

Novo Nordisk

Liraglutide (injection) NDA 22-341

Endocrine and Metabolic Drug Advisory Committee 2 April 2009

Novo Nordisk

**Liraglutide (injection) for the Treatment of Patients
with Type 2 Diabetes**

NDA 22-341

Briefing Document

**Endocrine and Metabolic Drug Advisory Committee
2 April 2009**

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1 Executive Summary

Introduction

This New Drug Application (NDA 22-341) was submitted on 23 May 2008 and seeks approval of liraglutide as an adjunct to diet and exercise and for use in combination therapy with oral antidiabetic agents (OADs), to improve glycemic control in patients with type 2 diabetes mellitus. Liraglutide is an analog of human glucagon-like peptide-1 (GLP-1) classified as a GLP-1 receptor agonist, developed for once-daily s.c. administration.

The liraglutide NDA was comprised of 38 completed clinical trials including five long-term phase 3 trials. The subsequent 120-day Safety Update included two additional completed clinical trials, leading to a total of 40 completed clinical trials with 26 phase 1 trials, seven phase 2 trials, and seven phase 3 trials, of which five constituted the long-term phase 3 trials in the NDA.

This Briefing Document provides background information on the clinical development program for liraglutide and summarizes nonclinical and clinical information as included in the NDA and in the 120-day Safety Update.

Clinical Development Program

The safety database for the 40 completed trials includes more than 6,800 subjects of whom 4,655 were treated with liraglutide (2,412 subjects for 24 weeks or more, 840 subjects for 50 weeks or more and 495 subjects for 76 weeks or more). Based on both completed and ongoing trials, more than 700 subjects were treated with liraglutide for 76 weeks. All data beyond 52 weeks are exclusively from open-label, but controlled, extension studies. That is, all subjects who continued in the open-label extension part of the studies maintained the original randomized treatment assignments.

The primary objective of all five long-term phase 3 trials was to assess the effect of liraglutide on glycemic control as measured by change from baseline in glycosylated hemoglobin A1c (HbA_{1c}) in subjects with type 2 diabetes mellitus. Achievement of good glycemic control with available diabetes therapies is often associated with an increase in body weight. Results from the early clinical trials in the clinical development program demonstrated that treatment with this agent is associated with a weight loss. Change from baseline in body weight was therefore a pre-specified secondary efficacy endpoint in all five long-term phase 3 trials. Other investigations of efficacy parameters included additional assessments of blood glucose control and beta-cell function, cardiovascular biomarkers, blood pressure and lipid profiles.

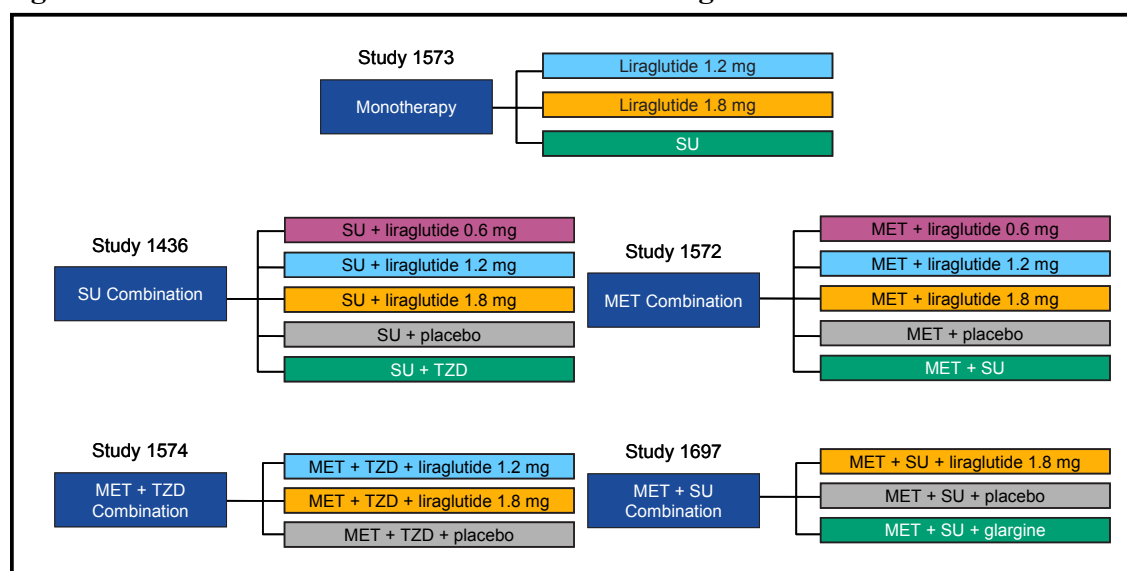
The five long-term phase 3 trials were randomized, double-blind, double-dummy, parallel-group, multi-center trials. In all studies except the monotherapy study, subjects were switched from their usual diabetes therapy to a specific drug regimen during the run-in phase of each trial. Moreover, in each trial, subjects entered on diet, monotherapy or combination therapy. For some subjects, this

meant a substitution of medications and for others a substitution of one medication and the addition of another medication.

