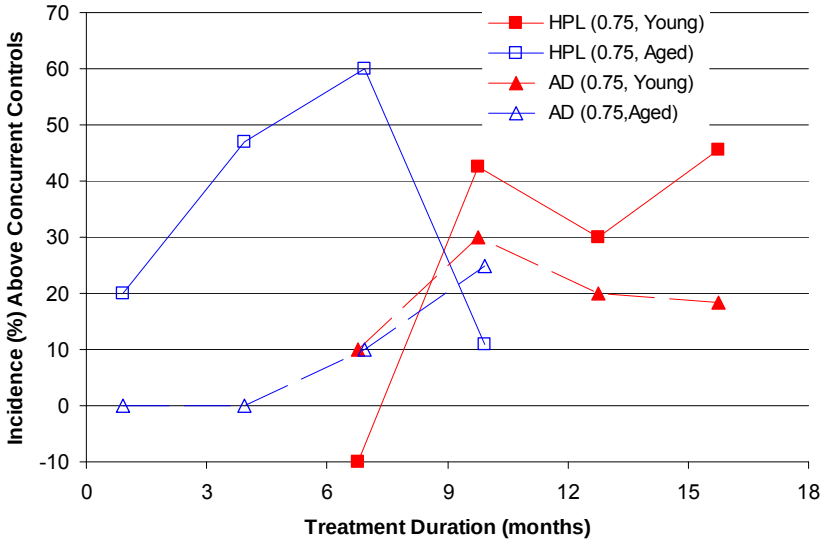


Figure 5. Effect of Treatment Duration on the Incidence of Focal C-cell Hyperplasia (HPL) or Adenomas (AD) in Young and Aged Male Rats* Treated with 0.75 mg/kg Liraglutide

*Young male rats were 2 months old when treatment was started and aged males were 8 months old.

Comparing the incidence of focal c-cell hyperplasia and adenomas in young and old rats by age shows liraglutide increased the incidence of age-dependent focal hyperplasia, but it didn't accelerate its onset (Figure 6). Focal c-cell hyperplasia was age-dependent, and liraglutide increased the incidence of age-dependent focal c-cell hyperplasia in rats ≥ 9 months old.

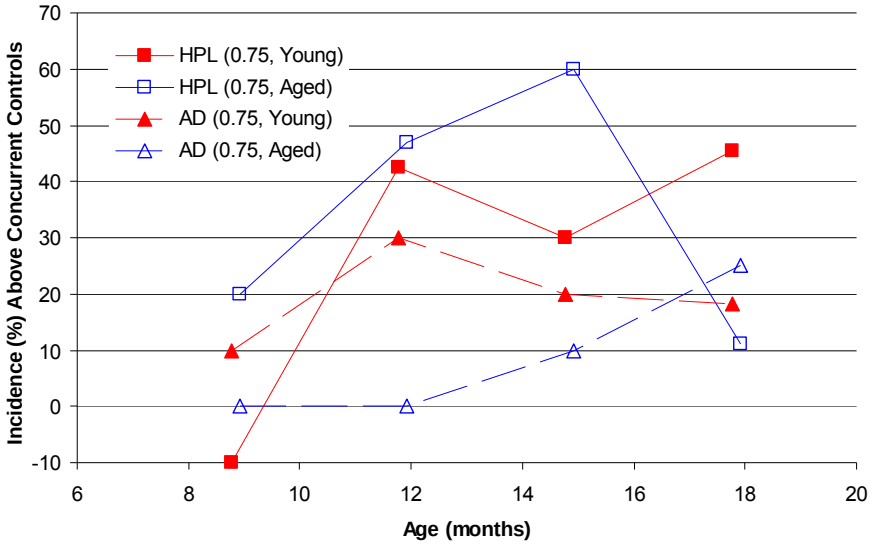


Figure 6. Effect of Age on the Incidence of Focal C-cell Hyperplasia (HPL) or Adenomas (AD) in Young or Aged Male Rats* Treated with 0.75 mg/kg/day Liraglutide.

*Young male rats were 2 months old when treatment was started and aged males were 8 months old.

Mice

Unlike rats, mice don't develop age-related proliferative c-cell lesions, so they're rare. The background incidence of focal c-cell hyperplasia, c-cell adenomas, and c-cell carcinomas in 2 year carcinogenicity studies in CD-1 mice is < 1%, and usually 0%. In mice, liraglutide induced progressive proliferative c-cell lesions in thyroid. Liraglutide causes focal c-cell hyperplasia after at least 4 weeks of treatment in females and after 9 weeks in males. Focal hyperplasia occurring after 9 weeks wasn't fully reversed after a 16 week recovery period (focal c-cell hyperplasia persisted in 1 high dose female mouse). A Pathology Working Group was convened by the applicant to review thyroid c-cell pathology findings from 4- and 13-week toxicity studies and a 9-week mechanistic study in mice. The Group concluded a few instances of c-cell hyperplasia originally diagnosed in the 4-week study were actually developmental disturbances due to incomplete fusion of the ultimobranchial duct with the thyroid resulting in only partial delivery of c-cells into the gland. However, since liraglutide-treated mice clearly develop focal c-cell hyperplasia after 9 weeks and c-cell focal hyperplasia and tumors in the carcinogenicity study, the distinction has little impact on safety assessment.

A time course for the development of focal c-cell hyperplasia, adenomas, and carcinomas in high dose liraglutide-treated CD-1 mice was constructed using data from 4-week (5 mg/kg HD) and 13-week (5 mg/kg HD) repeat dose toxicity studies, 2- and 9-week mechanistic studies (5 mg/kg HD), and a 104-week carcinogenicity study (3 mg/kg HD) (Figure 7). Proliferative c-cell lesions only occurred in liraglutide-treated mice. Liraglutide increased the incidence of focal c-cell hyperplasia after ≥ 4 - 9 weeks in females and after ≥ 9 weeks in males, but the incidence of diffuse hyperplasia was unaffected by treatment. Focal c-cell hyperplasia preceded c-cell tumors. C-cell tumors were not identified in mice treated for up to 13 weeks and in the 2 year

carcinogenicity study, c-cell tumors first occurred in high dose group decedents in week 64 in females (a malignant carcinoma) and in week 78 in males (a benign adenoma), but focal hyperplasia occurred 17 weeks earlier in high dose decedents from both sexes.

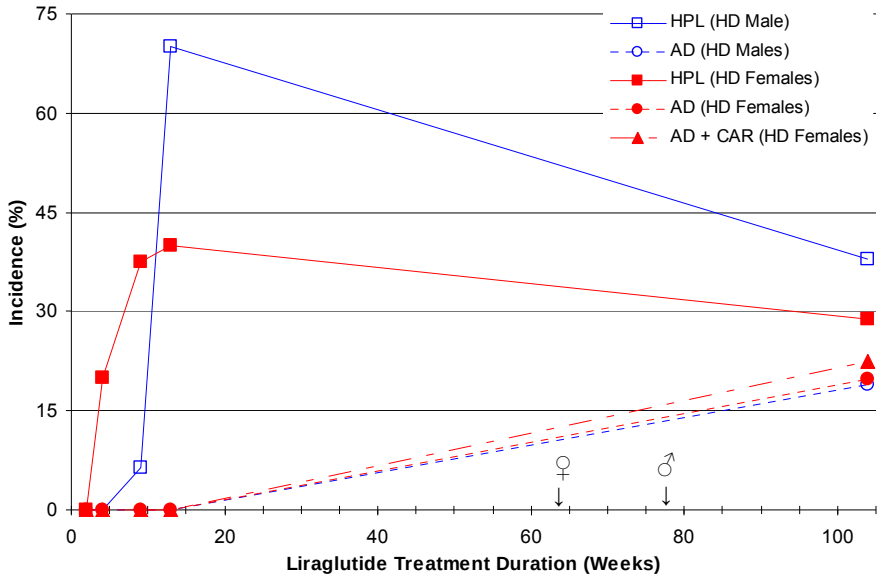
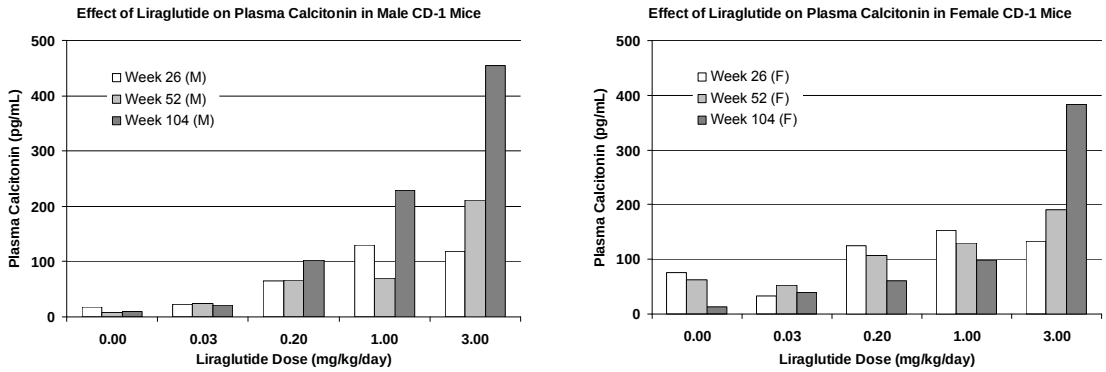


Figure 7. Focal C-cell Hyperplasia (HPL), Adenomas (AD), and Combined Adenomas and Carcinomas (AD + CAR) in Male (blue symbols) and Female (red symbols) Mice Treated with High Dose Liraglutide (≥ 3 mg/kg/day).

♀ and ♂ denote occurrence of first C-cell tumor in a decedent high dose female (carcinoma) and male (adenoma) in the 104 week carcinogen bioassay, respectively.

Single and repeat subcutaneous dosing with liraglutide increased plasma calcitonin. Plasma calcitonin levels were measured in weeks 26, 52, and 104 during the carcinogenicity study. Calcitonin levels were variable, but plasma calcitonin generally increased with liraglutide dose and treatment duration at ≥ 0.2 mg/kg/day in males and at 3 mg/kg/day in females.



A B

Figure 8. Plasma Calcitonin in Male (A) and Female (B) Mice Treated with Liraglutide for 26 (empty), 52 (gray), or 104 (dark gray) Weeks.

In rodent carcinogenicity studies, bolus subcutaneous injections of exenatide caused c-cell adenomas in female rats, but not in male rats or male and female mice. In a series of studies

in mice treated with exenatide submitted to NDA 22-341, the applicant showed differences in potency to induce c-cell tumors are likely due to pharmacokinetic differences between exenatide and liraglutide. Exenatide has a shorter elimination half life than liraglutide in mice and rats. Sustained subcutaneous infusion yielding pharmacologically relevant plasma levels of exenatide ($\geq$ 290 pM, based on pharmacodynamic/pharmacokinetic modeling of exenatide-induced increased plasma calcitonin) increased plasma calcitonin and caused focal c-cell hyperplasia in CD-1 mice. Administering 0.25 mg/kg/day exenatide by bolus injection once a day resulted in a low incidence of focal c-cell hyperplasia at 12 weeks and none at 16 weeks, but constant infusion caused a higher incidence of hyperplasia after 12 or 16 weeks (Table 5). Repeat dosing with up to 1 mg/kg exenatide for up to 3 times a day for up to 13 weeks did not cause focal c-cell hyperplasia in CD-1 mice, even though it increased plasma calcitonin and thyroid calcitonin mRNA. Pharmacokinetic / pharmacodynamic modeling of the effects of liraglutide and exenatide on plasma calcitonin in mice showed that sustained GLP-1 receptor activation, by daily subcutaneous injection of liraglutide or constant subcutaneous infusion of exenatide, results in persistent calcitonin secretion and focal C-cell hyperplasia. These results indicate persistent GLP-1 receptor activation induces increased plasma calcitonin and caused focal c-cell hyperplasia in mice, but to date, only liraglutide caused c-cell tumors in mice.

Table 5. Incidence of Focal C-cell Hyperplasia in Thyroid of CD-1 Mice Subcutaneously Administered Exenatide by Constant Infusion (Infusion, N = 18/group) or Once Daily Bolus Injection (SC, N = 12/group) for up to 16 Weeks.

		Sex	Males					Females				
		Route	Infusion			SC		Infusion			SC	
Exenatide Dose (mg/kg/day)			0	0.25	1.00	0	0.25	0	0.25	1.00	0	0.25
Finding	Week	Incidence										
Focal c-cell hyperplasia	12	#	1	6	9	0	0	0	5	11	0	2
		%	6	33	50	0	0	0	28	58	0	17
	16	#	1	7	5	0	0	0	6	10	1	0
		%	6	39	28	0	0	0	33	53	8	0

Evaluation of the Mode of Action

The mode of action for liraglutide-induced thyroid c-cell tumors requires further study for 3 reasons. First, the proposed mode of action does not account for the persistence of liraglutide-induced calcitonin secretion, when it occurs, or the absence of any counter-regulatory effect of increased calcitonin to inhibit calcitonin secretion. Second, other potential modes of action have not been ruled out including mechanisms of GLP-1 receptor agonist-induced transformation of thyroid c-cells through RET-dependent mechanisms. Activating mutations in RET are the most common molecular pathology in human MTCs. Third, liraglutide caused tumors in more than one tissue because in addition to c-cell tumors, it caused fibrosarcomas in the dorsal skin and subcutis in male mice, so GLP-1 receptor-independent mechanisms of liraglutide-induced thyroid c-cell tumors should be ruled out.

The weight of evidence from mechanistic studies of liraglutide-induced thyroid c-cell tumors do not support the proposed mode of action in rats because:

1. Although published studies demonstrate GLP-1 receptors in rat thyroid by autoradiographic tissue binding, GLP-1 receptor agonist increased calcium-dependent calcitonin release from perfused rat thyroid cells, and inactivating the GLP-1 receptor in mice reduces thyroid calcitonin transcript levels, the applicant's immunohistochemical and in situ hybridization studies did not conclusively demonstrate GLP-1 receptors localized to c-cells.

2. Calcitonin was not a biomarker for liraglutide-induced c-cell tumors in rats, and there was no consistent, sustained effect of liraglutide on plasma calcitonin.

3. Liraglutide did not consistently increase thyroid calcitonin mRNA.

4. Liraglutide increased the incidence of age-dependent focal c-cell hyperplasia, but without accelerating its onset and without causing diffuse c-cell hyperplasia.

5. The incidence of liraglutide-induced thyroid c-cell tumors in rats increased with treatment duration, but required at least 7 months of treatment in both young and aged male rats. Therefore, its tumorigenic effects were independent on the incidence of focal hyperplasia, which is higher in aged rats than in young rats.

The weight of evidence from mechanistic studies of liraglutide-induced thyroid c-cell tumors do not support the proposed mode of action in mice because:

1. Immunohistochemical localization and in situ hybridization studies of GLP-1 receptors in thyroid did not adequately demonstrate the receptor protein or transcript were localized to calcitonin immunoreactive c-cells. A published study showed that thyroid from 60% of mice (3/5) were positive for GLP-1 receptors detected by autoradiographic ligand binding, but GLP-1 binding activity wasn't localized to a specific cell-type.

2. Liraglutide caused focal c-cell hyperplasia, a preneoplastic lesion, without causing proliferation of normal c-cells (diffuse hyperplasia). These results indicate liraglutide transforms normal c-cells into preneoplastic c-cells in mice, a species lacking age-related increases in either plasma calcitonin or proliferative c-cell lesions.

Human Relevance of Liraglutide Induced Thyroid C-cell Tumors

Thyroid C-cells

Thyroid parafollicular cells, or c-cells, synthesize calcitonin and secrete it in response to elevated free calcium concentrations in blood. Calcitonin is a 32 amino acid peptide that protects against postprandial hypercalcemia by inhibiting osteoclast-mediated bone resorption when calcium is being absorbed from the gut. Feeding increases plasma calcitonin levels because gastrointestinal hormones, including gastrin, glucagon, cholecystokinin, and secretin stimulate its secretion (Wang 2002).

Unlike thyroid hormone synthesizing follicular cells which are derived from endoderm, C-cells arise from the ultimobranchial body composed of cells from the neural crest. Histologically, normal C-cells are difficult to discern from follicular epithelial cells by hematoxylin-eosin staining, but they are readily identified by immunochemical staining for calcitonin (Greaves 2007). There are some species differences in c-cell distribution within the thyroid gland. In humans, c-cells are concentrated at the junction of the upper and middle lobes, but in rats, c-cells are more widely distributed with higher concentrations occurring in the central region. The applicant determined that in thyroid from cynomolgus monkeys, c-cells are distributed in the middle third of the lobes in clusters of 2 to 10 cells. Therefore, c-cell density in the same thyroid region may vary in different species.

C-cell Proliferation and C-cell Tumors

C-cell proliferation occurs along a continuum ranging from diffuse hyperplasia, focal hyperplasia, adenomas, to carcinomas. Diffuse hyperplasia is considered a physiologic response while focal hyperplasia and adenomas are only differentiated by size; foci of c-cells > 5 average-

sized contiguous follicles are considered adenomas. Although focal c-cell hyperplasia occuring in mice was reversed in nearly all mice after a 15-week recovery period, it was not reversed in one mouse suggesting focal hyperplasia can develop into autonomous neoplastic growths. C-cell carcinoma occurs when c-cell nodules or cords develop stromal or vascular invasion.

Thyroid c-cell tumors in humans, or MTCs, are uncommon. Activating mutations in REarranged during Transfection (RET) proto-oncogene are the most common molecular pathology causing spontaneous and familial MTC in humans. RET is a plasma membrane receptor tyrosine kinase that regulates the growth of cells derived from the neural crest. Approximately 75% of MTC occurs sporadically and 25% is familial due to inherited autosomal dominant gain of function point mutations in RET. Somatic RET mutations occur in up to 50% of sporadic cases.

There are differences in the development of thyroid c-cell tumors in rats and mice (DeLillis 1979, van Zweiten 1983). In rats, plasma calcitonin and the incidence of diffuse c-cell hyperplasia, focal c-cell hyperplasia, and c-cell adenomas increase with age. Although age-related diffuse and focal C-cell hyperplasia and adenomas are common in common laboratory rat strains (incidence > 1%), c-cell carcinomas are rare (incidence < 1%). The incidence of proliferative C-cell lesions in rats is strain dependent and affected by diet. In both familial MTC in humans and strain-dependent age-related c-cell tumors in rats, a prolonged period of diffuse and nodular c-cell hyperplasia and elevated serum calcitonin precedes the development of tumors. However, the most common molecular pathology of MTC in humans, activating mutations in RET, have not been identified in rat strains susceptible to MTC, including WAG/Rij rats, a substrain of Sprague Dawley rats, and Long-Evans rats (De Miguel 2003). In mice, hypercalcitoninemia, c-cell hyperplasia, adenomas, and carcinomas are rare (incidence < 1%). However, genetically engineered mice expressing a human RET with an activating mutation that causes MTC in humans (CGRP-Ret^{C634R}) developed C-cell hyperplasia progressing to bilateral MTC and elevated calcitonin by the time they were 8 to 12 months old (Knostman 2007). Tumor penetrance of CGRP-Ret^{C634R} in mice depends on the background strain with 0% of FVB/N mice developing tumors compared to 98% of CBA/ca mice.

Drug-Induced C-cell Tumors in Rats and Mice

Liraglutide is unique in causing thyroid c-cell tumors in rats and mice. A search of drug information derived from approved labels (Drug Facts and Comparisons online, 2008) and review document databases in CDER did not identify any other approved or investigational drug causing thyroid c-cell tumors in mice. Seven approved drugs in 7 different pharmacologic classes cause c-cell tumors in rats (Table 6). There is no established mechanism for drug-induced rat thyroid c-cell tumors, and except for GLP-1 receptor agonists, no evidence of a pharmacologic class effect.

Table 6. Comparison of Thyroid C-cell Tumors in Rodent Carcinogenicity Studies of Liraglutide and Approved Drugs

Drug	Drug Class	Mice		Rats	
		Male	Female	Male	Female
liraglutide	GLP-1 receptor agonist	adenoma (NOAEL 2X)[1]	adenoma, combined adenoma & carcinoma (NOAEL 2X)[1]	adenoma, combined adenoma & carcinoma (NOAEL < 1X)[1], carcinoma (NOAEL 2X)[1]	adenoma, combined adenoma & carcinoma (NOAEL < 1X)[1]
Approved Drugs					
alendronate	bisphosphonate, osteoclast inhibitor	-	-	adenoma (NOAEL < 1X)[2]	-
arformoterol	$Beta_2$ receptor agonist	-	-	-	adenoma & carcinoma (NOAEL 55X)[1]
atenolol	$Beta_2$ receptor agonist	-	-	carcinoma (NOAEL 150X)[3]	-
colesevelam	bile acid sequestrant	-	-	-	adenoma (NOAEL 20X)[3]
naratriptan	$5\text{-}HT_{1D/1B}$ receptor agonist	-	-	adenoma[B] (NOAEL 29X)[1]	
palonosetron	$5\text{-}HT_3$ receptor antagonist	-	-	-	adenoma, combined adenoma & carcinoma (NOAEL 82X)[1]
exenatide	GLP-1 receptor agonist	-	-	-	adenoma[A] (NOAEL < 5X)[1]

[1]Human exposure multiple calculated using plasma AUC comparison.

[2]Human exposure multiple calculated using body surface area based dose comparison.

[3]Human exposure multiple calculated using weight based dose comparison.

[A]Incidences in female rats were 8% and 5% in the 2 control groups and 14%, 11%, and 23% in the low-, medium-, and high-dose groups, but increased tumor incidences in exenatide-treated groups were not statistically significant by trend analysis or control group pairwise comparison.

[B]According to the drug label "Two rat studies were conducted, 1 using a standard diet and the other a nitrite-supplemented diet (naratriptan can be nitrosated in vitro to form a mutagenic product that has been detected in the stomachs of rats fed a high nitrite diet)." Exposure multiples are based on results from the nitrite-diet supplemented study in which c-cell tumors occurred at lower exposures.

GLP-1 Receptor Agonist-Induced Thyroid C-cell Tumors

In life-time rodent carcinogenicity studies, liraglutide increased the incidence of benign c-cell adenomas in male and female rats and mice, c-cell carcinomas in male rats, and combined adenomas and carcinomas in male and female rats and female mice. Liraglutide had no effect on thyroid c-cells in chronic toxicity studies in rats (6 months) or monkeys (12 months) or in a 20 month repeat dose mechanistic study in cynomolgus monkeys, Liraglutide did cause focal c-cell hyperplasia, a preneoplastic lesion, in repeat-dose studies up to 13 weeks in CD-1 mice.

In rodent carcinogenicity studies, exenatide increased the incidence of benign c-cell adenomas in female rats (a no effect level was not identified), but not in mice. Although there were no thyroid findings in mice treated for up to 6 months with bolus subcutaneous injections of exenatide, continuous subcutaneous infusion of exenatide caused focal c-cell hyperplasia in mice

within 12 weeks. Preliminary results from a rat carcinogenicity study of another GLP-1 receptor peptide agonist showed it increased the incidence of c-cell adenomas in males and females and the incidence of combined carcinomas and adenomas in females. These data support the hypothesis that GLP-1 receptor peptide agonists cause thyroid c-cell tumors in rodents and that tumorigenic effects are related to the duraction of action, but the mode of action is uncertain.

Human Relevance of Rodent Thyroid C-cell Tumors

Liraglutide caused thyroid c-cell adenomas (benign) and carcinomas (malignant) in rats and mice and malignant fibrosarcomas in the dorsal skin and subcutis in male mice. Carcinogenicity studies in rats and mice, mechanistic studies of liraglutide-induced proliferative c-cell lesions, and clinical data are insufficient to conclude thyroid c-cell tumor findings in rodents are not relevant to human risk because:

1. Mechanistic studies did not adequately support the applicant's proposed novel mode of action for liraglutide-induced c-cell tumors in rats and mice.

2. After 26 to 28 weeks of treatment, liraglutide dose-dependently increased calcitonin in clinical study subjects, so if the proposed mode of action is correct, it may be operable in humans.

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Clinical Briefing Document
Major Adverse Cardiovascular Events, Thyroid Cancer and Hypercalcitoninemia
New Drug Application 22-341
Victoza® (liraglutide injection)

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3 Mar 2009

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I. Introduction

I.A. Product Description

Victoza® (liraglutide injection, hereafter 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.

I.B. Description of Clinical Trial Development Program

As of the date of submission of the NDA (14 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 cardiovascular and thyroid cancer safety review included review of pooled data from these trials, from subsequently submitted cardiovascular and thyroid safety information, from a safety

update submitted by the applicant on 23 Sep 2008, from the only approved GLP-1 analogue (Byetta®, exenatide injection), and from the medical literature.

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

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

Table I.B.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

Table I.B.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]
NN2211-1329	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
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

Table I.B.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]
NN2211-1571[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
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

Table I.B.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]
NN2211-1572 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
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

Table I.B.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]
NN2211-1334[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
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 (14 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 NN9233-1807 and pulmonary in 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.

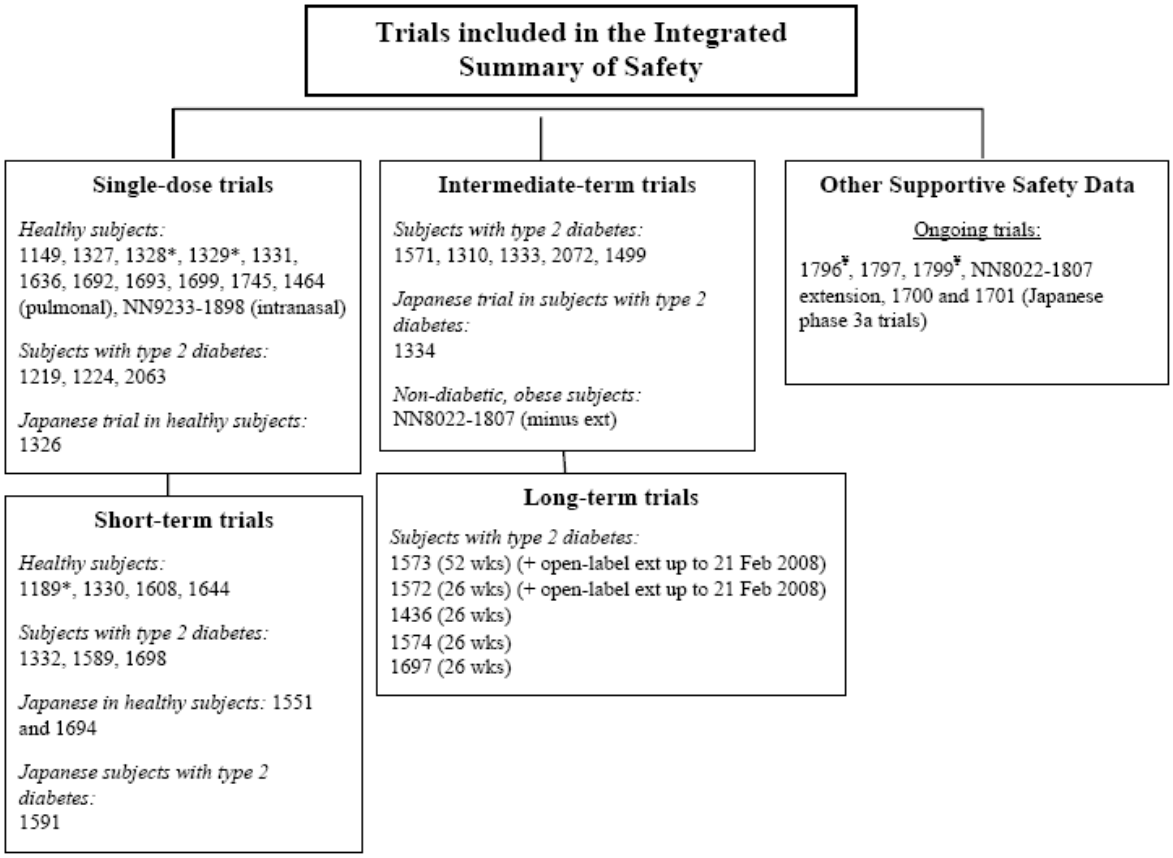
Table I.B.2: Summary of Design, Rescue and Extension for Phase 3 Studies

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	Exten-sion 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

The following figure displays the clinical trials grouped by duration:

Figure I.B: Liraglutide Clinical Trials Grouped by Duration



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

The applicant used the following definitions for the safety population and analysis sets in the NDA (source Module 2.7.4, pg 20):

Safety population: all subjects randomized into a clinical trial who were exposed to at least one dose of trial product(s)

Analysis sets:

- "All completed trials safety analysis set": all randomized and exposed subjects in the 38 completed clinical trials (including two open-label extensions to trials 1573 and 1572 with data up to the cut-off date of 21 Feb 2008)
- "Long-term trial safety analysis set": all randomized and exposed subjects in the five long-term trials (including two open-label extensions to trials 1573 and 1572 with data up to the cut-off date of 21 Feb 2008). Long-term trials included Studies 1436, 1572, 1573, 1574 and 1697.
- "Ongoing trials safety analysis set": all randomized and exposed subjects in four of the six ongoing trials (trials 1700, 1701, 1797 and NN8022-1807)

I.C. Baseline Characteristics and Exposure

I.C.1 Baseline Characteristics

Please see Dr. Derr's efficacy briefing document for summaries of demographics, general baseline characteristics, and disposition.

All intermediate and long-term trials had an exclusion criterion for patients with significant cardiovascular disease, and thus a high incidence of cardiovascular events would not be expected among the population studied in the development program. Examination of data from the Phase 3 trials did not reveal any marked imbalances in the incidence of baseline cardiovascular conditions or baseline concomitant cardiovascular medication use between liraglutide groups and comparator groups (Sources: Study 1436 report, Table 14.1.8, beg pg 230; Study 1572 report, Table 14.1.8, beg pg 263; Study 1573, Table 14.1-8, beg pg 186; Study 1574, Table 14.1-8, beg pg 167; Study 1697, Table 14.1.8, beg pg 209; Integrated Summary of Safety Table 1-21, beg pg 72).

The following table displays the baseline incidence of complications of diabetes in the long-term trials 1572, 1436 and 1697.

Table I.C.1: Number and Percentage of Patients with Baseline Complications of Diabetes in Long-term Trials 1436, 1572 and 1697

	Liraglutide Arms			Placebo Control	Active Control	Total
Trial 1436 (26 weeks; add-on to glimepiride 4 mg)	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**rosiglitazone 4 mg**	**Total**
Retinopathy	40 (17.2)	34 (14.9)	28 (12.0)	15 (13.2)	38 (16.4)	155 (14.9)
Neuropathy	53 (22.7)	39 (17.1)	45 (19.2)	19 (16.7)	52 (22.4)	208 (20.0)
Nephropathy	21 (9.0)	9 (3.9)	11 (4.7)	2 (1.8)	12 (5.2)	55 (5.3)
Macroangiopathy	19 (8.2)	23 (10.1)	23 (9.8)	6 (5.3)	27 (11.6)	98 (9.4)
Trial 1572 (26 weeks; add-on to metformin 2 g)	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**glimepiride 4 mg**	**Total**
Retinopathy	32 (13.2)	39 (16.2)	30 (12.4)	19 (14.8)	25 (10.2)	144 (13.2)
Neuropathy	48 (19.8)	38 (15.8)	44 (18.2)	22 (18.0)	38 (15.6)	190 (17.4)
Nephropathy	10 (4.1)	19 (7.9)	17 (7.0)	8 (6.6)	16 (6.6)	70 (6.4)
Macroangiopathy	37 (15.3)	26 (10.8)	23 (9.5)	10 (8.2)	31 (12.7)	127 (11.6)
Trial 1697 (26 weeks; add-on to glimepiride 4 mg + metformin 2 g)			**liraglutide 1.8 mg +**	**placebo**	**insulin glargine**	**Total**
Retinopathy			46 (19.8)	27 (23.5)	48 (20.5)	121 (20.8)
Neuropathy			51 (22.0)	20 (17.4)	51 (21.8)	122 (21.0)
Nephropathy			17 (7.3)	7 (6.1)	16 (6.8)	40 (6.9)
Macroangiopathy			31 (13.4)	16 (13.9)	37 (15.8)	84 (14.5)

Sources: Study 1436 report, Table 11-4, pg 96; Study 1572 report, Table 11-3, pg 104; Study 1697 report, Table 11-4, pg 95

Definitions for retinopathy, neuropathy, nephropathy and macroangiopathy were not provided in the application. The Division requested the definitions, and on 13 Feb 2009, the applicant responded that there had not been specific definitions. At screening, concomitant illness was recorded on the case report form, which specifically included sections for the above complications of diabetes. The applicant stated that "A specific diagnostic definition for the specific complications was not given and the recording was based on the investigator's assessment."

Across the development program, withdrawals due to adverse events were more common among LGT-treated patients than among comparator-treated patients. This excess withdrawal rate was due largely to gastrointestinal events, and 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. Withdrawals due to ineffectiveness of therapy were more common among placebo-treated patients than among liraglutide or active comparator group patients.

I.C.2. Exposure

At the time of NDA submission, across all trials, 4211 subjects had been exposed to liraglutide. Of these, 2086 had been exposed for at least 24 weeks, and 840 had been exposed for at least 50 weeks. At the time of submission of the 120-day safety update (23 Sep 2008), 4655 subjects had been exposed to liraglutide. Of these, 2412 had been exposed for at least 24 weeks, and the number of patients exposed for >50 weeks remained at 840.

The following table displays the number of patients exposed by treatment arm, study population and trial duration. The applicant has listed trials specifically required by Japanese regulatory authorities separately.

Table I.C.2.a: Liraglutide Exposure by Treatment Arm, Study Population and Trial Duration, All Completed Trials at Time of NDA Submission

Trial Duration	Study Population	LGT N	PBO N	Active Comp N
Single dose	**Healthy subjects**	288	23	24
	DM2	47	40	
	Healthy Japanese subjects	24	8	
Short-term (1-7 wks)	**Healthy subjects**	164	155	
	DM2	63	61	31
	Healthy Japanese subjects	36	12	
	Japanese DM2	11	4	
Intermediate-term (8-20 wks)[1]	**DM2**	526	151	62
	Japanese DM2	180	46	
	Obese, non-DM2	371	98	95
Long-term (≥ 26 wks)	**DM2**	2501	524	953
Total	**All**	**4211**	**1122**	**1165**

Source: Applicant's Table 1-2, pg 31, ISS, Module 5.3.5.3
1 In intermediate trials, Applicant included Study 1499, which was a 5-week trial
Abbreviations: Comp = comparator, DM2 = type 2 diabetes mellitus, LGT = liraglutide, PBO = placebo, wks = weeks

The following table displays liraglutide exposure by duration of exposure.

Table I.C.2.b: Liraglutide Exposure by Duration of Exposure, All Completed Trials at Time of NDA Submission

Trial Duration	Study Population	1 Day	>1 Day	≥5 Wks	≥12 Wks	≥24 Wks	≥50 Wks	≥76 Wks
Single dose	**Healthy subjects**	141	147					
	DM2	47						
	Healthy Japanese subjects	24						
Short-term (1-7 wks)	**Healthy subjects**	2	162	14				
	DM2	1	62	1				
	Healthy Japanese subjects		36	18				
	Japanese DM2		11					
Intermediate-term (8-20 wks)[1]	**DM2**		526	475	333			
	Japanese DM2		180	177	174			
	Obese, non-DM2	2	369	349	329	1		
Long-term (≥ 26 wks)	**DM2**	7	2494	2339	2222	2085	840	497
Total Subjects	**All**	**224**	**3987**	**3373**	**3058**	**2086**	**840**	**497**
Total Subject-Years	**All**	**1**	**2241**	**2214**	**2166**	**1865**	**1226**	**784**

Source: Applicant's Table 1-3, pg 34, ISS, Module 5.3.5.3
1 In intermediate trials, Applicant included Study 1499, which was a 5-week trial
Abbreviations: DM2 = type 2 diabetes mellitus, LGT = liraglutide, PBO = placebo, Wks = weeks

The following table displays liraglutide exposure by dose.

Table I.C.2.c: Liraglutide Exposure by Dose, All Completed Trials at Time of NDA Submission

Trial Duration	Study Population	SQ Daily Dose in Mg n (%)[1]							IV n (%)[1]	INH n (%)[1]
		<0.6	0.6	>0.6 - <1.2	1.2	>1.2 - <1.8	1.8	>1.8		
Single dose	**Healthy subjects**	48 (9.7)	30 (3.7)	192 (39.5)		12 (9.7)			6 (100)	39 (100)
	DM2	17 (3.4)	1 (0.1)	29 (6.0)						
	Healthy Japanese subjects	12 (2.4)	3 (0.4)	9 (1.9)						
Short-term (1-7 wks)	**Healthy subjects**	14 (2.8)	144 (18.0)	6 (1.2)	142 (12.3)		140 (9.9)			

Table I.C.2.c: Liraglutide Exposure by Dose, All Completed Trials at Time of NDA Submission

Trial Duration	Study Population	SQ Daily Dose in Mg n (%)[1]							IV n (%)[1]	INH n (%)[1]
		<0.6	0.6	>0.6 - <1.2	1.2	>1.2 - <1.8	1.8	>1.8		
	DM2	12 (2.4)	18 (2.2)	3 (0.6)	18 (1.6)		48 (3.4)			
	Healthy Japanese subjects	36 (7.3)	1 (0.1)	26 (5.3)		9 (7.3)		1 (0.3)		
	Japanese DM2	11 (2.2)		4 (0.8)						
Intermediate-term (8-20 wks)[2]	**DM2**	253 (51.2)	85 (10.6)	173 (35.6)		103 (83.1)		101 (35.1)		
	Japanese DM2	91 (18.4)	45 (5.6)	44 (9.1)						
	Obese, non-DM2				95 (8.3)		90 (6.4)	186 (64.6)		
Long-term (≥ 26 wks)	**DM2**		475 (59.2)		896 (77.8)		1130 (80.3)			
Total Subjects	**All**	**494 (100)**	**802 (100)**	**486 (100)**	**1151 (100)**	**124 (100)**	**1408 (100)**	**288 (100)**	**6 (100)**	**39 (100)**

Source: Applicant's Table 1-4, pg 35, ISS
1: % of all patients exposed to this dose; each column should add up to 100%
2 In intermediate trials, Applicant included Study 1499, which was a 5-week trial
Abbreviations: DM2 = type 2 diabetes mellitus, INH = inhaled, IV = intravenous, SQ = subcutaneous

Across the development program, the greatest number of patients exposed to liraglutide was at the 1.8 mg dose, which is the highest dose proposed by the applicant.

II. Major Adverse Cardiovascular Events (MACE)

II.A. 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 most recent 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 see the Guidance,

which is included in its entirety in the FDA Briefing Package. In that 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. To the extent possible, this briefing document 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.
- A specific effort was not made to include patients at high risk of cardiovascular events.
- 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.
- Relatively 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.

II.B. Description of Types of Analyses and Summaries

Initially, the Agency requested that Novo Nordisk, and the applicant for another recent New Drug Application, 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 II.D below. However, upon comparison, it was noted that the component terms chosen by the applicants were quite different for the two 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 to see a similar type of information for each of the two drugs. Therefore, the Division made a "uniform" request of each of the applicants. This "uniform" information request is included in the FDA Briefing Packet for the Committee's reference. A precisely identical format for data presentation is not possible for the two products, because the development programs differed in several ways. However, the endpoints are uniform, and to the extent possible, similar analyses are presented for each product. Results of the "uniform" analyses are presented in Section II.C below, and are likely the most useful for evaluation of the cardiovascular risk of liraglutide. In the interest of completeness, Section II.E 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 II.G.

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 II.B: 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 Briefing Document	**II.C**	**II.C**	**II.C**	**II.D**
Myocardial Infarction Terms				
Acute coronary syndrome	x		x	
Acute myocardial infarction	x	x	x	x
Blood creatine phosphokinase abnormal	x			

Table II.B: 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]**
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	
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	

Table II.B: 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]**
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
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	

Table II.B: 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]**
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			
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			

Table II.B: 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]**
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	
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 08, pg 6. Terms in this endpoint were selected from events which actually occurred, rather than from a MedDRA SMQ

II.C. "Uniform MACE Analyses"

Please see the Information Request which was sent to each of the applicants for the two products being presented. It 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 MedDRA Standard Queries for myocardial infarction and central nervous system hemorrhages and cerebrovascular accidents; and cardiovascular deaths. 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 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 could see data that were as similar as possible for each product. Please see Table II.B 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 II.B.

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. Because some of these data were collected after the cut-off for the original NDA submission, this includes additional exposure when compared to the exposure data in Section I.C.3 above. 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 vs. comparator. In these tables, Population A includes the randomized, controlled periods for all completed Phase 2 and Phase 3 trials of LGT, up to collection of the primary 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 NN8022-1807, 1572, 1573, 1700, 1701 and NN8022-1807. Exposure for these populations is as follows:

Table II.C.1: Exposure in Trials Included in 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 09
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 extension periods (after collection of the primary endpoint) of trials NN8022-1807, 1572, 1573, 1700, 1701 and NN8022-1807.
Abbreviations: MACE = major adverse cardiovascular events, Pop = 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 "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 14 May 08, 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 briefing 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, we did not identify one specific method of estimation that was preferable to others. For this reason, we 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 to us 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 we 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:

(1) 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.

(2) We 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.

(3) We 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, we constructed forest plots to depict the study-by-study estimates as well as the overall estimate.

We note that all three methods are stratified, reflecting our 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. We believe 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.

We note further that other estimation methods are available, and that this is not intended as a comprehensive list of all available methods. In addition, we note 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, and we are in the process of evaluating them. However, the focus in this briefing document is on the incidence ratio and the three methods we 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 we 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.

<u>Liraglutide vs. Total Comparator (Placebo and Active Controls)</u>

The stratified analyses that we 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 vs total comparator were < 1.0 and 11 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 II.C.8, II.C.9, II.C.10 and II.C.11 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. For this reason we concluded that the estimates for liraglutide vs. 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 II.C.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 vs. Placebo Control

The stratified analyses that we 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 vs 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 Population A exceeded 1.0; the Division considers Population A to be the primary 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 II.C.8, II.C.9, II.C.10 and II.C.11). 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. We believe that the sensitivity and the wide confidence intervals are due in part to the low event rates in the placebo arms.

The number of actual events for the liraglutide and placebo control groups is summarized in Table II.C.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. Because we and Novo conducted stratified analyses on the 12 studies that had placebo groups, we expect the distribution of baseline cardiovascular risk factors to be relatively similar among the randomized arms within each study. For this reason, we do 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.

Liraglutide vs. Active Control

The stratified analyses that we 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 vs active control were < 1.0. All of the upper 95% CI bounds were < 1.8, with one being < 1.3. (Table II.C.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 II.C.8, II.C.9, II.C.10 and II.C.11). For this reason we conclude that the estimates for the liraglutide vs. active control were somewhat sensitive to the choice of estimation methodology.

The number of actual events for the liraglutide and placebo control groups is summarized in Table II.C.7. The number of events was small in most analyses.

As mentioned earlier, Population A (in the Tables II.C.2 through II.C.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 II.C.2: Incidence Ratio, Liraglutide vs. 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 = population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events; CMH = Cochran Mantel-Haenszel

Table II.C.3: Number of Major Adverse Cardiovascular Events for Liraglutide vs. Pooled Comparator (Placebo + Active Comparator)

Agent	MACE Endpoint			Type of Events		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

Table II.C.3: Number of Major Adverse Cardiovascular Events for Liraglutide vs. Pooled Comparator (Placebo + Active Comparator)

Agent	MACE Endpoint			Type of Events		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		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 09. Also, Applicant's Tables 29, 33, 37 and 41; pgs 111, 125, 139, and 153, subm stamp date 13 Feb 09 (updated from 21 Jan 09 submission with addition of one event to active control for Custom FDA endpoint)
Abbreviations: CI = confidence interval, Pop = population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events

Table II.C.4: Incidence Ratio, Liraglutide vs. 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 09
Abbreviations: CI = confidence interval, Pop = population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events; CMH = Cochran Mantel-Haenszel

Table II.C.5: Number of Major Adverse Cardiovascular Events for Liraglutide vs. Placebo

Agent	MACE Endpoint			Type of Events		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

Table II.C.5: Number of Major Adverse Cardiovascular Events for Liraglutide vs. Placebo

Agent	MACE Endpoint			Type of Events		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		
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 09
Abbreviations: CI = confidence interval, Pop = population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events

Table II.C.6: Incidence Ratio, Liraglutide vs. 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 09. Also, Applicant's Tables 29, 33, 37 and 41; pgs 111, 125, 139, and 153, subm stamp date 13 Feb 09 (updated from 21 Jan 09 submission with addition of one event to active control for Custom FDA endpoint)
Abbreviations: CI = confidence interval, Pop = population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events; CMH = Cochran Mantel-Haenszel

Table II.C.7: Number of Events for Liraglutide vs. Active Comparator

Agent	MACE Endpoint			Type of Events		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 09. Also, Applicant's Tables 29, 33, 37 and 41; pgs 111, 125, 139, and 153, subm stamp date 13 Feb 09 (updated from 21 Jan 09 submission with addition of one event to active control for Custom FDA endpoint)
Abbreviations: CI = confidence interval, Pop = population, SMQ = Medical Dictionary for Regulatory Activities (MedDRA) Standard MedDRA Query, TEAE = treatment-emergent adverse events

Table II.C.8: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-Analysis Method with Continuity Correction, All Treatment-emergent MACE, Population A, FDA Custom Endpoint

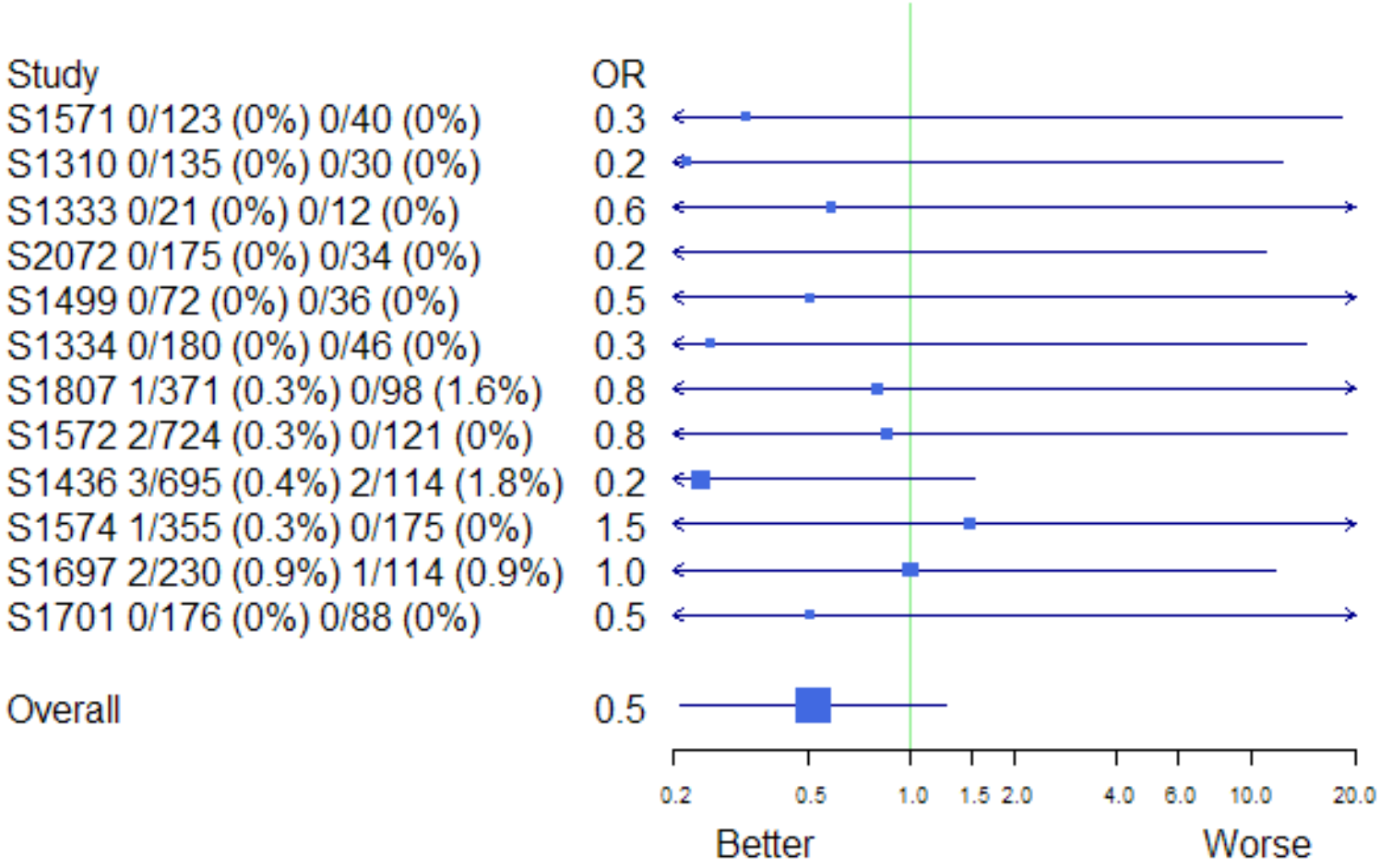
Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 1000 pt-yrs
Liraglutide	4257	1880	13	0.31%	6.92
Placebo	907	328	3	0.33%	9.14
Active Comparator	1474	718	10	0.68%	13.94
Total Comparators	2381	1046	13	0.55%	12.43

	# of studies included in the analysis (with at least 1 event in the comparator group)	Incidence Ratio (95% CI)	% of cases excluded from analysis (studies with 0 events in the comparator group)	Incidence Rate Ratio (95% CI)	% of pt-yrs excluded from analysis (studies with 0 events)
		Stratified, asymptotic (MH)[3]		***Stratified, asymptotic (MH)***[3]	
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 II.C.1, II.C.2 and II.C.3)

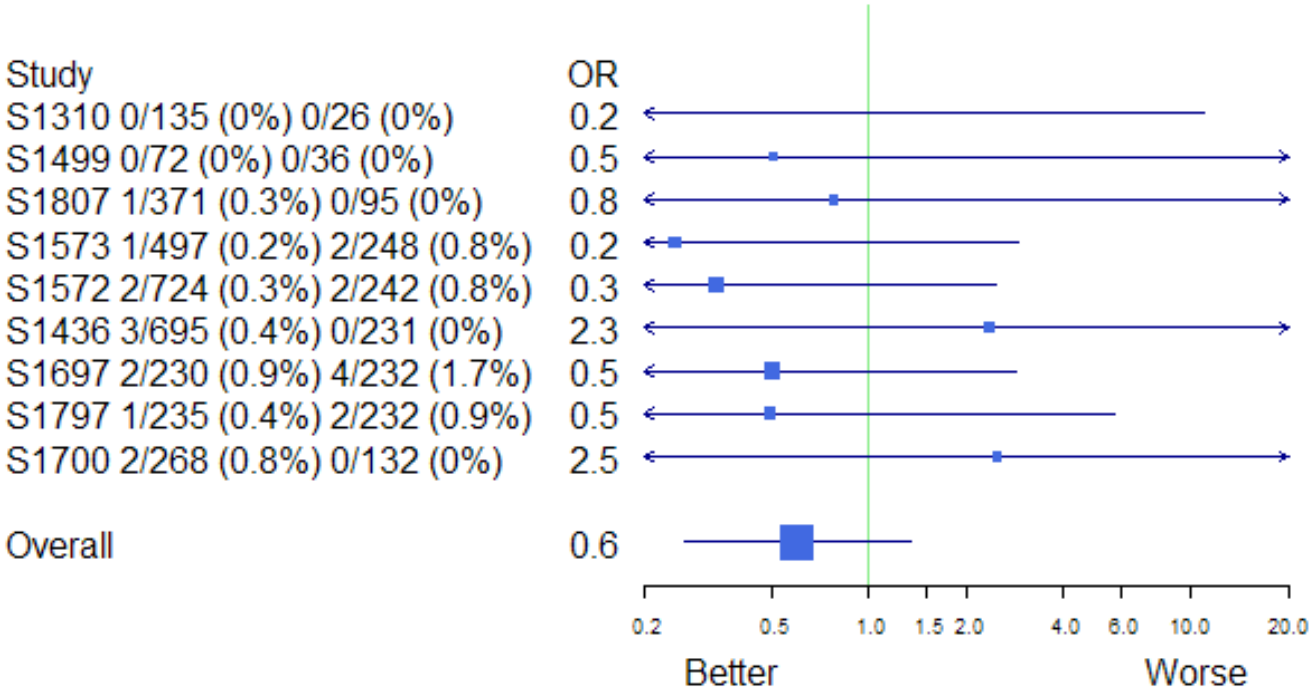
The following forest plots depict the odds ratio and 95% confidence intervals for each study and for the combined estimate from the stratified, fixed effects Mantel-Haenszel meta-analysis, with a continuity correction of +0.5 applied to studies with zero events in either arm or both arms. Studies with 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 II.C.1: Forest Plot for FDA Custom Endpoint, Liraglutide vs. Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population A. Values to the left of 1.0 favor liraglutide.



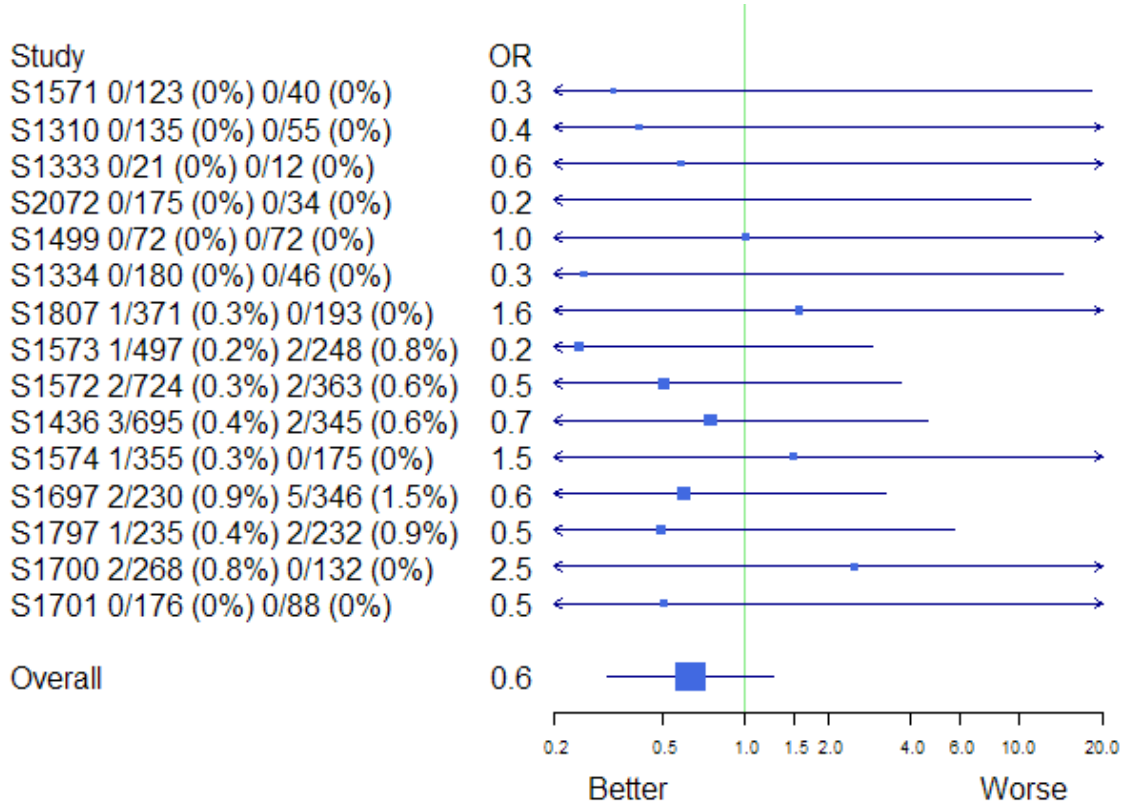
Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.2: Forest Plot for FDA Custom Endpoint, Liraglutide vs. Active Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population A. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.3: Forest Plot for FDA Custom Endpoint, Liraglutide vs. Total Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population A. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Table II.C.9: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All Treatment-emergent MACE, Broad SMQ Endpoint

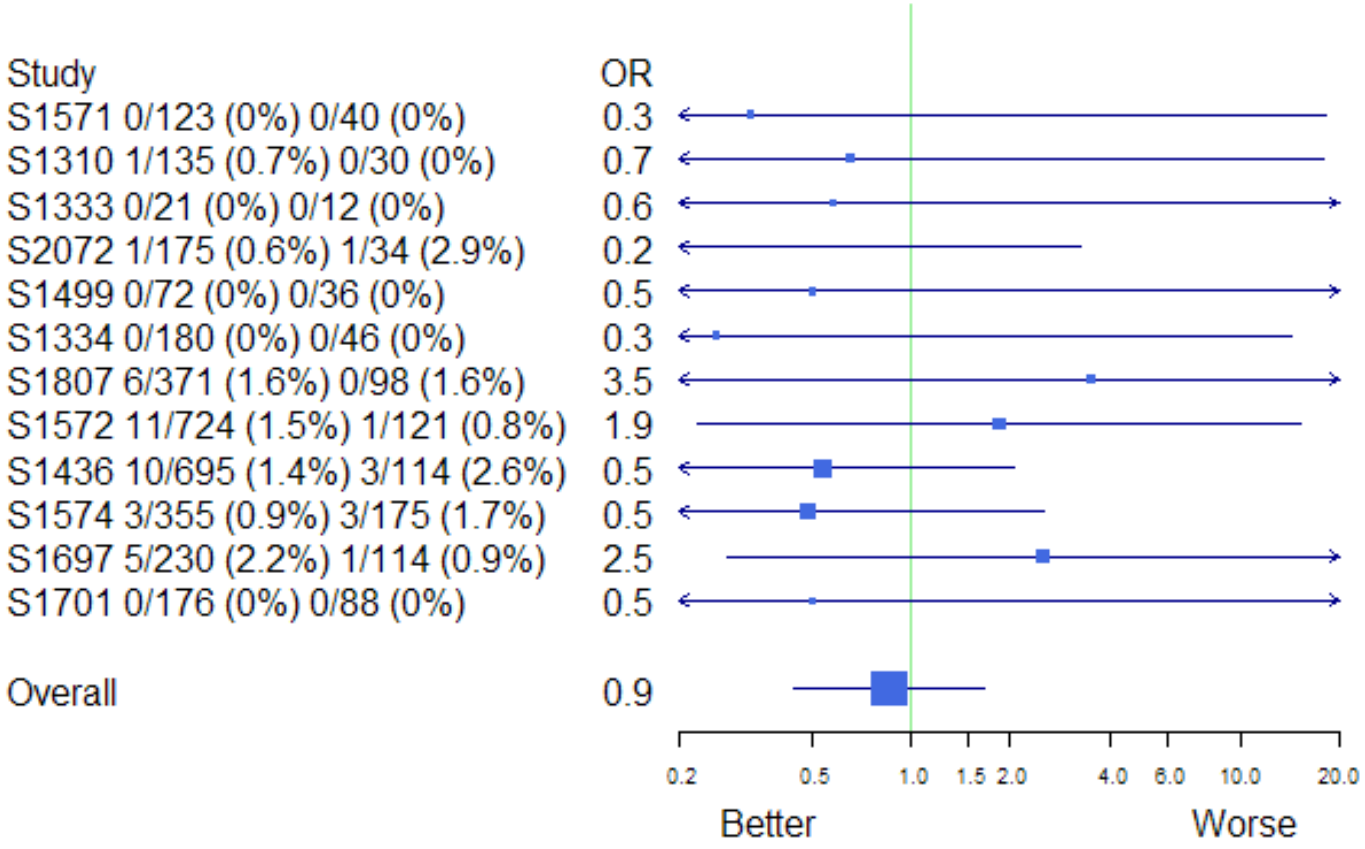
Group	N	Exposure (Pt-Yrs)	# of events	Incidence (%) Events/N	Incidence Rate Events/ 1000 pt-yrs
Liraglutide	4257	1880	51	1.20%	27.13
Placebo	907	328	9	0.99%	27.43
Active Comparator	1474	718	26	1.76%	36.23
Total Comparators	2381	1046	35	1.47%	33.47

	# 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	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 II.C.4, II.C.5, and II.C.6)

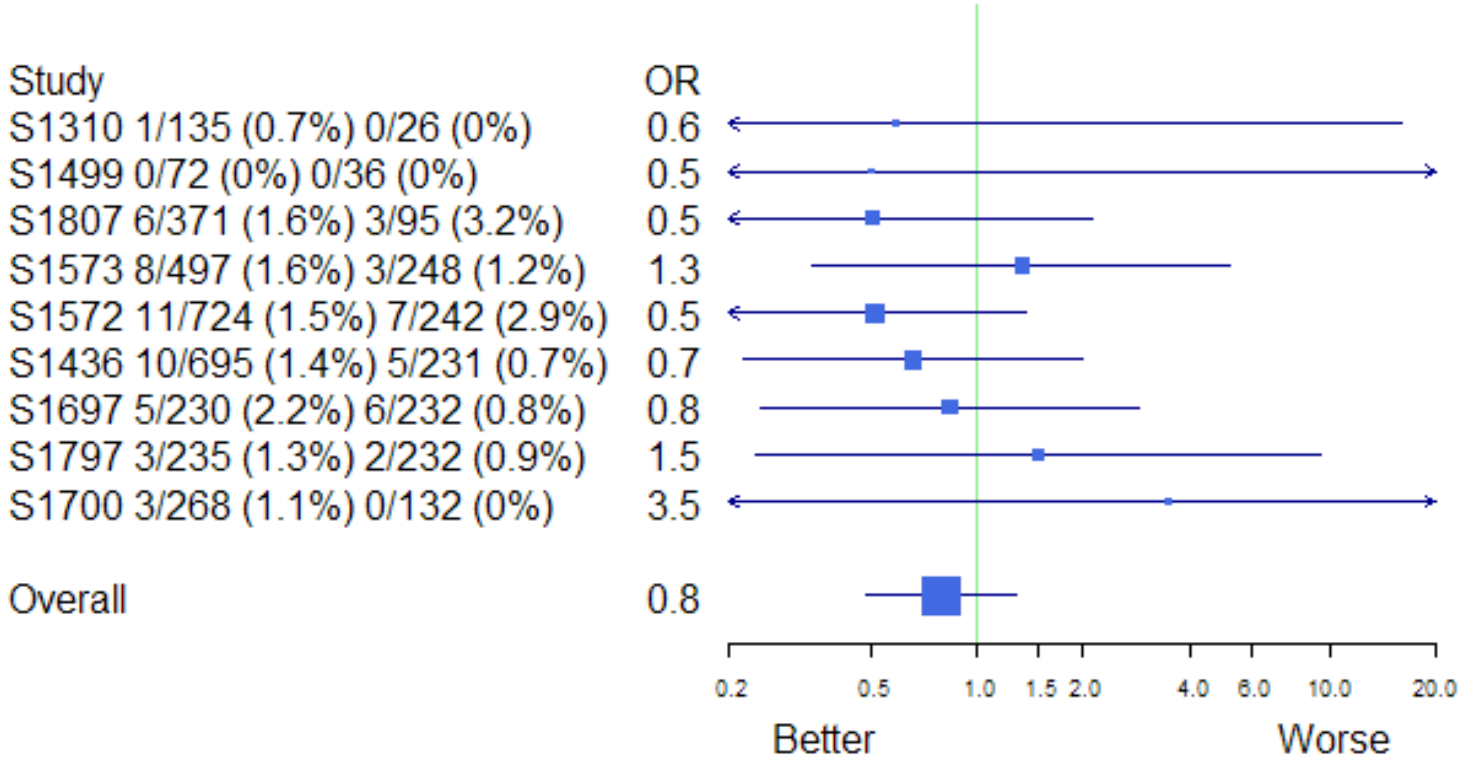
The following forest plots for the Broad SMQ endpoint display point estimates and 95% confidence intervals by study, and for the overall estimate, for Dr. Derr's analyses utilizing a stratified Mantel-Haenszel method with continuity correction applied.

Figure II.C.4: Forest Plot for Broad SMQ Endpoint, Liraglutide vs. Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction. Values to the left of 1.0 favor liraglutide.



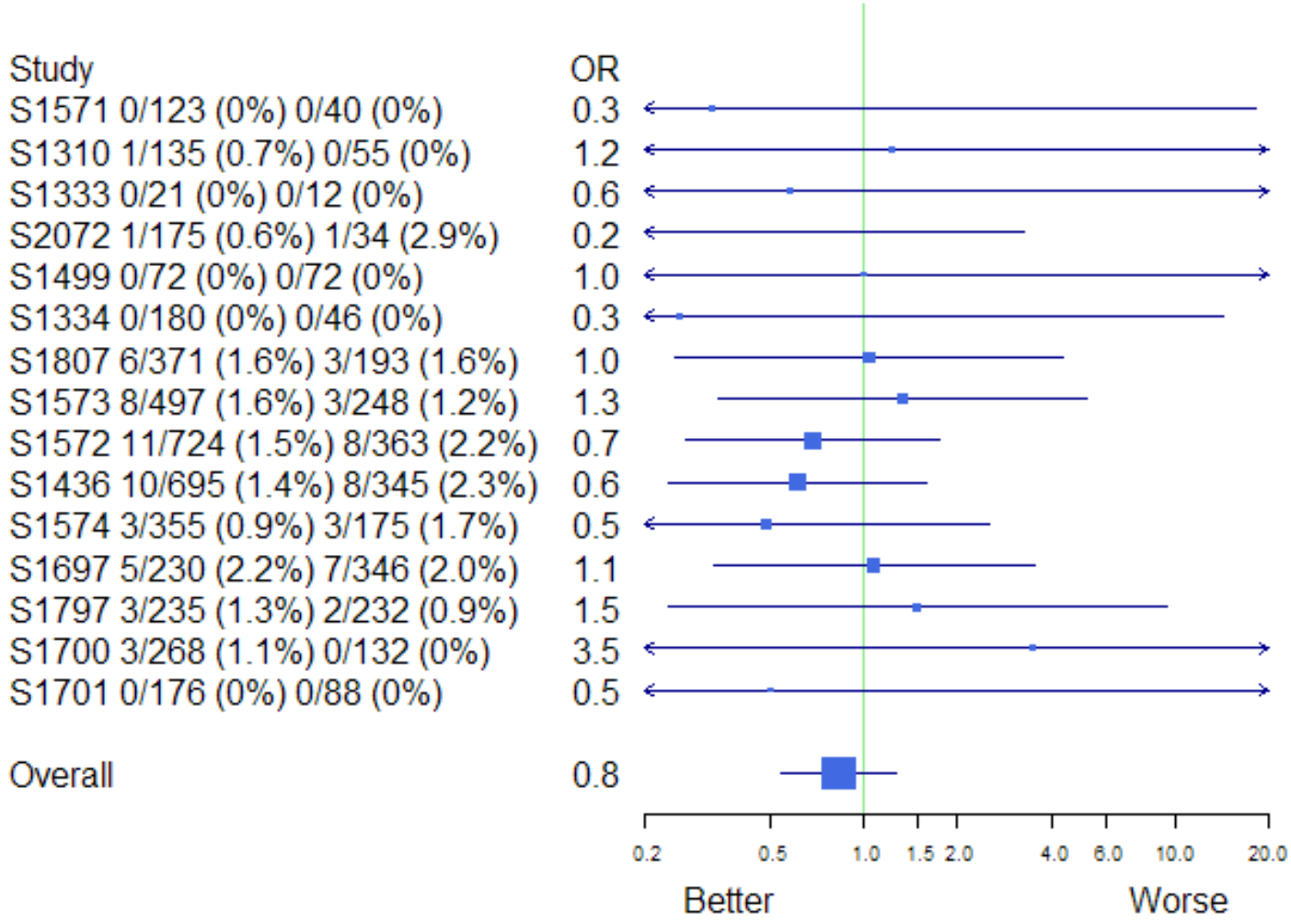
Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.5: Forest Plot for Broad SMQ Endpoint, Liraglutide vs. Active Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.6: Forest Plot for Broad SMQ Endpoint, Liraglutide vs. Total Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Table II.C.10: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All Treatment-emergent MACE, 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

	# 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	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

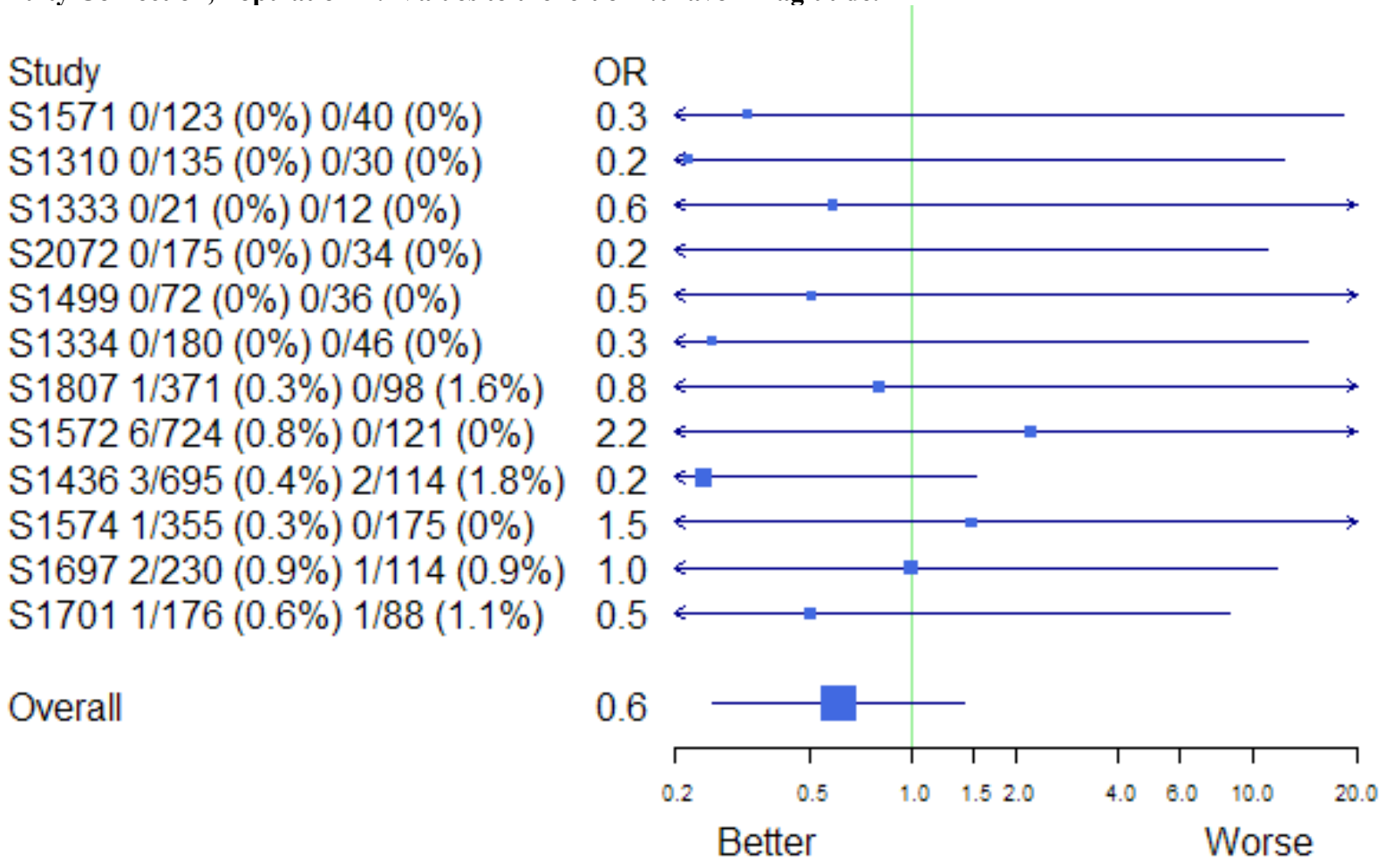
[4] Test conducted by Dr. Derr; the tests for homogeneity across studies could not be calculated on StatXact™ 7.0

[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.

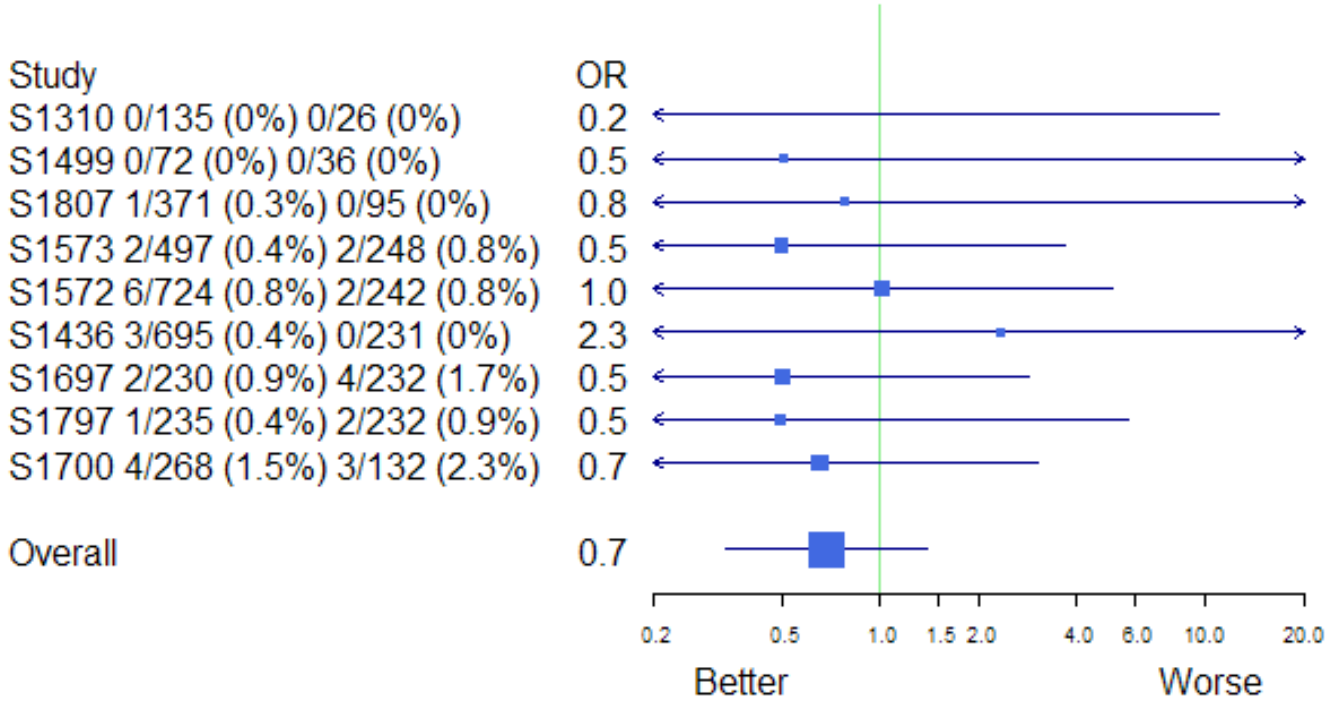
[7] Test conducted by Dr. Derr, forest plots provided, with continuity correction of 0.5 for arms with 0 MACE events (Figures II.C.7, II.C.8, and II.C.9)

Figure II.C.7: Forest Plot for FDA Custom Endpoint, Liraglutide vs. Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population B. Values to the left of 1.0 favor liraglutide.



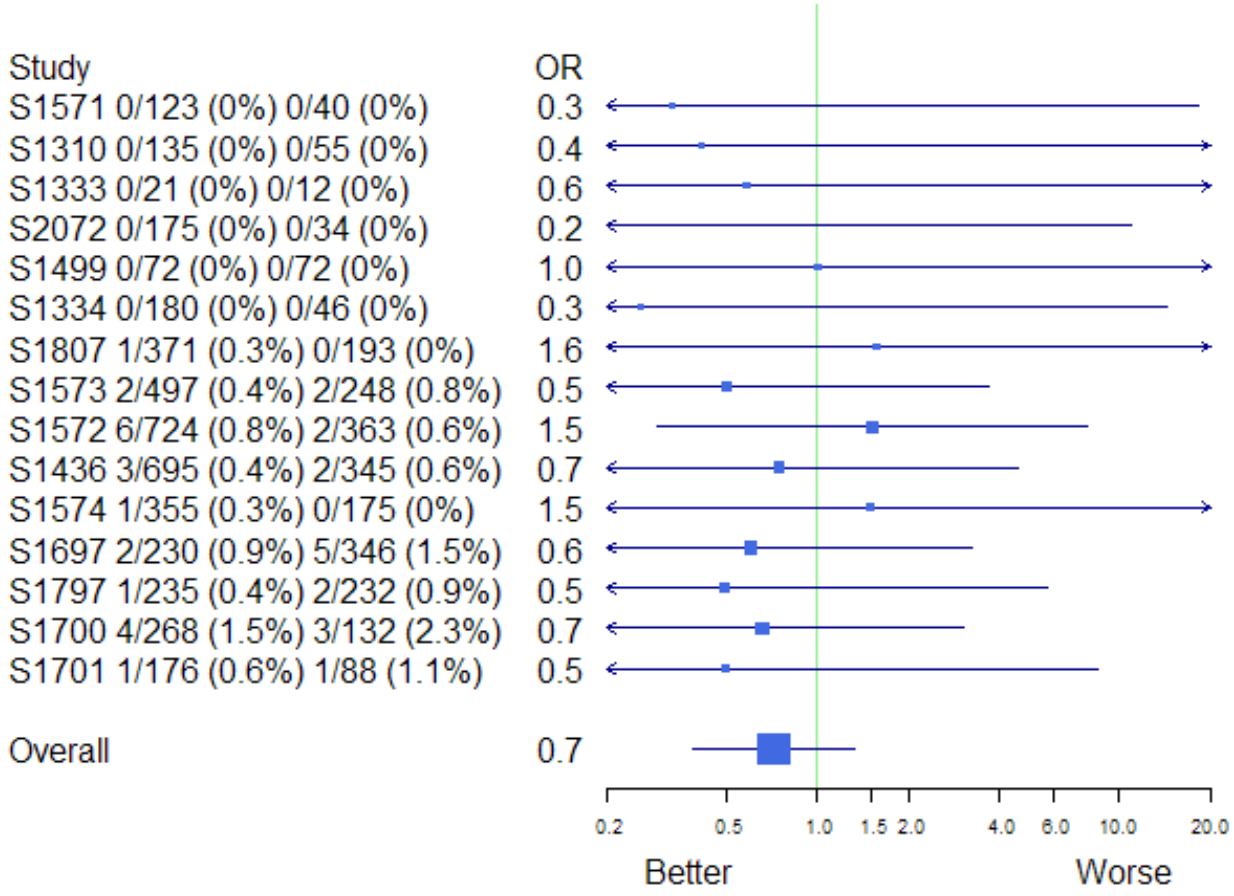
Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.8: Forest Plot for FDA Custom Endpoint, Liraglutide vs. Active Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.9: Forest Plot for FDA Custom Endpoint, Liraglutide vs. Total Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

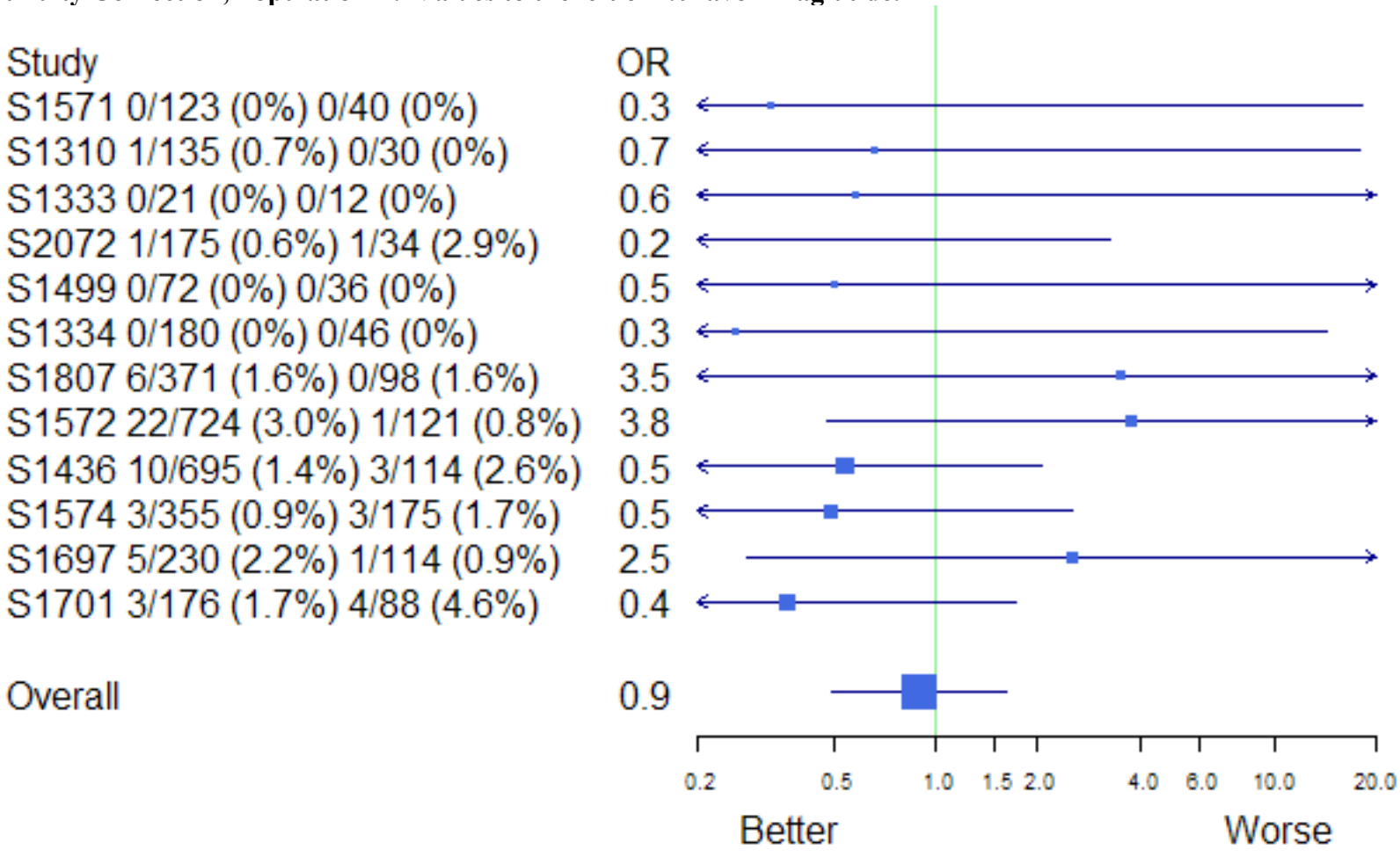
Table II.C.11: FDA Analyses by Exact Method, and by Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All Treatment-emergent MACE, Population B, Broad SMQ Endpoint

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

	# 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	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%		

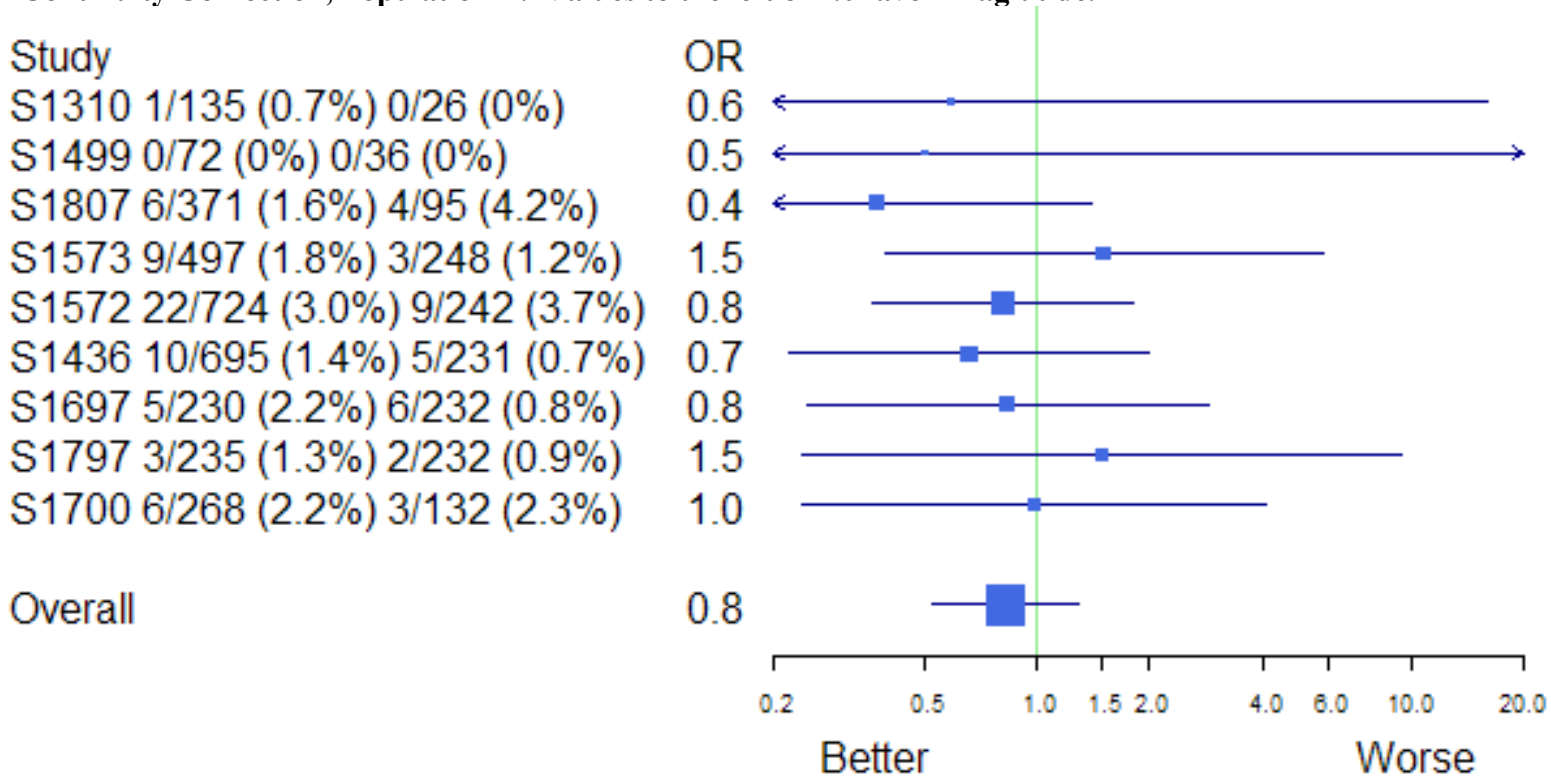
[1] Novo, submitted in response to FDA request for information 1/11/2009, Appendix B, Table 22 and Table 24
[2] Novo provided differences scaled as incidence events/N and incidence rates/pt yr (Appendix B, Table 14). The results are not reported in this table.
[3] Test conducted by Novo, MH = Mantel-Haenszel
[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 II.C. 10, II.C.11 and II.C.12)

Figure II.C.10: Forest Plot for Broad SMQ Endpoint, Liraglutide vs. Placebo, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population B. Values to the left of 1.0 favor liraglutide.



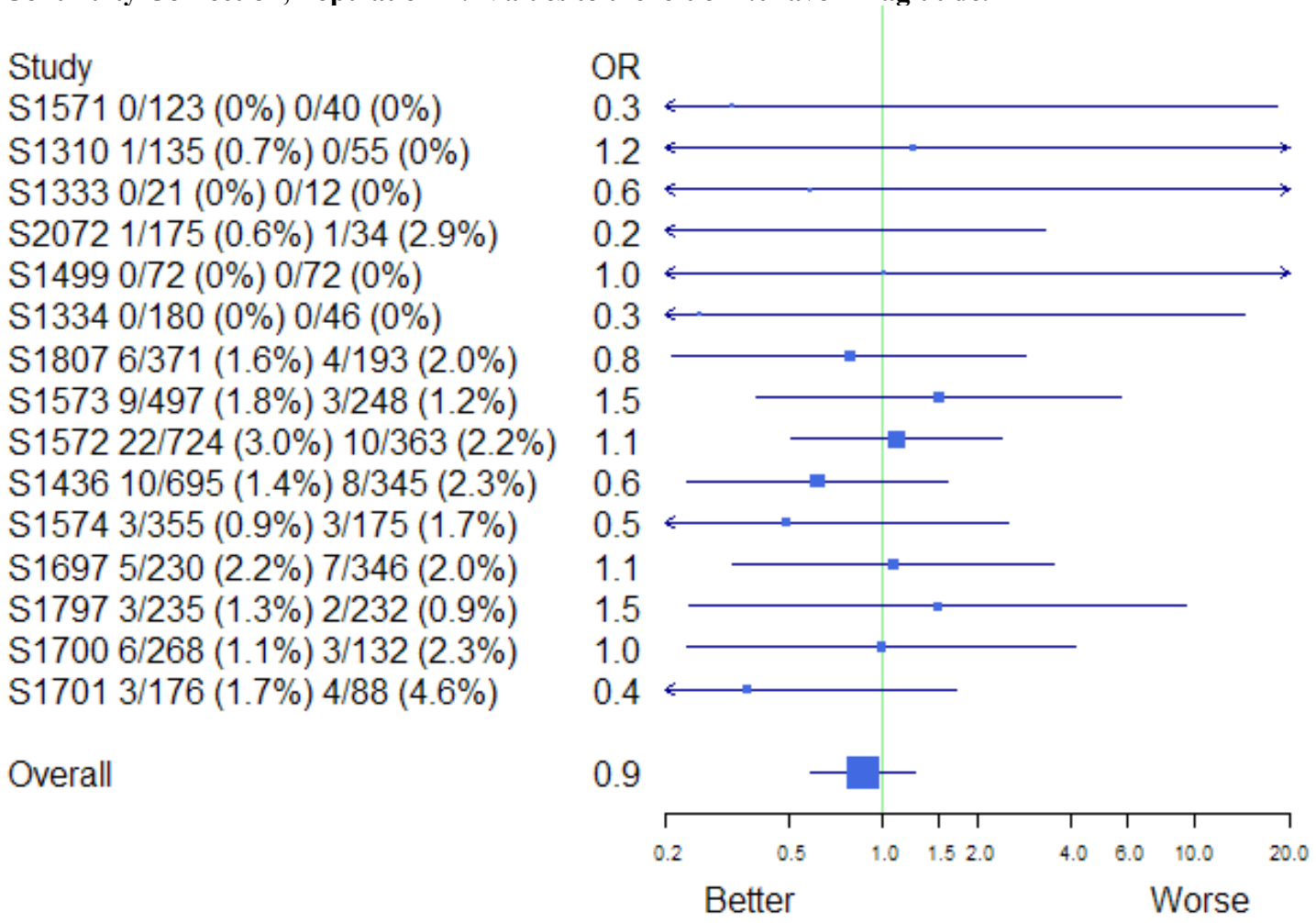
Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.11: Forest Plot for Broad SMQ Endpoint, Liraglutide vs. Active Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

Figure II.C.12: Forest Plot for Broad SMQ Endpoint, Liraglutide vs. Total Comparator, Stratified Mantel-Haenszel Analysis with Continuity Correction, Population B. Values to the left of 1.0 favor liraglutide.



Source: Dr. Janice Derr, FDA Biometrics

The following tables display Dr. Derr's analyses in a similar format to that presented for the Novo analyses in Tables II.C.2, II.C.4 and II.C.6 above.

Table II.C.12: Incidence Ratio, FDA Stratified Exact Analyses, All (Serious + Nonserious) Treatment-emergent MACE, Broad SMQ and FDA Custom Endpoints

Comparator			MACE Endpoint		Pop		Point Estimate (95% CI)
Total Comp	PBO	AC	FDA Custom	Broad SMQ	A	B	
x			x		x		0.72 (0.30, 1.74)
x				x	x		0.86 (0.55, 1.41)
x			x			x	0.80 (0.39, 1.64)
x				x		x	0.90 (0.60, 1.36)
	x		x		x		0.78 (0.19, 4.76)
	x			x	x		1.04 (0.48, 2.17)
	x		x			x	0.92 (0.28, 3.97)
	x			x		x	1.10 (0.56, 2.31)
		x	x		x		0.68 (0.26, 1.83)
		x		x	x		0.82 (0.48, 1.33)
		x	x			x	0.76 (0.35, 1.72)
		x		x		x	0.84 (0.53, 1.35)

Source: Dr. Derr's Tables II.C.8, II.C.9, II.C.10 and II.C.11 above

Table II.C.13: Incidence Ratio, FDA Asymptotic Fixed-Effects Mantel-Haenszel Meta-analysis Method with Continuity Correction, All (Serious + Nonserious) Treatment-emergent MACE, Broad SMQ and FDA Custom Endpoints

Comparator			MACE Endpoint		Pop		Point Estimate (95% CI)
Total Comp	PBO	AC	FDA Custom	Broad SMQ	A	B	
x			x		x		0.63 (0.32, 1.24)
x				x	x		0.83 (0.55, 1.27)
x			x			x	0.71 (0.39, 1.30)
x				x		x	0.86 (0.59, 1.24)
	x		x		x		0.52 (0.21, 1.25)
	x			x	x		0.86 (0.45, 1.65)
	x		x			x	0.60 (0.26, 1.39)
	x			x		x	0.89 (0.50, 1.60)
		x	x		x		0.60 (0.27, 1.31)
		x		x	x		0.79 (0.49, 1.28)
		x	x			x	0.68 (0.34, 1.37)
		x		x		x	0.83 (0.54, 1.27)

Source: Dr. Derr's Tables II.C.8, II.C.9, II.C.10 and II.C.11 above

The following listing shows all MACE events which occurred for the above 3 endpoints, and indicates which events were included in each endpoint. If a patient had more than one event, those events are listed here, but only the first event was included in the analyses.

Table II.C.14: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
4505	2072	LGT 0.6 mg	Cerebrovascular disorder	26	y	y		y	y
9410	1310	"	Cerebral hemorrhage	84	y	y		y	y
49002	1701	"	Cerebral arteriosclerosis	358				y	y
51002	1701	"	Blood CPK increased	249				y	
124003	1572	"	"	184	y			y	
213002	"	"	"	1	y			y	
227006	"	"	MI	416		y	y	y	y
270001	"	"	Acute MI	244		y	y	y	y
300015	"	"	"	299		y	y	y	y
358003	"	"	Coronary artery occlusion	187		y		y	y
372006	"	"	Acute coronary syndrome	16	y	y		y	y
394003	"	"	Hemorrhage intracranial	388		y		y	y
403005	"	"	Blood CPK incr	544				y	
587037	1436	"	"	182	y			y	
617010	"	"	"	1	y			y	
619002	"	"	"	1	y			y	
9024	1700	LGT 0.9 mg	MI	14	y	y	y	y	y
29001	"	"	Blood CPK incr	28	y	y		y	
"	"	"	"	330				y	
29003	1701	"	Cerebral infarction	178[1]			y	y	y
51003	1700	"	Acute MI	160	y	y	y	y	y
51004	"	"	Cerebral infarction	233			y	y	y
52002	"	"	MI	191		y	y	y	y
67002	"	"	TIA	191				y	y
131058	1807	LGT 1.2 mg	Blood CPK incr	99	y			y	
158005	1573	"	Carotid artery stenosis	40	y			y	y
194012	"	"	"	78	y			y	y
205016	"	"	Blood CPK incr	248	y			y	
213018	1572	"	"	84	y			y	
216005	1573	"	"	205	y			y	
239001	1572	"	"	558				y	

Table II.C.14: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
239004	“	“	“	280				y	
239005	“	“	“	184	y			y	
253002	“	“	Paresis	21	y			y	
288002	“	“	CVA	149	y	y	y	y	y
326009	“	“	Subarachnoid hemorrhage	292		y		y	y
332007	“	“	Acute MI	133	y	y	y	y	y
332025	1574	“	MI	183	y		y	y	y
375003	1572	“	“	337		y	y	y	y
403012	“	“	Blood CPK incr	1	y			y	
516011	1573	“	MI	167	y	y	y	y	y
547011	1436	“	TIA	88	y			y	y
562010	“	“	Blood CPK incr	85	y			y	
568002	“	“	Acute MI	89	y	y	y	y	y
120004	1573	LGT 1.8 mg	MI	367		y	y	y	y
121022	1807	“	CVA	13	y	y	y	y	y
136005	1573	“	Blood CPK incr	199	y			y	
172065	1807	“	“	113	y			y	
188010	1573	“	“	359	y			y	
217003	1572	“	“	84	y			y	
253010	1573	“	“	359	y			y	
273015	1572	“	“	272				y	
324019	1574	“	Coronary artery occlusion	26	y			y	y
326011	1797	“	Blood CPK incr	184	y			y	
343002	1572	“	“	184	y			y	
381003	1574	“	“	1	y			y	
401002	1797	“	Cerebellar infarction	103	y	y	y	y	y
496011	1436	“	ECG Q wave abnl	188	y			y	
514001	1797	“	Blood CPK incr	84	y			y	
546028	1436	“	“	86	y			y	
596001	“	“	Acute MI	182	y		y	y	y
622001	“	“	MI	181	y	y	y	y	y
659002	1697	“	Blood CPK incr	91	y			y	
714012	“	“	CVA	62	y	y	y	y	y
751001	“	“	Blood CPK incr	1	y			y	
826029	“	“	TIA	89	y			y	y
829002	“	“	Acute MI	154	y	y	y	y	y
121001	1807	LGT 2.4 mg	Blood CPK incr	142	y			y	

Table II.C.14: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
171039	"	LGT 3.0 mg	"	111	y			y	
172063	"	"	TIA	29	y	y		y	y
29004	1700	AC	Thalamus hemorrhage	199[1]				y	y
"	"	"	Cerebral infarction	305		y	y	y	y
62002	"	"	MI	233[1]		y	y	y	y
63006	"	"	Cerebral infarction	231		y	y	y	y
103006	1807	"	Blood CPK incr	229				y	
133036	"	"	"	87	y			y	
164001	1572	"	MI	176	y	y	y	y	y
171023	1807	"	Blood CPK incr	30	y			y	
171056	"	"	"	57	y			y	
178012	1572	"	Carotid arteriosclerosis	272				y	y
183012	1573	"	Blood CPK incr	84	y			y	
"	"	"	"	286	y			y	
201004	1572	"	MI	45	y	y	y	y	y
203004	"	"	Paralysis	16	y			y	
273002	1573	"	Acute MI	24	y	y	y	y	y
275001	"	"	MI	218	y	y	y	y	y
300004	1572	"	Blood CPK incr	1	y			y	
"	"	"	TIA	126	y			y	y
"	"	"	Carotid artery stenosis	135	y	y		y	y
300008	"	"	"	188				y	y
327016	1797	"	CVA	145	y	y	y	y	y
372010	1572	"	Blood CPK incr	182	y			y	
372011	"	"	"	182	y			y	
381007	"	"	"	1	y			y	
489004	1797	"	Acute MI	61	y	y	y	y	y
528012	1436	"	Blood CPK incr	87	y			y	
528019	"	"	"	82	y			y	
546009	"	"	"	92	y			y	
547008	"	"	"	84	y			y	
587017	"	"	"	1	y			y	
702006	1697	"	MI	153	y	y	y	y	y
713009	"	"	Acute MI	142	y	y	y	y	y
749007	"	"	TIA	153	y	y		y	y
"	"	"	Carotid artery stenosis	157	y			y	y
770002	"	"	Ischemic stroke	10	y	y	y	y	y
827005	"	"	Acute MI	117	y	y	y	y	y

Table II.C.14: Listing of All Events Which Actually Occurred for FDA Custom, Broad SMQ and Narrow SMQ Endpoints

Pt ID	Study	Tx	MedDRA Preferred Term	Time to Event (days)	Pop A	SAE	FDA Custom	Broad SMQ	Narrow SMQ
827020	"	"	Carotid artery stenosis	141	y	y		y	y
4812	2072	PBO	Cerebrovascular disorder	60	y	y		y	y
7009	1701	"	Carotid artery stenosis	308				y	y
9006	"	"	Blood CPK incr	252				y	
12002	"	"	"	308				y	
41002	"	"	Brain stem infarction	354			y	y	y
237005	1572	"	Blood CPK incr	1	y			y	
314006	1574	"	"	126	y			y	
381007	"	"	"	1	y			y	
388010	"	"	"	135	y			y	
431003	1436	"	MI	182	y	y	y	y	y
596002	"	"	MI	183	y		y	y	y
619010	"	"	Blood CPK incr	185	y			y	
689012	1697	"	Acute MI	78	y	y	y	y	y

Source: NDA 22341, subm stamp date 21 Jan 09, Appendix A, Applicant's Listings 1 and 2, pages 1-11
1 Patient had only month and year data for onset of event; date imputed to first day of month (Source: NDA 22341 subm stamp date 09 02 13, pg 7)
Abbreviations: abnl = abnormal, CPK = creatine phosphokinase, CVA = cerebrovascular accident, ECG = electrocardiogram, ID = identification, LGT = liraglutide, MedDRA = Medical Dictionary for Regulatory Activities, MI = myocardial infarction, Pop = population, Pt = patient, SAE = serious adverse event, SMQ = Standard MedDRA Query, TIA = transient ischemic attack, Tx = treatment

Observations related to the above table include:

- The most common events in the FDA Custom endpoint which occurred were myocardial infarction (15 events), acute myocardial infarction (11 events), cerebral infarction (4 events) and cerebrovascular accident (4 events).
- A large percentage of the events which occurred in the "Broad SMQ" endpoint, but not in the "FDA Custom" or "Narrow SMQ" endpoints were events of "blood creatine phosphokinase increased". A total of 55/120 (46%) of the total "Broad SMQ" events were these events of increased CPK. This event term accounted for 55/58 (95%) of events which occurred in the Broad SMQ but did not occur in the Narrow SMQ. Therefore, almost all of the increased specificity of the Narrow SMQ endpoint (compared to the Broad SMQ endpoint) was accounted for by this one term. The term accounted for 55/82 (67%) of events which occurred in the Broad SMQ but did not occur in the FDA Custom MACE. A total of 11/55 (20%) of the total events of increased CPK were reported to have occurred on Day 1 of study, which would suggest that, in these patients, elevation of CPK might have been present at baseline, and might not actually be a treatment effect.
- Other events which occurred in the Broad SMQ endpoint, but were not included in the FDA Custom endpoint, included carotid artery stenosis (2 LGT NSAE, 2 AC SAE, 2 AC

NSAE, 1 PBO NSAE), transient ischemic attack (1 LGT SAE, 3 LGT NSAE, 1 AC SAE, 1 AC NSAE), coronary artery occlusion (1 LGT SAE, 1 LGT NSAE), cerebrovascular disorder (1 LGT SAE, 1 PBO SAE), acute coronary syndrome (1 LGT SAE), cerebral hemorrhage (1 LGT SAE), hemorrhage intracranial (1 LGT SAE), subarachnoid hemorrhage (1 LGT SAE), carotid arteriosclerosis (1 AC NSAE), cerebral arteriosclerosis (1 LGT NSAE), electrocardiogram Q wave abnormal (1 LGT NSAE), paresis (1 LGT NSAE), paralysis (1 AC NSAE) and thalamus hemorrhage (1 AC NSAE).

There did not appear to be a relationship between LGT dose and the incidence of events within any of the three composite endpoints, as shown in the tables below. For each of the composite endpoints, among liraglutide-treated patients, the highest numerical incidence of events tended to occur in the 1.2 mg/day dose group.

Table II.C.15: Incidence of MACE Events by Liraglutide Dose, Population A, All Treatment-Emergent Events

Dose Group	N	FDA Custom		Broad SMQ		Narrow SMQ	
		n	%	n	%	n	%
LGT <0.6 mg	275	0	0	0	0	0	0
LGT 0.6 mg	693	0	0	7	1.0	2	0.3
LGT >0.6 and <1.2 mg	512	2	0.4	4	0.8	3	0.6
LGT 1.2 mg	991	5	0.5	16	1.6	8	0.8
LGT >1.2 and <1.8 mg	44	0	0	0	0	0	0
LGT 1.8 mg	1455	6	0.4	21	1.4	8	0.6
LGT >1.8 mg	287	0	0	3	1.1	1	0.4
Total LGT	4257	13	0.3	51	1.2	22	0.5
PBO	907	3	0.3	9	1.0	4	0.4
Active Comp	1474	10[1]	0.7	26	1.8	13	0.9
Total Comp	2381	12	0.5	35	1.5	17	0.7

Source: Applicant's Tables 1-3, beg pg 30, Appendix B, NDA 22341 submission received 21 Jan 09
1 The 21 Jan 09 submission included 9 events in this category, but one additional event reported in 13 Feb 09 submission

Table II.C.16: Incidence of MACE Events by Liraglutide Dose, Population A, Serious Treatment-Emergent Events

Dose Group	N	FDA Custom		Broad SMQ		Narrow SMQ	
		n	%	n	%	n	%
LGT <0.6 mg	275	0	0	0	0	0	0
LGT 0.6 mg	693	0	0	2	0.3	2	0.3
LGT >0.6 and <1.2 mg	512	2	0.4	4	0.8	3	0.6
LGT 1.2 mg	991	4	0.4	4	0.4	4	0.4
LGT >1.2 and <1.8 mg	44	0	0	0	0	0	0
LGT 1.8 mg	1455	5	0.3	5	0.3	5	0.3
LGT >1.8 mg	287	0	0	1	0.4	1	0.4
Total LGT	4257	11	0.3	16	0.4	15	0.4

Table II.C.16: Incidence of MACE Events by Liraglutide Dose, Population A, Serious Treatment-Emergent Events							
Dose Group	**N**	**FDA Custom**		**Broad SMQ**		**Narrow SMQ**	
		n	**%**	**n**	**%**	**n**	**%**
PBO	907	2	0.2	3	0.3	3	0.3
Active Comp	1474	10[1]	0.7	13	0.9	13	0.9
Total Comp	2381	11	0.5	16	0.7	16	0.7

Source: Applicant's Tables 4-6, beg pg 36, Appendix B, NDA 22341 submission received 21 Jan 09
1 The 21 Jan 09 submission included 9 events in this category, but one additional event reported in 13 Feb 09 submission

Results by liraglutide dose were qualitatively similar for the patients included in Population B (Source: NDA 22341, submission stamp date 21 Jan 2009, Tables 7-12, beginning serial page 42).

II.D. Other MACE Analyses

Prior to the "uniform" MACE information request described above, Novo had submitted other MACE analyses, using a different endpoint. Please see the column entitled "Prior Novo MACE" in Table II.B above for the terms included in this endpoint. This endpoint was defined post hoc, and included only terms for events that actually occurred, rather than prespecified terms from a Standard MedDRA Query. That is, the Broad Standard MedDRA Query endpoint included a predefined standard set of *terms*; from this broad set of event terms, there were some actual events which occurred, but for many terms, no event actually occurred. The "Prior Novo MACE" endpoint was picked by looking only at *events* which had actually occurred, and choosing those events which appeared to be relevant, rather than choosing a list of terms, and then seeing if any events from that list had occurred. As mentioned earlier, two terms which occurred in this endpoint, but which do not appear in the MedDRA Standard Queries, are cardiac arrest and circulatory collapse. The analyses included all completed phase 2 and phase 3 trials in diabetes and obesity, with or without the extension periods for these trials.

Table II.D.1: Incidence Ratio, Liraglutide vs. Comparator, Analyses of "Prior Novo MACE" Endpoint							
Comparator			Type of Events		Pop		Point Estimate (95% CI)
Total Comp	PBO	Active Comp	All TEAE	Serious Only	Main Period	Main + Ext	
x			x		x		0.63 (0.29, 1.35)
x				x	x		0.65 (0.25, 1.65)
x			x			x	0.80 (0.45, 1.42)
x				x		x	0.91 (0.46, 1.78)
	x		x		x		0.67 (0.21, 2.12)
	x			x	x		0.80 (0.16, 3.94)
	x		x			x	0.89 (0.33, 2.39)
	x			x		x	1.43 (0.32, 6.33)
		x	x		x		0.61 (0.26, 1.42)
		x		x	x		0.62 (0.23, 1.64)
		x	x			x	0.77 (0.41, 1.45)
		x		x		x	0.83 (0.41, 1.68)
Source: NDA 22341, submission stamp date 7 Oct 08, Applicant's Tables 2-3, 2-4 (pg 10), 2-5 (pg 11), and 2-6 (pg 12) Cox proportional hazard regression model, stratified by trial							

Qualitatively, the results of these analyses were similar to those for the FDA Custom, Broad SMQ and Narrow SMQ analyses. That is, for total and active comparator, the point estimate tended to be less than one, and the upper bound of the 95% confidence interval did not tend to exceed 1.8. For comparison to placebo, the upper bound did exceed 1.8, but as shown in Table II.D.2 below, the number of events in placebo groups was very small.

As with the Custom FDA, Broad SMQ and Narrow SMQ endpoints, the overall number of events was small, as shown in the following table.

Table II.D.2: Numbers of MACE Events for "Prior Novo MACE" Endpoint				
Type of Event	Total LGT N=4257 PY=2882	PBO N=907 PY=449	AC N=1474 PY=1038	Total Comp N=2381 PY=1486
CV deaths	0	1 (0.1)	1 (0.1)	2 (0.1)
Serious MACE	22 (0.5)	2 (0.2)	13 (0.9)	15 (0.6)
Nonserious MACE	8 (0.2)	4 (0.4)	3 (0.2)	7 (0.3)
Total MACE	29 (0.7)	5 (0.6)	16 (1.1)	21 (0.9)
Source: NDA 22341, submission stamp date 7 Oct 08, Applicant's Table 1, Appendix A, pg 15				

II.E. Overall Cardiovascular Event Summaries

The above analyses have focused on events of myocardial infarction, stroke and cardiovascular death. Other types of cardiovascular events occurred, and the following tables summarize the incidence of all potential cardiovascular events. Not all listed events are known to be cardiovascular in etiology. For example, the event terms "chest pain" and "edema" may have non-cardiovascular etiologies. However, these tables are provided to give the broadest possible overview of the incidence of potential cardiovascular events.

II.E.1. Serious Adverse Potentially Cardiovascular Events

The following table includes all serious adverse events that potentially involved the cardiac and vascular systems. This grouping will include more terms than those specified for the MACE analyses. Please note that this table includes events which had occurred at the time of the initial NDA submission. The MACE analyses above include additional data from the safety update which was submitted four months later, and therefore the number of events may differ slightly for certain MACE terms.

Table II.E.1: Serious Potential Cardiovascular Adverse Events by MedDRA System Organ Class and Preferred Term, Safety Analysis Set at Time of Initial 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
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
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	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

Table II.E.1: Serious Potential Cardiovascular Adverse Events by MedDRA System Organ Class and Preferred Term, Safety Analysis Set at Time of Initial 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**
	Hypertension	0	0	0	1	<0.1	0.9
Nervous system disorders	**Any (includes noncardiovascular events)**	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
	Hemorrhage intracranial	1	<0.1	0.4	0	0	0
	Loss of consciousness	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
	Ischemic stroke	0	0	0	1	<0.1	0.9
General disorders and administration site conditions	**Any (includes noncardiovascular events)**	8	0.2	3.6	6	0.3	5.3
	Chest pain	5	0.1	2.2	4	0.2	3.5
	Noncardiac chest pain	1	<0.1	0.4	1	<0.1	0.9
Respiratory, thoracic and mediastinal disorders	**Any (includes noncardiovascular events)**	5	0.1	2.2	4	0.2	3.5
	Pulmonary embolism	2	<0.1	0.9	1	<0.1	0.9
	Pulmonary edema	0	0	0	1	<0.1	0.9
Investigations	**Any (includes noncardiovascular events)**	2	<0.1	0.9	1	<0.1	0.9
	Heart rate increased	1	<0.1	0.4	0	0	0
	Electrocardiogram abnormal	0	0	0	1	<0.1	0.9

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

When considering all potential serious cardiovascular event terms, there did not appear to be an imbalance in any one term or group of terms for liraglutide vs. non-liraglutide groups. However, we note that the pooled safety data base is somewhat different from the database used to compare the incidence of MACE events in liraglutide vs. active comparator and liraglutide vs. placebo comparator groups. This is because the MACE analyses that we and Novo conducted were stratified by study, and involved only those studies with the pertinent comparator.

II.E.2. Combined Serious and Nonserious Adverse Cardiovascular Events

The following table includes all adverse events (serious and nonserious combined) that potentially involved the cardiac and vascular systems. This grouping will include more terms than those specified for the MACE analyses. Please note that this table includes events which had occurred at the time of the initial NDA submission. The MACE analyses above include

additional data from the safety update which was submitted four months later, and therefore the number of events may differ slightly for certain MACE terms. Liraglutide incidence is broken down by dose.

Table II.E.2.a: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
Cardiac	**Any**	25 (2.2)	32 (2.7)	57 (2.5)	6 (1.5)	31 (4.8)	3 (0.7)	46 (4.6)	2 (3.1)	45 (3.2)	6 (2.1)	139 (3.3)
	Palpitations	4 (0.4)	5 (0.4)	9 (0.4)	2 (0.5)	2 (0.3)		6 (0.6)		12 (0.9)	5 (1.7)	27 (0.6)
	Angina pectoris	3 (0.3)	3 (0.3)	6 (0.3)		9 (1.4)	1 (0.2)	5 (0.5)	1 (1.6)	4 (0.3)		20 (0.5)
	Tachycardia	2 (0.2)	3 (0.3)	5 (0.2)	2 (0.5)	2 (0.3)		5 (0.5)		4 (0.3)		13 (0.3)
	Myocardial infarction	2 (0.2)	4 (0.3)	6 (0.3)		1 (0.2)		3 (0.3)		2 (0.1)		6 (0.1)
	Ventricular extrasystoles	1 (0.1)	2 (0.2)	3 (0.1)		1 (0.2)		3 (0.3)		4 (0.3)		8 (0.2)
	Myocardial ischemia	1 (0.1)		1 (<0.1)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.3)	1 (1.6)	2 (0.1)		9 (0.2)
	AV block first degree	3 (0.3)	1 (0.1)	4 (0.2)		2 (0.3)	1(0.2)	2 (0.2)		1 (0.1)		6 (0.1)
	Acute myocardial infarction	1 (0.1)	3 (0.3)	4 (0.2)		2 (0.3)		2 (0.2)		2 (0.1)		6 (0.1)
	Atrial fibrillation		3 (0.3)	3 (0.1)		1 (0.2)				3 (0.2)	1 (0.3)	5 (0.1)
	Coronary artery disease		1 (0.1)	1 (<0.1)		1 (0.2)		2 (0.2)		3 (0.2)		6 (0.1)
	Bundle branch block left	2 (0.2)	2 (0.2)	4 (0.2)		1 (0.2)		1 (0.1)		1 (0.1)		3 (0.1)
	Bundle branch block right							1 (0.1)		4 (0.3)		5 (0.1)
	Supraventricular extrasystoles	1 (0.1)	1 (0.1)	2 (0.1)				2 (0.2)				2 (<0.1)
	Sinus tachycardia					2 (0.3)		2 (0.2)				4 (0.1)
	Left ventricular hypertrophy		2 (0.2)	2 (0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	Supraventricular tachycardia							1 (0.1)		2 (0.1)		3 (0.1)
	Sinus bradycardia	2 (0.2)		2 (0.1)						1 (0.1)		1 (<0.1)
	Cardiac failure							2 (0.2)		1 (0.1)		3 (0.1)
	Atrial flutter		1 (0.1)	1 (<0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	Ventricular tachycardia	1 (0.1)		1 (<0.1)						1 (0.1)		1 (<0.1)
	Tachycardia paroxysmal					1 (0.2)		1 (0.1)				2 (<0.1)
	Mitral valve incompetence	1 (0.1)	1 (0.1)	2 (0.1)								
	Left atrial dilatation		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)

Table II.E.2.a: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Extrasystoles		1 (0.1)	1 (<0.1)						1 (0.1)		1 (<0.1)
	Coronary artery stenosis	1 (0.1)	1 (0.1)	2 (0.1)								
	Coronary artery occlusion					1 (0.2)				1 (0.1)		2 (<0.1)
	Congestive cardiomyopathy							1 (0.1)				1 (<0.1)
	Cardiac failure							2 (0.2)				2 (<0.1)
	Cardiac arrest					1 (0.2)						1 (<0.1)
	Bundle branch block bilateral							1 (0.1)		1 (0.1)		2 (<0.1)
	Arrhythmia				2 (0.5)							2 (<0.1)
	Ventricular hypertrophy	1 (0.1)		1 (<0.1)								
	Tricuspid valve incompetence		1 (0.1)	1 (<0.1)								
	Sinus arrhythmia							1 (0.1)				1 (<0.1)
	Right ventricular failure									1 (0.1)		1 (<0.1)
	Pericardial effusion							1 (0.1)				1 (<0.1)
	Myocardial fibrosis							1 (0.1)				1 (<0.1)
	Mitral valve sclerosis									1 (0.1)		1 (<0.1)
	Ischemic cardiomyopathy		1 (0.1)	1 (<0.1)								
	Cardiac discomfort		1 (0.1)	1 (<0.1)								
	Bundle branch block					1 (0.2)						1 (<0.1)
	Bradycardia							1 (0.1)				1 (<0.1)
	AV block							1 (0.1)				1 (<0.1)
	Angina unstable							1 (0.1)				1 (<0.1)
	Acute coronary syndrome					1 (0.2)						1 (<0.1)
Vascular	**Any**	26 (2.3)	57 (4.9)	83 (3.7)	9 (2.2)	31 (4.8)	11 (2.6)	42 (4.2)	1 (1.6)	56 (4.0)	10 (3.5)	160 (3.8)
	Hypertension	15 (1.3)	40 (3.4)	55 (2.4)	5 (1.2)	15 (2.3)	1 (0.2)	21 (2.1)	1 (1.6)	30 (2.1)	1 (0.3)	74 (1.8)
	Vascular calcification	1 (0.1)	4 (0.3)	5 (0.2)		6 (0.9)		3 (0.3)		6 (0.4)	2 (0.7)	17 (0.4)
	Hematoma	3 (0.3)	2 (0.2)	5 (0.2)		4 (0.6)		1 (0.1)		4 (0.3)		9 (0.2)
	Hypotension		2 (0.2)	2 (0.1)			1 (0.2)	6 (0.6)		3 (0.2)	2 (0.7)	12 (0.3)

Table II.E.2.a: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Flushing	1 (0.1)		1 (<0.1)	2 (0.5)		1 (0.2)	2 (0.2)		2 (0.1)	2 (0.7)	9 (0.2)
	Hot flush		1 (0.1)	1 (<0.1)			3 (0.7)	1 (0.1)		3 (0.2)		7 (0.2)
	Aortic calcification		3 (0.3)	3 (0.1)		4 (0.6)				1 (0.1)	1 (0.3)	6 (0.1)
	Arteriosclerosis				1 (0.2)	3 (0.5)		1 (0.1)		2 (0.1)		7 (0.2)
	Varicose vein		1 (0.1)	1 (<0.1)				2 (0.2)		2 (0.1)	1 (0.3)	5 (0.1)
	Orthostatic hypotension	1 (0.1)		1 (<0.1)		1 (0.2)		3 (0.3)		1 (0.1)		5 (0.1)
	Pallor				1 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)				5 (0.1)
	Phlebitis		1 (0.1)	1 (<0.1)		1 (0.2)	1 (0.2)					2 (<0.1)
	Aortic arteriosclerosis		1 (0.1)	1 (<0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	Venous stasis	1 (0.1)		1 (<0.1)						1 (0.1)		1 <0.1)
	Thrombophlebitis						1 (0.2)				1 (0.3)	2 (<0.1)
	Lymphedema					1 (0.2)	1 (0.2)					2 (<0.1)
	Aortic aneurysm		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)
	Angiopathy					2 (0.3)						2 (<0.1)
	Venous thrombosis		1 (0.1)	1 (<0.1)								
	Vasodilation	1 (0.1)		1 (<0.1)								
	Thrombophlebitis superficial									1 (0.1)		1 (<0.1)
	Raynaud's phenomenon							1 (0.1)				1 (<0.1)
	Phlebitis superficial	1 (0.1)		1 (<0.1)								
	Peripheral vascular disorder									1 (0.1)		1 (<0.1)
	Peripheral arterial occlusive disease		1 (0.1)	1 (<0.1)								
	Ischemia		1 (0.1)	1 (<0.1)								
	Intermittent claudication		1 (0.1)	1 (<0.1)								
	Hypertensive crisis		1 (0.1)	1 (<0.1)								
	Essential hypertension										1 (0.3)	1 (<0.1)
	Deep vein thrombosis										1 (0.3)	1 (<0.1)
	Circulatory collapse	1 (0.1)		1 (<0.1)								

Table II.E.2.a: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Blood pressure fluctuation							1 (0.1)				1 (<0.1)
	Bleeding varicose vein									1 (0.1)		1 (<0.1)
	Arteriosclerosis obliterans		1 (0.1)	1 (<0.1)								
	Arterial stenosis limb	1 (0.1)		1 (<0.1)								
	Aneurysm						1 (0.2)					1 (<0.1)
Nervous system	**Any (includes non-CV events)**	189 (16.8)	184 (15.8)	371 (16.3)	63 (15.7)	90 (14.0)	73 (17.5)	195 (19.6)	12 (18.8)	295 (21.0)	58 (20.1)	786 (18.7)
	Syncope	3 (0.3)	1 (0.1)	4 (0.2)	2 (0.5)	1 (0.2)		1 (0.1)		5 (0.4)	1 (0.3)	10 (0.2)
	Syncope vasovagal	1 (0.1)		1 (<0.1)			1 (0.2)	1 (0.1)		2 (0.1)	1 (0.3)	5 (0.1)
	Carotid artery stenosis	4 (0.3)	4 (0.2)					2 (0.2)				2 (<0.1)
	TIA		2 (0.2)	2 (0.1)				1 (0.1)		1 (0.1)	1 (0.3)	3 (0.1)
	CVA							1 (0.1)		2 (0.1)		3 (0.1)
	Global amnesia		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)
	Cerebrovasc disorder	1 (0.1)		1 (<0.1)			1 (0.2)					1 (<0.1)
	Aphonia	1 (0.1)		1 (<0.1)						1 (0.1)		1 (<0.1)
	Visual field defect		1 (0.1)	1 (<0.1)								
	Subarachnoid hemorrhage							1 (0.1)				1 (<0.1)
	Paresis							1 (0.1)				1 (<0.1)
	Paralysis		1 (0.1)	1 (<0.1)								
	Pallanesthesia					1 (0.2)						1 (<0.1)
	Ischemic stroke		1 (0.1)	1 (<0.1)								
	Hemorrhage intracranial					1 (0.2)						1 (<0.1)
	Cerebral hemorrhage					1 (0.2)						1 (<0.1)
	Carotid arteriosclerosis		1 (0.1)	1 (<0.1)								
	Ataxia							1 (0.1)				1 (<0.1)
	Amnesia		1 (0.1)	1 (<0.1)								
Musculoskeletal and Connective Tissue Disorders	**Any (includes non-CV events)**	117 (10.4)	188 (16.1)	304 (13.4)	23 (5.7)	84 (13.1)	23 (5.5)	163 (16.4)	5 (7.8)	204 (14.5)	30 (10.4)	532 (12.6)

Table II.E.2.a: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Musculoskeletal chest pain	3 (0.3)	3 (0.3)	6 (0.3)		2 (0.3)		3 (0.3)		3 (0.2)	1 (0.3)	9 (0.2)
General disorders and administration site conditions	**Any (includes non-CV events)**	99 (8.8)	97 (8.3)	195 (8.6)	36 (9.0)	64 (10.0)	28 (6.7)	132 (13.3)	5 (7.8)	199 (14.1)	50 (17.4)	514 (12.2)
	Edema peripheral	19 (1.7)	19 (1.6)	38 (1.7)		3 (0.5)	1 (0.2)	16 (1.6)		12 (0.9)	2 (0.7	34 (0.8)
	Chest pain	7 (0.6)	12 (1.0)	19 (0.8)	1 (0.2)		2 (0.5)	7 (0.7)		7 (0.5)		17 (0.4)
	Chest discomfort	2 (0.2)		2 (0.1)			2 (0.5)	5 (0.5)		1 (0.1)		8 (0.2)
	Edema		3 (0.3)	3 (0.1)	1 (0.2)	3 (0.5)		1 (0.1)		1 (0.1)		6 (0.1)
	Noncardiac chest pain	1 (0.1)	1 (0.1)	2 (0.1)				1 (0.1)		2 (0.1)		3 (0.1)
	Gravitational edema	2 (0.2)		2 (0.1)	1 (0.2)			1 (0.1)				2 (<0.1)
	Pitting edema		1 (0.1)	1 (<0.1)				1 (0.1)				1 (<0.1)
	Generalized edema		1 (0.1)	1 (<0.1)	1 (0.2)			1 (0.1)				2 (<0.1)
	Local swelling		1 (0.1)	1 (<0.1)		1 (0.2)						1 (<0.1)
	Swelling		1 (0.1)	1 (<0.1)								
Metabolism and nutrition disorders	**Any (includes non-CV events)**	75 (6.7)	81 (7.0)	156 (6.9)	24 (6.0)	47 (7.3)	10 (2.4)	145 (14.6)	1 (1.6)	230 (16.3)	26 (9.0)	483 (11.5)
	Fluid retention		3 (0.3)	3 (0.1)				3 (0.3)		3 (0.2)		6 (0.1)
Respiratory, thoracic and mediastinal disorders	**Any (includes non-CV events)**	61 (5.4)	76 (6.5)	137 (6.0)	20 (5.0)	40 (6.2)	15 (3.6)	75 (7.6)	3 (4.7)	90 (6.4)	9 (3.1)	252 (6.0)
	Dyspnea	2 (0.2)	4 (0.3)	6 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	5 (0.5)	1 (1.6)	5 (0.4)		14 (0.3)
	Pulmonary embolism	1 (0.1)		1 (<0.1)				1 (0.1)		1 (0.1)		2 (<0.1)
	Pleural effusion							2 (0.2)				2 (<0.1)
	Pulmonary edema		1 (0.1)	1 (<0.1)								
	Dyspnea exertional							1 (0.1)				1 (<0.1)
Investigations	**Any (includes non-CV events)**	61 (5.4)	70 (6.0)	131 (5.8)	9 (2.2)	45 (7.0)	3 (0.7)	68 (6.8)		94 (6.7)	8 (2.8)	227 (5.4)
	Blood CPK incr	4 (0.4)	13 (1.1)	17 (0.7)		4 (0.6)		9 (0.9)		10 (0.7)	2 (0.7)	25 (0.6)
	Weight increased	1 (0.1)	13 (1.1)	14 (0.6)	1 (0.2)			3 (0.3)		6 (0.4)		10 (0.2)
	C-reactive protein increased	2 (0.2)	4 (0.3)	6 (0.3)		2 (0.3)		4 (0.4)		3 (0.2)		9 (0.2)
	Blood pressure increased	4 (0.4)	1 (0.1)	5 (0.2)				4 (0.4)		5 (0.4)		9 (0.2)

Table II.E.2.a: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	ECG abnl	3 (0.3)	3 (0.3)	6 (0.3)	2 (0.5)	3 (0.5)		1 (0.1)		1 (0.1)		7 (0.2)
	Plasminogen activator inhibitor increased	1 (0.1)	1 (0.1)	2 (0.1)		5 (0.8)		3 (0.3)		1 (0.1)		9 (0.2)
	Blood cholesterol increased	2 (0.2)	1 (0.1)	3 (0.1)		1 (0.2)		1 (0.1)		2 (0.1)		4 (0.1)
	Heart rate increased	1 (0.1)		1 (<0.1)		1 (0.2)		2 (0.2)		2 (0.1)		5 (0.1)
	Cardiac murmur	1 (0.1)		1 (<0.1)				3 (0.3)				3 (0.1)
	LDL incr	1 (0.1)	1 (0.1)	2 (0.1)						1 (0.1)		1 (<0.1)
	Brain natriuretic peptide increased		1 (0.1)	1 (<0.1)		1 (0.2)		1 (0.1)				2 (<0.1)
	ECG QT prolonged									2 (0.1)		2 (<0.1)
	ECG change		1 (0.1)	1 (<0.1)		1 (0.2)						1 (<0.1)
	Carotid bruit	1 (0.1)		1 (<0.1)				1 (0.1)				1 (<0.1)
	Blood CPK abnl	1 (0.1)		1 (<0.1)		1 (0.2)						1 (<0.1)
	VLDL incr					1 (0.2)						1 (<0.1)
	QRS axis abnl									1 (0.1)		1 (<0.1)
	Pulse absent									1 (0.1)		1 (<0.1)
	Pulse abnl					1 (0.2)						1 (<0.1)
	Lipids increased		1 (0.1)	1 (<0.1)								
	HDL decreased	1 (0.1)		1 (<0.1)								
	Heart sounds abnl									1 (0.1)		1 (<0.1)
	Heart rate irregular	1 (0.1)		1 (<0.1)								
	Heart rate decreased		1 (0.1)	1 (<0.1)								
	Free fatty acids incr				1 (0.2)							1 (<0.1)
	ECG T wave abnl				1 (0.2)							1 (<0.1)
	ECG ST-T change	1 (0.1)		1 (<0.1)								
	ECG Q wave abnl									1 (0.1)		1 (<0.1)
	ECG signs of myocardial ischemia	1 (0.1)		1 (<0.1)								
	Atrial natriuretic peptide incr		1 (0.1)	1 (<0.1)								

Table II.E.2.a: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
Surgical and medical procedures	**Any (includes non-CV events)**	3 (0.3)	9 (0.8)	12 (0.5)		4 (0.6)		8 (0.8)		5 (0.4)	1 (0.3)	18 (0.4)
	Coronary artery stent insertion	1 (0.1)		1 (<0.1)								

Source: NDA 22341, submission stamp date 09 01 16
Abbreviations: AC = active control, AV = atrioventricular, CPK = creatine phosphokinase, CV = cardiovascular, CVA = cerebrovascular accident, ECG = electrocardiogram, incr = increased, LDL = low density lipoprotein cholesterol, PBO = placebo, TIA = transient ischemic attack, VLDL = very low density lipoprotein cholesterol

Among the events in the above table, few occurred with higher frequency among liraglutide-treated patients than among comparator-treated patients. However, we note that the pooled safety data base is somewhat different from the database used to compare the incidence of MACE events in liraglutide vs. active comparator and liraglutide vs. placebo comparator groups. This is because the MACE analyses that we and Novo conducted were stratified, and involved only those studies with the pertinent comparator.

The following table includes those events that occurred in at least 3 liraglutide-treated patients, and which occurred with a frequency ≥0.2% higher in a liraglutide group than in a comparator group.

Table II.E.2.b: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) Which Occurred in at Least 3 Liraglutide-treated Patients and Occurred With a Numerically Higher (≥0.2% Higher) Frequency in a Liraglutide Group than in a Comparator Group, by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg) <0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
Cardiac	**Any**	25 (2.2)	32 (2.7)	57 (2.5)	6 (1.5)	31 (4.8)	3 (0.7)	46 (4.6)	2 (3.1)	45 (3.2)	6 (2.1)	139 (3.3)
	Palpitations	4 (0.4)	5 (0.4)	9 (0.4)	2 (0.5)	2 (0.3)		6 (0.6)		12 (0.9)	5 (1.7)	27 (0.6)
	Angina pectoris	3 (0.3)	3 (0.3)	6 (0.3)		9 (1.4)	1 (0.2)	5 (0.5)	1 (1.6)	4 (0.3)		20 (0.5)
	Tachycardia	2 (0.2)	3 (0.3)	5 (0.2)	2 (0.5)	2 (0.3)		5 (0.5)		4 (0.3)		13 (0.3)
	Ventricular extrasystoles	1 (0.1)	2 (0.2)	3 (0.1)		1 (0.2)		3 (0.3)		4 (0.3)		8 (0.2)
	Myocardial ischemia	1 (0.1)		1 (<0.1)	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.3)	1 (1.6)	2 (0.1)		9 (0.2)

Table II.E.2.b: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) Which Occurred in at Least 3 Liraglutide-treated Patients and Occurred With a Numerically Higher (≥0.2% Higher) Frequency in a Liraglutide Group than in a Comparator Group, by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
	Atrial fibrillation		3 (0.3)	3 (0.1)		1 (0.2)				3 (0.2)	1 (0.3)	5 (0.1)
	Coronary artery disease		1 (0.1)	1 (<0.1)		1 (0.2)		2 (0.2)		3 (0.2)		6 (0.1)
	Bundle branch block right							1 (0.1)		4 (0.3)		5 (0.1)
Vascular	**Any**	26 (2.3)	57 (4.9)	83 (3.7)	9 (2.2)	31 (4.8)	11 (2.6)	42 (4.2)	1 (1.6)	56 (4.0)	10 (3.5)	160 (3.8)
	Hypertension	15 (1.3)	40 (3.4)	55 (2.4)	5 (1.2)	15 (2.3)	1 (0.2)	21 (2.1)	1 (1.6)	30 (2.1)	1 (0.3)	74 (1.8)
	Vascular calcification	1 (0.1)	4 (0.3)	5 (0.2)		6 (0.9)		3 (0.3)		6 (0.4)	2 (0.7)	17 (0.4)
	Hematoma	3 (0.3)	2 (0.2)	5 (0.2)		4 (0.6)		1 (0.1)		4 (0.3)		9 (0.2)
	Hypotension		2 (0.2)	2 (0.1)			1 (0.2)	6 (0.6)		3 (0.2)	2 (0.7)	12 (0.3)
	Flushing	1 (0.1)		1 (<0.1)	2 (0.5)		1 (0.2)	2 (0.2)		2 (0.1)	2 (0.7)	9 (0.2)
	Hot flush		1 (0.1)	1 (<0.1)			3 (0.7)	1 (0.1)		3 (0.2)		7 (0.2)
	Aortic calcification		3 (0.3)	3 (0.1)		4 (0.6)				1 (0.1)	1 (0.3)	6 (0.1)
	Arteriosclerosis				1 (0.2)	3 (0.5)		1 (0.1)		2 (0.1)		7 (0.2)
	Orthostatic hypotension	1 (0.1)		1 (<0.1)		1 (0.2)		3 (0.3)		1 (0.1)		5 (0.1)
Nervous system	**Any (includes non-CV events)**	189 (16.8)	184 (15.8)	371 (16.3)	63 (15.7)	90 (14.0)	73 (17.5)	195 (19.6)	12 (18.8)	295 (21.0)	58 (20.1)	786 (18.7)
	Syncope	3 (0.3)	1 (0.1)	4 (0.2)	2 (0.5)	1 (0.2)		1 (0.1)		5 (0.4)	1 (0.3)	10 (0.2)
Musculoskeletal and Connective Tissue Disorders	**Any (includes non-CV events)**	117 (10.4)	188 (16.1)	304 (13.4)	23 (5.7)	84 (13.1)	23 (5.5)	163 (16.4)	5 (7.8)	204 (14.5)	30 (10.4)	532 (12.6)
General disorders and administration site conditions	**Any (includes non-CV events)**	99 (8.8)	97 (8.3)	195 (8.6)	36 (9.0)	64 (10.0)	28 (6.7)	132 (13.3)	5 (7.8)	199 (14.1)	50 (17.4)	514 (12.2)
	Chest discomfort	2 (0.2)		2 (0.1)			2 (0.5)	5 (0.5)		1 (0.1)		8 (0.2)
	Edema		3 (0.3)	3 (0.1)	1 (0.2)	3 (0.5)		1 (0.1)		1 (0.1)		6 (0.1)
Metabolism and nutrition disorders	**Any (includes non-CV events)**	75 (6.7)	81 (7.0)	156 (6.9)	24 (6.0)	47 (7.3)	10 (2.4)	145 (14.6)	1 (1.6)	230 (16.3)	26 (9.0)	483 (11.5)
	Fluid retention		3 (0.3)	3 (0.1)				3 (0.3)		3 (0.2)		6 (0.1)
Respiratory, thoracic and mediastinal disorders	**Any (includes non-CV events)**	61 (5.4)	76 (6.5)	137 (6.0)	20 (5.0)	40 (6.2)	15 (3.6)	75 (7.6)	3 (4.7)	90 (6.4)	9 (3.1)	252 (6.0)
	Dyspnea	2 (0.2)	4 (0.3)	6 (0.3)	1 (0.2)	1 (0.2)	1 (0.2)	5 (0.5)	1 (1.6)	5 (0.4)		14 (0.3)

Table II.E.2.b: Potential Cardiovascular Adverse Events (Serious and Nonserious Combined) Which Occurred in at Least 3 Liraglutide-treated Patients and Occurred With a Numerically Higher (≥0.2% Higher) Frequency in a Liraglutide Group than in a Comparator Group, by MedDRA System Organ Class and Preferred Term, ITT Population at Time of Initial NDA Submission

SOC	Event	PBO N= 1122 n(%)	AC N= 1165 n(%)	All Comp N= 2272 n(%)	Liraglutide (mg)							
					<0.6 N= 401 n(%)	0.6 N= 641 n(%)	>0.6-<1.2 N= 416 n(%)	1.2 N= 993 n(%)	>1.2-<1.8 N= 64 n(%)	1.8 N= 1408 n(%)	>1.8 N= 288 n(%)	All LGT N= 4211 n(%)
Investigations	**Any (includes non-CV events)**	61 (5.4)	70 (6.0)	131 (5.8)	9 (2.2)	45 (7.0)	3 (0.7)	68 (6.8)		94 (6.7)	8 (2.8)	227 (5.4)
	Blood CPK incr	4 (0.4)	13 (1.1)	17 (0.7)		4 (0.6)		9 (0.9)		10 (0.7)	2 (0.7)	25 (0.6)
	Weight increased	1 (0.1)	13 (1.1)	14 (0.6)	1 (0.2)			3 (0.3)		6 (0.4)		10 (0.2)
	C-reactive protein increased	2 (0.2)	4 (0.3)	6 (0.3)		2 (0.3)		4 (0.4)		3 (0.2)		9 (0.2)
	Blood pressure increased	4 (0.4)	1 (0.1)	5 (0.2)				4 (0.4)		5 (0.4)		9 (0.2)
	ECG abnl	3 (0.3)	3 (0.3)	6 (0.3)	2 (0.5)	3 (0.5)		1 (0.1)		1 (0.1)		7 (0.2)
	Plasminogen activator inhibitor increased	1 (0.1)	1 (0.1)	2 (0.1)		5 (0.8)		3 (0.3)		1 (0.1)		9 (0.2)
	Cardiac murmur	1 (0.1)		1 (<0.1)				3 (0.3)				3 (0.1)
Surgical and medical procedures	**Any (includes non-CV events)**	3 (0.3)	9 (0.8)	12 (0.5)		4 (0.6)		8 (0.8)		5 (0.4)	1 (0.3)	18 (0.4)

Source: NDA 22341, submission stamp date 09 01 16

Overall cardiac and vascular System Organ Class events occurred with slightly numerically higher frequency for the total liraglutide-treated group than for the placebo-treated group, but with similar frequency to the active control and overall comparator group. Overall neurologic System Organ Class events occurred with slightly numerically higher frequency for the total liraglutide-treated group than for comparator groups. However, we note that the pooled safety data base is somewhat different from the database used to compare the incidence of MACE events in liraglutide vs. active comparator and liraglutide vs. placebo comparator groups. This is because the MACE analyses that we and Novo conducted were stratified, and involved only those studies with the pertinent comparator.

The terms “hypotension” and “orthostatic hypotension” occurred with slightly numerically higher frequency among liraglutide-treated patients than among comparator-treated patients. “Hypotension” occurred in 12 (0.3%) of liraglutide-treated patients and in 2 (0.1%) of comparator-treated patients. “Orthostatic hypotension” occurred in 5 (1%) of liraglutide-treated patients and in 1 (<0.1%) of comparator-treated patients. Other slight numerical imbalances of note include the terms “angina pectoris” (LGT n=20 [0.5%] vs. comp n=6 [0.3%]) and “myocardial ischemia” (LGT n=9 [0.2%] vs. comp n=1 [<0.1%]). The slightly higher incidence of the terms “flushing” and “hot flush” is potentially of some interest to the later discussion of thyroid cancer, because medullary thyroid carcinoma is a rare entity in the differential diagnosis

of flushing (Izikson 2006). Other causes of flushing are much more common, however. The overall incidence of each of the event terms discussed in this paragraph was low.

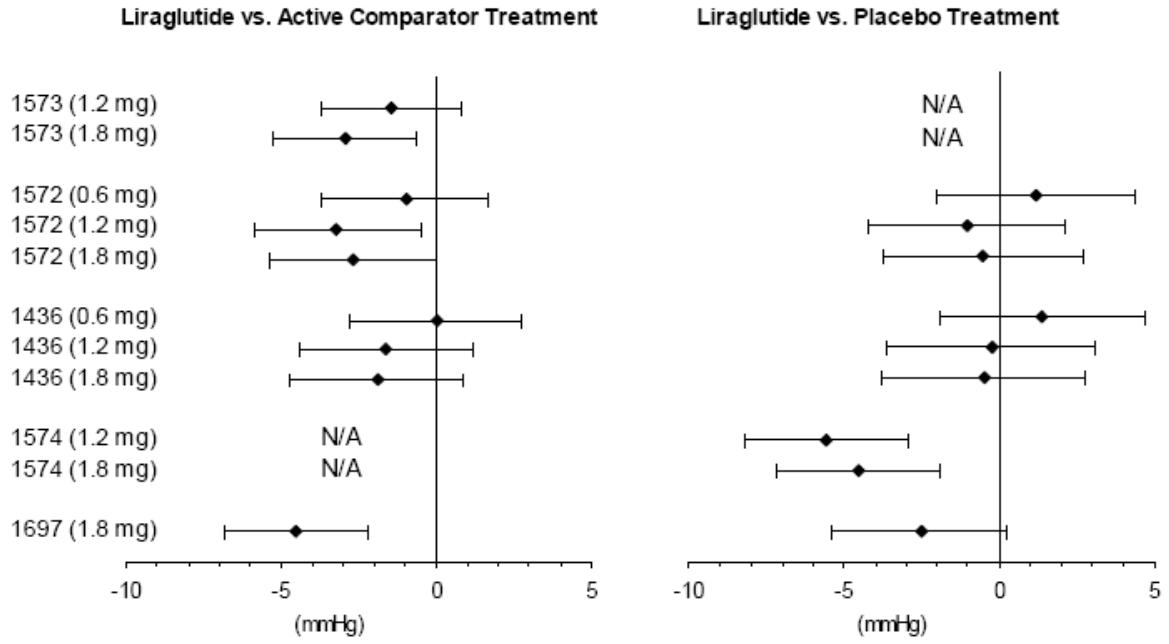
Otherwise, within each of these System Organ Classes, no particular potential cardiovascular event term appeared to show an unfavorable imbalance for liraglutide. Imbalances were not noted for dysrhythmias or cardiac failure events.

II.F. Changes From Baseline in Cardiovascular Risk Factors

Changes from baseline in cardiovascular risk factors (blood pressure, lipids, C-reactive protein et al) were efficacy endpoints. The review of clinical efficacy is being conducted by Dr. Yanoff, and is ongoing. The following sections summarize the applicant's statements regarding changes in these risk factors.

In the long-term (Phase 3) trials, liraglutide did not increase systolic blood pressure; most point estimates for liraglutide vs comparator favored liraglutide, particularly for comparisons to other active antidiabetic agents. The following figure displays point estimates and confidence intervals for change in systolic blood pressure.

Figure II.F.1. Change from Baseline in Systolic Blood Pressure, Liraglutide vs. Comparator, Long-term Trials



Source: Applicant's Figure 3-8, Summary of Clinical Efficacy, pg 117
Time period is from baseline to time of measurement of primary HbA1c efficacy endpoint

The applicant reports that there was no significant effect of liraglutide on diastolic blood pressure in the Phase 3 trials.

The applicant reports that liraglutide was associated with a small but statistically significant increase in heart rate in the long-term trials, as illustrated in the following repeated measurements analysis by the applicant. This analysis is under review.

Table II.F.1. Repeated Measurements Analysis (by Novo) of Heart Rate (Beats per Minute), Long-term Trials

Comparison of levels in Pulse after 26/28, 52 and 76/78 weeks of treatment

Treatment / Comparison	Estimates			P-value
Week 26/28				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	1053	77.55	(0.31)	
Liraglutide 1.2mg	805	77.14	(0.34)	
Liraglutide 0.6mg	471	77.73	(0.40)	
Active Comparator	851	75.82	(0.31)	
Placebo	501	75.03	(0.41)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	1.73	[1.01 ;	2.45]	<.0001
Lira 1.2 vs. Active	1.32	[0.55 ;	2.09]	0.0008
Lira 0.6 vs. Active	1.91	[1.01 ;	2.82]	<.0001
Lira 1.8 vs. Placebo	2.52	[1.67 ;	3.37]	<.0001
Lira 1.2 vs. Placebo	2.11	[1.22 ;	3.00]	<.0001
Lira 0.6 vs. Placebo	2.70	[1.69 ;	3.72]	<.0001
Week 52				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	389	76.84	(0.41)	
Liraglutide 1.2mg	392	77.11	(0.41)	
Liraglutide 0.6mg	173	77.27	(0.57)	
Active Comparator	394	74.94	(0.40)	
Placebo	52	74.38	(0.98)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	1.90	[0.88 ;	2.91]	0.0002
Lira 1.2 vs. Active	2.17	[1.15 ;	3.19]	<.0001
Lira 0.6 vs. Active	2.33	[1.03 ;	3.63]	0.0004
Lira 1.8 vs. Placebo	2.46	[0.44 ;	4.47]	0.0167
Lira 1.2 vs. Placebo	2.73	[0.71 ;	4.75]	0.0080
Lira 0.6 vs. Placebo	2.89	[0.72 ;	5.05]	0.0089
Week 76/78				
Least Square Means	N	LSMean	SE	
Liraglutide 1.8mg	180	76.58	(0.54)	
Liraglutide 1.2mg	194	77.16	(0.53)	
Liraglutide 0.6mg	105	77.49	(0.70)	
Active Comparator	161	75.89	(0.57)	
Placebo	22	74.69	(1.44)	
Estimated Treatment Differences	LSMean	95% CI		
Lira 1.8 vs. Active	0.69	[-0.77 ;	2.16]	0.3528
Lira 1.2 vs. Active	1.27	[-0.18 ;	2.72]	0.0851
Lira 0.6 vs. Active	1.61	[-0.10 ;	3.32]	0.0655
Lira 1.8 vs. Placebo	1.89	[-1.09 ;	4.86]	0.2135
Lira 1.2 vs. Placebo	2.46	[-0.50 ;	5.43]	0.1034
Lira 0.6 vs. Placebo	2.80	[-0.30 ;	5.90]	0.0766

The estimates are from an repeated measurement model with country, previous treatment, treatment, time, treatment by time as fixed effects and baseline pulse level as a covariate and subject as random effect
For complete treatment regimens in the individual trials, see Table 1-1

Cross-reference: Appendix 7.2, Table 243.

Source: Applicant's Table 4-1, Integrated Summary of Safety, pg 203

In general, liraglutide was not associated with significant changes in serum lipids vs. comparator agents. The following table by the applicant displays liraglutide's effect on lipids in the Phase 3 trials. For each trial, and for each lipid category, the table denotes whether liraglutide had no effect (O), had a statistically significant favorable effect (S), or had a statistically significant undesirable effect (I).

Table II.F.2. Effect of Liraglutide on Serum Lipid Parameters, Long-term Trials, Analyses by Novo

Trial ID	Weeks from Baseline	Treatment	FFA	LDL-C	TC	VLDL-C	TG	HDL-C	ApoB
Therapeutic Confirmatory Trials									
1573	52 weeks	Lira							
		vs. Glim	S	O	O	O	O	O	O
1572	26 weeks	Lira+Met							
		vs. Pla+Met	O	O	O	S	S	O	O
		vs. Glim+Met	O	O	O	O	O	O	O
1436	26 weeks	Lira+Glim							
		vs. Pla+Glim	O	O	S	O	O	O	O
		vs. Rosi+Glim	O	S	S	S	O	I	O
1574	26 weeks	Lira+Met+Rosi							
		vs. Pla+Met+Rosi	S	S	O	O	S	O	N/A
1697	26 weeks	Lira+Met+Glim							
		vs. Pla+Met+Glim	S	O	O	O	O	O	O
		vs. Iglar+Met+Glim	O	S	S	O	O	O	O
Therapeutic Exploratory Trials									
1571	14 weeks	Lira							
		vs. Pla	O	I	O	O	S	O	O
1333		Lira							
	1 week	vs. Pla	O	O	S	N/A	O	O	N/A
	8 weeks	vs. Pla	O	O	O	N/A	O	O	N/A
Japanese trial									
1334	14 weeks	Lira							
		vs. Pla	O	O	O	O	O	O	O

S: liraglutide statistically significantly superior
I: liraglutide statistically significantly inferior
O: no difference
N/A: not assessed
Glim: glimepiride, Iglar: insulin glargine, Lira: liraglutide, Met: metformin, Pla: placebo, Rosi: rosiglitazone.

Source: Applicant's Table 3-20, pg 119, Integrated Summary of Efficacy

Liraglutide had no significant effect on change from baseline in levels of hsCRP (highly sensitive C-reactive protein) in the applicant's analyses.

II.G. Total Mortality

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 II.G: Postrandomization Deaths Listing									
Treatment	**Trial**	**Ctr**	**Pt ID**	**Age (Yrs)**	**Gender**	**Dose (mg)**	**Pt-Time (Days)**	**Applicant's Listed Cause of Death**	**Clinical 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 and glimepiride 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 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. 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 consistent with acute and chronic pancreatitis.

II.H. Summary of Observations Regarding Major Adverse Cardiovascular Events

- The liraglutide development program was not prospectively designed to permit a systematic evaluation of cardiovascular events.
- Few major cardiovascular events occurred across the development program, limiting the ability to assess cardiovascular risk.
- Cardiovascular events did not undergo pre-planned adjudication.
- The development program was not designed to include a large number of patients at high risk of cardiovascular events. In fact, intermediate and long-term trials had an exclusion criterion for patients with significant cardiovascular disease, and thus a high incidence of cardiovascular events would not be expected among the population studied in the development program.
- The development program was not designed to facilitate the combination of its trials into a meta-analysis. Trials were of varying durations, and the blinded and open-label periods differed among major Phase 3 trials.
- Choice of endpoint, comparator, and analysis method can alter the results of cardiovascular event analyses.
- In general, when comparing liraglutide to overall pooled comparator (placebo and active comparator) for risk of major adverse cardiovascular events (cardiovascular death, myocardial infarction or stroke), using analysis methods stratified by study, the point estimates were <1, and 95% confidence intervals included 1. The upper bound of the 95% confidence interval usually exceeded 1.3. The estimates were not very sensitive to choice of estimation methodology.
- Comparisons of liraglutide to active comparator for MACE were qualitatively similar to comparisons of liraglutide to total comparator. The estimates were somewhat sensitive to choice of estimation methodology.

- Comparisons of liraglutide to placebo for MACE sometimes resulted in a point estimate >1 (not favoring liraglutide), with the confidence intervals including 1, and an upper bound of the 95% confidence interval >1.8, depending on analysis method. Patients in placebo groups were not at lower cardiovascular risk than patients in other treatment groups, and thus lower risk was not an explanation. Estimates were sensitive to choice of estimation methodology. Low event rates among placebo-treated patients (and low event rates in general) are likely to have contributed to the sensitivity to methodology.
- There did not appear to be a relationship between liraglutide dose and risk of a major adverse cardiovascular event.
- When considering all adverse events that were possibly cardiovascular in nature (not limited to cardiovascular death, stroke or myocardial infarction), there were few events or groups of events which appeared to occur with higher frequency among liraglutide-treated patients than among comparator-treated patients. Overall MedDRA System Organ Class events for the Cardiac Disorders and Vascular Disorders SOCs occurred with slightly numerically higher frequency for liraglutide-treated patients than for placebo-treated patients, but with similar frequency for liraglutide vs. active comparator and liraglutide vs. overall comparator. These were observations of pooled data, and not stratified analyses.
- There were slightly numerically more patients who had events of "hypotension", "angina pectoris" and "myocardial ischemia" in the overall liraglutide group than in the overall comparator group, but the overall incidence of these individual event terms was low. These were observations of pooled data, and not stratified analyses.
- Overall, deaths from any cause occurred at a low rate, and occurred with approximately equal frequency among liraglutide-treated patients and comparator-treated patients.

III. Thyroid Cancer and Hypercalcitoninemia

III.A. Introduction to the Review of Thyroid Cancer and Hypercalcitoninemia

Carcinogenicity studies in rats and mice have demonstrated an increased incidence of thyroid C-cell adenomas and carcinomas associated with liraglutide administration in these species. Please see Dr. Parola's briefing document for details of the findings of these animal studies.

After a finding of increased carcinogenicity risk in animals, it is sometimes difficult to determine whether that finding translates to increased human risk. There are species differences in susceptibility to certain tumors, and there are other differences between rodents and humans which may be relevant. Dr. Parola's review and presentation will address these relevant differences. The clinical review sought to determine whether medullary thyroid cancer occurred in any patients, whether other types of thyroid cancer occurred, and whether potential precancerous signs of medullary thyroid carcinoma, e.g. hypercalcitoninemia or C-cell hyperplasia, occurred.

Medullary thyroid cancer (MTC) is a relatively rare form of thyroid cancer, accounting for only about 5% of all thyroid carcinomas in the United States (Hundahl 1998). It arises from the C-cells of the thyroid gland. The C-cells normally secrete calcitonin, a hormone which is involved in calcium homeostasis. In medullary thyroid carcinoma, calcitonin is often secreted in excess. Most cases of medullary thyroid carcinoma are sporadic, but familial forms exist, in which

medullary thyroid carcinoma is autosomally dominantly inherited, either as the carcinoma alone, or as part of a multiple endocrine neoplasia syndrome. These familial forms of medullary thyroid carcinoma are often associated with mutations in the "rearranged during transfection" (RET) proto-oncogene. Sporadic medullary thyroid carcinoma usually occurs as a single thyroid tumor; familial MTC is often bilateral and multicentric.

In addition to secreting calcitonin, medullary thyroid carcinomas may secrete other substances, including corticotropin, carcinoembryogenic antigen, histamine, and other vasoactive peptides.

The 10-year survival rate of patients with MTC averaged 75% in 1998 (Hundahl 1998), but has probably been improving due to improved early detection and early thyroidectomy for familial forms. Survival is strongly linked to tumor stage and patient age (Modigliani 1998). Sporadic MTC tends to present at a later age and more advanced stage than familial MTC (Massoll 2004).

Sporadic cases of MTC usually present as an isolated thyroid nodule or as part of a multinodular goitre, often asymptomatic and of long standing (Massoll 2004). Metastases are often present at diagnosis. The tumor may sometimes have a history of recent rapid growth with hoarseness, dysphagia or dyspnea; or it may present with systemic symptoms of diarrhea, flushing or bone pain. However, most tumors do not have these features of rapid growth or hormonal manifestations.

Most cases of familial thyroid carcinoma are now diagnosed through testing of the kin of patients with known MTC. The multiple endocrine neoplasia 2A (MEN2A) syndrome may also include pheochromocytoma and/or hyperparathyroidism. The MEN2B syndrome includes a Marfanoid habitus and mucosal neuromata, and may include pheochromocytoma and/or ganglineuromata. In the MEN 2 syndromes, MTC tends to present at an earlier age than in familial MTC outside an MEN syndrome; in MEN2B, MTC may even present in infancy. Guidelines have been established for identification of familial cases, and the timing of surgical intervention, through detection of RET proto-oncogene mutations (current predominant method) and measurement of serum calcitonin (Brandi 2001).

Early complete surgical excision through total thyroidectomy and lymph node dissection is essentially the only curative therapy at this point, although external beam radiotherapy may be effective in eradicating small foci of incompletely resected tumor (Hyer 2000, Massoll 2004, Rougier 1983).

To date, there has not been a clearly-described association between a particular drug and known increased risk of human medullary thyroid carcinoma.

III.B. Liraglutide and Human Thyroid Cancer

III.B.1. Events of Thyroid Cancer

At the time of submission of the NDA, there had been four cases of papillary thyroid cancer among LGT-treated patients and one case among comparator-treated patients. In completed trials, this corresponds to rates of 1.8 and 0.9 events per 1000 patient-years of exposure,

respectively. With the 120-day safety update, an additional case of papillary thyroid cancer was reported for a liraglutide-treated patient (Patient 175008).

The following table provides information regarding these six cases.

Table III.B.1: Papillary Thyroid Cancer Cases from the Liraglutide Development Program

Study	Pt ID	Age	Gender	Tx	Exp	Outcome	Comment
1334	16004	70	f	LGT 0.6	99 d	Thyroid surgery; adjuvant treatment not mentioned; long-term outcome not mentioned	
1573	261006	62	f	LGT 1.2	356 d	"	Elevated calcitonin preop; C-cell hyperplasia on path
	175008	64	m	LGT 1.8	26 d	"	Elevated baseline calcitonin; C-cell hyperplasia on path, "may also be referred to as 'medullary carcinoma in situ'"
1436	506001	59	m	LGT 1.8 + GLIM	175 d	"	Elevated calcitonin preop
1574	326016	53	f	LGT 1.8 + MET + RSG	50 d	"	Elevated calcitonin preop
	326008	59	m	MET + RSG	61 d[1]	"	Elevated calcitonin preop

Source: Applicant's Table 2-23 and narratives, Module 2.7.4, beg pg 115
Abbreviations: Exp = duration of exposure to study medication prior to time cancer was noted, f = female, GLIM = glimepiride, ID = patient identification number, LGT = liraglutide, m = male, MET = metformin, Path = pathology results, preop = preoperatively, Pt = patient, RSG = rosiglitazone, Tx = study drug treatment
1 The applicant's table states that the exposure was 1 day, but the clinical reviewer calculates 61 days.

Brief narratives of these cases follow:

Patient 16004 was a 70 year old woman with a prior history of goitre who received liraglutide, 0.6 mg/day, for 99 days prior to receiving a diagnosis of papillary thyroid cancer. Two months prior to initiation of LGT, at screening, a thyroid ultrasound revealed a nodule in the inferior right lobe of the thyroid; fine needle aspiration (FNA) was suggestive of adenomatoid goitre. The patient completed planned participation in the trial. At or near the end of the trial, the patient underwent repeat fine needle aspiration twice. One FNA was consistent with papillary thyroid carcinoma, and the other was consistent with benign adenoma. Six weeks after cessation of LGT, the patient underwent "a subtotal removal of the right thyroid and D1 dissection". The applicant's narrative states that the pathological diagnosis was "papillary adenocarcinoma, follicular variant, T1bN0M0, EX0". Consistent with the classification, there was no capsular infiltration and no evidence of metastases. The actual surgical pathology report was not provided; it was requested from the applicant on 27 Oct 2008 and again on 11 Feb 2009. On 25 Feb 2009, the applicant reported that no surgical pathology report beyond the stated description was available, although the applicant did provide translations (from Japanese) of other medical records related to the patient's evaluation and treatment. These translations did not mention whether the patient was living in Japan at the time when radiation exposure from Hiroshima or

Nagasaki might have occurred. The patient was discharged seven days after the surgery; follow-up treatment was not reported.

Patient 261006 was a 63 year old woman who received LGT, 1.2 mg/day, for 356 days prior to receiving diagnoses of papillary thyroid cancer and diffuse C-cell hyperplasia. After about 12 months of LGT exposure, the patient had repeated calcium stimulation tests with high calcitonin results. There were no palpable thyroid nodules or enlargement. About 1 month later, ultrasound showed multinodular goitre, with the right lobe more enlarged than the left. One month later, repeat calcium stimulation test again showed "significantly abnormal level of calcitonin". Two months later, a total thyroidectomy was performed. The surgical pathology report was provided (NDA 22341, receipt date 14 Nov 2008, beg pg 139 of case report). Pathology did not reveal medullary thyroid cancer. There were multiple benign adenomatous nodules and a left-sided 1 mm focus of papillary thyroid carcinoma "confirmed by specific stain for papillary thyroid tumour markers". A specific immunohistochemical stain of C-cells showed evidence of C-cell hyperplasia (>50 cells in a single low power field) in multiple blocks. Margins were free of tumor. Tumor-node-metastasis (TNM) classification was not included in the applicant's narrative. The patient was discharged to home one day after surgery; follow-up treatment was not reported.

Patient 506001 was a 59 year old man who received LGT, 1.8 mg/day, for 175 days prior to receiving a diagnosis of papillary thyroid cancer. After about 3 months of LGT treatment, the patient had high calcitonin levels. Two months later, nodular goitre was diagnosed. Three months later, "subtotal thyroidectomy (left lobe)" was performed, which revealed papillary thyroid cancer. The actual surgical pathology report was not provided; it was requested from the applicant on 27 Oct 2008 and again on 11 Feb 2009. On 25 Feb 2009, the applicant provided a translation (from Russian) of a surgical note, which stated that the histology was consistent with "nodular colloid goitre and papillary microcarcinoma/cicatricial carcinoma with calcification (left lobe)". The TNM classification was not reported. The translation does not mention whether the patient had lived in an area with radiation exposure related to the Chernobyl nuclear accident. The patient was discharged to home 3 days after surgery. Two months later, I131 body scan showed no extrathyroidal activity, "and a thyroid stimulating hormone blood sample was normal". (Reviewer note: a normal thyroid-stimulating hormone level [TSH] at the time of radioactive [RAI] scanning may be undesirable. Elevated TSH [either endogenous or attained through exogenous administration] is desired to drive the RAI into any remaining thyroid cancer cells so that they are detectable on the scan.) The patient continued LGT, and completed the trial 7 months post-operatively.

Patient 326016 was a 53 year old woman who received LGT, 1.8 mg/day, for 50 days prior to receiving a diagnosis of papillary thyroid carcinoma. Early in the trial, elevated calcitonin levels were noted. Because of this, thyroid ultrasound was done after about 3 weeks of LGT exposure. Multinodular goitre was noted. One month later, subtotal thyroidectomy was performed. The surgical pathology report was provided (NDA 22341, receipt date 14 Nov 2008, beg pg 105 of case report). In the right lobe, there was a 0.9 cm papillary thyroid carcinoma, and three papillary microcarcinomata (two at 1 mm size, one at 2.5 mm size). The margins were free of tumor. There was evidence of nodular goitre and lymphocytic thyroiditis. There is no mention in the surgical pathology report of staining for calcitonin, and no mention of examination of C-

cells. One month later, completion total thyroidectomy was performed; there was a 2 mm focus of papillary carcinoma in the left lobe, and evidence of lymphocytic thyroiditis. The TNM classification and follow-up were not reported. Liraglutide was not discontinued.

Patient 326008 was a 59 year old man who appears to have received metformin and rosiglitazone for 61 days prior to receiving a diagnosis of papillary thyroid cancer. The applicant's Table 2-23 on page 115 of Module 2.7.4 states that the duration of therapy at onset was 1 day, but the clinical reviewer calculates 61 days. After two months of study drug treatment, the patient had an elevated serum calcitonin (19.4 ng/L, upper limit of normal for assay not mentioned). About six weeks later, thyroid ultrasound showed an enlarged thyroid with left lobe nodules. About one month later, left thyroid lobectomy was performed and pathology revealed papillary thyroid cancer. The surgical pathology report was provided (NDA 22341, receipt date 14 Nov 2008, beg pg 78 of case report). The focus of papillary thyroid carcinoma was in the left lobe and was 1 mm in size. The surgical pathology report specifically states that "No medullary carcinoma is identified". Nodular hyperplasia was noted.

Patient 175008 was a 64 year old man who received liraglutide 1.8 mg for 26 days prior to receiving a diagnosis of papillary thyroid cancer and C-cell hyperplasia. The patient had elevated calcitonin (22.3 ng/L) at baseline. The narrative states that "Though this was considered to be a sign of goitre, the condition was not recorded at baseline. The patient was referred to Primary Care Physician and endocrinologist. Per sponsor request, the patient was withdrawn from the study." The reason for discontinuation was listed as an elevated calcitonin level (NDA 22341 safety update, 23 Sep 2008, pg 62 of CRF), which was listed as occurring on Day 1 of therapy. However, the patient appears to have received liraglutide for 26 days prior to discontinuation. Three days after randomization, thyroid ultrasound showed a small hypoechoic lesion in the left upper pole. After 3.5 more months, the patient underwent thyroidectomy. The surgical pathology report, and a subsequent confirmatory surgical pathology consultation, were provided (NDA 22341, receipt date 25 Feb 2009, beg pg 8 of submission). The surgical pathology report, and the subsequent confirmatory consultation, give diagnoses of bilateral neoplastic C-cell hyperplasia (as opposed to reactive C-cell hyperplasia) and a microscopic (1 mm) papillary carcinoma in the left lobe. There were numerous perifollicular aggregations of atypical C-cells. These aggregations of C-cells were noted immediately adjacent to small collections of solid cell nests, which the pathologist stated were remnants of the ultimobranchial body which gives rise to C-cells. The consultative pathologist states that neoplastic C-cell hyperplasia may also be referred to as "medullary carcinoma in situ". There was a 1 mm focus of papillary carcinoma in the left lobe. There were multiple adenomatoid nodules in both lobes. The patient was discharged one day postoperatively. Five weeks postoperatively, serum calcitonin was reported as normal.

Observations regarding the above cases of papillary thyroid carcinoma include:

- Most cases (4/5 LGT-treated, and the comparator-treated case) were initially identified because of an elevated calcitonin level, rather than because of a palpable nodule.
- Most of the papillary carcinomas which had a size reported were very small (1-2.5 mm), with the largest being 9 mm. In the medical literature, the reported incidence of papillary microcarcinomata (<1 cm in size) has been increasing, but a growing consensus is that this is due to increased detection within thyroid pathology specimens (often from surgeries done for

reasons other than suspected thyroid cancer), rather than a true rise in the incidence of papillary thyroid cancer (Grodski 2008).

- One liraglutide-treated case had a specific report of neoplastic C-cell hyperplasia, which is sometimes referred to as "medullary carcinoma in situ". This patient appears to have had elevated baseline calcitonin.

Also of note is one case of neoplastic C-cell hyperplasia, also referred to as medullary carcinoma in situ, which was diagnosed in one patient 8 months after discontinuation from the active control arm of Study 1572, as described in the narrative below.

Patient 224012 was a 64 year old man who received metformin for 390 days and glimepiride for 370 days. Eight months after discontinuation of these active control drugs, he received a diagnosis of neoplastic C-cell hyperplasia, or medullary carcinoma in situ. The patient had a history of struma nodosa (term commonly used in Germany for multinodular goitre), and a normal calcitonin level at baseline. Three months after randomization, he had an elevated calcitonin level of 3.54 pmol/L (ref range upper limit of normal [ULN] 2.46 pmol/L). Calcitonin remained elevated, and the patient had an abnormal pentagastrin stimulation test near the end of study participation. He was eventually referred for surgery, and underwent total thyroidectomy eight months after discontinuation from study. The surgical pathology report was provided (NDA 22341, submission received 14 Nov 2008, pg 112 of submitted case report). This revealed bilateral nodular goitre. Immunohistochemical staining with antibodies to calcitonin revealed bilateral foci of calcitonin-positive cells, in several cases circumferentially disposed around pre-existing follicles and mostly in small groups. A diagnosis was made of "bilaterally detectable neoplastic-type C-cell hyperplasia (known as medullary carcinoma in situ)".

C-cell hyperplasia (CCH) and its pathologic classification are areas of some controversy within endocrinology. It would be useful to be able to reliably differentiate pathologically between what is termed "reactive" or "physiologic" CCH, which might not be a preneoplastic lesion, and "neoplastic" CCH. Complete resection is probably the only curative option for medullary thyroid carcinoma, and thus accurate early detection of those who are destined to develop it is highly desirable. However, not all individuals with CCH are destined to develop MTC. "Reactive" CCH has been reported in neonates; the elderly; and in patients with hyperparathyroidism, Hashimoto's thyroiditis, and follicular thyroid adenomata (Verga 2007, Guyetant 1994). The basic pathologic definition for CCH is the presence of an increased number of normal C-cells, typically ≥50 C-cells in at least one low power (100x) field (De Lillis 1981, Albores-Saavedra 2001). Perry (1996) proposed a definition for neoplastic CCH as that characterized by the presence of large, mildly to moderately atypical, round, polygonal, or spindle-shaped cells with nuclear pleomorphisms. However, there is controversy regarding whether this is a meaningful definition, whether one can truly distinguish between reactive and neoplastic CCH, whether the absence of these pathologic features is truly reassuring, and whether the presence of these features is reliably predictive of malignant potential (Verga 2007, LiVolsi 1997, Hinze 2001, Kaserer 2001). A specific difficulty with regard to interpretation of surgical findings of CCH in the liraglutide program is the fact that much of the pathology literature for CCH was developed from studies of kindreds with known familial MTC. It is unclear whether features of CCH in these kindreds is comparable to CCH (or early MTC) that is possibly induced by a drug.

There is one approved GLP-1 analogue (Byetta®, exenatide). The agency requested that the sponsor (Amylin Pharmaceuticals) for exenatide provide information on all cases of thyroid cancer in all clinical trials of exenatide. Amylin responded on 19 Dec 2008; as of 30 Sep 2008, there had been no cases of thyroid cancer in clinical trials of Byetta®, which have included >5500 subjects and >4600 subject-years of exposure. Calcitonin was not measured in any of the clinical trials of Byetta®. There had been nine spontaneous postmarketing reports of thyroid cancer (3 papillary and 6 unspecified type); there have been approximately 7 million prescriptions filled for Byetta® with an estimated cumulative exposure of 840,000 patient-years.

III.B.2. Nonmalignant Thyroid Adverse Events

The following table summarizes nonmalignant serious thyroid-related adverse events.

Table III.B.2.a: Nonmalignant Thyroid-related Serious Adverse Events

Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
	n	%	Rate/ 1000 PY	n	%	Rate/ 1000 PY
Benign neoplasm of thyroid gland	1	<0.1	0.4	0	0	0
Goitre	3	0.1	1.3	0	0	0
Thyroid disorder	1	<0.1	0.4	0	0	0

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

Patient 222002 had events of goitre and elevated blood calcitonin. This was a 56 year old German man who presented after 206 days of LGT at 1.8 mg/day with "struma nodosa". He also had an elevated calcitonin level of 7.05 pmol/L (normal range 0.2-2.46). His serum calcitonin continued to increase; 3 months later it was reported at 23.4 pg/mL (nl range <18.9). An ultrasound revealed a right thyroid nodule; scintigraphy was consistent with "struma nodosa". Medullary thyroid cancer was suspected. Six weeks after the ultrasound, the thyroid nodule was excised and was benign. He recovered from surgery uneventfully. Regular sonography and calcitonin levels were planned for follow-up.

Patient 232004 had events of goitre and elevated blood calcitonin. This was a 47 year old German woman who presented with elevated blood calcitonin (level not mentioned) and a solitary right thyroid nodule after 27 days of run-in metformin therapy. Although she was randomized to liraglutide, the narrative states she never received the drug. Eight months after the elevated calcitonin and the nodule were noted, she underwent resection of the nodule, which was benign. One month postoperatively, her calcitonin level was reported as normal.

Patient 261006 had events of benign neoplasm of thyroid gland, thyroid disorder, and papillary thyroid cancer. This patient is further discussed in Section III.B.1.

Patient 326016 had events of goitre and papillary thyroid cancer. This patient is further discussed in Section III.B.1.

Patient 769005 had an event of goitre. This was a 69 year old Slovak man who presented with asymptomatic "moderate struma nodosa" after 221 days of comparator therapy. The narrative states that papillary thyroid cancer was suspected, although no biopsy is mentioned. Thyroidectomy was recommended, but the patient refused. The trial drug appears to have been discontinued per protocol 18 days before the patient's presentation with goitre. The patient remained asymptomatic at last follow-up, which was approximately 74 days after presentation, and continued to refuse surgery.

There are too few cases of nonmalignant serious thyroid disorders to assign causality to liraglutide.

Across all trials of liraglutide at the time of NDA submission, thyroid adverse events occurred with higher numerical frequency among LGT-treated patients than among comparator-treated patients, as shown in the following table:

Table III.B.2.b: Overall Summary of Incidence of Thyroid Events, Safety Analysis Set, All Completed Trials

	LGT N=4211 PY=2241	**Non-LGT N=2272 PY=1139**
Number of subjects with serious thyroid adverse events (%)	7 (0.2)	1 (<0.1)
Number of serious thyroid adverse events	10	1
Total number of subjects with thyroid adverse events (serious + nonserious)	61 (1.4)	24 (1.1)
Total number of thyroid adverse events (serious + nonserious)	80	25
Number of serious thyroid adverse events per 1000 PY	4.5	0.9
Number of overall thyroid adverse events per 1000 PY (serious + nonserious)	35.7	22.0

Source: Applicant's Table 2-16, pg 107, ISS
Abbreviations: LGT = liraglutide, PY = patient-years

Thyroid adverse events also occurred at a higher numerical rate per unit of patient-time among LGT-exposed patients than among comparator patients.

In the four trials which were ongoing at the time of submission of the NDA, there was a similar imbalance of thyroid adverse events; some data are still blinded.

Table III.B.2.c: Summary of Incidence of Thyroid Events, Ongoing Trials at Time of NDA Submission

	LGT N=714 PY=602	**Non-LGT N=362 PY=294**	**Blinded N=467 PY=164**
Number of subjects with serious thyroid adverse events (%)	1 (0.1)	0	1 (0.2)
Number of serious thyroid adverse events	1	0	1
Total number of subjects with thyroid adverse events (serious + nonserious) (%)	10 (1.4)	2 (0.6)	5 (1.1)
Total number of thyroid adverse events (serious + nonserious)	10	2	6

Table III.B.2.c: Summary of Incidence of Thyroid Events, Ongoing Trials at Time of NDA Submission			
	LGT N=714 PY=602	**Non-LGT N=362 PY=294**	**Blinded N=467 PY=164**
Number of serious thyroid adverse events per 1000 PY	1.7	0	6.1
Number of overall thyroid adverse events per 1000 PY (serious + nonserious)	16.6	6.8	36.5
Source: Applicant's Table 2-17, pg 108, ISS			

The applicant reports that, although patient-time data are still blinded in the ongoing trials, it is known that three of the events occurred among patients treated with LGT 1.8 mg and two occurred among patients treated with exenatide. For LGT, one patient had an event of autoimmune thyroiditis and thyroid neoplasm (Patient 476001) and two patients had increased calcitonin (Patients 352004 and 352013). The thyroid events among exenatide-treated patients in the blinded studies were both events of hyperthyroidism (Patients 206005 and 207002).

Dose dependency was not noted for thyroid events in completed trials, as shown in the following table:

Table III.B.2.d: Rates of Thyroid Adverse Events by LGT Dose, Completed Trials							
	<0.6 mg	**0.6 mg**	**>0.6 and <1.2 mg**	**1.2 mg**	**>1.2 and <1.8 mg**	**1.8 mg**	**>1.8 mg**
Number of patients	377	641	417	993	73	1408	302
Number of patient-years	64	418	39	758	12	870	82
Number of serious thyroid adverse events per 1000 PY	0	4.8	0	5.3	0	4.6	0
Total number of thyroid adverse events per 1000 PY (serious + nonserious)	141.6	38.3	76.9	33.0	0	29.9	12.2
Source: Applicant's Table 2-18, pg 108, ISS							

The following table presents adverse thyroid events by System Organ Class and Preferred Term.

Table III.B.2.e: Thyroid Adverse Events, Safety Analysis Set at Time of NDA Submission							
System Organ Class	**Preferred Term**	**LGT N=4211 PY=2241**			**Non-LGT N=2272 PY=1139**		
		n	**%**	**Rate per 1000 PY**	**n**	**%**	**Rate per 1000 PY**
Any	**Any thyroid term**	61	1.4	35.7	24	1.1	22.0
Investigations	**Any thyroid term**	30	0.7	14.3	13	0.6	11.4
	Blood calcitonin increased	25	0.6	11.6	10	0.4	8.8
	Blood TSH increased	3	0.1	1.8	2	0.1	1.8
	Blood calcitonin abnormal	1	<0.1	0.4	0	0	0

Table III.B.2.e: Thyroid Adverse Events, Safety Analysis Set at Time of NDA Submission							
System Organ Class	**Preferred Term**	**LGT N=4211 PY=2241**			**Non-LGT N=2272 PY=1139**		
		n	**%**	**Rate per 1000 PY**	**n**	**%**	**Rate per 1000 PY**
	Thyroxine decreased	1	<0.1	0.4	0	0	0
	Blood TSH decreased	0	0	0	1	<0.1	0.9
Endocrine disorders	**Any thyroid term**	21	0.5	11.6	7	0.3	6.1
	Goitre	15	0.4	7.1	1	<0.1	0.9
	Hypothyroidism	3	0.1	1.3	4	0.2	3.5
	Hyperthyroidism	2	<0.1	0.9	0	0	0
	Thyroid cyst	2	<0.1	0.9	0	0	0
	Thyroid disorder	2	<0.1	0.9	0	0	0
	Autoimmune thyroiditis	1	<0.1	0.4	2	0.1	1.8
Neoplasms	**Any thyroid term**	19	0.5	9.8	5	0.2	4.4
	Thyroid neoplasm	15	0.4	7.1	4	0.2	3.5
	Papillary thyroid cancer	4	0.1	1.8	1	<0.1	0.9
	Benign neoplasm of thyroid gland	1	<0.1	0.4	0	0	0
	Parathyroid tumor benign	1	<0.1	0.4	0	0	0

Source: Applicant's Table 2-19, pg 110, ISS
Abbreviations: LGT = liraglutide, PY = patient-years, TSH = thyroid stimulating hormone

Events which occurred with a higher numerical frequency among LGT-treated patients than among comparator-treated patients included blood calcitonin increased, goitre, and thyroid neoplasm. One of the events listed under the Preferred Term "thyroid disorder" was a case of diffuse C-cell hyperplasia (Patient 261006).

Regarding the term thyroid neoplasm, 14/19 events (3 PBO, 11 LGT) came from a single study (1334), which was performed in Japan. This study was one of four studies in which thyroid ultrasounds were performed, and in this study, the appearance of thyroid nodules on ultrasound was reported as an adverse event for some, but not all, patients who were found to have a nodule on ultrasound. See Table III.B.2.f below.

The Preferred Term "goitre" was applied to a variety of verbatim descriptions of thyroid events, including "struma nodosa" (n=4), and one case each of "goitre nodular", "la goitre", "increase size thyroid left lobe", "increasing awareness of existing goitre", "multinodular goitre", "nodular goitre", "nontoxic struma unidosa right side", "struma unidosa nontoxic", "swollen thyroid right lobe", "thyroid enlargement", "thyromegaly", "thyromegaly left lobe with cystic mass" and "worsening of thyroid goitre".

As mentioned earlier in the discussion of cardiovascular events, the terms "flushing" and "hot flush" were reported slightly numerically more frequently for liraglutide-treated patients than for comparator-treated patients. Each of these terms was reported for only 1 comparator-treated patient (<0.1%). "Flushing" was reported for 9 (0.2%) of liraglutide-treated patients, and "hot flush" was reported for 7 (0.2%) of liraglutide-treated patients. Medullary thyroid carcinoma is a

rare entity in the differential diagnosis of flushing, although other causes of flushing are much more common.

Thyroid ultrasound was performed at baseline and end of study in four trials (1334, 1571, 1636 and 1694). In these trials, no patient had appearance of a new nodule ≥10 mm in diameter, and no patient had growth of an existing nodule by ≥10 mm. However, the longest duration of these trials was 14 weeks, which is a short observation time for the assessment of stimulation of thyroid nodule growth. In examining the study results for Study 1334, which was a 14-week study performed in Japan, new appearance of smaller thyroid nodules (<10 mm) was common, but did not appear to occur with significantly higher frequency among liraglutide-treated patients than among placebo-treated patients.

Table III.B.2.f: Incidence of New Thyroid Nodules <10 mm in Diameter, Week 14, Study 1334 (LOCF)

Treatment Group	N	# New Thyroid Nodules	% With New Thyroid Nodule
PBO	44	4	9.1
LGT 0.1 mg	45	6	13.3
LGT 0.3 mg	46	1	2.2
LGT 0.6 mg	45	5	11.1
LGT 0.9 mg	44	5	11.4
Any LGT	180	17	9.4

Source: Module 5, Clinical Trial Report for 1334, Table 12-13, pg 117

III.C. Hypercalcitoninemia

Calcitonin (CT) is a 32 amino acid peptide which is synthesized in mammals in a number of tissues, but especially in the C-cells of the thyroid gland. It has several known biologic effects. Its most prominent current uses in human medicine are related to its effect of lowering of plasma calcium due to an inhibitory effect on osteoclast-mediated bone resorption, and its role as a tumor marker for medullary thyroid cancer. This latter role is of interest for liraglutide.

In normal humans, circulating levels of calcitonin are very low (<10 pg/mL). Elevation of blood calcium concentration stimulates calcitonin release from C-cells, and low blood calcium levels inhibit calcitonin release. As mentioned earlier, medullary thyroid cancer cells often produce calcitonin in excess, and thus it is a tumor marker for this malignancy. Numerous other factors can also cause elevation of calcitonin levels, including smoking (d'Herbomez 2007), chronic renal failure, isolated C-cell hyperplasia in association with lymphocytic thyroiditis or follicular thyroid carcinoma, neuroendocrine tumors (Niccoli 1996), hypergastrinemia (Hadjadj 1997), sepsis (d'Herbomez 2001), acute pancreatitis, burns (Findlay 2004), and other conditions.

There is perhaps some interplay between glucose metabolism and calcitonin. Intravenous insulin administered to pigs has been shown to increase calcitonin levels, and infusion of insulin directly into surgically-isolated in situ pig thyroid gland produced an increase in the secretion rate of calcitonin in thyroid venous effluent blood (Care 1998). Care also demonstrated that intravenous glucose administration raised insulin and calcitonin levels in pigs. Specific binding of radiolabeled insulin has been demonstrated in pig thyroid plasma membranes, and in rat and

human medullary thyroid carcinoma C-cells (Care 1998). In rabbit cell models, removal of glucose from the extracellular medium inhibited the normal plateau of calcitonin-induced proton efflux (Santhanagopal 2001); such an effect in humans might result in a feedback-based increase in calcitonin release in response to glucose lowering. In rat liver cells, calcitonin stimulated glycogenolysis and gluconeogenesis (Yamaguchi and Williamson 1983). Addition of calcitonin to isolated rat pancreatic islets inhibited glucose-stimulated insulin release (Alwmark 1986). Administration of calcitonin to healthy humans has been associated with increased blood glucose and decreased blood insulin (Young 1995, Passariello 1989, Giugliano 1984, Petralito 1979) in some studies. Administration of calcitonin during oral glucose tolerance testing in healthy humans, and humans with impaired baseline glucose tolerance, showed an impairment of glucose tolerance with inhibition of glucose-induced insulin secretion and reduction of glucose-mediated glucagon suppression (Passariello 1981). In other studies, however, calcitonin administration resulted in no change in blood glucose, but still caused a fall in serum insulin (Stevenson 1985). The increased serum glucose noted with acute calcitonin administration may not be sustained with chronic administration (Giugliano 1982). The effects of other specific diabetes drugs (other than insulin) on calcitonin levels has not been well-described.

In humans with poorly controlled type 2 diabetes mellitus (Gregorio 1994), and in prepubertal children with type 1 diabetes mellitus (Verrotti 1988), serum calcitonin levels were normal. Human diabetic ketoacidosis, which is associated with insulin deficiency, was not associated with a change in calcitonin level in one study (Topaloglu 2005).

Several researchers have noted homology in amino acid sequences for the A-chain of insulin, calcitonin, the calcitonin-gene-related peptides, and amylin, suggesting that these are part of a superfamily of biologically active peptides (Cooper 1989).

Thus, although data are not entirely consistent, it appears that calcitonin can increase glucose levels in humans, and conversely, that glucose lowering or insulin elevation can increase calcitonin release. Liraglutide stimulates glucose-dependent insulin release, and therefore could have some effect on calcitonin levels which could be independent of a neoplastic effect on C-cells. However, some other antidiabetic agents, such as sulfonylureas, also increase insulin levels, and might also be expected to have a stimulatory effect on calcitonin release.

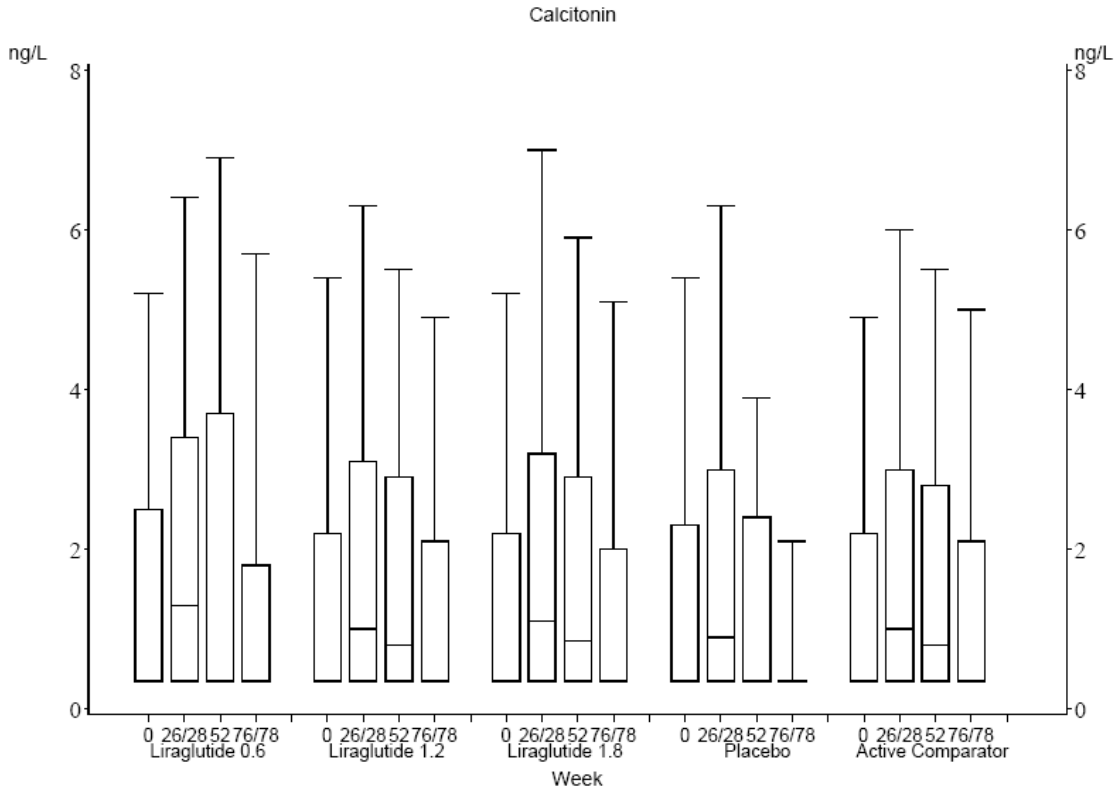
Routine measurement of calcitonin in all patients presenting with thyroid nodules has been advocated (Elisei 2008), with the rationale that the only curative treatment for medullary thyroid carcinoma is early surgical resection, and that serum calcitonin measurement is more sensitive than fine needle aspiration cytology in detecting MTC. In one analysis, measurement of serum calcitonin in the evaluation of thyroid nodules appeared to be comparably cost-effective to other cancer screening procedures such as colonoscopy and mammography (Cheung 2008). However, in the United States, serum calcitonin is not always measured in the routine evaluation of thyroid nodules, and published consensus guidelines do not yet advocate this routine measurement.

The applicant measured calcitonin in the five long-term clinical trials, and in one single-dose, three short-term and three intermediate-term trials. The applicant also performed calcium stimulation tests on a subpopulation of patients from long-term trials 1573 and 1574. The assay used had a lower limit of quantification (LLOQ) of 0.7 ng/L. Values below the LLOQ were

imputed as 0.35 ng/L. The upper limit of normal for the assay was 5.0 ng/L for women and 8.4 ng/L for men. The clinical review concentrated on data from the long-term trials (Studies 1436, 1572, 1573, 1574 and 1697), for which more extensive analyses were available.

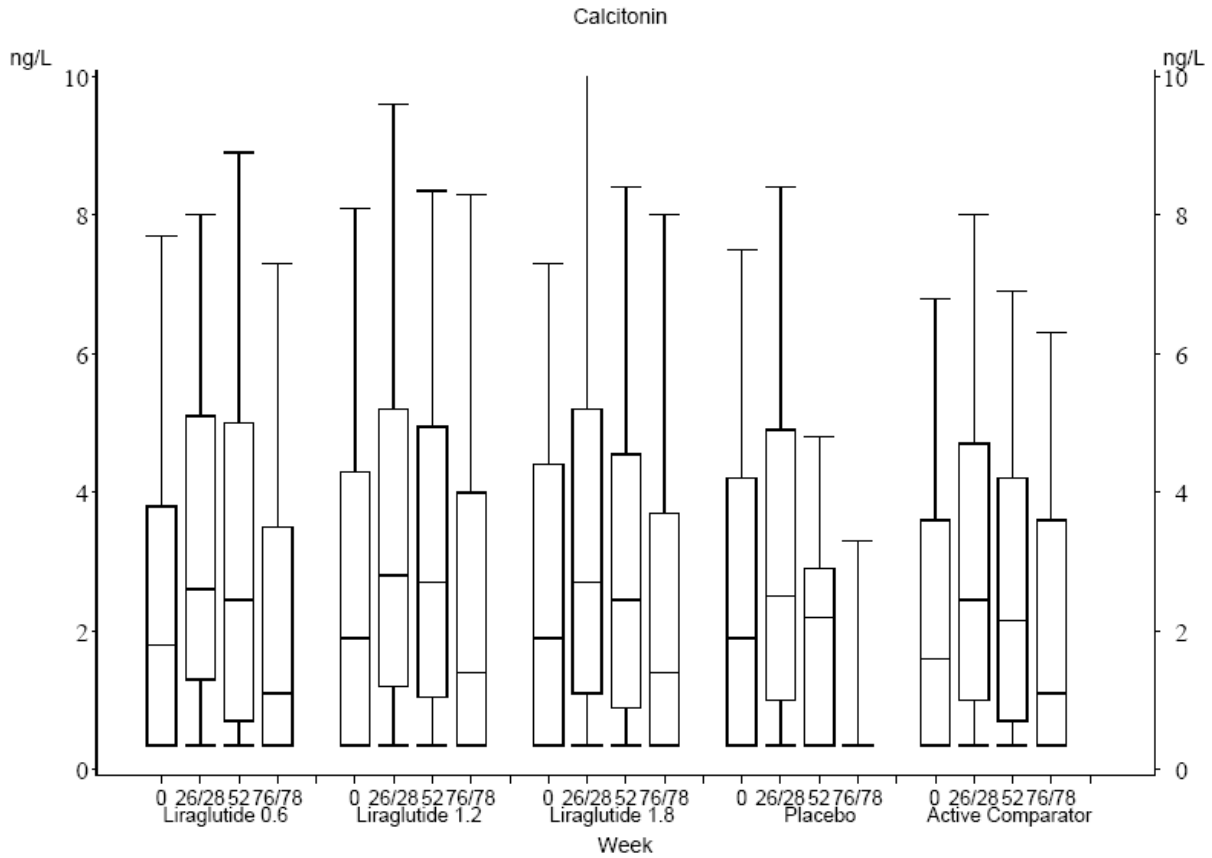
The following box plots present mean and other percentile data for women and men. Visual interpretation of the plots is somewhat complicated by the fact that 85% of women and 30% of men had baseline calcitonin levels below the LLOQ at baseline, and many had values below the LLOQ at other times also. For each box plot, the topmost horizontal line represents the 90th percentile; and the upper limit of the box represents the 75th percentile. If a box has a horizontal line within the box, that line represents the 50th percentile; if a box has no horizontal line within the box, the 50th percentile was at or below the LLOQ. The lower limit of the box represents the 25th percentile. If there is a horizontal line below the lower limit of the box, that line represents the 10th percentile; if there is no horizontal line below the lower limit of the box, the 10th percentile was at or below the LLOQ.

Figure III.C.1: Box Plots for Calcitonin Values for Women, All Long-term Trials



Source: Applicant's Figure 3-1, pg 176, ISS, Module 2.7.4

Figure III.C.2: Box Plots for Calcitonin Values for Men, All Long-term Trials



Source: Applicant's Figure 3-2, pg 177, ISS, Module 2.7.4

At baseline, calcitonin levels were comparable across treatment groups. As expected, women tended to have lower baseline calcitonin levels than men had. The treatment duration was 26 weeks for Studies 1572, 1436, 1574 and 1697, and 28 weeks for Study 1573. At 26-28 weeks, mean calcitonin levels went up in all treatment groups for both genders, and this increase did not differ significantly between groups when all trials were grouped, as in these figures. Mean values at subsequent time points trended toward lower values compared to the 26-28 week timepoints, and did not differ significantly between treatment groups.

The following tables show the percentages of patients whose calcitonin values shifted from baseline at given time points.

The table below shows the percentages of patients with calcitonin shifts from baseline to weeks 26-28 of treatment for the long-term trials. This span of time likely includes the most interpretable data, because trials were randomized and blinded to this point, and subsequent timepoints include some voluntary extension data, with the potential for confounding.

Table III.C.1: Percentages of Patients with Calcitonin Shifts, Baseline to Weeks 26-28 of Treatment, LOCF, All Long-term Trials

		Both sexes Endpoint After 26/28 weeks					Female Endpoint After 26/28 weeks					Male Endpoint After 26/28 weeks				
	Baseline	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤
Liraglutide 0.6mg	1 <LLOQ	34.5	13.7	-	-	1.1	65.8	15.6	-	-	2.0	12.0	12.3	-	-	0.4
	2 LLOQ-UNR	0.6	35.4	2.1	-	0.2	1.0	7.5	1.0	-	-	0.4	55.4	2.9	-	0.4
	3 >UNR-2*UNR	-	0.6	2.1	1.5	-	-	-	1.0	0.5	-	-	1.1	2.9	2.2	-
	4 >2*UNR	-	-	0.4	0.2	-	-	-	-	-	-	-	-	0.7	0.4	-
	5 Missing	0.8	4.2	0.2	-	2.3	1.0	2.0	-	-	2.5	0.7	5.8	0.4	-	2.2
Liraglutide 1.2mg	1 <LLOQ	37.8	14.1	0.1	-	0.2	63.7	16.8	0.2	-	0.2	12.2	11.3	-	-	0.2
	2 LLOQ-UNR	0.4	32.0	1.8	0.1	0.3	0.4	10.5	-	-	-	0.4	53.3	3.6	0.2	0.7
	3 >UNR-2*UNR	0.1	0.6	2.7	0.1	-	0.2	0.2	0.4	0.2	-	-	0.9	4.9	-	-
	4 >2*UNR	-	0.1	0.3	1.1	-	-	-	-	0.2	-	-	0.2	0.7	2.0	-
	5 Missing	1.5	2.3	0.1	-	4.1	2.7	0.9	-	-	3.1	0.2	3.8	0.2	-	5.1
Liraglutide 1.8mg	1 <LLOQ	34.1	15.7	-	-	0.4	59.5	19.2	-	-	0.6	11.9	12.6	-	-	0.3
	2 LLOQ-UNR	1.4	31.4	3.5	-	0.2	0.8	8.9	0.8	-	-	2.0	51.0	6.0	-	0.3
	3 >UNR-2*UNR	-	0.3	1.9	0.8	-	-	-	0.6	-	-	-	0.5	3.0	1.5	-
	4 >2*UNR	0.1	0.1	0.1	0.5	-	0.2	-	-	-	-	-	0.2	0.2	1.0	-
	5 Missing	1.8	3.1	0.5	0.2	4.0	3.2	1.7	-	-	4.6	0.5	4.3	1.0	0.3	3.5
Placebo	1 <LLOQ	36.1	13.7	0.2	-	0.2	63.6	14.8	0.4	-	0.4	13.5	12.8	-	-	-
	2 LLOQ-UNR	1.9	33.4	2.1	-	0.2	2.1	9.7	-	-	-	1.7	52.8	3.8	-	0.3
	3 >UNR-2*UNR	-	0.8	2.5	-	0.2	-	-	-	-	-	-	1.4	4.5	-	0.3
	4 >2*UNR	-	-	0.6	0.2	-	-	-	-	-	-	-	-	1.0	0.3	-
	5 Missing	1.9	1.9	-	-	4.2	2.1	2.1	-	-	4.7	1.7	1.7	-	-	3.8
Active Comparator	1 <LLOQ	35.9	14.4	0.2	-	0.3	62.2	14.5	0.2	-	0.7	13.9	14.3	0.2	-	-
	2 LLOQ-UNR	1.3	34.7	2.3	-	0.1	1.6	10.6	1.4	-	-	1.0	54.9	3.1	-	0.2
	3 >UNR-2*UNR	-	0.3	1.3	0.3	-	-	-	0.7	-	-	-	0.6	1.7	0.6	-
	4 >2*UNR	-	0.1	0.4	1.2	-	-	-	-	0.2	-	-	0.2	0.8	1.9	-
	5 Missing	1.0	2.1	0.2	-	3.9	1.8	2.1	-	-	3.9	0.4	2.1	0.4	-	3.9

1¤: <LLOQ, 2¤: LLOQ-UNR [upper limit of the normal range], 3¤: >UNR-2*UNR, 4¤: >2*UNR, 5¤: Missing
Endpoint recorded at Wk 26 for Studies 1572, 1436, 1574 and 1697; and at Wk 28 for Study 1573
Source: Applicant's Table 215, pg 1531, Module 5.3.5.3, Appendix 7.2

From baseline to 26-28 weeks, there was a dose-dependent trend for liraglutide-treated women to shift from calcitonin values below the LLOQ to values within the range of quantitation. The percentage of women who exhibited this shift was numerically higher for each of the LGT dose groups than for either placebo or active comparator. This trend was not noted for men.

The table below sums the total percentage of patients who had an upward shift of any degree in calcitonin values from baseline to 26-28 weeks.

Table III.C.2: Total Percentages of Patients Who had any Upward Shift in Calcitonin Levels From Baseline to 26-28 Weeks, LOCF, All Long-term Trials

Treatment	Both Genders %	Women %	Men %
LGT 0.6 mg	17.3	17.1	17.8
LGT 1.2 mg	16.2	17.2	15.1
LGT 1.8 mg	20.0	20.0	20.1
PBO	16.0	15.2	16.6
Active Comparator	17.2	16.1	18.2

Source: Derived from Table III.C.1 above

When examining the total percentage of patients who had an upward shift of any degree in calcitonin values from baseline to 26-28 weeks, the treatment group with the highest percentage of upward shifters was the LGT 1.8 mg group for both genders. The 1.8 mg dose group had a numerically higher percentage of shifters than either of the other LGT doses, and a higher

percentage than the placebo and active comparator groups. However, LGT dose-dependency was not noted.

The following two tables include information on shifts from baseline to 52 weeks, and from baseline to 76/78 weeks, respectively, for the two trials which had data beyond 28 weeks. These data should be interpreted with caution, because data beyond 26/28 weeks include some open-label extension periods, with the possibility for confounding.

Table III.C.3: Percentages of Patients with Calcitonin Shifts, Baseline to Weeks 52 of Treatment, LOCF, Long-term Trials 1573 (Continued Main Trial) and 1572 (Continued into Open Label Extension)

		Both sexes Endpoint After 52 weeks					Female Endpoint After 52 weeks					Male Endpoint After 52 weeks				
	Baseline	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤
Liraglutide 0.6mg	1 <LLOQ	41.8	6.0	-	-	-	81.1	2.7	-	-	-	15.5	8.2	-	-	-
	2 LLOQ-UNR	4.3	31.0	2.7	-	-	2.7	4.1	1.4	-	-	5.5	49.1	3.6	-	-
	3 >UNR-2*UNR	-	-	2.7	1.6	-	-	-	1.4	-	-	-	-	3.6	2.7	-
	4 >2*UNR	-	-	0.5	-	-	-	-	-	-	-	-	-	0.9	-	-
	5 Missing	4.9	3.8	0.5	-	-	6.8	-	-	-	-	3.6	6.4	0.9	-	-
Liraglutide 1.2mg	1 <LLOQ	34.7	10.0	-	-	0.2	58.1	9.3	-	-	0.5	11.2	10.7	-	-	-
	2 LLOQ-UNR	3.0	26.8	2.3	-	-	2.8	7.4	0.5	-	-	3.3	46.3	4.2	-	-
	3 >UNR-2*UNR	-	0.7	1.9	-	-	-	0.5	0.5	-	-	-	0.9	3.3	-	-
	4 >2*UNR	-	-	0.2	0.5	-	-	-	-	0.5	-	-	-	0.5	0.5	-
	5 Missing	2.8	1.2	-	-	15.6	5.1	-	-	-	14.9	0.5	2.3	-	-	16.4
Liraglutide 1.8mg	1 <LLOQ	31.4	10.0	0.2	-	-	57.7	9.3	0.5	-	-	8.8	10.6	-	-	-
	2 LLOQ-UNR	3.8	27.6	1.9	-	-	1.5	7.2	1.5	-	-	5.8	45.1	2.2	-	-
	3 >UNR-2*UNR	-	0.2	1.0	1.4	-	-	-	0.5	-	-	-	0.4	1.3	2.7	-
	4 >2*UNR	-	-	0.5	-	-	-	-	-	-	-	-	-	0.9	-	-
	5 Missing	4.3	2.4	0.5	0.5	14.3	5.7	1.0	-	-	14.9	3.1	3.5	0.9	0.9	13.7
Placebo	1 <LLOQ	39.3	11.5	-	-	-	66.7	12.5	-	-	-	21.6	10.8	-	-	-
	2 LLOQ-UNR	6.6	31.1	1.6	-	-	4.2	-	-	-	-	8.1	51.4	2.7	-	-
	3 >UNR-2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	4 >2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5 Missing	8.2	1.6	-	-	-	16.7	-	-	-	-	2.7	2.7	-	-	-
Active Comparator	1 <LLOQ	31.6	11.8	-	-	0.2	54.1	9.3	-	-	0.5	13.1	13.9	-	-	-
	2 LLOQ-UNR	4.2	26.9	2.1	-	-	4.1	6.2	1.5	-	-	4.2	43.9	2.5	-	-
	3 >UNR-2*UNR	-	0.5	0.5	0.2	-	-	-	-	-	-	-	0.8	0.8	0.4	-
	4 >2*UNR	-	0.2	-	0.9	-	-	-	-	-	-	-	0.4	-	1.7	-
	5 Missing	0.9	2.1	-	-	17.9	1.0	1.5	-	-	21.6	0.8	2.5	-	-	14.8

1¤: <LLOQ, 2¤: LLOQ-UNR, 3¤: >UNR-2*UNR, 4¤: >2*UNR, 5¤: Missing
Source: Applicant's Table 216, pg 1532, Module 5.3.5.3, Appendix 7.2

Table III.C.4: Percentages of Patients with Calcitonin Shifts, Baseline to Weeks 76-78 of Treatment, LOCF, Long-term Trials 1572 and 1573 (Both Trials Continued into Open Label Extension)

		Both sexes Endpoint After 76/78 weeks					Female Endpoint After 76/78 weeks					Male Endpoint After 76/78 weeks				
	Baseline	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤	1¤	2¤	3¤	4¤	5¤
Liraglutide 0.6mg	1 <LLOQ	44.0	2.2	-	-	-	81.1	-	-	-	-	19.1	3.6	-	-	-
	2 LLOQ-UNR	14.1	20.1	1.1	-	-	6.8	-	-	-	-	19.1	33.6	1.8	-	-
	3 >UNR-2*UNR	-	0.5	2.2	1.6	-	-	1.4	-	-	-	-	-	3.6	2.7	-
	4 >2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5 Missing	4.3	2.7	-	-	7.1	5.4	-	-	-	5.4	3.6	4.5	-	-	8.2
Liraglutide 1.2mg	1 <LLOQ	43.1	6.4	-	-	-	67.9	6.7	-	-	-	17.9	6.2	-	-	-
	2 LLOQ-UNR	10.4	23.9	2.1	0.3	-	3.6	8.5	-	-	-	17.3	39.5	4.3	0.6	-
	3 >UNR-2*UNR	0.3	1.2	1.2	0.3	-	0.6	-	-	-	-	-	2.5	2.5	0.6	-
	4 >2*UNR	-	-	0.3	0.6	-	-	-	-	0.6	-	-	-	0.6	0.6	-
	5 Missing	4.0	0.6	-	-	5.2	6.1	-	-	-	6.1	1.9	1.2	-	-	4.3
Liraglutide 1.8mg	1 <LLOQ	36.6	7.0	-	-	-	63.5	6.1	-	-	-	14.4	7.8	-	-	-
	2 LLOQ-UNR	13.1	22.0	2.4	-	-	5.4	6.8	0.7	-	-	19.4	34.4	3.9	-	-
	3 >UNR-2*UNR	-	0.9	1.5	0.3	-	-	-	0.7	-	-	-	1.7	2.2	0.6	-
	4 >2*UNR	-	-	0.3	0.3	-	-	-	-	-	-	-	-	0.6	0.6	-
	5 Missing	6.1	1.8	0.3	0.3	7.0	8.1	0.7	-	-	8.1	4.4	2.8	0.6	0.6	6.1
Placebo	1 <LLOQ	37.7	3.3	-	-	-	66.7	4.2	-	-	-	18.9	2.7	-	-	-
	2 LLOQ-UNR	19.7	8.2	1.6	-	-	-	4.2	-	-	-	32.4	10.8	2.7	-	-
	3 >UNR-2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	4 >2*UNR	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5 Missing	8.2	-	-	-	21.3	16.7	-	-	-	8.3	2.7	-	-	-	29.7
Active Comparator	1 <LLOQ	39.1	8.8	-	0.3	-	64.7	9.0	-	0.8	-	20.9	8.6	-	-	-
	2 LLOQ-UNR	12.2	22.2	2.8	-	-	5.3	8.3	0.8	-	-	17.1	32.1	4.3	-	-
	3 >UNR-2*UNR	-	0.6	0.9	-	-	-	-	-	-	-	-	1.1	1.6	-	-
	4 >2*UNR	-	0.3	-	0.9	-	-	-	-	-	-	-	0.5	-	1.6	-
	5 Missing	2.5	1.6	-	-	7.8	3.8	-	-	-	7.5	1.6	2.7	-	-	8.0

1¤: <LLOQ, 2¤: LLOQ-UNR, 3¤: >UNR-2*UNR, 4¤: >2*UNR, 5¤: Missing
Endpoint recorded at Wk 76 for Study 1573 and Wk 78 for Study 1572
Source: Applicant's Table 217, pg 1533, Module 5.3.5.3, Appendix 7.2

As mentioned earlier, data from the above two tables should be interpreted with caution, because they include some open-label extension data from voluntary extensions. The percentage of missing data is higher for these time periods than for the period from baseline to 26/28 weeks. Both these factors may result in confounding. Clear patterns of upward shifts which distinguish liraglutide from comparators are not identified. It appears that overall, a lower percentage of patients at these points still had a calcitonin value which remained above their baseline, indicating that some patients who had shifted above normal earlier in the trial might later have returned to baseline, but the confounding factors prevent assurance in this observation.

The applicant performed a repeated measurement analysis on data from Weeks 12 and 26/28 from the long-term trials. These analyses are presented in the following table. We recommend that the p-values from this statistical analysis model be viewed as exploratory findings, because this analysis is part of a larger exploratory evaluation of many safety endpoints. The statistical estimates and p-values from this analysis model may be useful in identifying possible trends and relationships for further study. We also note that the pooled safety database combines data from studies that are each designed somewhat differently, with respect to the study arms and to the patient population. For this reason, relationships identified from this statistical analysis model should be viewed as exploratory findings.

Table III.C.5: Repeated Measurement Analyses for Calcitonin, All Long-term Trials, Safety Analysis Set

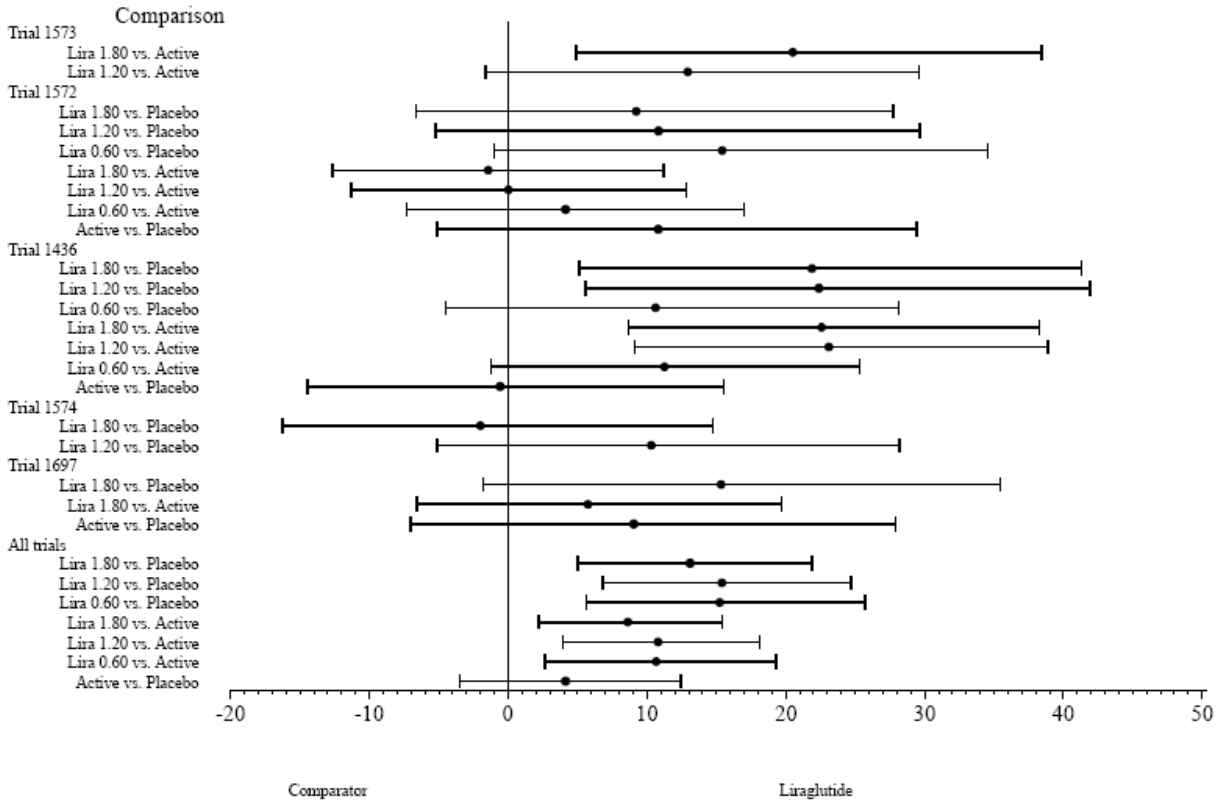
Week	Treatment	Calcitonin (ng/L) LS Mean (95% CI)	Comparison	Relative Difference % (95% CI)	p-value
12	LGT 1.8 mg	0.76 (0.72, 0.81)			
	LGT 1.2 mg	0.78 (0.73, 0.83)			
	LGT 0.6 mg	0.78 (0.72, 0.84)			
	AC	0.70 (0.66, 0.74)			
	PBO	0.67 (0.63, 0.73)			
			LGT 1.8 vs. PBO	13.0 (4.8, 21.8)	0.0014
			LGT 1.2 vs. PBO	15.4 (6.7, 24.7)	0.0003
			LGT 0.6 vs. PBO	15.2 (5.5, 25.7)	0.0015
			LGT 1.8 vs. AC	8.6 (2.2, 15.4)	0.0080
			LGT 1.2 vs. AC	10.9 (3.9, 18.3)	0.0017
			LGT 0.6 vs. AC	10.7 (2.6, 19.4)	0.0084
			AC vs. PBO	4.0 (-3.7, 12.4)	0.3118
26	LGT 1.8	1.01 (0.95, 1.06)			
	LGT 1.2	0.99 (0.94, 1.05)			
	LGT 0.6	0.96 (0.90, 1.04)			
	AC	0.97 (0.91, 1.02)			
	PBO	0.89 (0.83, 0.95)			
			LGT 1.8 vs. PBO	13.6 (6.1, 21.6)	0.0003
			LGT 1.2 vs. PBO	11.8 (4.1, 20.2)	0.0023
			LGT 0.6 vs. PBO	8.8 (0.3, 17.9)	0.0428
			LGT 1.8 vs. AC	4.3 (-1.6, 10.4)	0.1542
			LGT 1.2 vs. AC	2.7 (-3.5, 9.2)	0.4024
			LGT 0.6 vs. AC	-0.1 (-7.1, 7.3)	0.9683
			AC vs. PBO	8.9 (1.5, 16.9)	0.0181

Source: Applicant's Table 3-4, Module 2.7.4, pg 185
For description of analysis methods, see pages 183-184 of Module 2.7.4. Repeated measurement analysis for normal censored data. Logarithm of calcitonin was censored response. Trial time, treatment, gender and treatment by time interaction were fixed effects. Subjects entered as random effects. Calcitonin values at LLOQ (0.7 ng/L) were considered censored results; incorporated into statistical model by adding the information into the likelihood function. The contribution to the likelihood function for the censored terms corresponds to the distribution function taken at 0.7 ng/L.

At Week 12, mean calcitonin levels were higher for all three LGT dose groups than for either PBO or active comparator. Relative percent differences were statistically significant for comparisons of all LGT doses vs. either PBO or active comparator. At Week 26, relative percent differences remained statistically significantly different for comparisons of LGT to PBO, but not for LGT vs. active control.

The following two forest plots display relative differences between treatment arms in each of the long-term trials at 12 and 26 weeks.

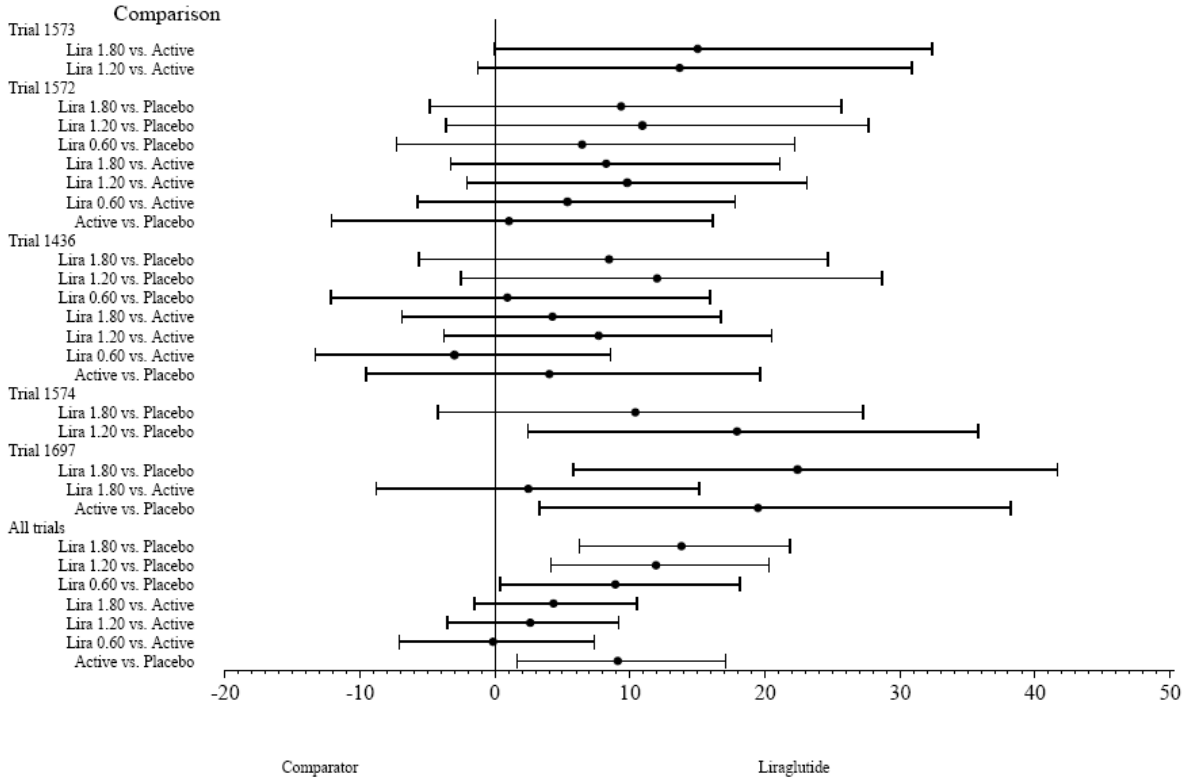
Figure III.C.3: Forest Plot of Calcitonin Continuous Analysis (Percent Relative Difference), Long-term Trials, Week 12



Source: Applicant's Figure 83, Module 5.3.5.3, pg 2982

At Week 12, for the combined data, all relative differences between liraglutide and comparator are statistically significantly different. In individual trials, the point estimate for the relative difference for most treatment comparisons is consistent with higher calcitonin values for liraglutide than comparator, although many of these confidence intervals include zero. Liraglutide dose dependency for calcitonin relative differences is not demonstrated.

Figure III.C.4: Forest Plot of Calcitonin Continuous Analysis (Percent Relative Difference), Long-term Trials, Week 26/28



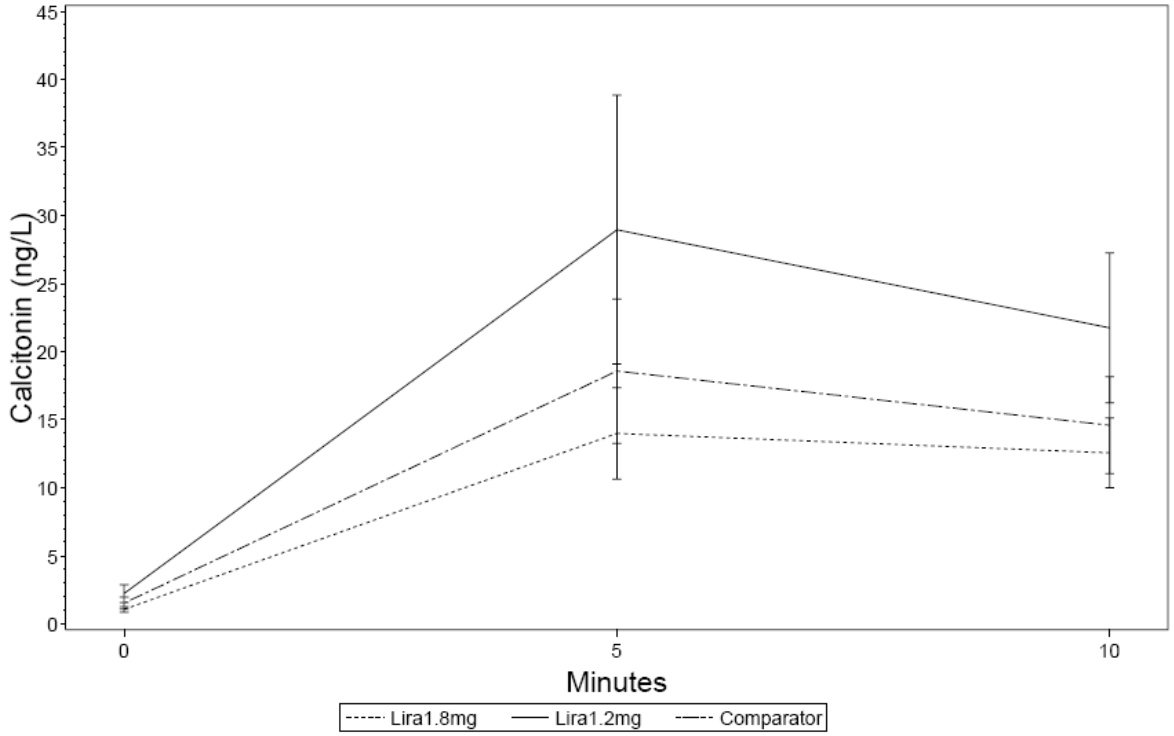
Source: Applicant's Figure 3-9, Module 2.7.4, pg 192

At 26/28 weeks, fewer relative differences are statistically significantly different for liraglutide vs. comparator. Point estimates for almost all treatment comparison are consistent with higher calcitonin values for liraglutide than for comparator, although many of these confidence intervals include zero. In the combined trials, there appears to be a pattern of liraglutide dose-dependence for increasing calcitonin relative differences. Overall, relative differences are higher for liraglutide vs. placebo than for liraglutide vs. active comparator.

Calcium stimulation tests were performed on a subset of patients (total N=144) from Study 1573 (Weeks 0 and 52; 90 patients included) and Study 1574 (Weeks 0 and 26; 54 patients included). Calcium or pentagastrin stimulation tests were used in the past (prior to the availability of RET proto-oncogene testing) in the evaluation of family members of patients with known medullary thyroid carcinoma, in an effort to identify MTC in family members at an early stage. Use of the stimulation test was based on the observation that basal calcitonin levels were sometimes not elevated in patients with C-cell hyperplasia or small tumors, but often increased to abnormally high levels after stimulation with calcium and/or pentagastrin (Becker 1995). Calcium stimulation tests are not used as commonly now. The usefulness of this test in the setting of evaluation of a potential drug-induced C-cell disorder is unknown. In this test, fasting subjects received 2 mg elemental calcium (as calcium gluconate) per kg of body weight, infused intravenously over 5 minutes. Blood samples were obtained at times 0, 5 and 10 minutes.

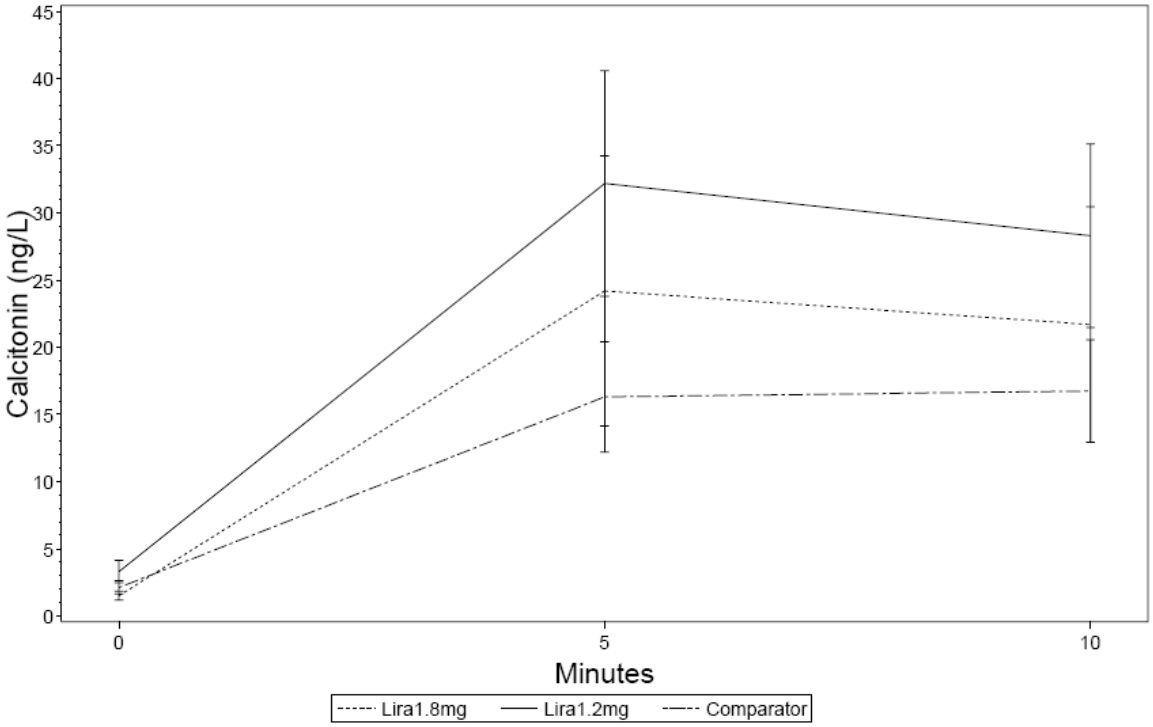
Treatments included LGT 1.8 mg, LGT 1.2 mg, and comparator. Study 1573 used an active comparator (glimepiride), and Study 1574 used an add-on placebo-controlled design, in which either LGT or PBO was added to baseline combination metformin and rosiglitazone. At both time zero and end of trial (26 or 52 weeks, LOCF), stimulated calcitonin values were highest in the 1.2 mg LGT group, intermediate in the 1.8 mg LGT group, and lowest in comparator. There was no statistically significant difference between LGT and comparator, as illustrated in the following graphs. However, stimulated calcitonin levels were higher at end of study than at baseline in the LGT groups.

Figure III.C.5: Mean Calcitonin Values (ng/L) During Calcium Stimulation Test, Week Zero, Studies 1573 and 1574



Source: Applicant's Figure 124, pg 3023, Module 5.3.5.3

Figure III.C.6: Mean Calcitonin Values (ng/L) During Calcium Stimulation Test, End of Study (LOCF), Studies 1573 and 1574



Source: Applicant's Figure 125, pg 3024, Module 5.3.5.3

III.D. Summary of Observations Regarding Thyroid Cancer and Hypercalcitoninemia

- Carcinogenicity studies in rats and mice have demonstrated an increased incidence of thyroid C-cell adenomas and carcinomas associated with liraglutide administration in these species.
- The applicability of these rat and mouse findings to humans is not fully understood.
- There have not been clear-cut cases of medullary thyroid carcinoma in humans who received liraglutide.
- In clinical trials of liraglutide, there have been five cases of papillary thyroid carcinoma among liraglutide-treated patients, and one case in a comparator-treated patient. At the time of submission of the NDA, the rates for papillary thyroid carcinoma were 1.8 vs. 0.9 events per 1000 patient-years for liraglutide vs. comparator.
- Four out of the five liraglutide-treated patients who had papillary thyroid carcinoma also had elevated calcitonin preoperatively, as did the single comparator-treated patient who had papillary thyroid carcinoma. The remaining liraglutide-treated patient who had papillary thyroid carcinoma had a thyroid nodule at baseline.
- Most of the reported papillary thyroid cancers were very small. Papillary microcarcinomata (<1 cm diameter) are common in the general population, and are often incidental findings. However, given the relatively short duration of observation in the liraglutide trials, and the often indolent nature of many thyroid cancers (papillary thyroid cancer in general, and many medullary thyroid cancers), large tumors might not be expected in the clinical trials, even if the tumors were drug-induced.

- Regarding the numerical imbalance in cases of papillary thyroid cancer, a question arises regarding whether liraglutide was inducing papillary thyroid cancer, or whether it was "inducing" thyroidectomies (for hypercalcitoninemia and/or thyroid nodules), with the subsequent incidental discovery of papillary microcarcinomata.
- One of the cases of papillary thyroid cancer also had "neoplastic C-cell hyperplasia", which the pathologist stated is sometimes referred to as "medullary carcinoma in situ".
- Among comparator-treated patients, there was one patient who was found to have neoplastic C-cell hyperplasia eight months after discontinuation of active comparator. The pathology report for this case also stated that this is sometimes referred to as "medullary carcinoma in situ".
- The clinical importance of these cases of "medullary carcinoma in situ" is not clear. It is also not clear whether the difference in temporal association between the liraglutide-associated case and the comparator-associated case makes a difference in clinical interpretation.
- One other liraglutide-treated patient who had papillary thyroid carcinoma also had C-cell hyperplasia.
- It is difficult to know whether the literature regarding the pathologic features of human C-cell hyperplasia is fully relevant to a possible drug-induced condition, because most of the literature is derived from studies of kindreds with familial medullary thyroid carcinoma.
- The only approved GLP-1 analogue, exenatide, has not had any cases of thyroid cancer in clinical trials, although calcitonin measurements (which prompted further evaluation and subsequent detection of 4/5 cases of thyroid cancer in patients treated with liraglutide) were not routinely performed in the exenatide clinical trials. There have been 9 spontaneous postmarketing reports of thyroid cancer (3 papillary and 6 unspecified type) for exenatide. There have been approximately 7 million prescriptions filled for exenatide, with an estimated cumulative exposure of 840,000 patient-years.
- Adverse events of goitre were reported numerically more frequently for liraglutide-treated patients than for comparator-treated patients.
- In long-term clinical trials of liraglutide, there was a dose-dependent trend for liraglutide-treated women to shift from calcitonin values below the lower limit of quantitation to within the range of quantitation, from baseline to 26 or 28 weeks of treatment.
- In long-term trials, when examining the total percentage of patients (men or women) who had an upward shift of any degree in calcitonin values from baseline to 26 or 28 weeks of treatment, the treatment group with the highest percentage of upward shifters was the liraglutide 1.8 mg dose group. The 1.8 mg dose group had a numerically higher percentage of shifters than either of the other liraglutide doses (1.2 or 0.6 mg), and a higher percentage than the placebo and active comparator groups. However, liraglutide dose-dependency was not noted in this observation.
- In long-term trials, repeated measurement analyses showed that at Week 12, mean calcitonin levels were statistically significantly higher for all doses of liraglutide vs. placebo, and for all doses of liraglutide vs. active control. At Week 26, differences remained significant for liraglutide vs. placebo, but not for liraglutide vs. active control. These analyses should be considered exploratory in nature.
- When examining a forest plot of calcitonin data from all long-term trials, in the combined trials, there appears to be a pattern of liraglutide dose-dependence at Week 26/28 but not at Week 12. That is, the point estimates for liraglutide vs. comparator at Week 26/28 are successively higher for the 0.6, 1.2 and 1.8 mg liraglutide doses. Relative differences are

greater for liraglutide vs. placebo than for liraglutide vs. active comparator, but the pattern of liraglutide dose-dependence occurs for both comparators.

- Previous medical literature has described some interplay between calcitonin and glucose metabolism, with a possible tendency toward increasing calcitonin levels with increases in insulin and/or declines in glucose. It is unknown whether this contributed in part to the observed increases in calcitonin with liraglutide. The specific effects of other individual diabetes drugs (other than insulin) on calcitonin levels have not been well-described.
- If liraglutide is approved, questions may arise regarding whether baseline evaluation of thyroid nodule status or serum calcitonin is needed. There may also be questions regarding the need for ongoing monitoring.
- Thyroid nodules are common (2-6% with palpation, 19-35% with ultrasound, 8-65% at autopsy [Dean 2008]). If liraglutide is approved, questions may arise regarding what a physician should do if a patient who is treated with liraglutide is found to have a thyroid nodule. Questions may also arise regarding when surgery is indicated for liraglutide-treated patients with thyroid nodules and/or elevated serum calcitonin values.
- Enhanced monitoring for thyroid nodules or elevated calcitonin could result in an increased rate of thyroidectomy. Thyroidectomy has some known risks, such as recurrent laryngeal nerve injury with vocal cord dysfunction, hypoparathyroidism and anesthetic complications. Patients with diabetes may have a higher risk of postoperative complications in general, such as impaired wound healing. An increased likelihood of thyroidectomy, especially in patients with diabetes, might be considered a risk in itself.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-341 **INFORMATION REQUEST LETTER**

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your May 23, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Victoza (liraglutide) Injection.

In anticipation of the upcoming Advisory Committee meeting for your product, we request that you submit for our review the following data regarding major adverse cardiovascular events (MACE).

Submit the requested data no later than January 21, 2009, to ensure that there is sufficient time for review.

Please provide information and analyses regarding MACE events as follows:

I. Analysis population(s):

A. The main analysis population should include the randomized, double-blind, controlled periods for all completed Phase 2 and Phase 3 trials of your product.

B. An additional analysis population should include the randomized, controlled periods for all completed Phase 2 and Phase 3 trials of your product. That is, include unblinded periods if they remain controlled, and include controlled data past the primary HbA1c efficacy measurement, if applicable. Do not include uncontrolled extension periods.

II. Endpoints: Use the following two endpoints, which will be referred to hereafter as “SMQ MACE” and “Custom MACE”. We acknowledge that there may be many opinions about what precise terms should be included in these endpoints, but these are the terms we want you to use. For nonfatal events, use MedDRA Preferred Terms as they were originally assigned in your NDA submission. Do not use post hoc adjudication for nonfatal events. Adjudication of cardiovascular deaths is acceptable. Do not add or subtract Preferred Terms from either endpoint. If you wish to provide separate analyses with independent external post hoc

adjudication of nonfatal events from the specified endpoints, you may do so, but you must submit the analyses with unadjudicated Preferred Terms for nonfatal events as requested.

"SMQ MACE": Use a composite endpoint of cardiovascular death, and all Preferred Terms in the Standardised MedDRA Queries for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents".

"Custom MACE": Use a composite endpoint of cardiovascular death and the following MedDRA Preferred Terms:

- Acute myocardial infarction
- Basilar artery thrombosis
- Brain stem infarction
- Brain stem stroke
- Brain stem thrombosis
- Carotid arterial embolus
- Carotid artery thrombosis
- Cerebellar infarction
- Cerebral artery embolism
- Cerebral artery thrombosis
- Cerebral infarction
- Cerebral thrombosis
- Cerebrovascular accident
- Coronary artery thrombosis
- Embolic cerebral infarction
- Embolic stroke
- Hemorrhagic cerebral infarction
- Hemorrhagic stroke
- Hemorrhagic transformation stroke
- Ischemic cerebral infarction
- Ischemic stroke
- Lacunar infarction
- Lateral medullary syndrome
- Moyamoya disease
- Myocardial infarction
- Papillary muscle infarction
- Postprocedural myocardial infarction
- Postprocedural stroke
- Silent myocardial infarction
- Stroke in evolution
- Thalamic infarction
- Thrombotic cerebral infarction
- Thrombotic stroke
- Wallenberg syndrome

III. Types of Analyses

A. Listing

List all events (including those from uncontrolled portions of the trials) from both the "SMQ MACE" and the "Custom MACE" endpoints, including both the first event observed and any subsequent events observed. The listing should be sorted by treatment group and patient ID. For patients with multiple events, the events should be listed in order of occurrence. The events should be defined by MedDRA Preferred Terms. A proposed format for this listing is shown below:

Table 1 (example) Listing of MACE events sorted by treatment group and type of event for all studies

Pt ID	Study	Treatment	MedDRA Preferred Term	Date of event	Time on study at time of event	In the main analysis population?	Serious event?	SMQ MACE?	Custom MACE?

B. Summaries

1. Summary of the incidence of SMQ MACE and Custom MACE events in the main analysis population and in the additional analysis populations by dose of the study drug. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 2 (example) Incidence of SMQ MACE events in the main analysis population, by dose of study drug

	Dose 1	Dose 2	Dose 3	All Doses	Placebo Comparator	Active Comparator
Pooled	x/X (y%)					
Study 1						
Study 2						
Study 3						
Study 4						

x= number of events for that group
X=total number of randomized patients in the safety database for that group
y=x/X times 100

2. Summaries of the incidence of SMQ MACE events and Custom MACE events in the main analysis population and the additional analysis population, combined across doses of the study drug in separate tables. Only the first MACE event for each patient is counted in these analyses. If a study has more than one type of comparator group, report the incidence of SMQ MACE events and Custom MACE events from the placebo comparator group separately from the active comparator group. A proposed format for this summary table is shown below.

Table 3 (example) Incidence of SMQ MACE events in the main analysis population, combined across doses of study drug, reported separately by study

Study	Group	N	Exposure (Pt-Yrs)	# Events	Incidence (events/N)	Incidence ratio, 95% CI	Incidence difference, 95% CI	Incidence rate (events/Pt-yrs)	Incidence rate ratio, 95% CI	Incidence rate difference, 95% CI
Study 1	Study Drug									
	Active Comparator									
	Placebo Comparator									
Study 2	Study Drug									
	Active Comparator									
	Placebo Comparator									
etc	etc									
etc	etc									
Overall results stratified by study										

C. Analyses

For SMQ MACE and custom MACE, analyze both the incidence (events/N) and the incidence rate (events/patient-year) using the analysis populations described under I. A. and B. of this document. If the set of Phase 2 and 3 studies has more than one type of comparator group, we recommend making three comparisons: a) the study drug compared to the placebo; b) the study drug compared to the active comparator; and c) the study drug compared to the placebo and the active comparator groups combined. Analysis c) is the analysis that should be presented in the last line of Table 3 and the Forest plots discussed in Section D.

The analyses should be stratified by study and we recommend that a stratified exact method be included as one of the analyses. However, we acknowledge that multiple studies may have 0

MACE events in one or more groups and that pooling studies for an unstratified analysis may be a reasonable alternative.

D. Forest Plots

For SMQ MACE and custom MACE, provide a forest plot depicting the incidence ratio results from the individual studies and the results from the overall stratified analysis for the primary analysis population described in I. A.

E. Electronic Data Files

Please provide a dataset with a single observation for each patient which includes the following:

- Study identifier
- Unique patient identifier
- Demographic data
- Date of randomization
- Treatment group
- Date of completion/rescue/discontinuation of the randomized, controlled, double-blind period of the study
- Exposure time in the randomized, controlled, double-blind period of the study
- Participated in extension study (Yes/No)
- For each of the composite endpoints (”SMQ MACE” and “Custom MACE”), include the following set of variables:
    a) Duration of time from randomization to date of first event or censoring
    b) Indicator for whether or not the event took place during the double blind period
    c) Censoring variable
    d) Date of event or censoring
- MedDRA Preferred Term for “SMQ MACE”
- MedDRA Preferred Term for “Custom MACE”

If you have any questions, call John Bishai, Ph.D., Regulatory Project Manager, at 301-796-1311.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	022341/0
Drug Name:	Victoza™ (liraglutide) injection
Indication(s):	Treatment of type 2 diabetes mellitus
Applicant:	Novo Nordisk Inc
Date(s):	Submission date: May 23, 2008
	PDUFA Goal Date (extended): May 23, 2009
	Advisory Committee Date: April 2, 2009
	Briefing document: March 2, 2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewers:	J. Todd Sahlroot, Team Leader and Deputy Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Karen Mahoney, M.D., Medical Reviewer
	Lisa Yanoff, M.D., Medical Reviewer
	Hylton Joffe, M.D., Medical Team Leader
	Mary H. Parks, M.D., Division Director
Project Manager:	John Bishai, Ph.D.

Keywords: clinical studies, NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Efficacy Conclusions: Based on an evaluation of the five key Phase 3 studies, I conclude that the efficacy of liraglutide 1.2 mg and 1.8 mg is supported by the comparisons to placebo and to active control comparators in a range of background antidiabetic therapies. The efficacy of liraglutide 0.6 mg is less well supported.

Monotherapy: Liraglutide monotherapy resulted in a net average reduction in HbA1c at week 52 of 0.33 for the 1.2 mg dose and 0.62 for the 1.8 mg dose compared to the active comparator glimepiride 8 mg monotherapy. These comparisons were statistically significant in the direction of superiority of liraglutide monotherapy to the active control monotherapy.

Add-on therapy: Liraglutide as an add-on therapy resulted in net average reductions in HbA1c at week 26 that ranged from 0.78 to 1.36 compared to placebo, with a range of background antidiabetic therapies, for the 1.2 mg dose and the 1.8 mg dose. These reductions were statistically significant in the direction of superiority to liraglutide add-on therapy. The background therapies were metformin 2 g, glimepiride 4 mg, metformin 2 g + rosiglitazone 8 mg *(4 mg BID)*, and glimepiride 4 mg + metformin 2 g.

With these same background therapies, liraglutide compared to an active control resulted in either a non-inferior HbA1c response or superior HbA1c response, as summarized below:

- Liraglude was non-inferior to glimepiride 4 mg for both the 1.2 mg dose and the 1.8 mg dose (metformin 2 g background therapy).

- Liraglutide was superior to rosiglitazone 4 mg, for both the 1.2 mg dose and the 1.8 mg dose (glimepiride 4 mg background therapy). Caveat: by trial design, the active comparator dose of rosiglitazone was one half the maximal FDA approved dose of 8 mg.

- Liraglutide 1.8 mg was superior to insulin glargine (glimepiride 4 mg + metformin 2 g background therapy); this statistical review does not address the adequacy of the glargine titration.

The efficacy of liraglutide 0.6 mg is less well supported. Liraglutide 0.6 mg was non-inferior to rosiglitazone 0.4 mg (glimepiride background therapy). However, liraglutide 0.6 mg did not meet the criteria for non-inferiority to glimepiride 4 mg (metformin background therapy).

Although the studies were not powered for a comparison between liraglutide dose arms, and these comparisons were not included in the pre-specified sequential testing protocol, it can be noted that the 95% confidence intervals of the average HbA1c change from baseline for the 1.2

mg and 1.8 mg dose arms overlapped to a great extent in three of the four studies in which both doses were evaluated. In the other study, the 95% confidence interval of the 1.8 mg dose arms overlapped less with the 95% CI of the 1.2 mg dose, in the direction of a greater average reduction in HbA1c with the larger dose.

Results for fasting plasma glucose supported the efficacy of liraglutide as monotherapy and as an add-on to background therapy with the other anti-diabetic drugs used in these studies.

The average HbA1c response in the younger and older age groups (< 65 and ≥ 65 years) and in males and females were relatively similar. Most subjects were Caucasian in each of the five key studies. In the two studies with subjects from the U.S., the numbers of subjects in the other identified race categories were small and did not support an evaluation of potential race-related difference in HbA1c reduction. These two studies had reasonable representation in the Hispanic/Latino ethnicity subgroup, and the average HbA1c response was relatively similar in this subgroup compared to the non-Hispanic/Latino subgroup.

The results from the phase 3 studies support the conclusion that liraglutide is associated with an average net loss in weight at 26 weeks and 52 weeks compared to several of the background diabetic therapies used in the studies. This may be a clinically relevant finding, considering that a range of 43% to 74% of subjects in the five phase 3 studies were classified as obese at baseline with a BMI ≥ 30 kg/m^2. Approximately half of the subjects (ranging from 40% to 62%) in the liraglutide arms lost from 0% to 5% of their baseline body weight at the study endpoint.

Safety Conclusions: Conclusions regarding the safety of liraglutide are addressed in the clinical review by Dr. Karen M. Mahoney.

Recommendations: Specific recommendations for labeling are not included in this review and will be covered in a later communication.

1.2 Brief Overview of Clinical Studies

The clinical development of liraglutide included efficacy studies of liraglutide monotherapy and add-on combination therapy with other common oral anti-diabetic drugs (glimepiride, metformin, rosiglitazone or insulin). Two general populations of subjects with type 2 diabetes mellitus were examined. A monotherapy phase 3 study was performed in subjects who had never received pharmacologic therapy or had received only minimal therapy. Add-on combination therapy studies were conducted in subjects who were inadequately controlled by their existing therapy. The design of the five Phase 3 studies shared some common features and also had some differences. All studies were randomized, controlled and double-blind. The monotherapy study had an active control comparator arm, and the primary efficacy endpoint was evaluated after 52 weeks of treatment. The four add-on studies were evaluated after 26 weeks of treatment. Three of the add-on studies included both a placebo comparator arm and an active control comparator arm. One of the add-on studies had a placebo control arm but not an active

control arm. Three dose levels of liraglutide, 0.6 mg, 1.2 mg and 1.8 mg were evaluated in the Phase 3 program, but not all three arms were included in each study.

The primary efficacy criterion in all major studies was the change from baseline to study endpoint (week 26 or 52) in glycated hemoglobin (HbA1c). Change in body weight was a key secondary efficacy endpoint. A total of 3992 subjects were randomized in five Phase 3 clinical studies. These five key studies are the focus of this statistical review.

1.3 Statistical Issues and Findings

Based on an evaluation of the five key Phase 3 studies, I conclude that the efficacy of liraglutide 1.2 mg and 1.8 mg is supported by the comparisons to placebo and to active control comparators in a range of background antidiabetic therapies. The efficacy of liraglutide 0.6 mg is less well supported. The estimated effects of liraglutide on HbA1c change from baseline at week 26 and week 52 in the different target populations and background antidiabetic therapies are summarized in TABLE 8.

Support for the efficacy of liraglutide compared to a placebo control and compared to an active control also comes from a consistent pattern of early withdrawals due to ineffective therapy, when observed across the five studies. In the four studies that had a placebo add-on arm, subjects in this arm were more likely to withdraw early due to ineffective therapy than subjects in the liraglutide arms. In the four studies that had an active comparator arm, subjects in this arm were about equally likely to withdraw early due to ineffective therapy as subjects in the liraglutide arms.

A potential concern for the statistical analysis of the primary endpoint arose for the monotherapy study, because of the occurrence of a substantial percentage of subjects with HbA1c $\leq$ 7.0 at baseline. In the monotherapy study, conducted with an active control comparator, 11.7% of subjects had baseline HbA1c levels $\leq$ 7.0, and another 18.1% of subjects had baseline HbA1c between 7.0 and 7.5. This relatively high proportion of subjects who were in reasonable diabetic control at baseline raised the concern that both the active control comparator and the liraglutide arms would tend to have a small average change from baseline HbA1c at the study endpoint. This assumption comes from a general finding across clinical studies of anti-diabetic drugs that subjects with lower levels of HbA1c at baseline tend to experience smaller decreases in HbA1c at the study endpoint compared to subjects with higher levels at baseline. In this situation, the assay sensitivity of the comparison may not have supported a non-inferiority margin of 0.4. However, the two liraglutide arms were superior to the active control arm for the primary endpoint, with statistically significant differences for both comparisons. For this reason, the proportion of subjects in reasonable diabetic control at baseline was not a review issue. However, this topic is an important consideration for future active-controlled studies.

The inclusion of both an active control arm and a placebo control arm in three of the studies presented an opportunity to estimate the placebo-adjusted effect of the active control comparator within the study. In all three studies, the placebo-adjusted effect was statistically significantly different from 0. The net effect of glimepiride was similar to the results from the three historical placebo-controlled studies of glimepiride that were used to support the non-inferiority margin of 0.4.

2. INTRODUCTION

2.1 Overview

Type 2 diabetes mellitus (diabetes) is a complex metabolic disorder characterized by abnormal glucose metabolism. The pathogenesis is not fully understood but is heterogeneous, involving environmental, lifestyle, and genetic factors. This leads to chronic hyperglycemia caused by abnormal beta-cell function, peripheral tissue insulin resistance, and abnormal glucose metabolism in the liver. Diet and exercise are important and effective measures for maintaining glycemic control in individuals with insulin resistance, impaired glucose tolerance, and overt diabetes, and are particularly effective in the early stages of disease progression. In cases where diet and exercise alone fail to adequately maintain glycemic control, oral anti-diabetic drugs can be used. Major classes of oral antidiabetic drugs that are currently available are biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, and meglitinides[1].

Victoza™ (liraglutide) is a member of an additional class of antidiabetic drug intended for the treatment of diabetes. Liraglutide is an analogue to human glucagon-like peptide-1 (GLP-1), classified as a GLP-1 receptor agonist. GLP-1 has been shown to reduce hyperglycemia in subjects with type 2 diabetes, perhaps by compensating for an impaired incretin effect. Studies with native GLP-1 have shown that the primary mechanisms of action are to stimulate insulin secretion and decrease glucagon secretion, to delay gastric emptying and to reduce appetite. Already approved drugs with GLP-1 mediated mode of action include the GLP-1 receptor agonist exenetide (Byetta™) and the DPP-IV inhibitor sitagliptin (Januvia™). Exenatide is administered by twice daily subcutaneous injections in relation to meals, and sitagliptin is administered orally once daily[2].

Scope of Statistical Review: Pivotal Efficacy and Safety Studies

[1] The sources of this paragraph (paraphrased) are part 1 (Product Development Rationale) in the clinical overview of this submission, and Harrison's Principles of Internal Medicine, 16th Ed, Part Fourteen: Endocrinology and Metabolism; Section 1; Endocrinology; Diabetes Mellitus (2005; from online.statref.com).

[2] The source of this paragraph (paraphrased) is part 1 (Product Development Rationale) in the clinical overview of this submission.

The statistical review covers five key Phase 3 studies that were designed to assess the efficacy and safety of liraglutide 0.6, 1.2 and 1.8 mg (by subcutaneous injection once a day) for the treatment of diabetes, either as monotherapy adjunct to diet and exercise, or as add-on therapy to other antidiabetic medications. Liraglutide was given once daily as monotherapy (Trial 1573), added to one oral antidiabetic drug (OAD; Trials 1572 and 1436) or to two OADs (Trial 1574 and 1697). Three different dose levels of liraglutide (0.6, 1.2 and 1.8 mg) were evaluated in the five key trials, but not all dose levels were evaluated in every trial. The duration of treatment in four of the five trials was 26 weeks. The duration of treatment in Trial 1573 was 52 weeks. An overview of the treatment regimens is given in TABLE 1. All studies were randomized, controlled and double-blind.

Depending on the trial, treatment with liraglutide was compared with placebo and/or a specific active comparator drug. One trial evaluated liraglutide monotherapy (1.2 and 1.8 mg) compared with glimepiride during 52 weeks of treatment (Trial 1573). The other four trials evaluated 26 weeks of treatment with liraglutide in combination with one or two OADs compared with placebo and/or an additional OAD active comparator (Trials 1572, 1436, 1574 and 1697).

Two of the therapeutic confirmatory trials were extended by open-labeled treatment periods. Trial 1573 was extended to a total of 5 years and Trial 1572 was extended to a total of 2 years.

TABLE 1 Overview of treatment regimens in the five therapeutic confirmatory trials

Trial	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo	Active Comparator
1573	N/A	Liraglutide 1.2 mg + placebo (glimepiride)	Liraglutide 1.8 mg + placebo (glimepiride)	N/A	Glimepiride 8 mg + placebo (liraglutide)
1572	Liraglutide 0.6 mg + placebo (glimepiride) + metformin 2 g	Liraglutide 1.2 mg + placebo (glimepiride) + metformin 2 g	Liraglutide 1.8 mg + placebo (glimepiride) + metformin 2 g	Placebo (liraglutide) + placebo (glimepiride) + metformin 2 g	Glimepiride 4 mg + placebo (liraglutide) + metformin 2 g
1436	Liraglutide 0.6 mg + placebo (rosiglitazone) + glimepiride 4 mg	Liraglutide 1.2 mg + placebo (rosiglitazone) + glimepiride 4 mg	Liraglutide 1.8 mg + placebo (rosiglitazone) + glimepiride 4 mg	Placebo (liraglutide) + placebo (rosiglitazone) + glimepiride 4 mg	Rosiglitazone 4 mg + placebo (liraglutide) + glimepiride 4 mg
1574	N/A	Liraglutide 1.2 mg + metformin 2 g + rosiglitazone 8 mg	Liraglutide 1.8 mg + metformin 2 g + rosiglitazone 8 mg	Placebo (liraglutide) + metformin 2 g + rosiglitazone 8 mg	N/A
1697	N/A	N/A	Liraglutide 1.8 mg + glimepiride 4 mg + metformin 2 g	Placebo (liraglutide) + 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).
N/A: not assessed

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

The five key studies involved 3992 randomized subjects, of whom 982 (24.6%) were enrolled at sites in the U.S. (TABLE 2). Only two studies, Trial 1573 and Trial 1574, enrolled subjects in the U.S. The numbers of randomized subjects, centers and countries for each study are summarized in TABLE 2.

TABLE 2 Number of randomized subjects and sites by country for each of the five Phase 3 studies

	Trial 1436		Trial 1572		Trial 1573		Trial 1574		Trial 1697	
Region	***# sites***	**# pts.**	***# sites***	**# pts.**	***# sites***	**# pts.**	***# sites***	**# pts.**	***# sites***	**# pts.**
US		**0**		**0**	*126*	**575**	*71*	**407**		**0**
Rest of the Americas		**81**		**51**		**171**		**126**		**52**
Argentina	*7*	81	*4*	51					5	52
Canada							*17*	126		
Mexico					*12*	171				
Western Europe		**153**		**526**		**0**		**0**		**241**
Austria									*7*	35
Belgium			*6*	36						
Denmark			*9*	54					*7*	35
Finland	*10*	72							*5*	12
France	*8*	35							*9*	28
Germany			*33*	200						
Ireland			*4*	22						
Italy	*5*	13	*10*	29					*8*	27
The Netherlands			*5*	20					*8*	22
Norway			*8*	51					*5*	12
Spain			*14*	48					*9*	44
Sweden			*8*	57						
Switzerland	*5*	33								
United Kingdom			*11*	9					*12*	26
Eastern Europe		**336**		**240**		**0**		**0**		**177**
Bulgaria	*6*	69	*1*	26						
Croatia	*3*	36	*2*	20						
Czech Republic	*7*	40								
Hungary			*5*	58						
Poland	*15*	126							*5*	48
Romania	*5*	65	*3*	31						
Russia			*6*	51					*4*	30
Serbia and Montenegro									*4*	63
Slovakia			*7*	54					*6*	36
Asia / India		**311**		**77**		**0**		**0**		**84**
Hong Kong	*1*	23								
India	*4*	66	*5*	77					*5*	65
Korea	*3*	33								
Malaysia	*3*	93								
Philippines	*4*	42							*4*	19
Taiwan	*4*	37								
Thailand	*3*	17								
Africa / Middle East		**118**		**65**		**0**		**0**		**27**
Israel	*3*	34								
South Africa	*5*	56	*7*	65					*4*	27
Turkey	*6*	28								
Australia / New Zealand		**42**		**132**		**0**		**0**		**0**
Australia	*9*	42	*19*	126						
New Zealand			*3*	6						
Totals	***116***	**1041**	***170***	**1091**	***138***	**746**	***88***	**533**	***107***	**581**

Sources: DEMOG.xpt files for Trials 1436, 1572, 1573, 1574 and 1697

Study populations: All subjects entering into these studies were required to have type 2 diabetes with inadequate glycemic control prior to randomization. Key inclusion criteria specific to each study are summarized below:

- Trial 1573 included subjects treated with diet/exercise or one OAD for at least two months. If treated with an OAD (sulphonylureas, meglitinides, amino acid derivatives, biguanides, alpha-glucosidase inhibitors or thiazolidinediones), the dose was to be no more than half maximal dose, except subjects previously treated with metformin (≤ 1500 mg) or pioglitazone (≤ 30 mg) were eligible for the trial. HbA1c at screening was to be in the range 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 was to be in the range 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 was to be in the range 7.0-10.0% for subjects on combination therapy including OADs and/or exenetide.

- Trial 1697 included subjects treated with OAD(s) for at least 3 months. HbA1c at screening was to be in the range 7.5-10.0% for subjects on OAD monotherapy and 7.0-10.0% for subjects on OAD combination therapy.

Stratification: In all trials, subjects were stratified with respect to previous diabetes treatment (diet/exercise treated versus OAD monotherapy in Trial 1573 and OAD monotherapy versus OAD combination therapy in Trials 1572, 1436, 1574 and 1697).

Maintaining the blind: All trials made use of placebo pills and placebo injections to maintain the blind.

Pre-randomization and post-randomization titration schedules: Each trial had a pre-specified protocol regarding the OAD and liraglutide therapy associated with the trial. All trials used the following titration schedule for liraglutide in the two-week period following randomization: After randomization, subjects randomized to receive liraglutide started on 0.6 mg for the first week. For subjects randomized to receive 1.2 mg or 1.8 mg, the dose was increased to 1.2 mg for the second week. Subjects randomized to receive 1.8 mg of liratude started on this dose at the third week.

The protocol for OAD therapy associated with each trial is described below:

Trial 1436: Subjects who were identified as eligible at the screening visit were to discontinue their usual OAD(s) and start 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 (FIGURE 1). 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.

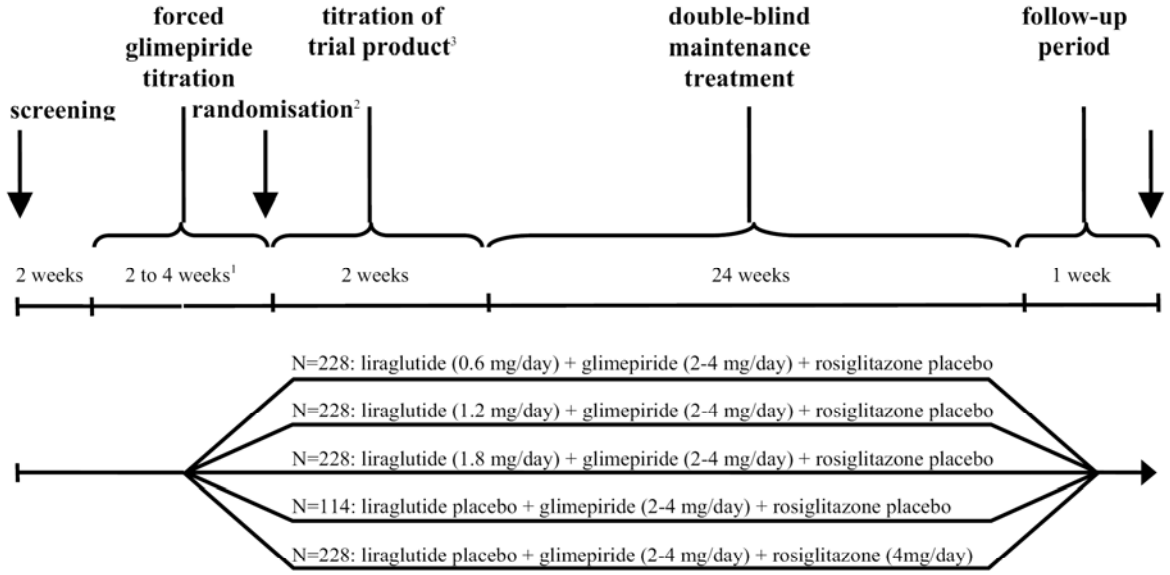
- Glimepiride: After randomization, the dose level of glimepiride could, at the discretion of the investigator, be decreased to a minimum of 2 mg/day in case of unacceptable hypoglycemia or other adverse events. The glimepiride dose could also be increased again to 4 mg/day, also at the discretion of the investigator. If a dose level less than 2 mg/day or more than 4 mg/day was required, the subject was to be withdrawn from the trial.

- Rosiglitazone: Rosiglitazone was to be kept at 4 mg/day. There was no titration schedule for rosiglitazone.

- Liraglutide: Liraglutide was up-titrated as described for all of the trials.

Clinic visits from randomization on took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 18 26 and 27. The double-blind portion of the trial took place from May 29, 2006 to May 7, 2007.

FIGURE 1 Design of Trial 1436



[1] Depending on glimepiride dose level at entry into the titration phase.
[2] Only if FPG is between 7.0 and 12.8 mmol/L (126-230 mg/dL) (both incl.usive).
[3] Up-titration of liraglutide (blinded) and glimepiride (open-label).

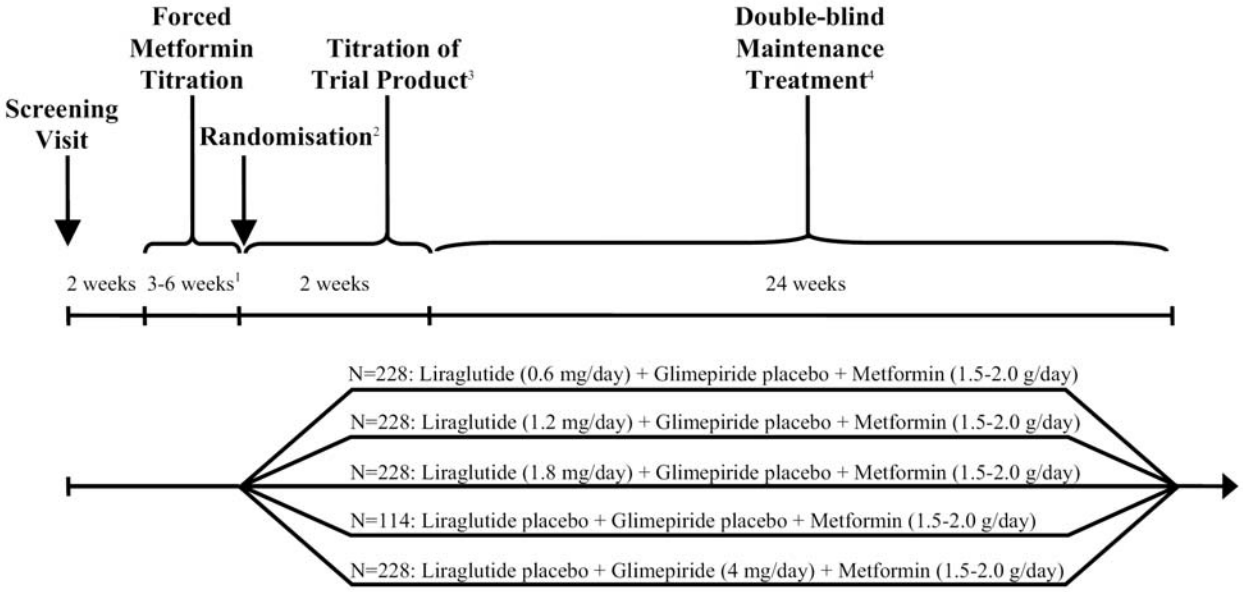
Source: Trial 1436 clinical report, Figure 9-1

Trial 1572: Subjects who were identified as eligible at screening discontinued their usual OAD(s) and started an open 3-week run-in period with forced titration of metformin therapy increasing to 2000 mg/day followed by a 3-week maintenance period. Subjects on current metformin therapy could go through a modified titration period or advance directly to the 3-week maintenance period at the discretion of the investigator.

After randomization, subjects assigned to glimepiride were started at 2 mg for the first two weeks, increased to 4 mg for the third week and to 4 mg for week 4 and beyond. Liraglutide was up-titrated as described for all of the trials (FIGURE 2). Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 18, 26 and 27. The double-blind portion of the trial took place from May 30, 2006 to May 4, 2007.

Extension to Trial 1572: At visit 10 at 26 weeks after randomization, all subjects were asked to confirm their continued participation in an 18-month 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.

FIGURE 2 Design of Trial 1572



[1] Depending on metformin dose level at entry into the titration phase.
[2] Only if FPG is between 7.0 and 12.8 mmol/L (126-230 mg/dL) (both incl.).
[3] Double-blind up-titration of liraglutide and glimepiride (active and/or placebo) (see section 9.4.1).
[4] Subjects not participating in the open-label extension had a follow-up visit 1 week after termination of the double-blind maintenance treatment period.

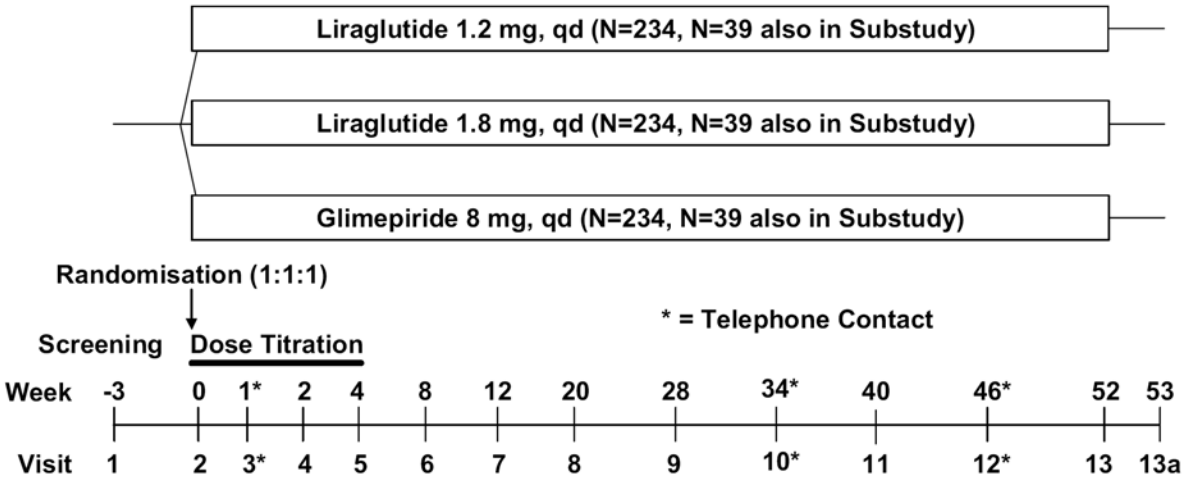
Source: Trial 1572 clinical report, Figure 9-1

Trial 1573: The protocol for Trial 1573 did not specify a pre-treatment period. A dose titration period for liraglutide or glimepiride followed randomization. Glimepiride was started at 2 mg for the first two weeks, increased to 4 mg for the third week and to 8 mg for week 4 and beyond (FIGURE 3). Liraglutide was up-titrated as described for all of the trials.

Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 20, 28, 40, 52 and 53. The double-blind portion of the trial took place from February 7, 2006 to November 2, 2007.

Extension to Trial 1573: This trial had a 52-week double-blind treatment period followed by a 52-week open-label 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.

FIGURE 3 Design of Trial 1573



Source: Trial 1573 study report, Figure 9-1

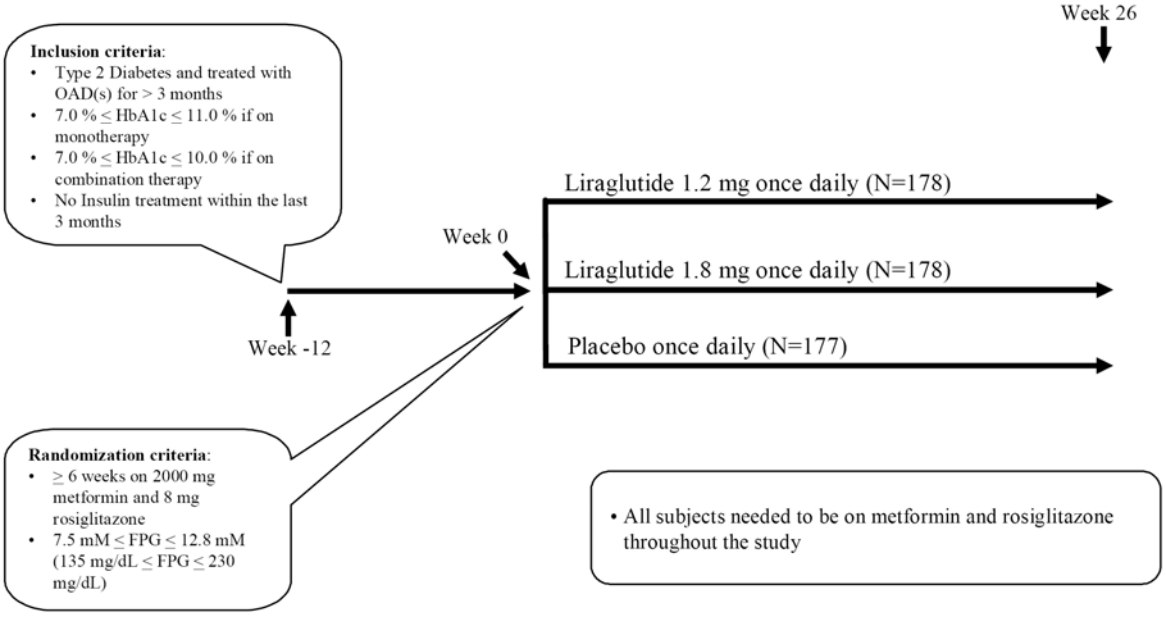
Trial 1574: At randomization, all subjects had been titrated (as needed) and maintained on rosiglitazone 8 mg/day and metformin 2000 mg/day for at least six weeks (FIGURE 4). These doses were achieved as follows:

- Rosiglitazone: Before randomization, rosiglitazone was initiated at 4 mg once daily and was increased after 2 weeks to 8 mg/day (4 mg BID). Subjects who entered the trial on rosiglitazone therapy could start titration at the dose that they were currently taking or go directly to the maintenance dose of 8 mg at the discretion of the investigator. All subjects had a six-week maintenance period with 8 mg rosiglitazone prior to randomization at week 0.

- Metformin: Before randomization, subjects who were not currently treated with metformin underwent an open-label forced titration, initiated at 500 mg with weekly increments of 500 mg to a final dose of 2000 mg/day. Subjects on current metformin therapy could start at the dose they were currently treated with or go directly to the maintenance metformin dose of 2000 mg at the discretion of the investigator. All subjects had a six-week maintenance period with 2000 mg prior to randomization.

Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 19, 26 and 27. The double-blind portion of the trial took place from May 30, 2006 to August 14, 2007.

FIGURE 4 Design of Trial 1574

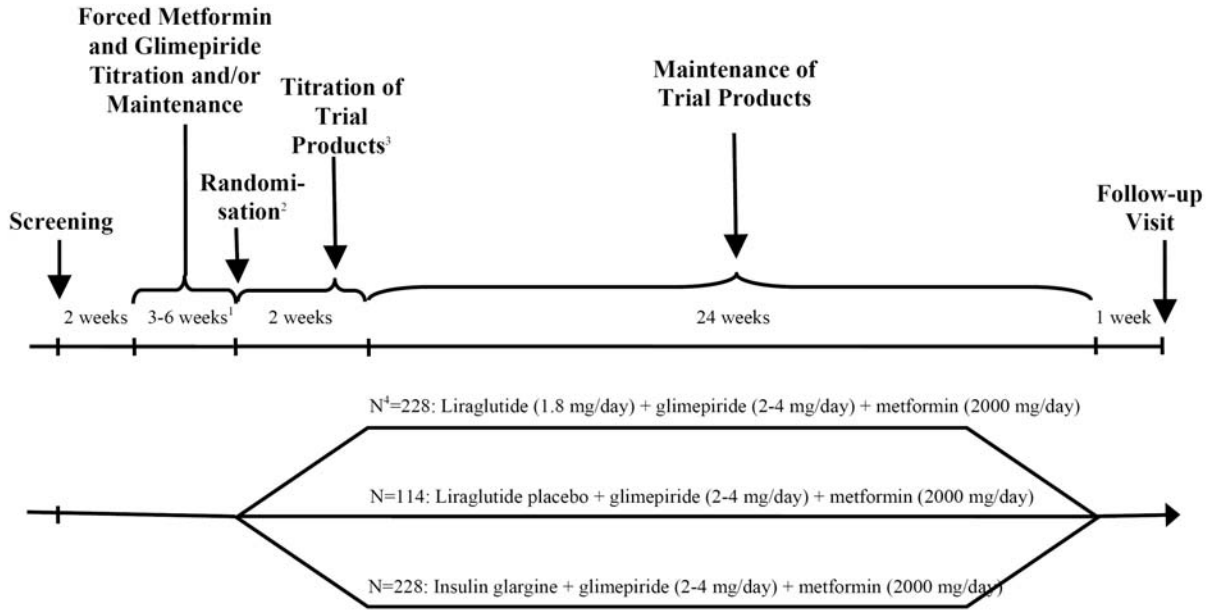


Source: Trial 1574 clinical report, Figure 9-1

Trial 1697: Subjects who were identified as eligible at screening discontinued their usual OADs at visit 2 and initiated an open 3-week period with forced titration of glimepiride and metformin therapy. The glimipiride and metformin therapy increased to 4 mg/day and 2000 mg/day, respectively, and the titration period was followed by a mandatory 3-week maintenance period. Subjects on current glimepiride and metformin combination therapy could go through a modified titration period or advance directly to the 3-week maintenance period at the discretion of the investigator (FIGURE 5).

Clinic visits from randomization to the end of the double-blind period took place at day 0 (randomization), weeks 1, 2, 4, 8, 12, 18, 26 and 27. The double-blind portion of the trial took place from May 30, 2006 to April 20, 2007.

FIGURE 5 Design of Trial 1697



[1] Depending on metformin and/or glimepiride dose level at entry into the titration phase.
[2] Only if FPG is between 7.5 and 12.8 mmol/L (135-230 mg/dL) (both inclusive).
[3] Up-titration of liraglutide (active and/or placebo) through doses of 0.6 mg and 1.2 mg liraglutide and titration of insulin glargine according to guideline (Sections 9.4.1 and 9.4.5).

Source: Trial 1697 clinical report, Figure 9-1

Number of subjects in each trial: The following assumptions were used for all five trials for the HbA1c endpoint (expressed as a change from baseline at week 26 for Trials 1436, 1572, 1574 and 1697, and at week 52 for Trial 1573):

- A margin of 0.4% for non-inferiority comparisons
- A net effect of liraglutide of 0.5% for superiority comparisons
- Desired statistical power of at least 85%
- A two-tailed α of 0.05 for superiority comparisons
- A one-tailed α of 0.025 for non-inferiority comparisons

Trial 1436: With a 2:2:2:2:1 allocation ratio to the liraglutide 0.6 mg + glimepiride : liraglutide 1.2 mg + glimepiride : liraglutide 1.8 mg + glimepiride : rosiglitazone + glimepiride : glimepiride arms, an estimated standard deviation of 1.2%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 1026, allocated as 228:228:228:228:114. In the study, 1041 subjects were randomized, allocated as 233:228:234:232:114.

Trial 1572: With a 2:2:2:2:1 allocation ratio to the liraglutide 0.6 mg + metformin : liraglutide 1.2 mg + metformin : liraglutide 1.8 mg + metformin : glimepiride + metformin : metformin arms, an estimated standard deviation of 1.2%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 1026, allocated as 228:228:228:228:114. In the study, 1091 subjects were randomized, allocated as 242:241:242:244:122.

Trial 1573: With a 1:1:1 allocation ratio to the liraglutide 1.2 mg : liraglutide 1.8 mg : glimepiride arms, an estimated standard deviation of 1.2%, and a drop out rate of 30%, the applicant determined that the total number of subjects to be randomized was 702, allocated as 234:234:234. In the study, 746 subjects were randomized, allocated as 246:251:248.

Trial 1574: With a 1:1:1 allocation ratio to the liraglutide 1.2 mg + metformin + rosiglitazone : liraglutide 1.8 mg + metformin + rosiglitazone : metformin + rosiglitazone arms, an estimated standard deviation of 1.3%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 492, allocated as 164:164:164. In the study, 533 subjects were randomized, allocated as 178:178:177.

Trial 1697: With a 2:2:1 allocation ratio to the liraglutide 1.8 mg + glimepiride + metformin : glargine + glimepiride + metformin : glimepiride + metformin arms, an estimated standard deviation of 1.2%, and a drop out rate of 25%, the applicant determined that the total number of subjects to be randomized was 570, allocated as 228:228:114. In the study, 581 subjects were randomized, in the ratio 232:234:115.

Non-inferiority margin: The selection of a non-inferiority margin for comparison of liraglutide with glimepiride (Amaryl™) in subjects who had not achieved adequate glycemic control on diet and exercise alone was based in part on an analysis of the effect of glimepiride monotherapy in three placebo-controlled studies. The estimated effect, combined across studies with a random effects meta-analysis, was -1.6%, with an upper 95% confidence bound of -1.3%, for HbA1c change from baseline after 14 weeks of therapy. Because the sponsor's proposed margin, 0.4%, is less than half of the upper bound, in the direction of inferiority of liraglutide compared to glimepiride, the proposed margin is acceptable from the statistical review perspective. A more detailed description of the methodology used to combine results across studies is in the statistical review of protocol 1573, submitted to IND 061040 on January 10, 2006 (amendment 060).

However, as noted in the statistical review of protocol 1573, the margin of difference of 0.4% is subject to the condition that the effect of glimepiride does not decline appreciably between 14 weeks and 52 weeks of therapy. Results from long-term extension studies that are described briefly in the Amaryl® label suggest that it may be reasonable to extend the 14-week results in HbA1c out to 52 weeks of therapy.

The non-inferiority margin 0.4% was used for several active control comparators and background therapies in the range of target populations of the Phase 3 studies. For this reason, I conducted a post-hoc evaluation of the non-inferiority margin from the results of the three studies that included both an active control arm and a placebo control arm.

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown in TABLE 3. Individual study reports were submitted for each study.

TABLE 3 Data sources for studies

Document: NDA 022341.0
CDER EDR link: \\CDSESUB1\N022341\
Company: Novo Nordisk
Drug: Liraglutide
Submission date: May 23, 2008

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1. Subject disposition

Ineffective therapy: Subjects who were withdrawn early from the liraglutide studies due to hyperglycemia were classified as having "ineffective therapy." The criteria for ineffective therapy were based on fasting plasma glucose (FPG). The FPG criteria were relatively similar across studies, but there were some differences (TABLE 4). In each study, subjects who met the criteria for being classified as having ineffective therapy had a final clinical visit, and then were withdrawn from the study. The last observation of HbA1c and other efficacy endpoints was carried forward to represent this subject's endpoint response to therapy.

TABLE 4 Fasting Plasma Glucose criteria for the "ineffective therapy" classification

Trial	Criteria for "ineffective therapy" classification
1436	From weeks 8 to 26: FPG > 239 mg/dL
1572	Double-blind period: • From weeks 8 to 26: FPG > 239 mg/dL Open-label extension period: • From weeks 26 to 52: FPG > 220 mg/dL From weeks 52 to 105: FPG > 200 mg/dL
1573	Double-blind period: • From weeks 8 to 28: FPG > 240 mg/dL • From week 28 to 52: FPG > 220 mg/dL Open-label extension period: • From week 52 to 104: FPG > 220 mg/dL
1574	From weeks 8 to 26: FPG > 240 mg/dL
1697	From weeks 8 to 26: FPG > 239 mg/dL

Notes:
- Subjects who met the criteria for ineffective therapy were removed from the study.
- "Weeks" refer to the weeks post randomization

Sources: Section 9.3.3 ("Removal of patients from therapy and assessment") in the report of each study

Patterns of disposition across studies: 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, when observed across the five studies. In the four studies

that had a placebo add-on arm, subjects in this arm were more likely to withdraw early due to ineffective therapy than subjects in the liraglutide arms (see Trials 1436, 1572, 1574 and 1697; TABLE 5). In the four studies that had an active comparator arm, subjects in this arm were about equally likely to withdraw early due to ineffective therapy as subjects in the liraglutide arms (see Trials 1436, 1572, 1697 and 1573; TABLE 5).

The possibility that the two larger doses of liraglutide may result in withdrawal due to adverse events when given in combination with metformin is suggested by the pattern of disposition in three of the studies that had metformin as background therapy (metformin in Trial 1572, metformin + rosiglitazone in Trial 1574, and metformin + glimepiride in Trial 1697). A greater percentage of subjects withdrew early due to adverse events in the liraglutide 1.2 mg + metformin and liraglutide 1.8 mg + metformin arms than in the metformin comparator arm within each of these studies (TABLE 5). This pattern was not observed in Trial 1436 which had glimepiride as background therapy rather than metformin. This pattern may suggest an increase in adverse events when liraglutide at the two higher dosages is combined with metformin. This finding is supported by the greater percentage of gastrointestinal adverse events (such as nausea, diarrhea, and vomiting) reported for liraglutide + metformin and liraglutide + metformin + glimepiride arms compared to liraglutide + glimepiride arms (summary not shown).

<u>Patterns of disposition within studies</u>:

- In Trial 1436 (glimepiride background therapy), the percentage of subjects who did not complete the study in the liraglutide arms ranged from 9% to 14%, of which the contribution due to ineffective therapy and adverse events was relatively similar and ranged from 2% to 5% (TABLE 5; FIGURE 6). In contrast, 27% of subjects in the placebo arm did not complete the study, of whom 18% (absolute) withdrew due to ineffective therapy. The disposition pattern in the rosiglitazone arm was similar to the pattern in the liraglutide arms.

- In Trial 1572 (metformin background therapy), the percentage of subjects who did not complete the study in the liraglutide arms ranged from 14% to 21% (TABLE 5; FIGURE 6). The largest contributor to this percentage was ineffective therapy in the liraglutide 0.6 mg arm (7.9%), and adverse events in the liraglutide 1.2 mg and liraglutide 1.8 mg arms (9.5% and 12.0% respectively). The placebo arm had the greatest percentage of subjects withdrawing from the study, 39%, compared to the other arms, with the majority of these early withdrawals, 24%, classified as "ineffective therapy." The percentage of early withdrawals in the glimepiride arm was 14%, which was relatively evenly distributed across the four different reasons for withdrawal.

- Trial 1573 (monotherapy) was a 52-week study, and the percentage of subjects who withdrew early was evaluated at week 52. All three arms of Trial 1573 had relatively large percentages of subjects who withdrew before week 52, ranging from 30% to 39% (TABLE 5). By week 26, the percentage of subjects who had withdrawn from the study was approximately 20%, which is broadly similar to the disposition pattern of the 26-week studies

(FIGURE 6). The most frequently cited reason for early withdrawal in each arm was "other," ranging from 15% to 21%. The two most common text entries accompanying the "other" classification were "withdrew consent" (44/125) and "lost to follow-up" (37/125).

- In Trial 1574 (metformin + rosiglitazone background therapy), 25% of subjects withdrew from the liraglutide 1.2 mg arm, of which the most frequently cited reason (15%; absolute) was adverse events (TABLE 5; FIGURE 6). A smaller percentage, 14%, withdrew from the liraglutide 1.8 mg arm; adverse events was also the most frequently cited reason (6%). The placebo arm had the greatest percentage of withdrawals (32%) of all three arms, and ineffective therapy was the most frequently cited reason (16%).

- Trial 1697 (glimepiride + metformin background therapy) had the smallest percentage of subjects withdraw from the study compared to the other four studies, ranging from 6% to 11% (TABLE 5; FIGURE 6). The most frequently cited reason for withdrawal was adverse events (5%) and other (5%) in the liraglutide 1.8 mg arm, ineffective therapy (11%) in the placebo arm, and adverse events (2%) and non-compliance with the protocol (2%) in the insulin arm.

TABLE 5 Subject disposition in each study

Trial 1436 (26 weeks) add-on to glimepiride 4 mg	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**rosiglitazone 4 mg**	**Total**
Randomized	233	228	234	114	232	1041
Exposed	233	228	234	114	231	1040
Completed	208 (89.3%)	196 (86.0%)	213 (91.0%)	83 (72.8%)	194 (83.6%)	894 (85.9%)
Withdrawn:	25 (10.7%)	32 (14.0%)	21 (9.0%)	31 (27.2%)	38 (16.4%)	147 (14.1%)
Ineffective therapy	*12 (5.2%)*	*8 (3.5%)*	*7 (3.0%)*	*20 (17.5%)*	*16 (6.9%)*	*63 (6.1%)*
Adverse events	*5 (2.1%)*	*11 (4.8%)*	*9 (3.8%)*	*6 (5.3%)*	*7 (3.0%)*	*38 (3.7%)*
Non-compliance with protocol	*3 (1.3%)*	*5 (2.2%)*	*3 (1.3%)*	*2 (1.8%)*	*6 (2.6%)*	*19 (1.8%)*
Other	*5 (2.1%)*	*8 (3.5%)*	*2 (0.9%)*	*3 (2.6%)*	*9 (3.9%)*	*27 (2.6%)*

Trial 1572 (26 weeks) add-on to metformin 2 g	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**glimepiride 4 mg**	**Total**
Randomized	242	241	242	122	244	1091
Exposed	242	240	242	121	242	1087
Completed	208 (86.0%)	197 (81.7%)	191 (78.9%)	74 (60.7%)	210 (86.1%)	880 (80.7%)
Withdrawn:	34 (14.0%)	44 (18.3%)	51 (21.1%)	48 (39.3%)	34 (13.9%)	211 (19.3%)
Ineffective therapy	*19 (7.9%)*	*8 (3.3%)*	*13 (5.4%)*	*29 (23.8%)*	*9 (3.7%)*	*78 (7.1%)*
Adverse events	*11 (4.5%)*	*23 (9.5%)*	*29 (12.0%)*	*2 (1.6%)*	*8 (3.3%)*	*73 (6.7%)*
Non-compliance with protocol	*2 (0.8%)*	*4 (1.7%)*	*4 (1.7%)*	*4 (3.3%)*	*5 (2.0%)*	*19 (1.7%)*
Other	*2 (0.8%)*	*9 (3.7%)*	*5 (2.1%)*	*13 (10.7%)*	*12 (4.9%)*	*41 (3.8%)*

Trial 1573 (52 weeks) monotherapy	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**glimepiride 8 mg**	**Total**
Randomized	247	251	248	746
Exposed	246	251	248	745
Completed	173 (70.0%)	162 (64.5%)	152 (61.3%)	487 (65.3%)
Withdrawn:	74 (30.0%)	89 (35.5%)	96 (38.7%)	259 (34.7%)
Ineffective therapy	*9 (3.6%)*	*15 (6.0%)*	*25 (10.1%)*	*49 (6.6%)*
Adverse events	*18 (7.3%)*	*25 (10.0%)*	*15 (6.0%)*	*58 (7.8%)*
Non-compliance with protocol	*11 (4.5%)*	*11 (4.4%)*	*5 (2.0%)*	*27 (3.6%)*
Other	*36 (14.6%)*	*38 (15.1%)*	*51 (20.6%)*	*125 (16.8%)*

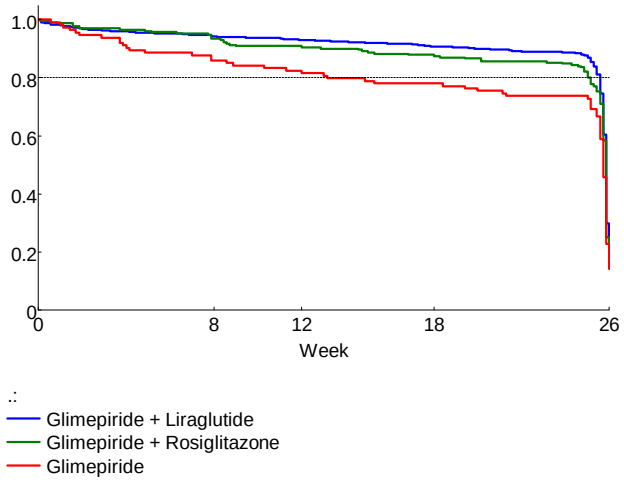
Trial 1574 (26 weeks) add-on to metformin 2 g + rosiglitazone 8 mg *(4 mg BID)*	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**Total**
Randomized	178	178	177	533
Exposed	178	177	175	530
Completed	133 (74.7%)	153 (86.0%)	121 (68.4%)	407 (76.4%)
Withdrawn:	45 (25.3%)	25 (14.0%)	56 (31.6%)	126 (23.6%)
Ineffective therapy	*3 (1.7%)*	*3 (1.7%)*	*29 (16.4%)*	*35 (6.6%)*
Adverse events	*27 (15.2%)*	*11 (6.2%)*	*6 (3.4%)*	*44 (8.3%)*
Non-compliance with protocol	*4 (2.2%)*	*4 (2.2%)*	*5 (2.8%)*	*13 (2.4%)*
Other	*11 (6.2%)*	*7 (3.9%)*	*16 (9.0%)*	*34 (6.4%)*

Trial 1697 (26 weeks) add-on to glimepiride 4 mg + metformin 2 g	**liraglutide 1.8 mg**	**placebo**	**insulin glargine**	**Total**
Randomized	232	115	234	581
Exposed	230	114	232	576
Completed	207 (89.2%)	96 (83.5%)	219 (93.6%)	522 (89.8%)
Withdrawn:	25 (10.8%)	19 (16.5%)	15 (6.4%)	59 (10.2%)
Ineffective therapy	*2 (0.9%)*	*13 (11.3%)*	*1 (0.4%)*	*16 (2.8%)*
Adverse events	*11 (4.7%)*	*1 (0.9%)*	*5 (2.1%)*	*17 (2.9%)*
Non-compliance with protocol	*1 (0.4%)*	*1 (0.9%)*	*5 (2.1%)*	*7 (1.2%)*
Other	*11 (4.7%)*	*4 (3.5%)*	*4 (1.7%)*	*19 (3.3%)*

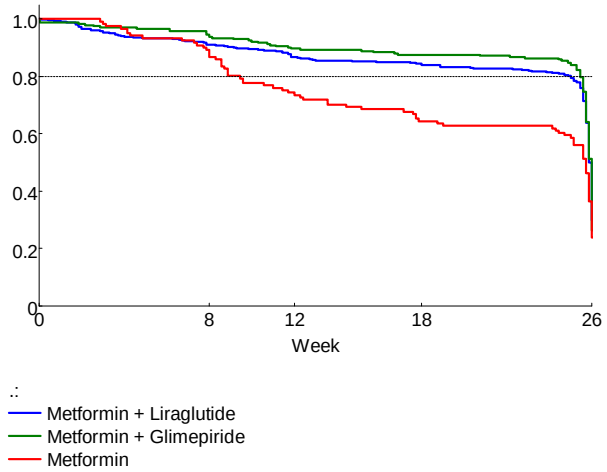
Sources:
Trial 1436 clinical report, Table 10-1
Trial 1572 clinical report, Table 10-1
Trial 1573 clinical report, Table 10-1
Trial 1574 clinical report, Table 10-1
Trial 1697 clinical report, Table 10-1

FIGURE 6 Disposition by week on study; Kaplan-Meier plots (horizontal axis shows the clinic visits where HbA1c was determined)

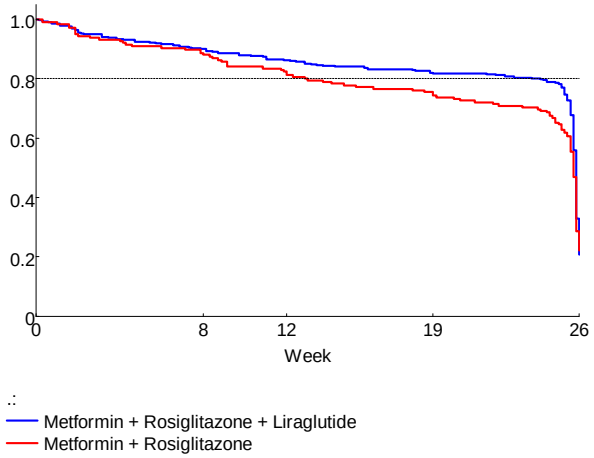
Trial 1436



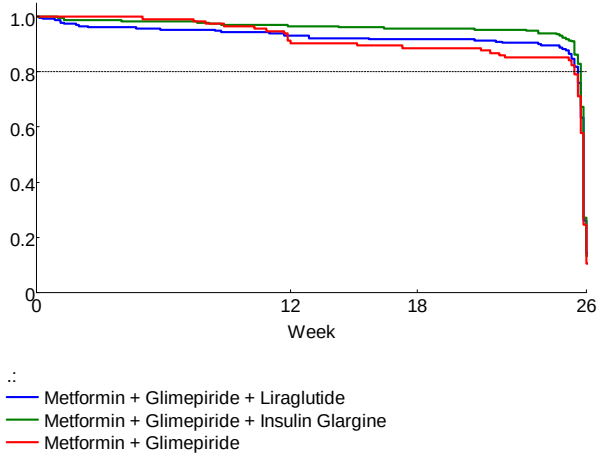
Trial 1572



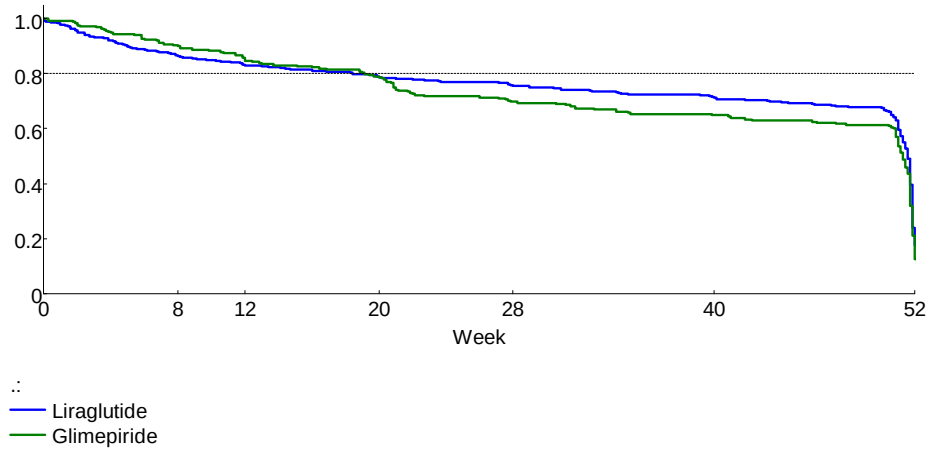
Trial 1574



Trial 1697



Trial 1573



3.1.2. Subject demographic and baseline characteristics

Certain subject demographic and baseline characteristics were relatively similar among studies (TABLE 6). Each study had approximately equal numbers of males and females. The average age was relatively similar among studies, ranging from 53 to 58 years. The majority of subjects in each study were Caucasian, ranging from 64% to 87%. The majority of subjects in each study were younger than 65 years, ranging from 78% to 85% (TABLE 6). Within each study, the distribution of demographic and baseline characteristics was relatively similar among the randomized arms (not shown in the table).

Differences among studies reflect differences among the target populations with respect to the progression of diabetes. The shortest median duration of diabetes, 3.8 years, was observed in the monotherapy study, Trial 1573 (TABLE 6). This study was also the only study that used the "diet/exercise" category of "previous antidiabetic treatment," with 37% of subjects reporting this category. The two longest median durations of diabetes, 7.9 and 8.4 years, were observed in the two studies with liraglutide added on to two OADs, Trial 1574 and Trial 1697 respectively. These two studies also had the largest percentages of subjects reporting "combination therapy" for "previous antidiabetic treatment" (83% and 94% respectively; TABLE 6).

A potential concern for the statistical analysis of the primary endpoint arises in certain studies because of the occurrence of subjects with HbA1c ≤ 7.0 at baseline. Within each study, the distribution of baseline HbA1c levels was relatively broad, including values less than 7.0 and values greater than 10.0 (TABLE 7, FIGURE 7). While the general screening range for HbA1c for the five studies was 7.0-10.0 (with some exceptions, see Part 2.1), four of the studies included a pre-randomization titration schedule of several weeks' duration. During this period of time, most subjects experienced changes in their background OAD therapy (see Part 2.1). These changes may account for the occurrence of baseline HbA1c levels less than 7.0 or greater than 10.0 in some subjects. The percentage of subjects with baseline HbA1c levels less than 7.0 ranged from 5.4% to 11.7% across the five studies (FIGURE 7). Trial 1573 did not have a pre-randomization titration schedule.

Subjects with HbA1c ≤ 7.0 at baseline represent a potential concern for Trial 1573, which had an active comparator arm but not a placebo add-on arm. This concern is based on the assumption that subjects in an active therapy arm who are already at a reasonable level of diabetic control at baseline are not likely to change much from their baseline levels over the course of the study. This assumption comes from a general finding across clinical studies of anti-diabetic drugs that subjects with lower levels of HbA1c at baseline tend to experience smaller decreases in HbA1c at the study endpoint compared to subjects with higher levels at baseline. In Trial 1573, 11.7% of subjects had baseline HbA1c levels ≤ 7.0, and another 18.1% of subjects had baseline HbA1c levels between 7.0 and 7.5, for a total of 28.8% at these lower baseline levels of HbA1c (FIGURE 7). With a relatively high proportion of subjects who are in reasonable diabetic control at baseline, both the liraglutide and the active comparator arms may tend to have a small average change from baseline HbA1c at the study endpoint. In this situation, the assay sensitivity of the comparison may not support a non-inferiority margin of 0.4. I evaluated this issue further in my analysis of the HbA1c endpoint in Trial 1573.

Subjects with HbA1c ≤ 7.0 at baseline represent less of a potential concern for studies that had both an active comparator arm and a placebo add-on arm. This design, used in Trials 1436, 1572 and 1697, permits an internal comparison of the active comparator to the placebo. The non-inferiority margin of 0.4 can be compared to the placebo-adjusted effect of the active comparator in each study.

Subjects with HbA1c ≤ 7.0 at baseline do not represent a particular concern for superiority comparisons of the liraglutide arm with a placebo add-on arm. Trials 1436, 1572, 1574 and 1697 include superiority comparisons.

TABLE 6 Subject demographic and baseline characteristics in the randomized subjects in each of the five key studies

	Trial 1436 n=1041	**Trial 1572 n=1091**	**Trial 1573 n=746**	**Trial 1574 n=533**	**Trial 1697 n=581**
Age (years)					
Mean ± SD	56.1 ± 9.8	56.8 ± 9.5	53.0 ± 10.9	55.1 ± 10.2	57.5 ± 9.9
Median	56.0	57.0	53.0	55.0	58.0
Range	24 to 80	25 to 79	19 to 79	23 to 80	24 to 80
≥ 65 years (n, %)	212 (20.4%)	243 (22.3%)	108 (14.5%)	93 (17.4%)	146 (17.4%)
Sex					
Male (n, %)	514 (49.4%)	635 (58.2%)	371 (49.7%)	298 (55.9)	328 (56.5%)
Female (n, %)	527 (50.6%)	456 (41.8%)	375 (50.3%)	235 (44.1)	253 (43.5%)
Race[1]					
Caucasian	670 (64.4%)	950 (87.1%)	578 (77.5%)	441 (82.7%)	436 (75.0%)
Black	29 (2.8%)	26 (2.4%)	94 (12.6%)	63 (11.8%)	21 (3.6%)
Asian/Pacific Islander	337 (32.4%)	98 (9.0%)	---	---	91 (15.7%)
Native Hawaiian / Pacific Islander	---	---	2 (0.3%)	0 (0.0%)	---
Asian	---	---	26 (3.5%)	10 (1.9%)	---
American Indian / Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	---	---	28 (4.8%)
Other	5 (0.5%)	17 (1.6%)	46 (6.2%)	15 (2.8%)	5 (0.9%)
Ethnicity[2]					
Hispanic/Latino	---	---	261 (35.0%)	81 (15.2%)	---
Not Hispanic/Latino	---	---	485 (65.0%)	452 (84.8%)	---
Diabetes duration (yr)					
Mean ± SD	7.9 ± 5.4	7.4 ± 5.2	5.4 ± 5.3	9.0 ± 5.6	9.4 ± 6.2
Median	6.6	6.5	3.8	7.9	8.4
Range	0.1 to 32.6	0.3 to 40.6	0.2 to 40.3	0.3 to 36.7	0.4 to 43.5
Previous anti-diabetic treatment					
Diet / Exercise[3]	---	---	272 (36.5%)	---	---
Monotherapy	315 (30.3%)	385 (35.3%)	474 (63.5%)	90 (16.9%)	33 (5.7%)
Combination therapy	726 (69.7%)	706 (64.7%)	---	443 (83.1%)	548 (94.3%)

	Trial 1436 n=1041	**Trial 1572 n=1091**	**Trial 1573 n=746**	**Trial 1574 n=533**	**Trial 1697 n=581**
Weight (kg)					
Mean ± SD	81.6 ± 17.4	88.6 ± 17.3	92.6 ± 19.6	97.0 ± 18.9	85.4 ± 18.3
Median	80.3	88.5	90.7	95.0	84.0
Range	40.3 to 138.1	42.0 to 151.0	46.7 to 163.3	54.0 to 165.1	45.6 to 150.0
BMI (kg/m^2)					
Mean ± SD	29.9 ± 5.1	31.0 ± 4.7	33.1 ± 5.8	33.5 ± 5.2	30.5 ± 5.3
Median	29.3	30.8	32.3	33.2	30.0
Range	17.5 to 45.5	17.0 to 41.4	20.8 to 47.1	20.5 to 46.0	17.0 to 45.2

Notes:

[1] In Trials 1573 and 1574 (with sites in the U.S.), racial groups were categorized differently than they were in Trials 1436, 1572 and 1697 (with no sites in the U.S.).

[2] In Trials 1573 and 1574 (with sites in the U.S.), Hispanic/Latino status was coded in an ethnicity category separately from the race category. In Trials 1436, 1572 and 1697 (with no sites in the U.S.), this ethnicity category was not recorded.

[3] In Trial 1573 (monotherapy) previous antidiabetic treatment was classified as "diet/exercise" and "monotherapy", and in Trials 1436, 1572, 1574 and 1697 (combination therapies), previous antidiabetic treatment was classified as "monotherapy and "combination therapy."

Baseline characteristics and demographics were recorded at screening and/or at randomization. If an item was recorded in both visits, and if not otherwise specified, the value from the randomization visit was used when summarizing the study population.

Sources:

Clinical reports from Trial 1436 (Table 11-2), Trial 1572 (Table 11-1), Trial 1573 (Table 11-1), Trial 1574 (Table 14.1-1), Trial 1697 (Table 11-2), and additional analysis by this reviewer

TABLE 7 Baseline levels of HbA1c in randomized subjects in each of the five key studies (by arm)

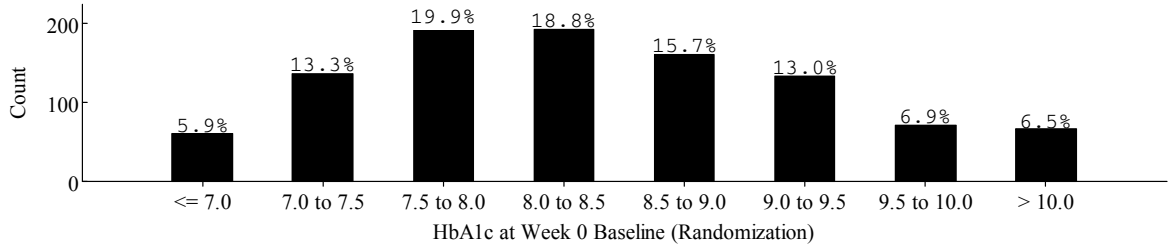
Trial 1436 add-on to glimepiride 4 mg	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**rosiglitazone 4 mg**
n	227	228	229	111	229
Mean ± SD	8.4 ± 1.0	8.5 ± 1.1	8.5 ± 0.9	8.4 ± 1.0	8.4 ± 1.0
Median	8.2	8.4	8.5	8.4	8.3
Range	6.3 to 11.8	6.3 to 13.2	6.1 to 11.4	6.4 to 11.0	6.3 to 11.1
Trial 1572 add-on to metformin 2 g	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**glimepiride 4 mg**
n	240	238	240	122	239
Mean ± SD	8.4 ± 0.9	8.3 ± 1.0	8.4 ± 1.0	8.4 ± 1.1	8.4 ± 1.0
Median	8.3	8.3	8.3	8.4	8.2
Range	6.4 to 10.9	5.8 to 12.9	6.4 to 12.7	4.8 to 12.1	6.4 to 11.5
Trial 1573 monotherapy		**liraglutide 1.2 mg**	**liraglutide 1.8 mg**		**glimepiride 8 mg**
n		251	247		248
Mean ± SD		8.2 ± 1.1	8.2 ± 1.1		8.2 ± 1.1
Median		8.0	7.9		8.0
Range		5.9 to 11.7	6.2 to 11.5		4.9 to 11.2
Trial 1574 add-on to metformin 2 g + rosiglitazone 8 mg *(4 mg BID)*		**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	
n		178	178	177	
Mean ± SD		8.5 ± 1.2	8.6 ± 1.2	8.4 ± 1.2	
Median		8.2	8.4	8.2	
Range		6.1 to 12.0	6.6 to 12.8	6.1 to 12.6	
Trial 1697 add-on to glimepiride 4 mg + metformin 2 g			**liraglutide 1.8 mg**	**placebo**	**insulin glargine**
n			232	113	234
Mean ± SD			8.3 ± 0.9	8.3 ± 0.9	8.2 ± 0.9
Median			8.2	8.2	8.1
Range			6.1 to 10.9	6.5 to 10.7	5.2 to 10.9

Note: Baseline HbA1c was recorded at randomization.

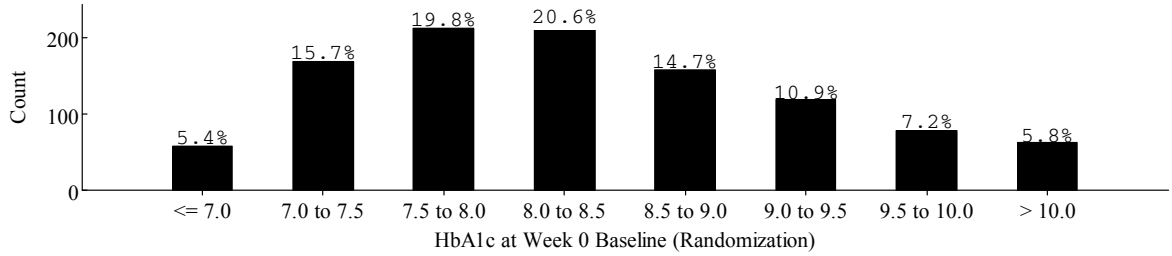
Sources: Clinical reports from Trial 1436 (Table 11-3), Trial 1572 (Table 11-3), Trial 1573 (Tables 11-2 and 14.1-4), Trial 1574 (Tables 11-2 and 14.1-4), Trial 1697 (Table 11-3)

FIGURE 7 Distribution of HbA1c at baseline

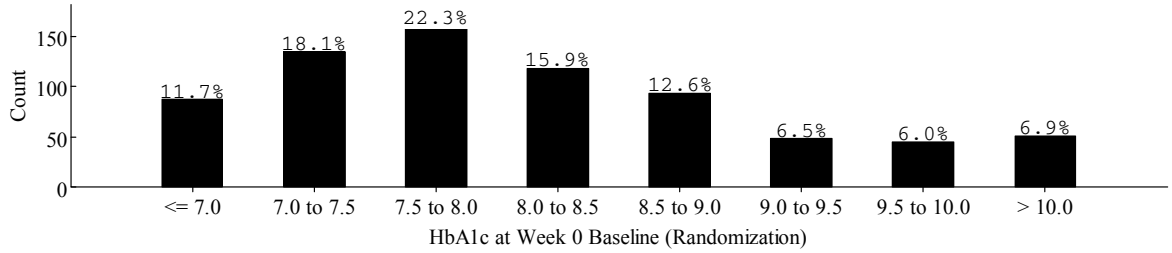
Trial 1436



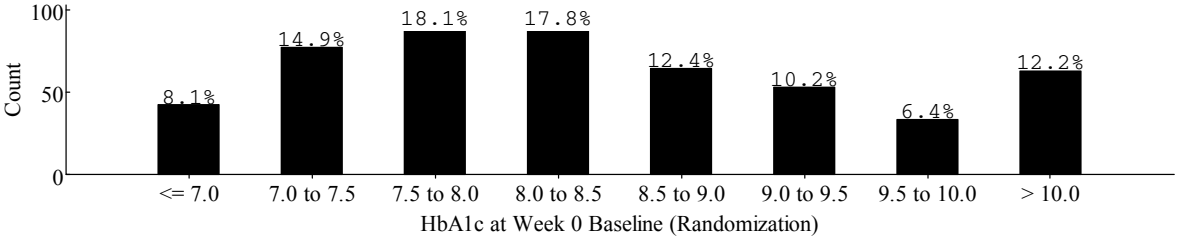
Trial 1572



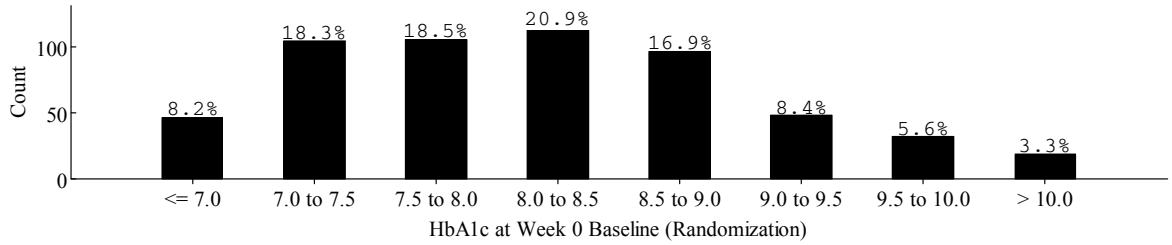
Trial 1573



Trial 1574



Trial 1697



Source: Analysis by this reviewer

3.1.3. Analysis populations

All five studies used the same definitions for the analysis populations, with exceptions as described below:

Intention to Treat (ITT) analysis set: The ITT analysis set consisted of all randomized subjects who were exposed to at least one dose of trial product(s). Subjects were analyzed according to the randomized treatment assignment. For Trials 1436, 1572, 1574 and 1697, missing baseline values were not imputed, i.e., subjects without a baseline value of HbA1c were excluded from the analysis. For Trial 1573, missing values of HbA1c at baseline were imputed using the screening value, because there was no change in OAD medication between screening and randomization. For all five studies, subjects who discontinued early had their HbA1c level in the last assessment carried forward to the study endpoint. Similarly, subjects who were withdrawn early due to hyperglycemia ("ineffective therapy"; see TABLE 4) had the HbA1c level in the last assessment prior to withdrawal carried forward to the study endpoint.

A sensitivity analysis for the HbA1c endpoint used a modified version of the ITT analysis set, with no imputation for missing endpoint values of HbA1c.

Per Protocol analysis set (PP): The PP analysis set consisted of all exposed subjects who completed the blinded treatment period (week 26 for Trials 1436, 1572, 1574 and 1697, and week 52 for Trial 1573) with an evaluable HbA1c observation at that week, and who also had no major protocol violations. Subjects were analyzed according to the randomized treatment assignment.

Safety analysis set: The safety analysis set consisted of all randomized subjects who were exposed to at least one dose of trial product(s). If a subject received a different treatment than he/she was randomized to, data for the subject was analyzed, tabulated and/or listed according to the actual treatment he/she received.

3.1.4. Primary efficacy variable

The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment, for Trials 1436, 1572, 1574 and 1697, and after 52 weeks of treatment for Trial 1573.

3.1.5. Statistical analysis methods for primary efficacy endpoint

Primary analysis model: The primary analysis was performed for the ITT analysis set using analysis of covariance (ANCOVA). The primary model included study treatment, country and

previous anti-diabetic treatment stratification categories as fixed effects and baseline HbA1c as a covariate. Supportive analyses were conducted using the PP analysis set, and the modified ITT analysis set (with no imputation), using the same ANCOVA model.

Approach to multiplicity: With the concurrence of the Agency, the applicant used a gate-keeping strategy to control for the overall Type I error associated with the set of comparisons that was used to evaluate the efficacy of liraglutide within each study. The sequence of hypothesis tests for each study was pre-specified in the statistical analysis plan. They encompass comparisons of liraglutide arms against the comparators in each study. The pre-specified sequences do not include comparisons of the active control comparator against placebo comparator in Trials 1436, 1572 and 1697. These comparisons can be used to confirm the efficacy of the active control comparator under the conditions of the study but they were not included in the primary evaluation.

In the statistical analysis plan (SAP) that covered all five Phase 3 studies, the applicant described the hierarchical testing procedure that was used to protect the type I family-wide error. The following description is summarized from the SAP[3]:

Three factors were identified that contribute to multiple testing: (a) up to three different doses or liraglutide treatment in the trials; (2) up to two comparators in the trials; and (c) several secondary endpoints in addition to the primary endpoint.

For the primary HbA1c endpoint, the three doses of liraglutide were tested hierarchically for descending doses of liraglutide: (I) 1.8 mg liraglutide + add-on vs. comparator; (II) 1.2 mg liraglutide + add on vs. comparator; (III) 0.6 mg liraglutide + add-on vs. comparator, where "add-on" refers to the background antidiabetic therapy. The gate-keeping sequence meant that a hypothesis test for a given dose of liraglutide, of superiority or non-inferiority, would only be done if the hypotheses in the gate-keeping sequence were rejected for all higher ranked doses.

For the primary endpoint comparisons with two comparators (i.e., the active control arm and the placebo control arm), the comparisons were done hierarchically within each dose level: (I) Liraglutide + add-on vs. the placebo; (II) Liraglutide + add-on vs. the active control. This means that for the primary endpoint a given liraglutide dose was only tested against the active control if it was superior to the placebo control. Superiority to the placebo control was evaluated at a 2-tailed α of 0.05, and non-inferiority to the active control was evaluated at a 1-tailed α of 0.025.

In the event that a conclusion of non-inferiority to the active control is supported for a given dose of liraglutide, then that dose is tested for superiority to the active control. However, the outcome of the superiority evaluation is not part of the gate-keeping sequence.

The applicant noted that this procedure protects the Type I family-wise error at α for the primary endpoint for each study.

[3] See the Statistical Analysis Plan (Statistical Methods), Section 7.1

Body weight was a key secondary efficacy endpoint in all trials. Hypotheses for body weight were tested conditional on the outcome of the hypothesis tests for the primary endpoint. The SAP specified that the comparisons of liraglutide to the active comparator were of greatest clinical interest. Dunnett's method was used to protect the family-wise error among this set of pair-wise comparisons involving the active comparator.

3.1.6. Results of the statistical analysis of efficacy

Monotherapy: HbA1c at week 52 – baseline: Liraglutide 1.2 mg and 1.8 mg monotherapy produced reductions in HbA1c at week 52 compared to baseline that supported a conclusion of superior efficacy to glimepiride monotherapy ($p<0.01$; TABLE 8; Trial 1573). The net differences between the liraglutide arms and the glimepiride arm were 0.33 for liraglutide 1.2 mg and 0.62 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to glimepiride 8 mg. Analyses of the PP analysis set and the ITT analysis set at week 52 had similar results (not tabulated in this review).

Add-on therapy: HbA1c at week 26 – baseline: In general, all three doses of liraglutide resulted in a greater average reduction in HbA1c at week 26 compared to baseline when given as an add-on to the other anti-diabetic drugs. The net differences between the liraglutide add-on arms and the placebo add-on arms in the four phase 3 studies ranged from 0.78 to 1.36, in the direction of superior efficacy to liraglutide compared to placebo ($p<0.0001$, TABLE 8; Trials 1436, 1572, 1574 and 1697). Specific results for each study are as follows:

Trial 1572 (metformin background therapy): The net differences between the liraglutide arms and the placebo arm were 0.78 for liraglutide 0.6 mg, 1.06 for liraglutide 1.2 mg and 1.09 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to the placebo arm (TABLE 8). The liraglutide 1.2 mg and 1.8 mg arms were non-inferior to the active comparator arm, glimepiride 4 mg. Analyses of the PP analysis set and the ITT analysis set at week 52 had similar results for the comparisons of liraglutide 1.2 mg and liraglutide 1.8 mg (not tabulated in this review).

The liraglutide 0.6 mg arm did not meet the criterion for non-inferiority to the active comparator arm, and in fact the 95% CI of this comparison was entirely in the region of inferiority to the active comparator arm (TABLE 8). However, the applicant noted that non-inferiority of liraglutide 0.6 mg to glimepiride was demonstrated when the analysis was performed on the PP analysis set and on the ITT/no LOCF analysis set, with the 95% CIs for treatment difference (0.01, 0.36) and (0.04, 0.38) respectively. These confidence intervals are entirely in the region of inferiority of liraglutide 0.6 mg to glimepiride, but the upper bound is less than the margin of 0.4. The applicant suggested that the difference in results between the analysis sets may be due to the larger percentage of early withdrawals due to ineffective therapy in the liraglutide 0.6 mg arm than in the glimepiride arm. For this reason, the applicant chose to evaluate the non-inferiority

of change in body weight for liraglutide 6 mg compared to glimepiride, even though doing so did not strictly follow the pre-specified procedure for evaluating this key secondary efficacy endpoint.

Trial 1436 (glimepiride background therapy): The net differences between the liraglutide arms and the placebo arm were 0.83 for liraglutide 0.6 mg, 1.31 for liraglutide 1.2 mg and 1.36 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to the placebo arm (TABLE 8). The liraglutide 1.2 mg and 1.8 arms were statistically significant in the direction of superiority to the active comparator arm, rosiglitazone 4 mg. The liraglutide 0.6 mg arm met the criterion for non-inferiority to the active comparator arm but was not statistically significant in the direction of superiority (TABLE 8). The same analysis model applied to the ITT analysis set but without data imputation, and on the PP analysis set demonstrated similar results (not tabulated in this review). It is important to note, however, that in this trial, the highest proposed doses of liraglutide are being compared to the half maximal dose of rosiglitazone. 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 and Trial 1574 (4 vs. 8 mg/day). Therefore, one should be cautious in concluding that liraglutide is superior to rosiglitazone given at the maximal FDA approved dose.

Trial 1574 (metformin + rosiglitazone background therapy): The net differences between the liraglutide and the placebo arm were 0.94 for liraglutide 1.2 mg and 0.94 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to the placebo arm (TABLE 8). Analyses of the PP analysis set and the ITT analysis set at week 26 had similar results (not tabulated in this review).

Trial 1697 (glimepiride + metformin background therapy): The net difference between the liraglutide 1.8 mg arm and the placebo arm was 1.09 in the direction of a greater reduction of HbA1c compared to the placebo arm (TABLE 8). The liraglutide arm was statistically significant in the direction of superiority to the active comparator arm, insulin glargine (TABLE 8). The same analysis model applied to the ITT analysis set but without data imputation, and on the PP analysis set demonstrated similar results (not tabulated in this review).

I confirmed the results of the primary efficacy analysis from all five studies. The means and 95% confidence intervals of the net differences between the liraglutide arms and the placebo add-on arms, and between the liraglutide arms and the active comparator arms are depicted in FIGURE 8 for each study. The dose response relationship between the 0.6, 1.2 and 1.8 mg doses of liraglutide is illustrated in FIGURE 8. Although the studies were not powered for a comparison between liraglutide dose arms, and these comparisons were not included in the pre-specified sequential testing protocol, it can be noted that the 95% confidence intervals for the 1.2 mg and 1.8 mg dose arms are relatively similar in three of the four studies in which both doses were evaluated (Trials 1436, 1572 and 1574; FIGURE 8). In Trial 1573 the 95% confidence intervals of the 1.8 mg dose arms overlapped less with the 95% CI of the 1.2 mg dose in the direction of a

greater average reduction in HbA1c with the larger dose. The time course of mean HbA1c is illustrated for all five studies in FIGURE 9.

Post-hoc exploration of the active control compared to the placebo control. I conducted a post-hoc exploration of the active control arm in the three studies that were designed with both an active control and a placebo control arm. My purpose in doing this was to gain some insights into the pre-specified non-inferiority margin of 0.4 by comparing it to the placebo-adjusted effect of the active control arm. In doing so I acknowledge the limitations of this assessment compared to a full assessment of historical placebo-controlled studies that would be used to establish the non-inferiority margin for an antidiabetic drug. In addition, from a practical perspective, the assay sensitivity of the active control drugs in these Phase 3 studies was not a review issue, the results supported the superiority of liraglutide 1.2 mg and 1.8 mg compared to the active control.

Trial 1572 (metformin background therapy): The placebo-adjusted mean effect of glimepiride 4 mg was statistically significantly different from 0, and was similar to the placebo-adjusted effects of glimepiride (1 to 8 mg; -1.1, -1.9 and -1.9) in the clinical studies reported in the Amaryl™ label[4] (TABLE 9).

Trial 1436 (glimepiride background therapy): The placebo-adjusted mean effect of the active control comparator, rosiglitazone 4 mg, was statistically significantly different from 0 (TABLE 9). The mean effect was smaller than the effects reported in the Avandia™ label (-1.1 and -0.9, reported in Table 5 of the Avandia label, for combination studies of Avandia plus sulfonylurea in 24 to 26 weeks. The smaller effect may be due to the population of Trial 1473 which included patients in reasonable glycemic control.

Trial 1697 (glimepiride + metformin background therapy): Placebo-adjusted effects of insulin glargine are not reported in the Lantus™ label. Given that insulin can be titrated to effect, the placebo-adjusted mean effect of insulin glargine in this study is challenging to interpret beyond noting that it was statistically significantly different from 0 (TABLE 9).

[4] The placebo-adjusted effects are not available on the Amaryl label, but are reported in references to the clinical studies used to support the approval of Amaryl; Schade, et al. 1998, J Clin Pharmacol 38:636-641; Goldberg et al. 1996 Diabetes Care 19: 849-856; and Rosenstock et al. 1996, Diabetes Care 19: 1194-1997.

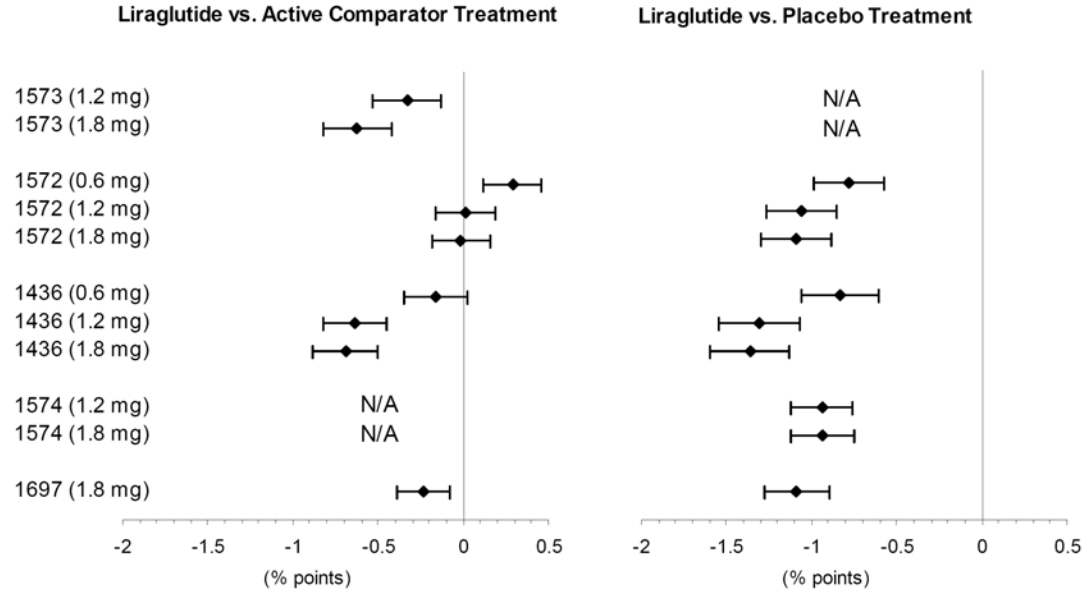
TABLE 8 Analysis of HbA1c, change from baseline (LOCF, ITT analysis set)

				Placebo			Comparator#		
	N	LS Mean	SEM	LS Mean Treatment Diff	95% CI	P-value	LS Mean Treatment Diff	95% CI	P-value
Trial 1573									
Liraglutide 1.2 mg	236	-0.84	(0.080)				-0.33	[-0.53;-0.13]	0.0014
Liraglutide 1.8 mg	234	-1.14	(0.081)				-0.62	[-0.83;-0.42]	<.0001
Comparator	241	-0.51	(0.077)						
Trial 1572									
Liraglutide 0.6 mg	239	-0.70	(0.067)	-0.78	[-0.99;-0.57]	<.0001	0.29	[0.12;0.46]	0.0009
Liraglutide 1.2 mg	232	-0.97	(0.069)	-1.06	[-1.27;-0.85]	<.0001	0.01	[-0.16;0.19]	0.8775
Liraglutide 1.8 mg	236	-1.00	(0.066)	-1.09	[-1.30;-0.88]	<.0001	-0.02	[-0.19;0.15]	0.8592
Placebo	120	0.08	(0.090)						
Comparator	234	-0.99	(0.068)						
Trial 1436									
Liraglutide 0.6 mg	224	-0.60	(0.071)	-0.83	[-1.07;-0.60]	<.0001	-0.16	[-0.35; 0.02]	0.0857
Liraglutide 1.2 mg	223	-1.08	(0.072)	-1.31	[-1.54;-1.08]	<.0001	-0.64	[-0.82;-0.45]	<.0001
Liraglutide 1.8 mg	226	-1.13	(0.072)	-1.36	[-1.60;-1.13]	<.0001	-0.69	[-0.88;-0.51]	<.0001
Placebo	107	0.23	(0.100)						
Comparator	224	-0.44	(0.071)						
Trial 1574									
Liraglutide 1.2 mg	174	-1.48	(0.078)	-0.94	[-1.12;-0.76]	<.0001			
Liraglutide 1.8 mg	177	-1.48	(0.075)	-0.94	[-1.12;-0.75]	<.0001			
Placebo	167	-0.54	(0.080)						
Trial 1697									
Liraglutide 1.8 mg	224	-1.33	(0.088)	-1.09	[-1.28;-0.90]	<.0001	-0.24	[-0.39;-0.08]	0.0029
Placebo	110	-0.24	(0.106)						
Comparator	225	-1.09	(0.090)						

The P-values corresponds to a two-sided test for superiority on a 5% significant level (statistical significance for p <0.05).
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.

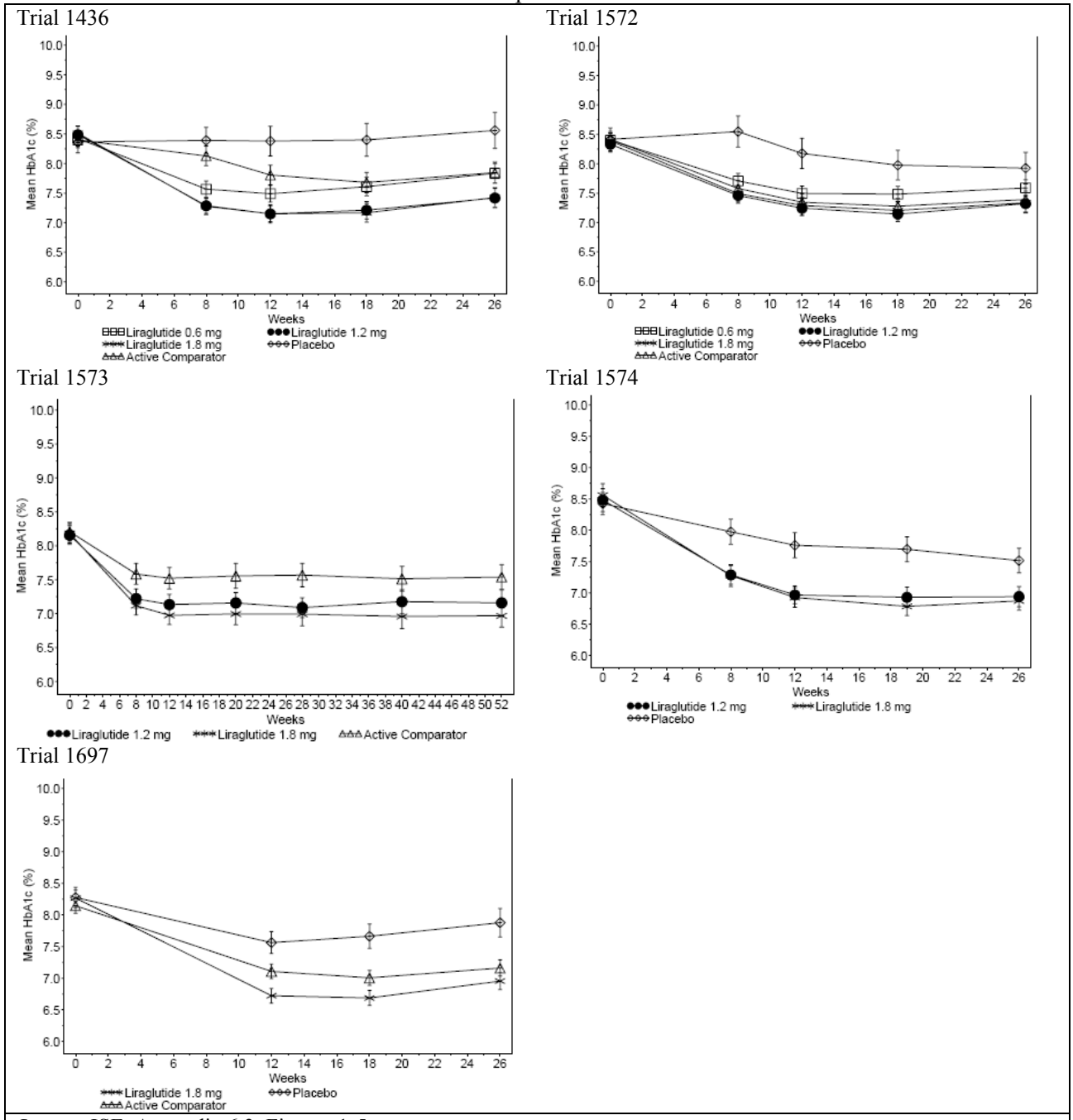
Source: Clinical Overview, Table 4-2

FIGURE 8 Forest plot of HbA1c, estimated mean difference ± 95% CI (LOCF, ITT analysis set)



Source: Clinical Overview, Figure 4-1

FIGURE 9 Mean HbA1c over time in the five phase 3 studies



Source: ISE, Appendix 6.3, Figures 1-5.
Note: ITT analysis set, with error bars representing ± 2 SEM

TABLE 9 Comparison of active control comparator arm with placebo control arm, HbA1c primary endpoint (change from baseline), ANCOVA primary model, LOCF/ICC primary analysis population

	Active Control Comparator Arm				Placebo Control Arm				Active - Placebo		
		N	LSMean	SE		N	LSMean	SE	LSMean	95% CI	p-value
Trial 1436 (26 weeks)	rosiglitazone 4 mg + glimepiride 4 mg	224	-0.44	0.07	glimepiride 4 mg	107	0.23	0.10	-0.67	(-0.90, -0.44)	<0.0001
Trial 1572 (26 weeks)	glimepiride 4 mg + metformin 2 g	234	-0.98	0.07	metformin 2 g	120	0.09	0.09	-1.07	(-1.28, -0.86)	<0.0001
Trial 1697 (26 weeks)	insulin glargine + glimepiride 4 mg + metformin 2 g	225	-1.09	0.09	glimepiride 4 mg + metformin 2 g	110	-0.24	0.11	-0.85	(-1.04, -0.66)	<0.0001

Sources: Clinical Reports from Trial 1436 (Table 14.2.16), Trial 1572 (Table 14.2.15), Trial 1697 (Table 14.2.17)

3.1.7. Other Efficacy Endpoints:

Body Weight

Body weight was pre-specified as a key secondary efficacy endpoint in the phase 3 studies. With 43% to 74% of subjects in the five studies classified as obese at baseline with a BMI ≥ 30 kg/m^2 (EXHIBIT 1-EXHIBIT 5), weight loss or gain is an important consideration. In my opinion, the results from the phase 3 studies support the conclusion that liraglutide is associated with an average net loss in weight at 26 weeks or at 52 weeks compared to several of the oral antidiabetic therapies used in the phase 3 studies. An overview of the weight change at study endpoint compared to baseline in the five phase 3 studies is given in FIGURE 10.

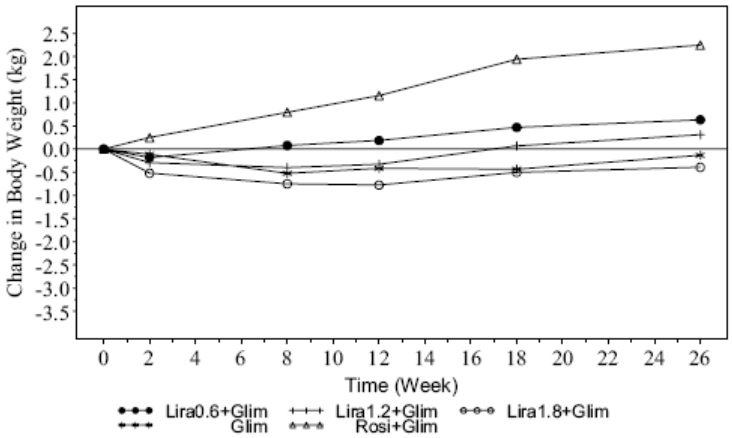
Liraglutide monotherapy resulted in an average net weight loss of 3.2 kg (liraglutide 1.2 mg) and 3.6 kg (liraglutide 1.8 mg) after 52 weeks, compared to glimepiride monotherapy (EXHIBIT 3; Trial 1573). However, liraglutide as an add-on to glimepiride did not result in an additional weight loss at 26 weeks compared to glimepiride monotherapy (EXHIBIT 1; Trial 1436). The liraglutide arms did result in a average net weight loss ranging from 1.4 kg to 2.3 kg compared to the rosiglitazone arm (EXHIBIT 1). This finding is consistent with findings reported elsewhere concerning the potential for rosiglitazone to cause a weight gain.

Liraglutide as an add-on to background antidiabetic therapies resulted in an average net weight loss ranging from 1.1 kg to 3.4 kg (EXHIBIT 2 - EXHIBIT 5).

About half of the subjects in the liraglutide arms (ranging from 40% to 62%) lost from 0 to 5% of their baseline body weight at the study endpoint. The percentage of subjects who lost 5% or more ranged from 4% to 33%, and the percentage of subjects who gained weight ranged from 17% to 54% across the liraglutide arms of the phase 3 studies (EXHIBIT 1-EXHIBIT 5). The summaries reported in EXHIBIT 1-EXHIBIT 5 are based on the ITT/LOCF analysis set. The applicant provided additional summaries based on the subset of ITT subjects who completed the study, and concluded that the two analysis sets resulted in similar findings. I evaluated a selection of these additional summaries and agree that the set of completers and the ITT/LOCF analysis set produce similar results with respect to body weight.

EXHIBIT 1 Body weight at baseline and change from baseline in Trial 1436

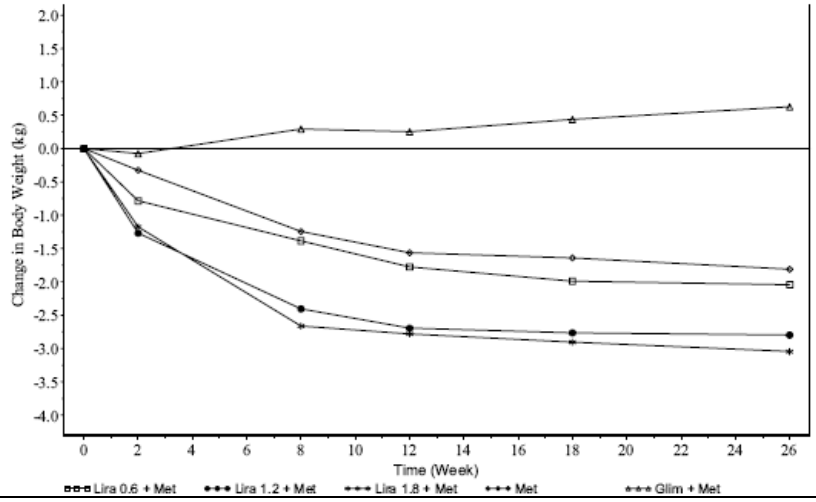
Trial 1436 add-on to glimepiride 4 mg	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**rosiglitazone 4 mg**
n in ITT analysis set	233	228	234	114	231
Baseline BMI categories (kg/m^2)					
< 25	37 (15.9%)[1]	39 (17.1%)	37 (11.1%)	16 (14.0%)	49 (21.2%)
25-30	85 (36.5%)	89 (39.0%)	93 (39.7%)	43 (37.7%)	82 (35.5%)
30-35	74 (31.8%)	55 (24.1%)	69 (29.5%)	34 (29.8%)	66 (28.6%)
≥ 35	36 (15.5%)	45 (19.7%)	34 (14.5%)	21 (18.4%)	33 (14.3%)
Baseline Body weight (kg)					
Mean ± SD	82.6 ± 17.7	80.0 ± 17.1	83.0 ± 18.1	81.9 ± 17.1	80.6 ± 17.0
Median	82.0	79.0	81.0	81.0	79.6
Min, Max	43.5, 183.1	40.3, 124.0	43.6, 138.0	50.0, 135.0	51.0, 130.0
Change from baseline at 26-week endpoint (LOCF)					
LS Mean ± SEM	0.72 ± 0.20	0.32 ± 0.20	-0.23 ± 0.20	-0.10 ± 0.27	2.11 ± 0.20
Net Change vs. Glimepiride arm					
LSMean, 95% CI, p-value[2]	0.82 (0.04, 1.60) p=0.0355	0.42 (-0.37, 1.20) p=0.4546	-0.14 (-0.92, 0.64) p=0.9702		
Net Change vs. Rosiglitazone + Glimepiride arm					
LSMean, 95% CI, p-value[2]	-1.38 (-2.03, -0.74) p<0.0001	-1.79 (-2.44, -1.13) p<0.0001	-2.34 (-2.99, -1.69) p<0.0001		
Weight loss as a % of baseline weight (% of ITT set; LOCF)					
No weight loss	126 (54.1%)[1]	110 (48.2%)	98 (41.9%)	46 (40.4%)	171 (74.0%)
0% to < 5%	92 (39.5%)	104 (45.6%)	109 (46.6%)	59 (51.8%)	52 (22.5%)
5% to < 10%	13 (5.6%)	8 (3.5%)	23 (9.8%)	7 (6.1%)	6 (2.6%)
≥ 10%	0 (0.0%)	2 (0.9%)	2 (0.9%)	0 (0.0%)	0 (0.0%)



Sources: Clinical reports from Trial 1436 (Table 11-15, Table 11-16, Table 11-17, Table 11-18, Figure 11-3)
Notes:
[1] Percentage of the ITT analysis set
[2] ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 2 Body weight at baseline and change from baseline in Trial 1572

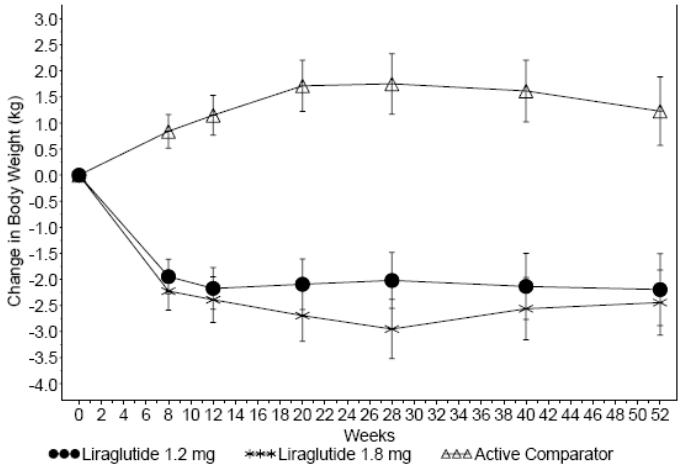
Trial 1572 add-on to metformin 2 g	**liraglutide 0.6 mg**	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**	**glimepiride 4 mg**
n in ITT analysis set	242	240	242	121	242
Baseline BMI categories (kg/m^2)					
< 25	33 (13.6%)[1]	22 (9.2%)	23 (9.5%)	8 (6.6%)	20 (8.3%)
25-30	84 (34.7%)	85 (35.4%)	86 (35.5%)	33 (27.3%)	79 (32.6%)
30-35	78 (32.2%)	72 (30.0%)	80 (33.1%)	50 (41.3%)	91 (37.6%)
≥ 35	47 (19.4%)	61 (25.4%)	53 (21.9%)	29 (24.0%)	50 (20.7%)
Baseline Body weight (kg)					
Mean ± SD	87.8 ± 17.1	88.5 ± 19.1	88.0 ± 16.3	91.0 ± 17.0	89.0 ± 16.8
Median	86.2	87.3	88.5	91.8	89.7
Min, Max	43.5, 141.0	43.4, 151.0	48.1, 135.2	52.5, 132.0	42.0, 148.0
Change from baseline at 26-week endpoint (LOCF)					
LS Mean ± SEM	-1.78 ± 0.23	-2.58 ± 0.24	-2.79 ± 0.23	-1.51 ± 0.31	0.95 ± 0.23
Net Change vs. Metformin arm					
LSMean, 95% CI, p-value[2]	-0.28 (-1.15, 0.60) p=0.8198	-1.07 (-1.94, -0.19) p=0.0117	-1.29 (-2.16, -0.41) p=0.0016		
Net Change vs. Glimepiride + Metformin arm					
LSMean, 95% CI, p-value[2]	-2.73 (-3.47, -2.00) p<0.0001	-3.53 (-4.27, -2.79) p<0.0001	-3.75 (-4.48, -3.01) p<0.0001		
Weight loss as a % of baseline weight (% of ITT set; LOCF)					
No weight loss	55 (22.7%)[1]	35 (14.6%)	40 (16.5%)	30 (24.8%)	149 (61.6%)
0% to < 5%	139 (57.4%)	148 (61.7%)	121 (50.0%)	71 (58.7%)	71 (29.3%)
5% to < 10%	45 (18.6%)	40 (16.7%)	66 (27.3%)	16 (13.2%)	16 (6.6%)
≥ 10%	3 (1.2%)	13 (5.4%)	14 (5.8%)	4 (3.3%)	1 (0.4%)



Sources: Clinical reports from Trial 1572 (Table 11-14, Table 11-15, Table 11-16, Table 11-17, Figure 11-3)
Notes:
[1] Percentage of the ITT analysis set
[2] ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 3 Body weight at baseline and change from baseline in Trial 1573

Trial 1573 monotherapy	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**glimepiride 8 mg**
n in ITT analysis set	251	246	248
Baseline BMI categories (kg/m^2)			
< 25	17 (6.8%)[1]	20 (8.1%)	15 (6.0%)
25-30	59 (23.5%)	73 (29.7%)	57 (23.0%)
30-35	90 (35.9%)	64 (26.0%)	84 (33.9%)
≥ 35	79 (31.5%)	83 (33.7%)	92 (37. 1%)
Baseline Body weight (kg)			
Mean ± SD	92.1 ± 19.0	92.6 ± 20.8	93.3 ± 19.0
Median	90.3	89.4	92.2
Min, Max	50.3, 154.0	49.9, 163.3	46.7, 159.2
Change from baseline at 52-week endpoint (LOCF)			
LS Mean ± SEM[2]	-2.05 ± 0.28	-2.45 ± 0.28	1.12 ± 0.27
Net Change vs. Glimepiride arm			
LSMean, 95% CI, p-value[2]	-3.17 (-3.87, -2.47) p<0.0001	-3.57 (-4.28, -2.87) p<0.0001	
Weight loss as a % of baseline weight (% of ITT set; LOCF)			
No weight loss	66 (26.3%)[1]	60 (24.4%)	154 (62.1%)
0% to < 5%	125 (49.8%)	116 (47.2%)	81 (32.7%)
5% to < 10%	42 (16.7%)	51 (20.7%)	11 (4.4%)
≥ 10%	12 (4.8%)	13 (5.3%)	2 (0.8%)



Sources: Clinical reports from Trial 1573 (Table 11-8, Table 11-9, Table 11-10, Table 14.2-6-6, Figure 21(ISE, Appendix 6.3))

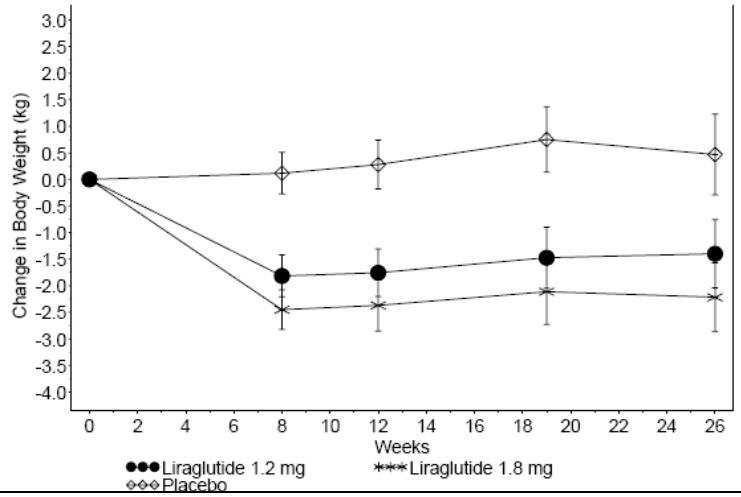
Notes:

[1] Percentage of the ITT analysis set

[2] ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 4 Body weight at baseline and change from baseline in Trial 1574

Trial 1574 add-on to metformin 2 g + rosiglitazone 8 mg *(4 mg BID)*	**liraglutide 1.2 mg**	**liraglutide 1.8 mg**	**placebo**
n in ITT analysis set	177	178	175
Baseline BMI categories (kg/m^2)			
< 25	10 (5.6%)[1]	7 (3.9%)	8 (4.6%)
25-30	45 (25.4%)	41 (23.0%)	35 (20.0%)
30-35	66 (37.3%)	63 (35.4%)	66 (37.7%)
≥ 35	55 (31.1%)	67 (37.6%)	64 (36.6%)
Baseline Body weight (kg)			
Mean ± SD	95.3 ± 18.3	94.9 ± 19.2	98.5 ± 18.2
Median	93.7	93.4	96.4
Min, Max	54.2, 152.0.6	52.4, 160.6	53.1, 150.1
Change from baseline at 52-week endpoint (LOCF)			
LS Mean ± SEM[2]	-1.01 ± 0.33	-2.02 ± 0.32	0.60 ± 0.34
Net Change vs. Metformin + Rosiglitazone arm			
LSMean, 95% CI, p-value[2]	-1.62 (-2.39, -0.85) p<0.0001	-2.62 (-3.39, -1.84) p<0.0001	
Weight loss as a % of baseline weight (% of ITT set; LOCF)			
No weight loss	59 (33.3%)[1]	36 (20.2%)	87 (49.7%)
0% to < 5%	83 (46.9%)	99 (55.6%)	72 (41.1%)
5% to < 10%	29 (16.4%)	38 (21.3%)	12 (6.9%)
≥ 10%	5 (2.8%)	5 (2.8%)	2 (1.1%)



Sources: Clinical reports from Trial 1574 (Table 11-8, Table 11-9, Table 11-10, Table 14.2-6-6, Figure 24 (ISE, Appendix 6.3))

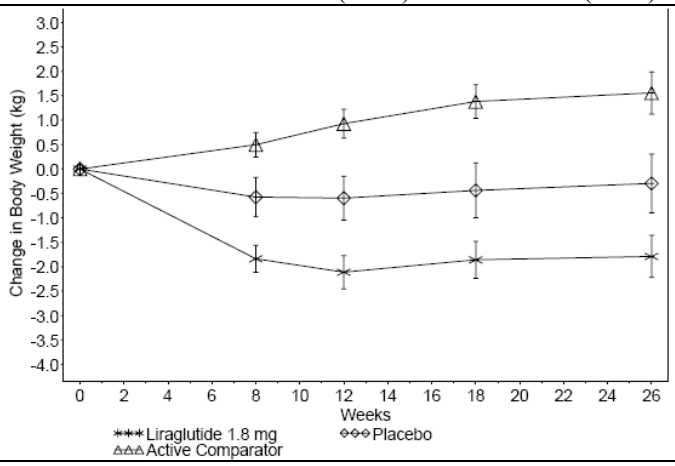
Notes:

[1] Percentage of the ITT analysis set

[2] ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

EXHIBIT 5 Body weight at baseline and change from baseline in Trial 1697

Trial 1697 add-on to glimepiride 4 mg + metformin 2 g	**liraglutide 1.8 mg**	**placebo**	**insulin glargine**
n in ITT analysis set	230	114	232
Baseline BMI categories (kg/m^2)			
< 25	38 (16.5%)[1]	11 (9.6%)	33 (14.2%)
25-30	79 (34.3%)	39 (34.2%)	87 (37.7%)
30-35	71 (30.9%)	40 (35.1%)	68 (29.3%)
≥ 35	42 (18.3%)	23 (20.2%)	43 (18.5%)
Baseline Body weight (kg)			
Mean ± SD	85.8 ± 19.3	85.4 ± 16.3	85.2 ± 17.9
Median	83.7	85.9	84.0
Min, Max	50.4, 149.5	56.9, 132.2	45.6, 136.0
Change from baseline at 26-week endpoint (LOCF)			
LS Mean ± SEM[2]	-1.81 ± 0.33	-0.42 ± 0.39	1.62 ± 0.33
Net Change vs. Glimepiride + Metformin arm			
LSMean, 95% CI, p-value[2]	-1.39 (-2.10, -0.69) p=0.0001		
Net Change vs. Glimepiride arm +Metformin + Insulin Glargine arm			
LSMean, 95% CI, p-value	-3.43 (-4.00, -2.86) p<0.0001		
Weight loss as a % of baseline weight (% of ITT set; LOCF)			
No weight loss	64 (27.8%)[1]	47 (41.2%)	166 (71.6%)
0% to < 5%	110 (47.8%)	55 (48.2%)	55 (23.7%)
5% to < 10%	48 (20.9%)	9 (7.9%)	4 (1.7%)
≥ 10%	5 (2.2%)	2 (1.8%)	2 (0.9%)



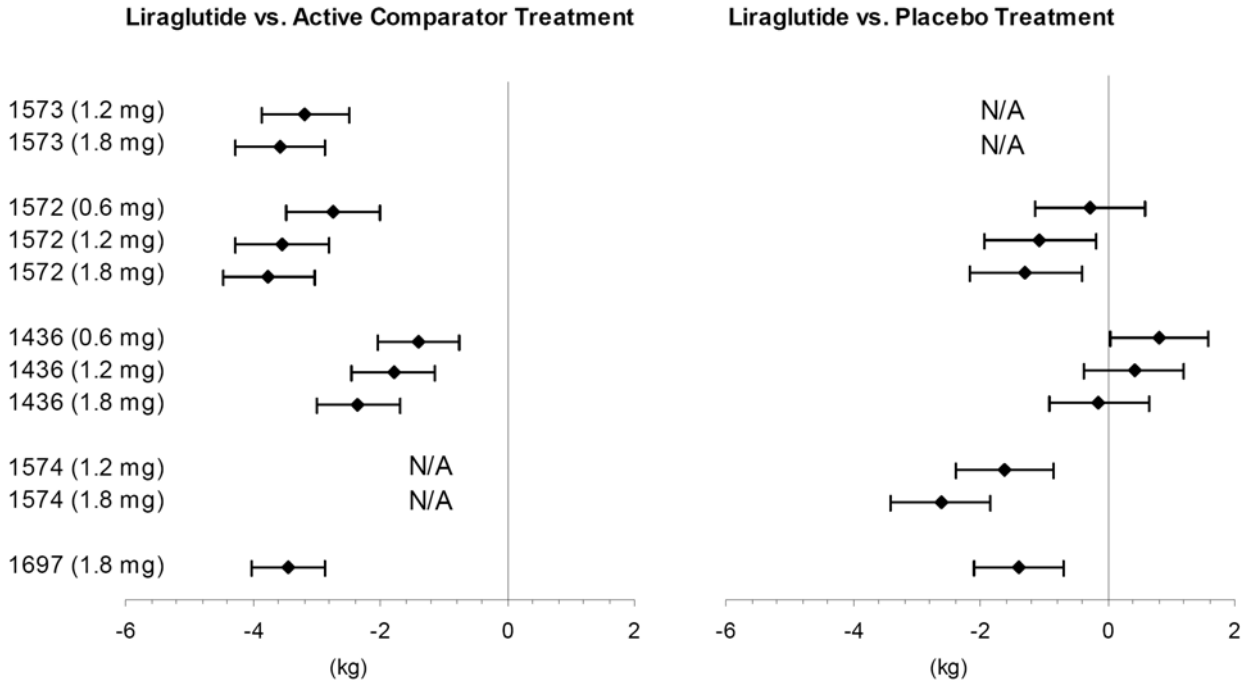
Sources: Clinical reports from Trial 1697 (Table 11-16, Table 11-17, Table 11-18, Table 11-19, Figure 25 (ISE, Appendix 6.3))

Notes:

[1] Percentage of the ITT analysis set

[2] ANCOVA model with treatment, country, previous treatment as fixed effects and baseline weight as covariate.

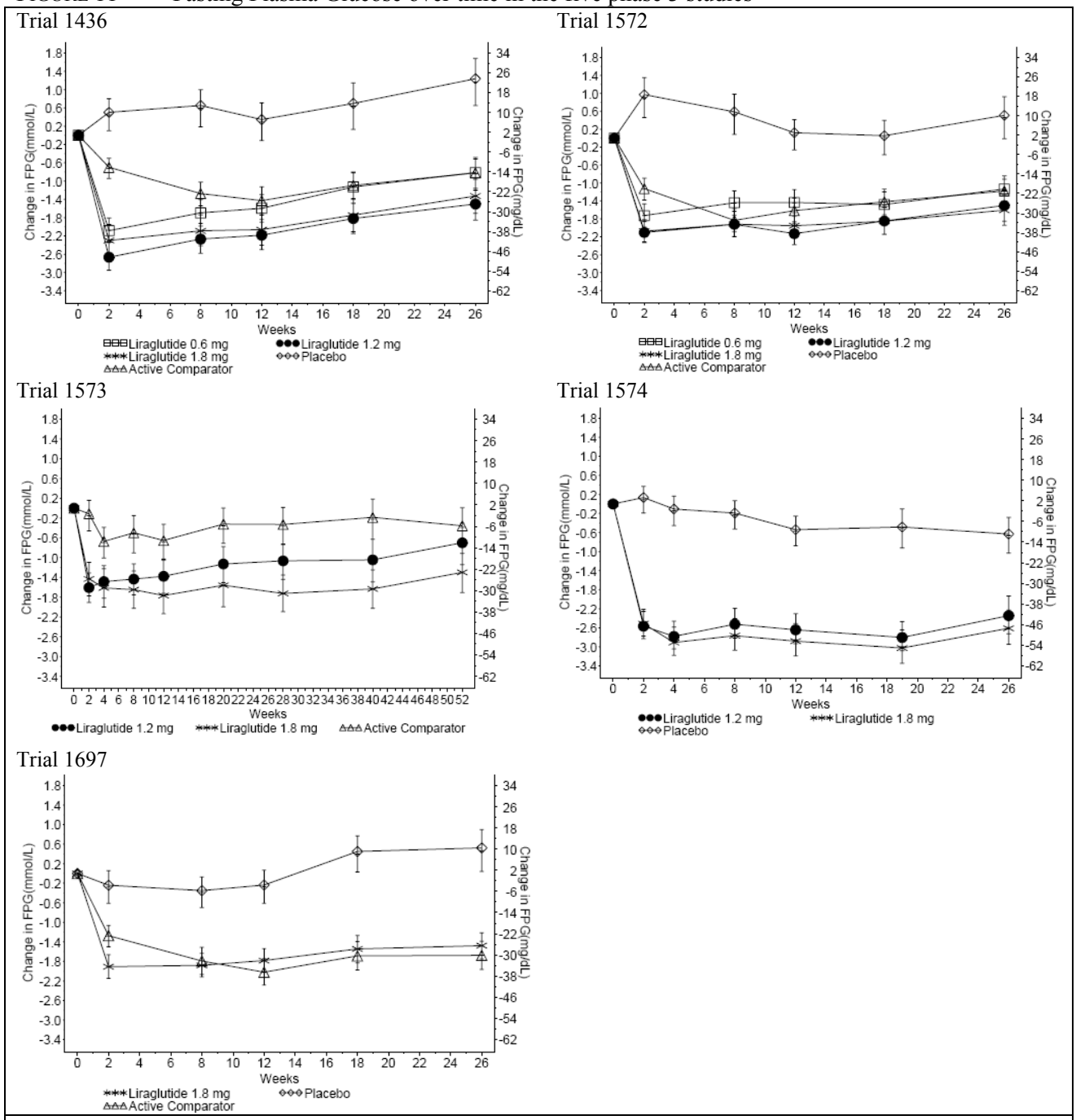
FIGURE 10 Forest plot of body weight (kg), estimated mean difference ± 95% CI (LOCF, ITT analysis set)



Source: Clinical Overview, Figure 4-2

Fasting Plasma Glucose (FPG): Treatment with liraglutide in the five phase 3 studies resulted in a decrease in mean FPG compared to baseline over the first 2-4 weeks of the double blind period, followed by a steady increase over the remaining period of the studies (FIGURE 11). In general, the active control arm followed a similar pattern. The placebo add-on arm did not show a decrease in mean FPG in the first 2-4 weeks. This pattern is supportive of the efficacy of liraglutide as monotherapy and as an add-on to background therapy with the other anti-diabetic drugs used in these studies.

FIGURE 11 Fasting Plasma Glucose over time in the five phase 3 studies



Source: ISE, Appendix 6.3, Tables 26-30
Notes: The ITT analysis set is depicted, with error bars representing ± 2 SEM

3.2 Evaluation of Safety

An evaluation of safety is covered in the FDA clinical review by Dr. Karen M. Mahoney.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Across the five key studies, the average HbA1c response to liraglutide was not significantly affected by age group or gender (TABLE 10 - TABLE 14). With respect to race, the pattern of average HbA1c response was consistent with a possible difference between Caucasian and Asian/Pacific Islander racial subgroups. The majority race in all five studies was Caucasian, ranging from 64% to 87% (TABLE 6). Trials 1436 and 1697 included 32% and 16% Asian/Pacific Islander, respectively, as the next most common racial group. In these two studies, the interaction of treatment by racial group had p-values < 0.1, which can indicate a potential relationship between the HbA1c response to liraglutide and racial group (TABLE 10 and TABLE 14. A further exploration of these two studies, conducted in sites outside the U.S., suggests that the Asian/Pacific Islander subgroup may have less net reduction in HbA1c with liraglutide compared to the placebo arm, relative to the Caucasian subgroup. With respect to ethnicity, the two studies that enrolled subjects from the U.S., Trials 1572 and 1573, also evaluated the interaction between Hispanic/Latino ethnicity and response to liraglutide. This interaction was not significant in either study (TABLE 11 and TABLE 12).

TABLE 10 Trial 1436; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender and race

Trial 1436	**liraglutide 0.6 mg**			**liraglutide 1.2 mg**			**liraglutide 1.8 mg**			**placebo**			**rosiglitazone 4 mg**		
add-on to glimepiride 4 mg	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)															
<65	180	8.4	-0.4 (1.1)	171	8.5	-1.0 (1.1)	184	8.5	-1.0 (1.2)	89	8.4	0.4 (1.1)	187	8.4	-0.3 (1.1)
≥ 65	47	8.4	-0.7 (0.9)	57	8.4	-0.9 (1.0)	45	8.5	-1.0 (1.2)	22	8.2	-0.1 (1.0)	41	8.3	-0.6 (0.7)
Sex															
Male	124	8.4	-0.5 (1.2)	102	8.4	-0.9 (1.1)	123	8.5	-0.9 (1.1)	52	8.3	0.2 (1.1)	108	8.3	-0.2 (1.2)
Female	103	8.4	-0.5 (0.8)	126	8.6	-1.0 (1.1)	106	8.5	-1.0 (1.2)	59	8.4	0.4 (1.1)	120	8.5	-0.5 (0.9)
Race															
Caucasian	153	8.4	-0.6 (1.0)	143	8.4	-0.9 (1.0)	145	8.4	-1.0 (1.1)	76	8.2	0.2 (1.1)	149	8.4	-0.4 (1.0)
Black	7	8.0	0.1 (1.1)	7	9.5	-2.2 (1.5)	9	9.0	-1.6 (1.4)	1	8.8	3.0 (---)	5	8.9	-0.8 (0.8)
Asian / Pacific Islander	67	8.6	-0.3 (1.1)	78	8.5	-1.0 (1.1)	74	8.6	-0.8 (1.2)	33	8.7	0.5 (1.0)	71	8.4	-0.2 (1.2)
Other							1	8.5	-1.7 (---)	1	8.6	-1.2 (---)	3	8.3	0.8 (2.7)

Notes:
Treatment (5 levels) by age group (2 levels) interaction p=0.3930; Treatment (5 levels) by sex (2 levels) interaction p=0.4170; Treatment (5 levels) by race (4 levels) interaction p=0.0026; from the following ANCOVA models: Change from baseline to endpoint = baseline value + treatment + country + previous antidiabetic drug + factor of interest (age, race or sex) + factor by treatment interaction.

Sources: Clinical Report from Trial 1436, Tables 14.2.25, 14.2.26 and 14.2.27

TABLE 11 Trial 1572; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender and race

Trial 1572	**liraglutide 0.6 mg**			**liraglutide 1.2 mg**			**liraglutide 1.8 mg**			**placebo**			**glimepiride 4 mg**		
add-on to metformin 2 g	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)															
<65	183	8.4	-0.6 (1.0)	184	8.3	-0.9 (1.1)	188	8.4	-0.9 (1.1)	97	8.5	0.1 (1.2)	191	8.4	-0.9 (0.9)
≥ 65	57	8.3	-0.6 (0.8)	54	8.5	-0.9 (1.0)	52	8.3	-0.8 (1.1)	24	8.1	0.3 (1.0)	48	8.4	-1.1 (1.0)
Sex															
Male	150	8.4	-0.6 (1.0)	127	8.2	-0.8 (0.9)	140	8.4	-0.9 (1.1)	72	8.3	0.2 (1.1)	138	8.4	-0.9 (0.9)
Female	90	8.5	-0.7 (1.0)	111	8.4	-1.0 (1.2)	100	8.4	-1.0 (1.2)	49	8.6	0.1 (1.4)	101	8.4	-1.0 (1.0)
Race															
Caucasian	200	8.4	-0.6 (0.9)	208	8.3	-0.8 (1.0)	212	8.3	-1.0 (1.0)	106	8.3	0.2 (1.0)	211	8.4	-0.9 (0.9)
Black	4	8.8	-1.1 (1.1)	9	9.1	-1.5 (2.2)	5	9.8	-1.7 (3.0)	3	10.4	-1.8 (3.5)	5	8.9	-1.9 (0.7)
Asian / Pacific Islander	31	8.7	-0.5 (1.2)	19	8.5	-1.2 (1.1)	18	8.4	-0.3 (1.2)	9	8.9	-0.3 (1.5)	21	8.5	-0.6 (1.0)
Other	5	8.0	-0.2 (1.4)	2	8.7	-0.8 (1.7)	5	8.8	-0.2 (1.3)	3	8.7	1.3 (1.8)	2	8.9	0.6 (0.7)

Notes:
Treatment (5 levels) by age group (2 levels) interaction p=0.8910; Treatment (5 levels) by sex (2 levels) interaction p=0.8089; Treatment (5 levels) by race (4 levels) interaction p=0.1180; from the following ANCOVA models: Change from baseline to endpoint = baseline value + treatment + country + previous antidiabetic drug + factor of interest (age, race or sex) + factor by treatment interaction.

Sources: Clinical Report from Trial 1572, Tables 14.2.28, 14.2.29 and 14.2.30

TABLE 12 Trial 1573; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender, race and ethnicity

Trial 1573	**liraglutide 1.2 mg**			**liraglutide 1.8 mg**			**glimepiride 8 mg**		
monotherapy	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)									
<65	208	8.2	-0.7 (1.4)	222	8.2	-1.0 (1.3)	208	8.3	-0.4 (1.2)
≥ 65	43	8.0	-0.8 (1.0)	24	7.7	-0.8 (0.9)	40	7.8	-0.5 (0.8)
Sex[1]									
Male	117	8.2	-0.7 (1.3)	121	8.2	-1.0 (1.4)	133	8.2	-0.5 (1.2)
Female	134	8.2	-0.8 (1.3)	125	8.2	-1.0 (1.1)	115	8.2	-0.4 (1.1)
Race									
Caucasian	200	8.1	-0.7 (1.4)	185	8.3	-0.7 (1.4)	192	8.2	-0.5 (1.1)
Black	34	8.5	-0.8 (1.1)	30	7.7	-0.9 (0.9)	30	8.3	0.0 (1.2)
Asian	5	7.8	-1.0 (0.8)	12	8.3	-1.1 (1.0)	9	9.0	-0.9 (1.0)
Native Hawaiian	---			2	7.4	0.2 (0.6)	---		
Other	12	8.2	-0.8 (1.4)	17	8.3	-0.8 (1.8)	17	8.5	-0.8 (1.5)
Ethnicity									
Hispanic/Latino	81	8.2	-0.7 (1.5)	87	8.5	-1.1 (1.5)	93	8.4	-0.5 (1.3)
not Hispanic/Latino	170	8.2	-0.8 (1.3)	159	8.0	-0.9 (1.1)	155	8.1	-0.4 (1.1)

Notes:
Treatment (3 levels) by age group (2 levels) interaction p=0.6587; Treatment (3 levels) by sex (2 levels) interaction p=0.3182; Treatment (3 levels) by race (5 levels) interaction p=0.3597; Treatment (5 levels) by ethnicity (2 levels) interaction p=0.6360; from the following ANCOVA models: Change from baseline to endpoint = baseline value + treatment + country + previous antidiabetic drug + factor of interest (age, race, sex or ethnicity) + factor by treatment interaction.

Sources: Clinical Report from Trial 1573, Tables 14.2.5-13, 14.2-5-14, 14.2-5-15, and 14.2-5-16

TABLE 13 Trial 1574; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender, race and ethnicity

Trial 1574	**liraglutide 1.2 mg**			**liraglutide 1.8 mg**			**placebo**		
add-on to metformin 2 g + rosiglitazone 8 mg *(4 mg BID)*	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)									
<65	146	8.5	-1.5 (1.0)	141	8.6	-1.5 (1.1)	151	8.5	-0.5 (1.0)
≥ 65	31	8.6	-1.3 (0.7)	37	8.6	-1.4 (1.0)	24	8.1	-0.6 (0.6)
Sex[1]									
Male	101	8.6	-1.4 (0.9)	87	8.7	-1.4 (0.9)	107	8.6	-0.5 (1.0)
Female	76	8.4	-1.5 (1.1)	91	8.4	-1.6 (1.1)	68	8.2	-0.6 (0.8)
Race									
Caucasian	144	8.5	-1.6 (0.9)	148	8.5	-1.5 (1.0)	148	8.4	-0.5 (0.9)
Black	26	8.0	-1.1 (0.9)	18	8.5	-1.6 (1.4)	18	8.3	-0.7 (0.8)
Asian	2	9.3	-0.1 (2.2)	5	8.7	-1.3 (1.1)	2	7.9	-0.6 (0.7)
American Indian	1	9.9	-3.1 (---)	1	8.3	-1.2 (---)	2	7.9	-1.1 (0.4)
Other	4	9.1	-1.3 (1.0)	6	9.1	-1.9 (1.4)	5	8.8	-0.8 (0.8)
Ethnicity									
Hispanic/Latino	23	8.7	-1.7 (1.1)	29	8.6	-1.5 (1.1)	29	8.7	-0.8 (0.9)
not Hispanic/Latino	154	8.5	-1.5 (0.9)	149	8.6	-1.5 (1.0)	146	8.4	-0.5 (0.9)

Notes:
Treatment (3 levels) by age group (2 levels) interaction p=0.1780; Treatment (3 levels) by sex (2 levels) interaction p=0.7338; Treatment (3 levels) by race (5 levels) interaction p=0.1337; Treatment (3 levels) by ethnicity (2 levels) interaction p=0.5375; from the following ANCOVA models: Change from baseline to endpoint = baseline value + treatment + country + previous antidiabetic drug + factor of interest (age, race, sex or ethnicity) + factor by treatment interaction.

Sources: Clinical Report from Trial 1574, Tables 14.2.5-13, 14.2-5-14, 14.2-5-15, and 14.2-5-16

TABLE 14 Trial 1697; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by age, gender and race

Trial 1697	**liraglutide 1.8 mg**			**placebo**			**insulin glargine**		
add-on to glimepiride 4 mg + metformin 2 g	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Age (years)									
<65	173	8.3	-1.3 (0.9)	83	8.3	-0.1 (1.1)	172	8.2	-0.9 (0.8)
≥ 65	57	8.3	-1.3 (1.0)	29	8.2	-0.4 (1.0)	60	8.1	-1.1 (0.8)
Sex[1]									
Male	130	8.3	-1.2 (1.0)	56	8.4	-0.2 (1.0)	139	8.1	-0.9 (0.8)
Female	100	8.2	-1.4 (0.8)	56	8.1	-0.2 (1.2)	93	8.3	-1.1 (0.9)
Race									
Caucasian	176	8.3	-1.4 (0.9)	87	8.2	-0.3 (1.0)	171	8.1	-1.0 (0.8)
Black	9	8.7	-1.5 (0.9)	5	9.5	0.4 (2.6)	7	8.4	-1.0 (1.1)
Asian / Pacific Islander	32	8.3	-1.0 (1.0)	14	8.0	-0.2 (0.7)	40	7.9	-0.9 (0.8)
Other	2	7.9	-0.3 (0.0)	1	8.9	-0.8 (---)	2	8.1	-0.9 (0.7)

Notes:
Treatment (3 levels) by age group (2 levels) interaction p=0.3722; Treatment (3 levels) by sex (2 levels) interaction p=0.7634; Treatment (3 levels) by race (2 levels) interaction p=0.0407; from the following ANCOVA models: Change from baseline to endpoint = baseline value + treatment + country + previous antidiabetic drug + factor of interest (age, race or sex) + factor by treatment interaction.

Sources: Clinical Report from Trial 1697, Tables 14.2.26, 14.2.27 and 14.2.28

4.2 Other Special/Subgroup Populations

Baseline HbA1c and change from baseline in HbA1c at week 26 (or week 52): Across the five key studies, subjects in subgroups with higher baseline HbA1c values generally had greater average reductions in HbA1c compared to subjects in subgroups with lower baseline HbA1c values in the liraglutide arms compared to placebo (TABLE 15 through TABLE 19). This relationship is illustrated not only in the liraglutide groups, but also in the arms with other antidiabetic drugs, including the placebo comparator groups and the active control comparator groups. Several explanations are consistent with this finding: (1) The antidiabetic drugs may all promote a greater reduction in HbA1c in subjects with higher baseline values; (2) The regression to the mean effect will tend to cause a greater change from baseline in subjects who had higher than average HbA1c levels at baseline by chance; and (3) The general improvement in diabetes care and management in subjects who participate in these studies may have a greater impact on subjects with higher baseline HbA1c.

In two studies, the interaction between baseline HbA1c and treatment group had p-values < 0.1, suggesting that the relationship between change in HbA1c and baseline HbA1c may be different among treatment arms (Trial 1574, TABLE 18 and Trial 1697, TABLE 19). In Trial 1574 (metformin + rosiglitazone background therapy), the average change from baseline in the liraglutide arms appeared to be greater at higher levels of baseline HbA1c than in the placebo comparator arm. In Trial 1697 (metformin + glimepiride background therapy), the average change from baseline in the liraglutide arm and the insulin glargine arm appeared to be greater at higher levels of baseline HbA1c than in the placebo comparator arm.

Baseline BMI: Differences in HbA1c response between categories of baseline BMI were not consistent across the five key studies (TABLE 15 through TABLE 19). Only one of the five studies had a p-value < 0.1 for the baseline BMI by treatment interaction. In Trial 1697, the average change from baseline in the liraglutide arm was greater in subjects with a higher average BMI, while this relationship was not apparent in the other two arms of the study (TABLE 19). This distinction among the arms may explain the interaction effect.

TABLE 15 Trial 1436; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA1c category and baseline BMI category

Trial 1436	**liraglutide 0.6 mg**			**liraglutide 1.2 mg**			**liraglutide 1.8 mg**			**placebo**			**rosiglitazone 4 mg**		
add-on to glimepiride 4 mg	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Baseline HbA1c (%)															
≤ 7.0	15	6.8	0.1 (0.9)	18	6.8	-0.4 (0.6)	9	6.8	-0.6 (0.5)	7	6.8	0.6 (0.9)	11	6.8	-0.2 (0.7)
7.0 < HbA1c ≤ 8.0	81	7.7	-0.4 (0.9)	70	7.6	-0.6 (0.8)	68	7.6	-0.7 (1.0)	38	7.5	0.5 (1.1)	83	7.6	-0.2 (1.1)
8.0 < HbA1c ≤ 9.0	70	8.5	-0.5 (1.0)	72	8.5	-0.9 (1.0)	95	8.5	-1.1 (1.1)	41	8.6	0.3 (1.1)	75	8.5	-0.4 (1.1)
> 9.0%	61	9.7	-0.7 (1.2)	68	9.7	-1.5 (1.3)	57	9.8	-1.2 (1.5)	25	9.7	-0.1 (1.0)	59	9.7	-0.5 (1.1)
Baseline BMI (kg/m^2)															
< 25	36	8.5	-0.6 (0.9)	39	8.7	-1.3 (1.0)	37	8.6	-0.9 (1.1)	16	8.6	0.3 (0.7)	49	8.5	-0.2 (1.0)
25 to < 30	82	8.4	-0.6 (1.0)	89	8.5	-1.0 (1.1)	90	8.6	-1.0 (1.3)	43	8.4	0.5 (1.1)	80	8.3	-0.3 (1.1)
30 to < 35	73	8.5	-0.6 (1.1)	55	8.4	-0.8 (1.1)	68	8.3	-0.9 (1.1)	32	8.4	0.1 (1.2)	66	8.4	-0.5 (1.1)
≥ 35	35	8.2	-0.2 (0.9)	45	8.4	-0.8 (1.0)	33	8.5	-1.2 (1.1)	20	8.0	0.3 (1.1)	32	8.4	-0.4 (1.0)

Notes:
Treatment (5 levels) by Baseline HbA1c (linear component) interaction p=0.3387; Treatment (5 levels) by BMI (4 levels) group interaction p=0.2067; from the following ANCOVA models: Change from baseline to endpoint = baseline HbA1c + treatment + country + previous antidiabetic drug + factor of interest (for the baseline BMI analysis) + factor by treatment interaction.

Sources: Clinical Report from Trial 1436, Table 14.2.28 (BMI) and additional analysis by this reviewer (HbA1c)

TABLE 16 Trial 1572; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA1c category and baseline BMI category

Trial 1572	**liraglutide 0.6 mg**			**liraglutide 1.2 mg**			**liraglutide 1.8 mg**			**placebo**			**glimepiride 4 mg**		
add-on to metformin 2 g	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Baseline HbA1c (%)															
≤ 7.0	9	6.8	-0.3 (0.6)	16	6.6	-0.5 (0.4)	9	6.8	-0.4 (0.8)	8	6.6	0.2 (0.6)	16	6.8	-0.3 (0.8)
7.0 < HbA1c ≤ 8.0	82	7.5	-0.3 (0.7)	85	7.6	-0.6 (0.7)	91	7.6	-0.7 (0.9)	39	7.6	0.2 (0.9)	85	7.7	-0.7 (0.7)
8.0 < HbA1c ≤ 9.0	84	8.5	-0.5 (1.0)	86	8.5	-0.8 (0.9)	86	8.5	-0.9 (1.0)	41	8.5	0.4 (1.1)	83	8.5	-0.9 (0.9)
> 9.0%	65	9.6	-1.1 (1.1)	51	9.7	-1.6 (1.4)	54	9.8	-1.4 (1.6)	33	9.7	-0.1 (1.6)	55	9.9	-1.4 (1.1)
Baseline BMI (kg/m^2)															
< 25	33	8.3	-0.7 (0.8)	22	8.2	-0.8 (0.8)	23	8.4	-0.7 (0.9)	8	9.3	0.0 (1.6)	20	8.7	-1.0 (0.9)
25 to < 30	83	8.4	-0.7 (1.0)	84	8.5	-0.9 (1.0)	84	8.4	-0.9 (1.0)	33	8.5	0.0 (1.5)	78	8.3	-1.1 (0.9)
30 to < 35	77	8.4	-0.5 (0.9)	72	8.3	-0.9 (1.1)	79	8.4	-0.9 (1.1)	50	8.4	0.3 (1.0)	89	8.5	-1.0 (1.0)
≥ 35	47	8.5	-0.5 (1.2)	60	8.3	-0.9 (1.1)	53	8.4	-1.1 (1.4)	29	8.1	0.1 (1.1)	50	8.4	-0.6 (0.8)

Notes:
Treatment (5 levels) by baseline HbA1c (linear component) interaction p=0.2491; Treatment (5 levels) by BMI group (4 levels) interaction p=0.2086; from the following ANCOVA models: Change from baseline to endpoint = baseline HbA1c + treatment + country + previous antidiabetic drug + factor of interest (for the baseline BMI analysis) + factor by treatment interaction.

Sources: Clinical Report from Trial 1572, Table 14.2.31 (BMI) and additional analysis by this reviewer (HbA1c)

TABLE 17 Trial 1573; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA1c category and by baseline BMI category

Trial 1573 monotherapy	liraglutide 1.2 mg n	Base-line mean	Change from baseline (SD)	liraglutide 1.8 mg n	Base-line mean	Change from baseline (SD)	glimepiride 8 mg n	Base-line mean	Change from baseline (SD)
Baseline HbA1c (%)									
≤ 7.0	24	6.8	-0.4 (0.7)	31	6.8	-0.3 (0.7)	28	6.8	-0.1 (1.1)
7.0 < HbA1c ≤ 8.0	100	7.5	-0.3 (1.1)	94	7.6	-0.7 (1.0)	94	7.6	-0.2 (0.9)
8.0 < HbA1c ≤ 9.0	69	8.5	-0.8 (1.3)	64	8.6	-1.1 (1.4)	70	8.5	-0.5 (1.2)
> 9.0%	43	10.0	-1.7 (1.5)	45	9.9	-2.0 (1.3)	49	9.9	-1.0 (1.4)
Baseline BMI (kg/m^2)									
< 25	18	7.8	-0.5 (1.4)	21	8.8	-1.5 (1.0)	15	8.1	-0.5 (1.4)
25 to < 30	61	8.1	-0.6 (1.3)	75	8.1	-1.0 (1.2)	57	8.1	-0.4 (1.4)
30 to < 35	93	8.3	-1.0 (1.3)	66	8.2	-1.2 (1.3)	84	8.5	-0.5 (1.2)
35 to < 40	40	8.2	-0.6 (1.2)	43	8.3	-0.7 (1.4)	57	8.1	-0.4 (1.1)
≥ 40	39	8.0	-0.5 (1.5)	41	8.0	-0.9 (1.3)	35	8.1	-0.5 (0.9)

Notes:
Treatment (3 levels) by baseline HbA1c (linear component) interaction p=0.3619; Treatment (3 levels) by BMI group (5 levels) interaction p=0.5765; from the following ANCOVA models: Change from baseline to endpoint = baseline HbA1c + treatment + country + previous antidiabetic drug + factor of interest (for the baseline BMI analysis) + factor by treatment interaction.

Sources: Clinical Report from Trial 1573, Table 14.2-5-17 (BMI), and additional analysis by this reviewer (HbA1c)

TABLE 18 Trial 1574; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA1c category and by baseline BMI category

Trial 1574	**liraglutide 1.2 mg**			**liraglutide 1.8 mg**			**placebo**		
add-on to metformin 2 g + rosiglitazone 8 mg *(4 mg BID)*	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Baseline HbA1c (%)									
≤ 7.0	19	6.7	-0.8 (0.4)	11	6.8	-0.7 (0.3)	12	6.7	-0.2 (0.4)
7.0 < HbA1c ≤ 8.0	55	7.6	-1.0 (0.5)	54	7.6	-1.9 (0.7)	62	7.6	-0.4 (0.7)
8.0 < HbA1c ≤ 9.0	46	8.5	-1.6 (0.8)	66	8.5	-1.4 (0.8)	44	8.5	-0.5 (0.9)
> 9.0%	54	10.0	-2.1 (1.1)	46	10.2	-2.3 (1.2)	49	9.9	-0.7 (1.2)
Baseline BMI (kg/m^2)									
< 25	7	9.4	-1.6 (1.7)	11	8.5	-1.2 (1.0)	8	8.5	-0.2 (0.5)
25 to < 30	41	9.0	-1.4 (1.1)	45	8.5	-1.4 (1.1)	35	8.5	-0.5 (1.0)
30 to < 35	63	8.4	-1.5 (0.9)	66	8.5	-1.5 (0.9)	66	8.4	-0.6 (0.9)
35 to < 40	39	8.5	-1.5 (1.1)	33	8.3	-1.5 (0.9)	43	8.4	-0.4 (0.9)
≥ 40	28	8.3	-1.5 (1.1)	22	8.7	-1.7 (1.0)	23	8.4	-0.7 (1.0)

Notes:
Treatment (3 levels) by baseline HbA1c (linear component) interaction p=0.0004; Treatment (3 levels) by BMI group (5 levels) interaction p=0.9503; from the following ANCOVA models: Change from baseline to endpoint = baseline HbA1c + treatment + country + previous antidiabetic drug + factor of interest (for the baseline BMI analysis) + factor by treatment interaction.

Sources: Clinical Report from Trial 1697, Table 14.2-5-17 (BMI) and additional analysis by this reviewer (HbA1c)

TABLE 19 Trial 1697; Mean changes from baseline in HbA_{1c} (%) at endpoint: subgroup analysis of the ITT/LOCF population by baseline HbA1c category and by baseline BMI category

Trial 1697	**liraglutide 1.8 mg**			**placebo**			**insulin glargine**		
add-on to glimepiride 4mg + metformin 2g	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**	**n**	**Base-line mean**	**Change from baseline (SD)**
Baseline HbA1c (%)									
≤ 7.0	17	6.7	-0.8 (0.6)	7	6.7	-0.2 (0.8)	23	6.6	-0.5 (0.5)
7.0 < HbA1c ≤ 8.0	83	7.5	-1.0 (0.7)	37	7.6	0.0 (1.0)	91	7.6	-0.7 (0.6)
8.0 < HbA1c ≤ 9.0	85	8.5	-1.3 (0.8)	50	8.5	-0.3 (1.0)	82	8.5	-1.1 (0.8)
> 9.0%	45	9.7	-1.9 (1.2)	18	9.7	-0.3 (1.4)	36	9.6	-1.7 (1.1)
Baseline BMI (kg/m^2)									
< 25	38	8.2	-1.1 (0.8)	11	8.6	-0.3 (1.1)	33	7.9	-1.2 (1.1)
25 to < 30	79	8.3	-1.3 (1.0)	38	8.3	-0.1 (1.2)	87	8.1	-1.0 (0.7)
30 to < 35	71	8.4	-1.4 (1.0)	39	8.1	-0.3 (0.8)	68	8.2	-1.1 (0.8)
≥ 35	42	8.2	-1.4 (0.7)	23	8.4	-0.1 (1.1)	43	8.3	-0.7 (0.8)

Notes:
Treatment (3 levels) by baseline HbA1c (linear component) interaction p=0.0111; Treatment (3 levels) by BMI group (4 levels) interaction p=0.0874; from the following ANCOVA models: Change from baseline to endpoint = baseline HbA1c + treatment + country + previous antidiabetic drug + factor of interest (for the baseline BMI analysis) + factor by treatment interaction.

Sources: Clinical Report from Trial 1697, Table 14.2.29 (BMI), and additional analysis by this reviewer (HbA1c)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

I evaluated the collective evidence in support of the efficacy of liraglutide from the results of five key Phase 3 studies. I confirmed a selection of the efficacy results for the primary endpoint, HbA1c at week 26 and 52, expressed as a change from baseline. I concurred with the pre-specified statistical methodology used in evaluating the primary endpoint. Results from the sensitivity analysis of the HbA1c endpoint supported the efficacy of liraglutide 1.2 mg and 1.8 mg. The efficacy of liraglutide 0.6 mg was less well supported, with results from one study supporting a non-inferiority conclusion and results from another study failing to meet the non-inferiority margin.

5.2 Conclusions

Monotherapy: HbA1c at week 52 – baseline: Liraglutide 1.2 mg and 1.8 mg monotherapy produced reductions in HbA1c at week 52 compared to baseline that supported a conclusion of superior efficacy to glimepiride monotherapy. The net differences between the liraglutide arms and the glimepiride arm were 0.33 for liraglutide 1.2 mg and 0.62 for liraglutide 1.8 mg in the direction of a greater average reduction of HbA1c compared to glimepiride 8 mg. Analyses of the PP analysis set and the ITT analysis set at week 52 had similar results.

Add-on therapy: HbA1c at week 26 – baseline: In general, all three doses of liraglutide resulted in a greater average reduction in HbA1c at week 26 compared to baseline when given as an add-on to the other anti-diabetic drugs. The net differences between the liraglutide add-on arms and the placebo add-on arms in the four phase 3 studies ranged from 0.78 to 1.36, in the direction of superior efficacy to liraglutide compared to placebo. Analyses of the PP analysis sets were supportive of the results from the ITT/LOCF analysis sets.

The inclusion of both an active control arm and a placebo control arm in three of the studies presented an opportunity to estimate the placebo-adjusted effect of the active control comparator within the study. In all three studies, the placebo-adjusted effect was statistically significantly different from 0. The net effect of glimepiride was similar to the results from the three historical placebo-controlled studies of glimepiride that were used to support the non-inferiority margin of 0.4.

Specific recommendations for labeling are not included in this review and will be covered in a later communication.

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Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Ilan Irony at 301-796-2290.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2008
Clinical/Medical

Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2008
Clinical/Medical

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Guidance for Industry[1]
Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment and prevention of diabetes mellitus. The intention of this guidance is to serve as a focus for continued discussions among the review divisions, pharmaceutical sponsors, academic community, and the public.[2] The organization of the guidance parallels the development plan for a particular drug or biologic. In the following discussion, we briefly describe type 1 and type 2 diabetes mellitus and treatment goals, discuss issues relevant to preclinical development, and then provide guidance on issues related to trial design, endpoints appropriate for different phases of development, and eligible populations. These issues are addressed for both type 1 and type 2 diabetes mellitus.

Although this guidance focuses more on the development of drug and therapeutic proteins to target the metabolic control of blood glucose in patients with diabetes, it also provides guidance on the development of products intended to prevent diabetes mellitus in high-risk individuals. Since the development of products for the prevention of diabetes is a relatively novel area, it is possible that specific guidances will be developed in the future for this topic as regulatory experience accrues. Therapeutic approaches to mitigate or reverse other clinical or pathophysiological hallmarks of what is often termed the metabolic syndrome are not addressed in this guidance.

[1] This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of diabetes drug or biological products. The FDA/NIH Joint Symposium on Diabetes, held on May 13 and 14, 2004, in Bethesda, Maryland, gathered relevant perspectives from academia and industry on issues covered in this guidance.

In addition, we recognize other important topics surrounding the treatment and prevention of diabetes mellitus. However, the following discussions are beyond the scope of this guidance.

- A comprehensive treatment strategy involves dietary changes and interventions other than medications.

- Highly desirable treatments specifically targeted to have direct effects in preventing end organ damage and diabetes-associated acute and chronic complications.

- Significant advances in the development of treatments for diabetes have been made through experimental approaches other than drugs or therapeutic proteins, such as transplantation of pancreata, pancreatic islet cells, stem cells that may differentiate into insulin-producing cells, and closed-loop devices (or artificial pancreas) that constantly monitor blood or interstitial glucose and adjust automated insulin delivery via a pump accordingly.

- The expansion of available choices in diagnostic devices that allow accurate and instantaneous glucose measurements, continuous glucose monitoring, and the identification of parameters of glucose metabolism characterizing states of insulin resistance has been significant to patients and health care professionals.

Advice on the development of specific products for preventing or treating complications of diabetes (e.g., diabetic peripheral neuropathy) can be sought from the relevant review division and other existing guidances.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[3] Instead, this guidance focuses on specific drug development and trial design issues that are unique to the study of diabetes mellitus, as measured by changes in hemoglobin A1c (HbA1c, glycosylated hemoglobin, or glycohemoglobin). Reductions in HbA1c directly reflect improvements in glycemic control. Therefore, HbA1c is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus.

The FDA recognizes that diabetes mellitus is associated with an increased risk of macrovascular complications and that reducing long-term cardiovascular complications in patients with diabetes should be an important goal of disease management. However, a premarketing recommendation to demonstrate macrovascular risk reduction in the absence of a signal for an adverse cardiovascular effect may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy. A reasonable approach may be to conduct long-term cardiovascular studies post-approval in an established time frame. We recommend that the design of such trials be discussed with the FDA and perhaps with clinical

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

trialists and experts in endocrinology and cardiology. This approach is beyond the scope of this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND TREATMENT GOALS

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although there are several drug treatments currently available (see Appendix C), the FDA recognizes the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs, therapeutic biologics, and devices).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure and has a heritable basis). Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial (DCCT)[4] has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy. Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.[5] There are also reasonably strong data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control, although macrovascular risk reduction in this patient population is less conclusive.[6]

[4] N Engl J Med, 1993, 329:977-986

[5] Diabetes, 2006, 55:3556-3565

[6] Lancet, 1998, 352:837-853 and 854-865

Glycemic control in these studies has been based on changes in HbA1c. This surrogate endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. In addition, there is a growing recognition that addressing cardiovascular disease risk factors, such as hypertension, smoking, and dyslipidemia, in patients with diabetes is particularly important, as diabetes is now considered an atherosclerotic heart disease equivalent.

III. DIAGNOSING DIABETES MELLITUS

Based on studies that have established a relationship between plasma glucose concentrations, measures of glycemic exposure, and risk of diabetic retinopathy, the following criteria have been adopted for the diagnosis of diabetes mellitus:

- Fasting plasma glucose greater than or equal to 126 mg/dL (7.0 mmol/L)
- Plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) at 2 hours following ingestion of 75 g anhydrous glucose in an oral glucose tolerance test
- Random plasma glucose greater than 200 mg/dL (11.1 mmol/L) in a person with symptoms of diabetes

These criteria were recommended by the American Diabetes Association (ADA) and the World Health Organization (WHO) in 1997 and 1998, respectively.

Other important definitions include:

- Impaired glucose tolerance: a plasma glucose equal to or greater than 140 mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L) at 2 hours in the oral glucose tolerance test
- Impaired fasting glucose: fasting plasma glucose (FPG) equal to or greater than 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL
- Gestational diabetes mellitus (GDM):
  - According to the ADA criteria, GDM is detected based on two or more values meeting or exceeding any of the following threshold values during a 75- or a 100-g oral glucose tolerance test:
    - FPG greater than or equal to 95 mg/dL (5.3 mmol/L)
    - Plasma glucose greater than or equal to 180 mg/dL (10 mmol/L) at 1 hour
    - Plasma glucose greater than or equal to 155 mg/dL (8.6 mmol/L) at 2 hours
    - Plasma glucose greater than or equal to 140 mg/dL (7.8 mmol/L) at 3 hours (the optional 3-hour time point only applies to the 100-g test)
  - GDM is diagnosed by the WHO criteria if FPG is greater than or equal to 126 mg/dL (7.0 mmol/L) or if the 2-hour glucose after a 75-mg oral glucose load is greater than or equal to 140 mg/dL (7.8 mmol/L)

Impaired fasting glucose and impaired glucose tolerance have recently gained importance because they identify groups of people at high risk for developing overt diabetes mellitus over

time, and because recent studies have demonstrated reductions in the progression to overt disease in these groups with specific therapeutic interventions. These individuals, along with women who have had a history of gestational diabetes, have been targeted for clinical evaluation of diabetes prevention.

IV. PRECLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES[7]

Preclinical development often includes pharmacology studies in which efficacy is assessed in animal models appropriate to the diabetes type being targeted for therapy. Toxicology studies for antidiabetic therapies generally should be conducted in the standard nondiabetic animal models.

A. Type 1 Diabetes Mellitus

In preclinical models that most closely mimic type 1 diabetes in humans, animals manifest spontaneous insulitis and progressive beta-cell destruction. Non-obese diabetic (NOD) mice and diabetes-prone BioBreeding (BB) rats are the most commonly used rodent models for type 1 diabetes, in which proof-of-concept studies of prospective therapeutic agents can be conducted. Such studies examine parameters relevant to the treatment of human disease, such as preservation of beta cells and insulin secretory function and fasting and postprandial levels of C-peptide and glucose. Streptozotocin-induced diabetes in rats is a predictable metabolic model of human type 1 diabetes, but does not involve an autoimmune mechanism, and, therefore, should not be used in preclinical studies of immune-directed diabetes prevention strategies.

NOD mice develop type 1 diabetes by an autoimmune disease similar to humans. In these mice, approximately 90 percent of females and 60 percent of males become hyperglycemic and develop diabetes by 12 months of age.

Approximately 90 percent of mature diabetes-prone BB rats develop diabetes. Diabetes-resistant BB rats constitute a variant that develop type 1 diabetes after some environmental insult (e.g., Kilham rat viral infection).

B. Type 2 Diabetes Mellitus

Animal models of type 2 diabetes are characterized by insulin resistance, hyperglycemia, and hyperinsulinemia. Some of the most frequently used models of type 2 diabetes are the leptin-deficient mouse (*ob/ob*), the leptin-receptor-deficient mouse (*db/db*), the obese Zucker rat (*fa/fa*), the Wistar Kyoto rat (*fa/fa*), and knockout mice lacking relevant targets, such as insulin receptors or glucose transporter 4 genes.

For all peroxisome proliferator-activated receptor (PPAR) agonists, 2-year carcinogenicity evaluations in rats and mice should be conducted before the initiation of clinical studies longer than 6 months in duration, based on their known carcinogenic potential as a class. Additionally, for PPAR drugs with gamma agonist activity, the maximum tolerated dose for carcinogenicity

[7] See 21 CFR part 58 for the FDA's good laboratory practices for conducting nonclinical laboratory studies.

assessment should be defined as the dose that results in a 20 to 25 percent increase in heart weight in rodents in the 13-week dose finding studies. This recommended dose limitation is designed to prevent excess cardiac mortality in the 2-year bioassay secondary to fluid accumulation and cardiomegaly. Refer to Appendix A for further details on this issue.

C. Insulins and Insulin Analogues

In vitro studies of insulins and insulin analogues can be useful for describing insulin receptor binding affinities and dissociation rates, receptor autophosphorylation, phosphorylation of signaling elements, and promotion of mitogenesis. In addition, for insulin analogues, affinity to the insulin receptor relative to other targets of insulin action, such as the insulin-like growth factor 1 receptor, should be characterized and compared to that found with native-sequence human insulin.

V. CLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES[8]

A. Trial Design and Conduct

1. Optimization of Glucose Control and Diabetes-Associated Comorbid Conditions

Individualization of therapy is essential to optimum control of glycemia in patients with diabetes. Consequently, some studies permit use of other antidiabetic therapies before randomization to ensure enrollment of patients whose diabetes control will be acceptable for clinical investigational purposes. Such studies often allow entry of patients using a specific class of antidiabetic drugs (e.g., baseline metformin therapy in patients with type 2 diabetes), to which either the investigational drug (or biologic) or a placebo will be added during randomization. Addition of new noninvestigational drugs or substantial changes in the dose of permissible baseline drug therapy after randomization may confound the results and interpretability of both efficacy and safety. For the results to be interpretable, any changes to these other therapies should be carefully documented.

When planning exploratory phase 2 studies, we recommend that sponsors include a run-in period before randomization to allow for diabetes education and for optimization of compliance with diet and exercise. This 6- to 8-week run-in period also is intended to allow for stabilization of parameters of metabolic control (e.g., HbA1c, fructosamine), so that the magnitude of the effect of different doses of the product can be most accurately estimated. Absence of this run-in period can result in overestimation of the *real world* treatment effects, given the intensive reinforcement of hygienic measures and compliance during clinical trials that is not reflected in typical treatment settings. In addition, placebo run-in periods in phase 3 studies can help screen out noncompliant subjects. We recommend providing efficacy data with a new product that result from rigorously designed studies.

[8] See 21 CFR parts 312, 50, and 56 for regulations regarding investigational new drug applications and human subject protection, including informed consent.

Adequate control of diabetic comorbidities in accordance with current standards of care should be incorporated in the criteria for eligibility in the study protocol. The addition of therapies to control diabetic comorbidities after randomization should be carefully documented (as should be the use of these therapies at baseline), because these therapies may confound the interpretation of both safety and efficacy of the investigational drug or biologic.

Improvement in HbA1c has become the standard surrogate outcome measure in many trial designs for a variety of therapies. In patients with diabetes, the following situations also can be considered a benefit of therapy: 1) a meaningful reduction of insulin requirements (in either type 1 or type 2 diabetes), or 2) a reduction in the number or doses of oral antidiabetic agents (in type 2 diabetes mellitus), both in the context of stable or improved HbA1c. Even though HbA1c is appropriate as a surrogate endpoint in many study designs, documented improvement in a serious morbidity or mortality related to diabetes (i.e., outcome studies) may be more persuasive evidence of benefit for drugs in which substantial safety issues or questions arise (see sections V.B., Study Assessments and Endpoints, and V.E., Sample Size and Study Duration, for additional considerations).

2. Type 1 Diabetes Mellitus

As stated earlier, insulin is the essential glucose-lowering therapy for the treatment of patients with type 1 diabetes. Therefore, all experimental treatments for type 1 diabetes (and their matching placebos, as applicable) that are not insulin analogues or other insulin receptor ligands should be studied as add-on therapies to insulin.

Preclinical data or knowledge of a particular mechanism of action may indicate that an investigational product has the potential to cause or worsen hypoglycemia, either by binding to insulin receptors or by affecting other aspects of glucose absorption and metabolism. If the investigational product is anticipated to have the potential to lead to hypoglycemia, either directly or through potentiation of insulin effect, the study design should include allowance for insulin dose adjustments to protect trial subjects from hypoglycemia. However, pharmacodynamic interactions with insulin, as well as the need to adjust insulin doses to prevent hypoglycemia, may pose significant challenges for study design, interpretation, and inference of the new drug's efficacy. For example, given the need to titrate insulin to control for glycemia and to guard against hypoglycemia, the blinding of subject and investigator to treatment allocation may not be practical or acceptably safe. Unblinded, controlled trials may be appropriate in some circumstances, particularly for trials incorporating clearly objective endpoints. On the other hand, unblinding can severely limit the interpretability of subjective endpoints (i.e., patient-reported outcomes) that might be incorporated as secondary assessments of efficacy.

In phase 1 and phase 2 trials of products intended to prevent or delay the progression of type 1 diabetes, sponsors are encouraged to conduct randomized, placebo-controlled studies, while investigating early pharmacodynamic markers of effect as well as the safety of the tested product.

3. Type 2 Diabetes Mellitus

Efficacy and safety of new products for the treatment of type 2 diabetes can be evaluated in placebo-controlled monotherapy trials, placebo-controlled add-on therapy trials, and active-controlled trials. Given the progressive nature of type 2 diabetes and the requirement for multiple drug therapy, the clinical development program should involve evaluation of the investigational drug as monotherapy and in combination with many other approved antidiabetic drugs.

In the past, oral agents (i.e., sulfonylureas) to treat type 2 diabetes were approved largely on the basis of placebo-controlled trials with no underlying pharmacological therapy, in which all randomized subjects received only counseling for appropriate diet and an exercise program in addition to the product being tested. As medical care for diabetes has evolved, it may now be difficult to find patients who are appropriate candidates for purely placebo-controlled trials because a large proportion of those diagnosed with diabetes are receiving early pharmacological treatment. Considerations of withdrawal of existing therapy to enroll patients in a placebo-controlled trial of a new agent as initial monotherapy should include informed consent, severity and duration of disease, presence of diabetic comorbidities, and dose of the existing drug therapy. In addition, strict escape or withdrawal criteria for loss of glycemic control should be explicit in the study protocol.

The discontinuation of effective treatment for the purposes of making a patient eligible for inclusion in a placebo-controlled trial of significant duration (e.g., longer than 6 months) raises ethical issues, although placebo-controlled trials of 6 months or less in duration may be appropriate, provided that the protocol contains strict escape or rescue criteria related to hyperglycemia and poor glycemic control. In such trials, the number of patients meeting the escape criteria can be assessed as a measure of efficacy. In any case, we recognize that both placebo-controlled (with or without background therapy) and active-controlled studies can provide the essential safety and efficacy data to support approval.

a. Studies of a test agent as monotherapy

Many patients with type 2 diabetes who are potential candidates for studies of new therapeutic agents are likely being treated with one or more antidiabetic medications. Development of a new investigational product to support its indication as monotherapy in type 2 diabetes can be undertaken in subjects who are drug-naïve and whose diabetes is reasonably well controlled with diet and exercise. These subjects can participate in placebo- and dose-controlled studies for up to 24 weeks, provided that they continue to remain in reasonable metabolic control for the duration of the studies (see below for an example of escape or rescue criteria). Likewise, subjects on low doses of a single antidiabetic medication who are under reasonable glycemic control can discontinue their medications under strict glycemic supervision to participate in placebo-controlled studies of an agent to be used as monotherapy.

There also should be a reasonable expectation that placebo dropouts caused by further loss of glycemic control will be limited, thus enabling controlled assessments of both efficacy and safety.

For either phase 2 or phase 3 studies, regardless of HbA1c at entry, subjects whose hyperglycemia persists or worsens beyond prespecified thresholds should be appropriately monitored and treated throughout the study. In developing these escape or rescue criteria, it is useful to consider that even for drugs that show therapeutic effects only after a matter of weeks (e.g., thiazolidinediones/PPAR agonists), most responders experience a reduction in fasting blood glucose of greater than 20 mg/dL (1.1 mmol/L) by 6 weeks. For agents that lower postprandial rather than fasting glucose levels, a clinically meaningful reduction in HbA1c (e.g., 0.3 percentage units) also usually is evident by 6 weeks. The following are examples of rescue criteria based on thresholds for FPG or HbA1c:

- FPG greater than 270 mg/dL (15 mmol/L) from baseline to Week 6
- FPG greater than 240 mg/dL (13.3 mmol/L) from Week 6 to Week 12
- FPG greater than 200 mg/dL (11.1 mmol/L) or HbA1c greater than 8.0 percent from Week 12 to Week 24

For agents that lower postprandial rather than fasting glucose levels, the sponsor is encouraged to enforce specific rescue criteria based on thresholds of unacceptable postprandial glucose encountered during the first 12 weeks of the study and unacceptable HbA1c encountered thereafter.

Even if the escape criteria related to poor glycemic control result in early discontinuation of a substantial proportion of participating subjects, the trial may still be interpretable, at least from the standpoint of efficacy. (For more details, see section V.G., Important Statistical Considerations.) The rate of meeting withdrawal criteria also can provide an assessment of efficacy using a time-to-event analysis if events are collected or responder analysis based on a binary outcome of treatment success or failure. Subjects meeting glycemic rescue criteria ideally should remain in the study even after receiving the additional or alternative therapy to allow for the assessment of safety of the investigational drug or biologic.

Phase 2 or phase 3 studies investigating the efficacy of a new product as monotherapy in subjects already on active therapy for their diabetes can be more problematic. The majority of these subjects will probably experience significant worsening of glycemic control when their medications for diabetes are discontinued. These subjects require a washout period with careful monitoring of glucose. An unknown, and likely high, proportion of subjects simply will either not qualify for studies because of loss of control before randomization or will discontinue because of worsening glycemia in the initial weeks of treatment with poorly effective doses of the investigational drug or with placebo. The washout period should take into account the pharmacokinetic properties of the existing treatment (e.g., 5 half-lives) and the fact that HbA1c reflects mean glycemic control over 2 to 3 months. The length of treatment with the test agent before endpoint ascertainment should account for the duration of the pharmacodynamic effects of previous treatments and the expected timing of a pharmacodynamic effect (e.g., plasma glucose, HbA1c) of the test agent.

A difference between active drug and placebo (or between two active treatments such as a lower and higher dose of the test agent) in the proportion of subjects meeting criteria for glycemic rescue therapy can be used as a measure of efficacy.

b. Studies of new agents on a background of existing therapy

For subjects taking two or more antidiabetic agents to control glycemia, a potential approach in phase 2 or phase 3 can be a randomized study in which the investigational product or matching placebo is substituted for one of the drugs being taken. Sponsors can conduct extensive dose titration and dose exploration in phase 2 studies of this type, typically 12 to 16 weeks in duration.

For phase 3 studies of investigational agents as add-on therapy, the typical design is not that of substituting the investigational agent for an existing medication, but rather to add the investigational agent to the existing therapy. Typically, these studies are designed as placebo-controlled superiority or active-controlled noninferiority trials. In these studies, patients inadequately controlled on optimal or near-optimal doses of approved therapies should be randomized to one of several doses of the investigational agent or to placebo as add-on to the existing medications (or, in the case of active-controlled trials, to a therapy previously approved for such add-on use). Subjects should be on optimal or near-optimal doses of approved therapies for two reasons: 1) most practicing physicians titrate the dose of one therapeutic agent before considering addition of another antidiabetic agent to improve glycemic control; and 2) this approach allows for more rigorous assessment of the investigational product's efficacy by avoiding a confounding effect of any upward dose titration of the approved medication during the trial.

Another design less commonly used in studies directed at assessing efficacy is the randomized withdrawal. For example, all subjects can be treated with the test agent either as monotherapy or in addition to existing therapy. After a treatment period sufficient to reach pharmacodynamic steady state, subjects can be randomized, in double-blind fashion, either to continue test therapy or to switch to placebo for an additional period (e.g., 12 to 16 weeks). Subjects whose glycemic control deteriorates to the point of meeting escape criteria and requiring additional therapy may create a bias in the assessment of efficacy if the efficacy endpoint is defined as change of HbA1c from randomization to the study endpoint. The primary endpoint for the withdrawal design should be the time to therapeutic failure if event times are collected or, if not, the proportion of HbA1c treatment failures in each treatment group.

B. Study Assessments and Endpoints

1. General Considerations

Throughout development of new molecular entities, particularly within novel classes of therapeutic products, thorough safety evaluations are critical even in the early phase clinical studies. These early studies should be designed with conservative approaches to testing, initially in smaller numbers of subjects, with single doses, and with appropriate safety monitoring not only for glycemia-related parameters, but also for potential hazards identified based on

preclinical or in vitro study results or on known effects seen with other members of the drug class (if available).

a. Pharmacokinetics

In general, pharmacokinetic parameters of noninsulin therapeutics should be evaluated in phase 1 studies. These studies can be performed in healthy volunteers to determine the basic pharmacokinetic parameters (e.g., absolute bioavailability, area under the curve (AUC), C_{max}, T_{max}, $T_{1/2}$). Additionally, pharmacokinetic studies also may be appropriate in the intended patient population. We recommend that exposure-response data be obtained during the phase 2 dose-finding studies. (See the guidance for industry *Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*.)

In patients with diabetes, the high prevalence of altered glomerular filtration rates, delayed or deficient gastrointestinal transit and absorption, and the potential for interactions with commonly used medications usually dictate the need for the evaluation of the pharmacokinetics of new agents in the target population, beyond investigations in healthy volunteers. It is important to evaluate the in vivo and in vitro mechanisms of drug absorption and disposition. This information will provide the basis for the design of the drug interaction studies addressing the class effects of oral antidiabetic drugs (e.g., addressing the induction potential of CYP enzymes by thiazolidinediones, CYP2C-based interactions with sulfonylureas, and interactions with renal tubular secretion of metformin). We also recommend interaction studies with drugs that have a narrow therapeutic index and with drugs likely to be co-administered in the diabetic population. (See the draft guidance for industry *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling* for details.)[9]

Effects of food on pharmacokinetics should be evaluated in the development of therapeutic products that are intended to be administered orally in temporal proximity to meals (e.g., agents designed to exert effects on glycemia peri- or postprandially, such as meglitinides). Because patients with diabetes may be a particularly sensitive population in terms of polypharmacy and underlying, often subclinical, cardiac disease, we also encourage sponsors to address the effect of the drug on the QT interval by conducting a thorough QT study.[10]

b. Pharmacodynamic endpoints and biomarkers

Products whose pharmacodynamics, by design, are restricted to effects on postprandial glucose (e.g., meglitinides) should be tested in dose-finding, proof-of-principle, short-term, oral glucose challenge studies. However, such demonstrations of pharmacodynamic activity are not sufficient evidence of efficacy for new drug application (NDA) approval,[11] because the link between a modifying effect on postprandial glucose excursions to clinical outcomes is not sufficiently

[9] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[10] See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.

[11] See 21 CFR part 314 for regulations regarding NDAs.

strong to consider the use of this pharmacodynamic endpoint as a surrogate for efficacy. Such products should be shown to be safe and effective in improving overall glycemic control based on reduction in HbA1c. That said, description in labeling of the effects of the agent on excursions in postprandial serum glucose concentrations, thereby effecting reductions in overall glycemic exposure (as manifest by reductions in HbA1c), may be warranted in some cases to provide physicians with an understanding of the mechanism of action of the agent and its implication for method of use.

Glycated endogenous proteins with turnover rates faster than hemoglobin, such as fructosamine, can be used as preliminary indicators of a product's effects on integrated glycemic exposures in early phase studies of limited duration. Demonstration of reductions in HbA1c, with a concomitant meaningful decrease in mean daily insulin requirements in relevant patients, is desirable but not necessary for the preliminary inference of efficacy from these early studies. Changes in FPG, plasma glucose level after a standard meal, plasma glucose level after oral administration of 75 g of glucose, average blood glucose (mean of seven home measurements obtained before and after each meal and at bedtime), and fructosamine can be used as primary measures of efficacy in phase 2 studies. They also can be used as secondary, supportive measures of efficacy in phase 3 studies.

c. Efficacy endpoints

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. Superiority or noninferiority hypotheses may be appropriate depending on the trial design. Refer to section V.G., Important Statistical Considerations, for a discussion of issues related to noninferiority trials and choice of noninferiority margins as they relate to studies in diabetes. Also see the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

d. Effects on markers of insulin resistance and diabetes comorbidities

Treatment-associated reduction in endogenous hyperinsulinemia (in type 2 diabetes) or improvement in insulin sensitivity are arguably salutary health effects, but do not alone provide sufficient support of a new agent for approval purposes. Effects of antidiabetic agents on blood pressure and serum lipids are of obvious importance and can be described in labeling with disclaimers commensurate with the limitations of the trials regarding extrapolation of findings to conclusions about ultimate drug effects (i.e., on mortality or irreversible morbidity).

e. Effect of weight loss on diabetes

In recent years, the FDA has recommended to sponsors of weight loss products seeking an indication for the treatment of type 2 diabetes that they should demonstrate that the product's effect on glycemic control is independent of weight loss. The FDA has reconsidered the necessity of this recommendation. The FDA's current thinking is that a sponsor can gain approval for the treatment of type 2 diabetes for a drug or biologic whose principal mechanism

of action appears to be weight loss by showing a clinically meaningful and statistically significant improvement in glycemia.

The development program to support a diabetes indication for these products should be comparable to the development programs used for antidiabetic products not intended for weight loss. For example, the product would need to be studied in subjects with a wide range of body mass indices (from lean to obese), different duration of diabetes (new onset to long-standing), and under different conditions of use (monotherapy and combination therapy). Sponsors interested in the development of weight loss products for the treatment of type 2 diabetes should discuss their plans with the Division of Metabolism and Endocrinology Products.

2. Insulins

In the case of a new insulin with perhaps unique pharmacokinetic characteristics dictating a specific method of use (i.e., dosing interval, timing relative to meals), efficacy can be assumed based on pharmacodynamic (e.g., clamp) studies. However, studies of clinical safety and efficacy usually will be necessary to demonstrate that the method of use leads to effective diabetes management and that the treatment is not associated with undue hypoglycemia (e.g., relative to an approved insulin and standard regimen). (See Appendix B for a discussion on hypoglycemia). These studies should be directed at achieving actual reductions in glycemia (as opposed to simple maintenance of pretrial levels of control) from baseline to end of study. Test and comparator groups should be treated to similar goals. Similar degrees of glycemic control (test noninferior to reference) should be achieved so that comparisons among groups in frequency and severity of hypoglycemia will be interpretable in ultimate risk-benefit assessments.

a. Insulin mixes

When seeking approval of a new formulation of premixed short- and long-acting insulins, the sponsor should establish the distinctiveness and usefulness of the premixed products compared to each individual insulin component. We recommend that the premixed product's pharmacokinetic and pharmacodynamic profiles have a target difference of at least 20 percent from each of its single components (e.g., NPH and regular/rapid insulin) and also from each adjacent product within its product line. Such differences can be established by the maximum concentrations (C_{max}) and the various partial AUCs (e.g., $AUC_{0\text{-}4\ hr}$ and $AUC_{4\text{-}12\ hr}$) from insulin plasma exposure versus time profiles. From a pharmacodynamic perspective, the maximum glucose infusion rate (GIR) and the various partial AUCs (e.g., $AUC_{GIR0\text{-}4\ hr}$ and $AUC_{GIR4\text{-}12\ hr}$) from glucose infusion rate versus time profiles can be used. In addition, the bioavailability of the new premixed product should remain comparable to the total bioavailability of the short-acting insulin product.

b. Insulin use in pumps (continuous subcutaneous insulin infusion)

Endpoints to be used in the development of insulins for use in pumps should include ascertainment of compatibility between the insulin or analogue and the pump and infusion sets. Likewise, the stability, sterility, and appearance of insulin under laboratory conditions simulating

the conditions and stresses of actual use should be assessed. Assuming the use of approved pumps and approved insulins, clinical studies *per se* are not usually necessary for approval of the use of a particular insulin in a pump. However, glycemic control may need to be evaluated in a short-term clinical study for novel delivery systems. To clarify expectations for development and approval, additional discussion is encouraged between the FDA (including the Office of Combination Products) and sponsors of particular insulin pumps or insulins.[12]

c. New insulin analogues or insulin receptor binding agonists

In the development of new insulin analogues or insulin receptor binding agonists, sponsors should address the following three fundamental issues in randomized, controlled trials:

1. The risk of hypoglycemia under conditions of use ultimately recommended in labeling, relative to approved insulin products and regimens. In this regard, both test and control groups should achieve improved and similar glucose control as assessed by HbA1c.

2. Pharmacokinetic variability should be evaluated, according to injection site, thickness of fat layer, and other parameters known to affect absorption, distribution, metabolism, and excretion characteristics. Additionally, pharmacodynamic characteristics should be carefully studied to direct dosing interval (for long-acting products) and timing of dosing relative to meals (for short-acting products). Assessment of insulin receptor binding (affinity and dissociation rates), receptor autophosphorylation, phosphorylation of signaling elements and promotion of mitogenesis may add important data to the characterization of new insulin analogues.

3. As a complex biological protein, insulin has the potential to be immunogenic. Adequate assays should be developed that measure antibodies to the test product before the submission of an application. Antibody titers, the timing of their detection and disappearance (if applicable), and correlation with pharmacological effects should be ascertained. The potential for any of the antibodies to neutralize the effects of a new insulin should be assessed, particularly in the presence of high titers of antibodies, and in the presence of allergic reactions or suspicion of immune-complex deposition, or apparent loss of clinical effectiveness.

d. Inhaled insulins

Investigations of insulin delivered by inhalation should include preclinical safety, pulmonary safety, pharmacokinetics, pharmacodynamics, dose proportionality, and hypoglycemic risk. The extent of preclinical studies needed depend, in part, on the novelty of the formulation (e.g., what excipients are used) for the inhaled route. Typically, the minimum preclinical program should be comprised of two 14-day inhalation studies focusing on the histopathology of the respiratory tract, followed by a 6-month bridging study in the most appropriate species. The pharmacokinetics (including bioavailability), pharmacodynamics, and hypoglycemic risk of

[12] It should be noted that proposed labeling may affect the design of trials using a particular insulin with a particular pump.

inhaled insulin in humans should be compared to that of subcutaneously administered insulin. Intrasubject pharmacokinetic variability should be evaluated.

We encourage sponsors of inhaled insulin products to enroll at least some patients with underlying pulmonary disease, such as chronic obstructive pulmonary disease and asthma, to assess not only effects of inhaled insulin on their pulmonary function, but also the effects of their disease on insulin kinetics. Cigarette smoking affects inhaled insulin bioavailability, and airway status may lead to alterations in drug delivery to the absorption site. Therefore, sponsors should investigate the potential effect of cigarette smoking and inhalational drugs for pulmonary disease on the efficacy and safety of the inhaled insulin product, including assessments of the effects on insulin pharmacokinetic and pharmacodynamic endpoints and the rates and timing of hypoglycemia.

Sponsors developing inhaled insulin products should evaluate the pulmonary safety of these inhaled insulin products (including excipients). Safety assessments should include pulmonary function as measured by the full battery of pulmonary function tests, including spirometry, lung volumes, and diffusion capacity. Serial pulmonary function tests should be performed and the long-term effects of the inhaled insulin product on pulmonary function should be established. Additional safety assessments include high resolution computed tomography of the chest at baseline and on treatment. Because of the potential effects of diabetes mellitus on the pulmonary system, a comparator group is recommended for these safety assessments. In addition, assessment of anti-insulin antibody responses is essential in the overall safety assessment of the inhaled insulins, because the inhaled route may lead to a different propensity toward immune responses. Pre-use storage and in-use handling conditions during these studies should be designed to mimic actual use of the products. Accuracy of use and dosing should be assessed and documented.

3. Noninsulin Products

A reduction in insulin dose is not sufficient stand-alone evidence of efficacy for approval or labeling of a noninsulin product. In addition to showing a meaningful reduction in the insulin dose, the drug should be shown to independently reduce HbA1c, or at least show that no increase in HbA1c accompanies the insulin reduction. In this context, the elimination of the need for insulin entirely in patients with type 1 diabetes or simplification of the insulin regimen while maintaining or improving glycemia (i.e., optimum control with a nonintensive insulin regimen resulting in reduced hypoglycemic risks) is considered clinically meaningful.

Novel approaches to the treatment of type 2 diabetes, such as the use of gastrointestinal neuropeptides or products that inhibit degradation of these peptides, have been shown to have effects beyond the control of insulin secretion and insulin action, such as rate of gastric emptying, food intake, and glucose counterregulation. Nonetheless, the recommended endpoints for approval of such products specifically for the treatment of diabetes will be the same as the traditional approaches used in the development of currently approved insulin secretagogues or insulin sensitizers (i.e., change from baseline in HbA1c).

Products intended for the treatment of diabetes can be developed for use as monotherapy and for use in combination therapy regimens with other drug classes with different mechanisms of action.

A fixed-dose combination (FDC) of a new agent and an established agent should be studied in a manner that demonstrates that each of the individual components makes a contribution to the claimed effects of the FDC, and that the combination is acceptably safe. If the FDC consists of two currently approved and marketed drugs, and will be labeled for the same indications and patient populations as the separately approved therapies, and the safety and efficacy of these drugs have been established in co-administration, a full factorial efficacy trial may not be necessary to demonstrate the contribution of each FDC component to the claimed effects. In this setting, pharmacokinetic data defining any drug-drug interactions between the components generally should be sufficient. There are exceptions to this approach, such as situations where there are potential safety concerns with the co-administration of the two components. In addition, we recommend nonclinical toxicity studies for certain FDC products, even when the components are previously marketed drugs or biologics. For details, see the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

4. Prevention of Type 1 Diabetes Mellitus or Preservation of Beta-Cell Function in Patients Newly Diagnosed with Type 1 Diabetes Mellitus

Studies of products aimed at the prevention of type 1 diabetes in high-risk subjects, or at preservation of beta-cell function in recent-onset type 1 diabetes with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as the following:

- Fasting and postprandial glucose and glycemic excursion
- Frequency and severity of hypoglycemic events
- Fasting and stimulated C-peptide levels
- Daily insulin requirements in the subjects with diabetes, expressed in international units (IU) per kilogram of body weight

These studies also should evaluate the variations in serum or plasma levels of immune markers, such as anti-insulin, antiglutamic acid decarboxylase 65 and 67, ICA512, and IA-2 beta antibodies. Other markers of cellular immune response (T-cell subpopulations, cytokines) also can be used. In phase 2 studies for the prevention of type 1 diabetes, genotyping and assessments of specific populations of pathogenetically relevant T-cells are encouraged. In particular, the correlation between genotypes and immunoreactive T-cell subpopulations, biomarkers related to glycemic control, and response to treatment may lead to more successful phase 3 studies.

Phase 2 and phase 3 studies of immunosuppressive products or immunomodulators for the prevention of type 1 diabetes also should evaluate their effects on general immune responses, including T-cell proliferation in response to conventional antigens, immunoglobulin subclasses, and titers of antibodies in response to primary antigens and recall responses. Depending on the known or suspected mechanism of action, as well as findings from previous clinical and nonclinical studies, other endpoints should be considered in the overall safety evaluation. These

assessments should be conducted in patients with diabetes, and not borrow substantially from other patient populations, such as populations with neoplasia or post-transplant patients treated concomitantly with other immunosuppressants.

Phase 3 studies of investigational products intended for the prevention of type 1 diabetes mellitus in high-risk individuals typically will designate a delay in the diagnosis of type 1 diabetes as the criterion for defining efficacy. An appropriate endpoint to support efficacy can be the proportion of subjects in the treatment groups who develop frank diabetes after a prespecified period of time (the period being at least 1 year) compared across treatment groups.

Preservation of beta-cell function in patients recently diagnosed with type 1 diabetes is being actively pursued by the pharmaceutical industry and in government and academic collaborations. We acknowledge the evidence from the DCCT and other studies that have demonstrated clinical benefits in patients who achieve better glucose control, in terms of delaying the chronic complications of diabetes. Similarly, we acknowledge that patients who had greater preservation of endogenous insulin secretory function (as assessed by C-peptide in the serum) at baseline were more likely to have lower HbA1c with fewer hypoglycemic events over time.

Phase 3 development of investigational products intended to preserve endogenous beta-cell function in patients with newly diagnosed type 1 diabetes can designate a measure of C-peptide (e.g., AUC following a standardized mixed meal tolerance test) compared to control at 1 year as the primary efficacy endpoint. Sponsors should analyze the change from baseline to the study endpoint (typically 1 or 2 years) in both treatment groups, and demonstrate maintenance of C-peptide or an attenuation in the rate of decline compared to the control group. For this endpoint to provide convincing evidence of preserved endogenous beta-cell function, the trials should demonstrate a clinically meaningful reduction in mean daily insulin requirements accompanied by similar magnitude of glycemic control compared to the control arm. A favorable effect on these endpoints should be balanced against the risks of the particular intervention being tested. Subjects should continue to be monitored for an extended period (2 to 4 years or longer) to investigate both the durability of the effect and whether they experience a lower frequency of hypoglycemia, diabetic ketoacidosis, and long-term complications of diabetes.

As with most prevention claims, we generally will accept fewer risks for treatments intended to prevent type 1 diabetes compared with treatments that preserve endogenous beta-cell function in patients already diagnosed with type 1 diabetes.[13] This distinction is made because some individuals exposed to prevention strategies have no chance for benefit, as they are not inexorably destined to develop diabetes. Therefore, some patients (who presumably cannot be pre-identified) would be subject to the risks of the treatment with no hope of benefit.

5. Prevention of Type 2 Diabetes Mellitus

In phase 3 studies for products intended to prevent the development of type 2 diabetes in high-risk individuals (such as individuals with impaired glucose tolerance, impaired fasting glucose, or with a history of gestational diabetes), potential endpoints supporting approval include delay in type 2 diabetes diagnosis or reduction in the proportion of patients diagnosed with type 2

[13] See 21 CFR 56.111(a)(1)(i) regarding the unnecessary exposure of subjects to risk.

diabetes by ADA criteria, relative to placebo. These study designs should include a follow-up (washout) period to assess whether the tested agent truly delays progression to diabetes or only masks diabetes during the treatment period. Such studies will likely be of substantial duration (years) and size. The FDA cannot *a priori* define the magnitude of a clinically meaningful effect size.

For prevention studies of drugs with a pharmacological action of improving glycemic parameters (e.g., approved treatments used in the prevention setting), improvement in clinical parameters beyond those that would be expected from glucose lowering alone should be demonstrated, since the forestalling of a biochemical diagnosis of frank diabetes from the prediabetic state may not itself be a sufficiently tangible benefit against which one can appropriately judge the risks. Such supportive evidence can include a demonstration of a durable delay in the onset of type 2 diabetes after the prevention therapy is stopped, or can show that the delay in progression to type 2 diabetes mellitus is accompanied by other indicators of clinical benefit (e.g., delay or lessening in microvascular or macrovascular complications). That said, the more modest the treatment effect, the higher the standard for safety and the more restricted (e.g., to subjects at highest risk for near-term conversion to frank type 2 diabetes) the indicated target population.

C. Metabolic Syndrome

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. A host of therapies now exist to address individual or multiple components of the syndrome (e.g., lipid-altering agents, antihypertensives, insulin sensitizers). A therapeutic product intended to treat the metabolic syndrome ideally should normalize or improve all components of the syndrome and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality. As mentioned in the Introduction section, a full discussion of this syndrome is beyond the scope of this guidance.

D. Study Population Considerations

In general, premarket study populations should be representative of the population for which the product, once approved or licensed, is intended. Two specific considerations with regard to study populations are listed below.

1. Pediatric Populations

Under the Pediatric Research Equity Act (PREA), section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 355c), as amended by the Food and Drug Administration Amendments Act of 2007 (Public Law No. 110-85), sponsors must study a product in all relevant pediatric populations when submitting an application under section 505 of the Act (21 U.S.C. § 355) or section 351 of the Public Health Service Act (42 U.S.C. § 282) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. However, the PREA requirements may be waived or deferred in certain

circumstances. Although a detailed discussion of how sponsors may comply with the PREA requirements is beyond the scope of this guidance, several relevant points are addressed below.

In the case of new molecular entities, particularly for new classes of therapeutic products with novel mechanisms of action, the early studies should enroll adult subjects only, reserving pediatric exposure until the metabolism, pharmacodynamics, and safety of the agent are reasonably well-defined. The same precaution can be applied to already approved agents with known toxicities in nondiabetic populations, such as immunosuppressive or immune modulatory products. Because many of the general aspects of the clinical pharmacology and safety profiles of an approved therapeutic are better understood, it may be appropriate to dose pediatric patients earlier in the development programs of approved versus unapproved investigational products.

In the initial development of insulins and other agents with potential to cause hypoglycemia, we recommend that subjects with particularly labile glucose control and a substantial history of recent hypoglycemia be excluded. Because of the high representation of children and adolescents in the population with type 1 diabetes, patients in these demographic subsets usually should be included early in the clinical development of treatments for type 1 diabetes. However, it is not appropriate to study all products for type 1 diabetes in children before approval. For example, inhaled insulins, which represent simply an alternate route of administration for a well-established active ingredient, should be developed for adult use initially because of uncertainties in the safety of new inhalation dosage forms. After additional safety data are developed, these products can be studied in children, including during the postmarketing period. In such cases, the initial approved labeling should specifically address dosing and administration in adults. Labeling for pediatric use can be developed and approved after additional studies are conducted in pediatric patients.

Given the increasing representation of children and adolescents with type 2 diabetes, studies of therapeutic products intended for the treatment of type 2 diabetes should at some point include patients younger than 18 years of age, assuming no obvious contraindications to such use (e.g., hypothetical effects on growth and development based on mechanism of action).

Sponsors may contact the review division for further information with regard to meeting the PREA requirements.

2. Other Study Populations

Type 2 diabetes occurs more frequently in Latino, African American, and Native American patients relative to patients of northern European descent. Therefore, attempts should be made to enroll representative numbers of individuals from these ethnic groups during the clinical development program, particularly during the phase 3 trials. Attention also should be paid to considerations in geriatric patients, including decreased renal function, autonomic dysfunction, poor glucose-counterregulatory response, hypoglycemia unawareness, and potentially dangerous interactions with other commonly used drugs. It is desirable to determine whether demographic, genetic, metabolic (e.g., C-peptide, body mass index, previous antidiabetic therapy), or other factors predict responses to a new antidiabetic agent, predispose patients to certain toxicities, or otherwise affect tolerability and compliance.

E. Sample Size and Study Duration

The ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* recommends a total exposure of at least 1,500 subjects (300 to 600 for 6 months, 100 for 1 year) for the safety assessment of chronically administered drugs developed for the treatment of non-life-threatening conditions. However, exposures exceeding these recommendations should be used for products developed for the treatment of type 2 diabetes, given the large and growing size of the population with type 2 diabetes and the increasing complexity of treatment regimens. At the time of submission of the marketing application (either a biologics license application (BLA) or an NDA) for products intended for the treatment of type 2 diabetes mellitus, we recommend that phase 3 trial data be available for at least 2,500 subjects exposed to the investigational product with at least 1,300 to 1,500 of these subjects exposed to the investigational product for 1 year or more and at least 300 to 500 subjects exposed to the investigational product for 18 months or more.

These investigational products should be tested as monotherapy and in combination with antidiabetic medications with which they likely will be co-administered in clinical practice. As treatment of type 2 diabetes mellitus frequently requires combination therapy, overall exposures and length of duration should be weighted more in trials evaluating the investigational product with other antidiabetic medications. The guidance for industry *Premarketing Risk Assessment* also anticipates situations where larger numbers of exposures for longer periods might be needed, including for diseases where many sufficiently safe alternative treatments already exist or for a preventive treatment. Therefore, we encourage long-term extensions of 6- to 12-month controlled trials and anticipate that the safety information relevant for approval will be provided at the initial submission of an application.

Development of products intended to preserve beta-cell mass and function in type 1 or type 2 diabetes can be considered in enriched populations, where genetic or immunologic markers predicting the natural history of the disease exist. Testing the investigational product in high-risk populations enriched for such markers enhances power to detect an effect of the intervention (if one exists), as compared to testing the product in the general diabetic population. Even in enriched populations, pivotal studies may still need to be relatively long (e.g., 2 or more years) to show a meaningful effect, given the natural history of the decline in beta-cell function in the target populations and also recognizing the need for long-term safety information.

For all new development programs for drugs to treat diabetes, phase 3 studies should be sized to allow meaningful evaluation of the consistency of effects across subgroups based on sex, age, ethnic background, duration and severity of the disease (e.g., based on categories of HbA1c at baseline), interactions with other likely concomitant medications as combination therapies, and other relevant factors specific to the product and indication sought. Randomized treatment groups should be well balanced for these factors, and to fully ensure balanced assignment, randomization stratified for a limited number of factors may be desirable, with particular emphasis on those baseline variables hypothesized to affect either safety or efficacy.

Most patients taking products intended to treat diabetes are titrated to achieve a particular effect on serum or plasma glucose or on HbA1c. The primary efficacy parameter should be assessed substantially after the end of the titration period (e.g., 3 months) to better reflect the steady-state effect of the dose regimens studied.

Regardless of the choice of control used in phase 3 studies, the duration of the controlled phase in an efficacy trial is an important issue. In studies of recently approved products that lasted more than 1 year, sponsors have typically conducted a randomized, controlled study lasting at least 6 months, followed by an extension phase lasting 6 months or longer. Sponsors should weigh the advantages and disadvantages when deciding between a controlled and uncontrolled extension phase, and should ensure that the chosen design will provide interpretable long-term data.

Although uncontrolled extensions still allow for an expanded safety database (both in numbers exposed and duration of treatment), interpretability of both efficacy and safety data in an uncontrolled study period is limited by lack of a control group.

Since diabetic populations are prone to certain morbidities (such as cardiovascular disease and renal dysfunction), only longer term comparative safety data would allow for an assessment of the relative rates of these common, but important morbidities in subjects assigned to the investigational agent versus the control. Studies lasting longer than 1 year that employ an appropriate active comparator with adjudication of safety endpoints of interest by an endpoint committee blinded to treatment are strongly encouraged and may be needed if preclinical or phase 2 or phase 3 studies reveal a safety signal. Longer term controlled data also allow for better assessments of the comparative durability of effects on glycemia. Such studies, however, may have high rates of dropouts; therefore, treatment algorithms for maintenance of adequate glycemic control should be considered in the study design.

Of note, all drugs currently approved for the treatment of diabetes are indicated to improve glycemic control. The FDA currently bases approval of these drugs and biologics on HbA1c. We recognize that reducing long-term macrovascular complications in patients with diabetes should be an important goal of disease management. Although a recommendation to demonstrate macrovascular risk reduction premarketing may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy, sponsors should conduct large outcomes trials before submission of marketing applications for drugs in development that show nonclinical or clinical evidence of increasing macrovascular risk. Therapies that have not demonstrated a deleterious effect on cardiovascular outcome during extensive premarketing evaluation may need further post-approval assessment for their effects on long-term macrovascular disease. Interpretation of data resulting from such studies may be complicated by the need to identify conclusively the effect of a single drug within a multidrug regimen that usually is part of an adequate treatment for a complex, progressive condition such as type 2 diabetes and its associated comorbidities.

Phase 3 studies with a 6-month, placebo-controlled phase can be extended into a rigorously controlled, randomized, double-blind active-controlled phase that employs double-dummy agents.

Before submitting a marketing application, assessment of the immunogenic potential of therapeutic proteins, including insulins and insulin analogues, and of monoclonal antibodies, should be performed over a period of at least 6 to 12 months in study subjects reasonably representative of the intended population. If adverse events characteristic of allergic or immunologic reactions are identified, we may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of a marketing application or as a postmarketing commitment, based on the overall analysis of the risks and benefits of the product. The appropriate timing of additional studies in these circumstances can be discussed with the FDA at a pre-BLA meeting, pre-NDA meeting, or other similar advice meeting.

A licensed monoclonal antibody used only in allogeneic transplantation, where patients are immunosuppressed through multiple modalities, should be newly evaluated for immunogenic potential in the diabetic or high-risk prediabetic population.

F. Premarketing Safety Evaluation

The safety evaluation of a new drug is, in the end, directed by the findings of preclinical investigations, by concerns arising based on the mechanism of action of the drug, by known toxicities of agents with a similar chemical structure or mechanism of action, and by the findings of previous clinical trials. In other words, ultimately, the safety evaluation is an iterative process based on prior experience.

Additionally, new antidiabetic agents, used alone or in combination with approved agents, should be assessed for their tendency to cause or augment hypoglycemia, an event that is part of diabetes management. Acceptable hypoglycemic risk, although not defined in absolute terms, usually is risk that is comparable to existing therapies, to which the new drug is directly compared, when both drugs are used in trials in which subjects are treated to identical glycemic goals with comparable glycemic outcomes (e.g., ADA guidelines). Furthermore, patients with diabetes often use multiple medications, not only to control glycemia, but also to address cardiovascular disease risk factors, such as hypertension and hyperlipidemia, and microvascular and neuropathic complications of diabetes. Interactions between the new investigational product and these other medications can result in adverse events that should be considered, documented, and reported. Finally, worsening of comorbid conditions other than diabetes should be ascertained, reported, and analyzed in comparison to the rates of similar adverse events in the control group.

Findings of specific safety signals with a product or related product (whether cardiovascular or otherwise) during any development phase should be investigated further in controlled studies enriched with the population at risk for the signal. The timing of this investigation (pre-approval or post-approval) depends on the strength and nature of the signal and whether the treatment offers a major advance over existing therapies.

For general issues related to risk assessment, pharmacovigilance, and risk minimization plans, refer to the following guidances:[14]

- Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*
- Guidance for industry *Development and Use of Risk Minimization Action Plans*
- Guidance for industry *Premarketing Risk Assessment*
- ICH guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and addendum
- ICH guidance for industry *E2E Pharmacovigilance Planning*

G. Important Statistical Considerations

Standard statistical considerations apply to programs for drugs or biologics intended to treat diabetes. However, the following discussion highlights a few specific areas that are important to consider specifically for these therapeutic products.

1. Sample Size

Sample size calculations for superiority trials with HbA1c change from baseline as the primary endpoint should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes should represent clinically meaningful differences.

Sample sizes for noninferiority trials should be based on one-sided significance levels of 2.5 percent and at least 80 percent power. Because the calculations depend on the noninferiority margin, the sponsor should provide a rationale for the choice of margin and should be guided by the concept that this margin should not represent a clinically meaningful loss of efficacy relative to the active control. Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials. For additional guidance on noninferiority studies, refer to ICH E9 and ICH E10.

2. Preventing Missing Data from Subjects Who Prematurely Withdraw from Treatment

We encourage sponsors to obtain HbA1c measurements in all subjects, including those who withdraw prematurely or receive rescue medication because of poor glycemic control, near the calendar date at which they were scheduled to complete the trial. Complete data collection can facilitate the desired goal of a true intent-to-treat analysis (i.e., the analysis of all randomized subjects) and also serve as a measure of good clinical trial conduct.

[14] See http://www.fda.gov/cder/guidance/index.htm.

3. Analysis Methods

We recommend that the analysis of HbA1c change from baseline adjust for differences between groups in HbA1c at baseline (e.g., ANCOVA with baseline HbA1c as a covariate in the model). Factors in addition to treatment can be included in the model as appropriate, particularly variables with substantial correlation with the outcome and independence from the treatment, and variables used to stratify the randomization.

Although every reasonable attempt should be made to obtain complete HbA1c data on all subjects, dropouts are often unavoidable in diabetes clinical trials. The resulting missing data problems do not have a single general analytical solution. Statistical analysis using last observation carried forward (LOCF) is easy to apply and transparent in the context of diabetes trials. Assuming an effective investigational therapy, it is often the case that more placebo patients will drop out early because of a lack of efficacy, and as such, LOCF will tend to underestimate the true effect of the drug relative to placebo providing a conservative estimate of the drug's effect. The primary method the sponsor chooses for handling incomplete data should be robust to the expected missing data structure and the time-course of HbA1c changes, and whose results can be supported by alternative analyses. We also suggest that additional analyses be conducted in studies with missing data from patients who receive rescue medication for lack of adequate glycemic control. These sensitivity analyses should take account of the effects of rescue medication on the outcome.

The full analysis set as described in ICH E9 should be the primary analysis population for both superiority and noninferiority analyses. Supporting analyses in one or more subsets of the full analysis set also can be conducted and are encouraged in noninferiority analyses.

Analyses of data from studies using withdrawal designs depend on the type of primary endpoint. Survival analysis methods should be used if therapeutic failure times are collected. If the endpoint is therapeutic success or failure, categorical methods should be used.

If statistical significance is achieved on the primary endpoint, secondary assessments of efficacy can be considered. Type 1 error should be controlled across all clinically relevant secondary efficacy endpoints that may be intended for product labeling to provide statistical support for their inclusion in the label.

The sponsor should report least-square mean treatment differences and associated 95 percent confidence intervals from the primary statistical model for all continuous efficacy endpoints.

Rates of hypoglycemia should be compared statistically between groups. If count data are analyzed, the sponsor should use robust statistical methods that take account of the dependence of events within individual patients.

4. Graphical Methods

Graphical methods showing treatment effects over time for study completers should be presented. Additional graphical presentations of the data to illustrate the effect of the drug are

encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

APPENDIX A: PRECLINICAL CONSIDERATIONS FOR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS

Because of the effects of PPAR agonists on glucose and lipid metabolism, many compounds are being developed for the treatment of type 2 diabetes and/or dyslipidemia which activate PPARα, PPARγ, PPARα and γ (dual agonist), or PPARα, γ, and δ (pan agonist).

Recommendations for the Duration of Chronic Toxicology Studies

The ICH guidance regarding the duration of chronic toxicity studies in rodents and nonrodents has been adopted,[15] and for the nonrodent chronic toxicity study, a 9-month duration generally is appropriate for supporting chronic human use. However, since the no observed adverse effect levels for some of the toxicities associated with PPAR agonists can be adequately defined only after chronic administration, a 1-year study in nonrodents is recommended for drugs in the PPAR class.

Because of the prevalence of positive carcinogenicity findings with PPAR agonists, 2-year carcinogenicity evaluations in mice and rats are recommended. Since heart weight increases of 25 percent or greater after 13-week treatment with PPAR agonists have been predictive of excess cardiac mortality with longer-term chronic dosing (greater than or equal to 12 months) in all animal models, a dose that results in 20 to 25 percent increases in heart weight is considered to define the maximum tolerated dose for use in the 2-year carcinogenicity study for agonists with gamma activity.

Recommendations for the preclinical evaluation of PPAR-related toxicities are as follows:

- **Cardiac Effects.** The effects on the heart should be characterized by reviewing electrocardiograms, clinical chemistry, and cardiac histopathology in rats and nonrodents. QT prolongation potential should be thoroughly evaluated in multiple dose nonrodent toxicity studies. For compounds with PPAR alpha or delta agonist activity, biomarkers of direct cardiac toxicity such as Troponin I and T should be monitored in animal studies.

  Additional evaluations are recommended as follows:

  - Correlation of heart weights with thickness of ventricular free wall and ventricular septum in chronic toxicology studies in rats and nonrodents.
  - Morphometric measurements of ventricular myocardial hypertrophy in nonrodents.
  - Presence of karyomegaly in myocardium of ventricles.
  - Pattern and distribution of myocardial fibrosis.
  - Characterization of myocardial inflammatory infiltrates.
  - Determination of composition of serous effusions.
  - Presence of fatty changes detected by stained heart tissue. The sections can be stained with Sudan IV or Oil Red-O.

[15] See the ICH guidance for industry *S4 Duration of Chronic Toxicology Testing in Animals (Rodent and Nonrodent Toxicity Testing).*

  - Characterization in animals and humans of the potential for plasma volume expansion.

- **Hepatic Effects.** The cause of any liver enlargement observed should be determined (peroxisome proliferation, mitochondrial proliferation/swelling). Liver tissues should be stained to detect the presence of fatty changes. The sections can be stained with Sudan IV or Oil Red-O. Liver enzyme levels and biochemical markers of peroxisome proliferation (Acyl CoA and CYP 4A) should be analyzed in rodents and nonrodents.

- **Bone Marrow Effects.** Bone marrow smears from femur and sternum should be quantified to assess for effects on cellularity.

- **Renal Effects.** Drug-related increases in urothelial tumors have been observed in rodent carcinogenicity studies with PPAR agonists. If such tumors are observed, mechanistic studies (e.g., urinalysis assessing crystalluria, urine pH, urinary electrolytes) are recommended.

- **Muscle Toxicity.** Skeletal and/or cardiac muscle degeneration have been commonly observed for agonists with PPAR alpha or PPAR delta activity. Creatine kinase and troponin evaluations should be performed in preclinical studies for these subtypes. Histopathological evaluations of skeletal muscle should include multiple sites to evaluate effects on both type I and type II muscle (e.g., diaphragm, gastrocnemius, soleus, intercostals muscles).

- **Other Known Toxicities.** Thymic and lymphoid atrophy, reproductive organ toxicity, adipose proliferation, and infiltration are toxicities commonly associated with the administration of PPAR agonists in preclinical studies. Preclinical study designs should include adequate assessments for these potential toxicities.

- **Electron Microscopy.** Electron microscopy evaluations should be conducted on established target organs for PPAR agonists (liver and heart mandatory) and on other compound specific target tissues, as identified (e.g., renal proximal tubules, skeletal muscle).

APPENDIX B: HYPOGLYCEMIA

Severe episodes of hypoglycemia are often encountered when patients implement a program of intense glycemic control. These adverse occurrences are often the limiting factor in achieving improvements in metabolic control and reductions in HbA1c. There are often substantial differences in the interpretation and reporting of the severity of hypoglycemic episodes among investigators, studies, and clinical programs because of the diversity of the definitions used in clinical studies. To help in the interpretation of this important safety attribute of a new diabetes treatment that may cause hypoglycemia, we recommend standardization of definitions in individual protocols and across protocols within the development program. One recommended approach for such standardization is to use classifications of severity from well-accepted sources, such as the ADA.

The ADA Workgroup on Hypoglycemia classifies hypoglycemia as follows (Diabetes Care, 2005, 28: 1245):

- **Severe hypoglycemia.** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- **Documented symptomatic hypoglycemia.** An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).

- **Asymptomatic hypoglycemia.** An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65 to 70 mg/dL (3.6 to 3.9 mmol/L) and since antecedent plasma glucose concentrations of less than or equal to 70 mg/dL (3.9 mmol/L) reduce sympathoadrenal responses to subsequent hypoglycemia, this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes.

- **Probable symptomatic hypoglycemia.** An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as probable hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported.

- **Relative hypoglycemia**. An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (3.9 mmol/L). This classification reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels greater than 70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that level. Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and, therefore, may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported.

At a minimum, hypoglycemic events should be reported in each of the first three classifications: severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia.

Currently, there is no standardized convention for reporting the frequency of hypoglycemia in clinical studies. The ADA Workgroup recommends that both the proportion (percentage) of subjects affected and the event rates (e.g., episodes per subject-year or 100 subject-years) for each of the classifications of hypoglycemic events be reported. These data provide complementary information. In addition, we anticipate that the distribution of subjects having a specific number of hypoglycemic events will be reported (see also section V.G., Important Statistical Considerations). For the hypoglycemic episodes, sponsors should include information on potential precipitants (e.g., missed meal, exercise) and patterns (e.g., timing of the event during the course of the day or night).

APPENDIX C: CURRENTLY AVAILABLE DRUG TREATMENTS

A. Insulin Products

A variety of recombinant human insulins and insulin analogues are available and these products serve as the primary basis for treating the glucose metabolic defects in type 1 diabetes. Insulin and its analogues also have an important role in the treatment of type 2 diabetes, particularly as the disease progresses. These products are used in different combinations according to the pharmacokinetic profile of each insulin type, and some are available in premixed combinations of different proportions of short- and long-acting agents. These insulins also can be used in conjunction with oral agents (described below) to achieve control of blood glucose. There has been tremendous interest and some success in developing noninjectable insulins (e.g., inhaled insulin). However, current development of these products has been aimed at supplementing or replacing short-acting insulin only and would not represent a full alternative to injectable insulin and its analogues.

B. Oral Agents for Type 2 Diabetes

The first oral products for the treatment of diabetes mellitus were the sulfonylureas, which are long-acting insulin secretagogues. The meglitinides constitute another class of insulin secretagogues that are taken with meals and have short-term effects, primarily on the postprandial elevations of plasma glucose. Metformin exerts its effect on endogenous hepatic glucose production. PPAR agonists enhance insulin sensitivity. Alpha glucosidase inhibitors prevent intestinal glucose absorption and have primary effects on the excursion of postprandial glucose.

C. Newer Classes of Therapeutic Products

More recently, an analogue of human amylin, pramlintide, was approved for the treatment of type 1 or type 2 diabetic patients as an adjunct to mealtime short-acting or rapid-acting insulin. Amylin, a neuroendocrine hormone that is co-secreted with insulin from pancreatic beta cells, slows intestinal carbohydrate absorption through decreased gastric emptying and suppresses hepatic gluconeogenesis by inhibiting glucagon secretion postprandially. Additionally, exenatide, a glucagon-like peptide 1 (GLP-1) analogue (belonging to the new class of incretin mimetics) has been approved for type 2 diabetes, in combination with other oral antidiabetic agents. In response to nutrients in the lumen of the gut, GLP-1 is secreted from the intestinal L cells. Similar to amylin, GLP-1 decreases gastric emptying and glucagon secretion. In addition, GLP-1 stimulates insulin secretion. Because the effects of GLP-1 are glucose-dependent, GLP-1 mediates glucose homeostasis without causing hypoglycemia. Both pramlintide and exenatide are injectables.

There is a newer class of oral drugs known as dipeptidyl peptidase 4 (DPP4) inhibitors that has been the focus of intense development. DPP4 is a serine protease responsible for the rapid metabolism of endogenous GLP-1. By inhibiting this enzyme, DPP4 inhibitors prevent the rapid catabolism of endogenous GLP-1, thereby potentiating the incretin effect of GLP-1.

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

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U.S. Department of Health and Human Services
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Guidance for Industry[1]
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of diabetes mellitus.[2] Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

In March 2008, the FDA issued the draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.[3] Concerns related to cardiovascular risk will be addressed in the final version of that guidance. In the meantime, we are issuing this final guidance for immediate implementation to ensure that relevant issues related to minimizing cardiovascular risk are considered in ongoing drug development programs. We will address cardiovascular risk assessment for currently marketed antidiabetic therapies in a separate guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For discussion of general issues of clinical trial design or statistical analysis, see the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although several drug treatments currently are available, we recognize the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs and therapeutic biologics).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure). Both type 1 and type 2 diabetes have a heritable basis. Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy.[4] Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.[5]

There are also compelling data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control. Glycemic control in these studies has been based on changes in HbA1c. This endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. Therefore, reliance on HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus. However, diabetes mellitus is associated with an elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population. Although this excess cardiovascular risk is present in both type 1 and type 2 diabetes, the

[4] See N Engl J Med, 1993, 329:977-986.

[5] See Diabetes, 2006, 55:3556-3565.

absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical. For type 2 diabetes, the wider range of therapies available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type 2 diabetes.

On July 1 and 2, 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of cardiovascular assessment in the premarketing and postmarketing settings. After considering the discussion at this meeting as well as other available data and information,[6] we have determined that concerns about cardiovascular risk should be more thoroughly addressed during drug development.

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

[6] See Lancet, 1998, 352:837-853 and 854-865.

controlled trials, and to preserve the study level randomized comparison but include, when possible in the meta-analysis, important identifiers of study differences or other factors (e.g., dose, duration of exposure, add-on drugs). It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies.

- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible.

For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):

- Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be accomplished in several ways. The integrated analysis (meta-analysis) of the phase 2 and phase 3 clinical trials described above can be used. Or, if the data from all the studies that are part of the meta-analysis will not by itself be able to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8, then an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA submission. Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.

- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial.[7]

- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is less than 1.3 and the overall risk-benefit analysis supports approval, a postmarketing cardiovascular trial generally may not be necessary.

[7] See the Food and Drug Administration Amendments Act of 2007, Title IX, subtitle A, section 901. This section will become section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A).

- The report of this meta-analysis should contain sufficient detail for all the analyses; conventional graphical plots for meta-analysis finding by study, subgroup, and overall risk ratio; and all the analysis data sets that would allow a verification of the findings.

Sponsors are encouraged to contact the division to discuss specific issues that arise during the development of a new antidiabetic therapy to treat type 2 diabetes.