Trial 1573 (monotherapy) evaluated liraglutide monotherapy compared with 8 mg glimepiride during 52 weeks of treatment. The remaining four trials evaluated 26 weeks of treatment with liraglutide in combination with one or two oral antidiabetic drugs (OADs) (run-in therapy + liraglutide) compared with run-in therapy + placebo and/or run-in therapy + active comparator therapy (Trials 1572, 1436, 1574 and 1697) ([Figure 1-1](#)). All trials applied standardized and widely accepted treatment regimens during the run-in phase to provide a uniform baseline of treatment prior to addition of liraglutide, placebo or active comparator. The background treatment was titrated, i.e. in Trial 1572 (MET combination), subjects were on metformin 2 g for three weeks prior to randomization; in Trial 1436 (SU combination), the subjects were on glimepiride 4 mg for two weeks, etc. To obtain additional longer term clinical experience, two of the five long-term phase 3 trials included an open-label extension. Trial 1573 is being extended by 48 months to a total of five years with completion late 2010, and Trial 1572 was extended by 18 months to a total of two years. During these extensions, the subjects maintained the original randomized treatment assignments. Data up to 18 months exposure were included in the NDA and safety data up to 22 months from the extension periods were included in the 120-day Safety Update. In the period from the NDA to the 120-day Safety Update, an additional 208 subjects were exposed to liraglutide for more than 18 months, giving a total of approximately 700 subjects.

Subjects included in the five trials had to be uncontrolled with respect to glycemic control at the time of screening, as defined by an HbA_{1c} value in the range of 7.0–11.0%, depending on the trial. For the subjects to be eligible for randomization after the medication run-in phase, the subjects were also required to be out of glycemic control at the time of randomization, assessed by elevated fasting plasma glucose in the range of 126–250 mg/dL (7.0–13.9 mmol/L), depending on the trial.

Based on results from phase 2 clinical trials, three doses of liraglutide were selected for further evaluation in phase 3: 0.6 mg, 1.2 mg and 1.8 mg. All subjects randomized to liraglutide doses higher than 0.6 mg were titrated to their final dose in weekly increments of 0.6 mg. Based on the results from the five long-term phase 3 trials, the recommended dosing regimen is that for all patients, liraglutide treatment should be initiated at a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on clinical response and on the judgment of the medical doctor, the dose can be increased to 1.8 mg.

Figure 1–1 Outline of Treatment of the Five Long-term Phase 3 Trials

SU: Sulfonylurea (glimepiride), MET: metformin and TZD: thiazolidinedione (rosiglitazone).

Clinical Efficacy

Glycemic Control - HbA_{1c}

Change from baseline in HbA_{1c} was the primary regulatory efficacy endpoint. The fraction of subjects reaching the American Diabetes Association (ADA) target of HbA_{1c} < 7 % was a secondary endpoint.

Treatment with liraglutide resulted in a substantial and clinically relevant lowering of HbA_{1c}. All tested doses of liraglutide lowered HbA_{1c} significantly more than placebo. The 1.8 mg dose lowered HbA_{1c} by on average 0.94% to 1.36% points in comparison to placebo.

In the monotherapy trial, Trial 1573, both doses of liraglutide were superior to a maximum therapeutic dose of 8 mg of glimepiride. The liraglutide 1.8 mg dose was superior to liraglutide 1.2 mg. For single OAD combination therapy, the 1.2 mg and 1.8 mg doses in combination with metformin 2 g were non-inferior compared to metformin 2 g + glimepiride 4 mg (Trial 1572). Liraglutide doses at 1.2 mg and 1.8 mg in combination with glimepiride 4 mg were superior to rosiglitazone 4 mg + glimepiride 4 mg (Trial 1436). For dual OAD combination therapy, both doses of liraglutide 1.2 mg and 1.8 mg added to a background of metformin 2 g and rosiglitazone 8 mg were superior to metformin 2 g and rosiglitazone 8 mg (Trial 1574). For the last dual combination therapy trial, the addition of liraglutide 1.8 mg to metformin 2 g + glimepiride 4 mg was significantly better than adding on basal insulin glargine to the metformin 2 g and glimepiride 4 mg combination (Trial 1697). The difference was within the pre-specified non-inferiority limit of 0.4% (Table 1–1).

In two (Trials 1436 and 1697) out of the three combination therapy studies where an active comparator was administered (Trials 1572, 1436, and 1697), liraglutide lowered HbA_{1c} levels significantly more than the active comparators ([Table 1–1](#)).

Liraglutide consistently brought a greater percentage of subjects to the ADA target (HbA_{1c} < 7%) when compared to placebo. At the 1.8 mg dose liraglutide, this target was achieved in 42–54% of the trial population. When comparing to active comparator, the two higher liraglutide doses (1.2 mg and 1.8 mg) led to a larger proportion of subjects reaching the target than the active comparator treatment in all four trials in which an active comparator was tested. In three of four trials where both 1.2 mg and 1.8 mg were used, the 1.8 mg dose of liraglutide was superior to the 1.2 mg dose ([Figure 6–18](#)).

Table 1–1 Primary Endpoint (HbA_{1c}) in the Five Long-term Phase 3 Trials - Mean Change from Baseline (% Points) to End of Treatment

Trial (duration)	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo	Active Comparator
1573 (52 weeks) ^(a)	N/A	-0.84 (0.080)*	-1.14 (0.081)*	N/A	-0.51 (0.077) ^(b)
1572 (26 weeks)	-0.70 (0.067)**	-0.97 (0.069)**	-1.00 (0.066)**	0.08 (0.090)	-0.99 (0.068)
1436 (26 weeks)	-0.60 (0.071)**	-1.08 (0.072)*/**	-1.13 (0.072)*/**	0.23 (0.100)	-0.44 (0.071)
1574 (26 weeks) ^(c)	N/A	-1.48 (0.078)**	-1.48 (0.075)**	-0.54 (0.080)	N/A
1697 (26 weeks)	N/A	N/A	-1.33 (0.088)*/**	-0.24 (0.106)	-1.09 (0.090)

*Statistically significantly better than active comparator. **Statistically significantly better than placebo. ^a Trial 1573 did not include a placebo group. ^b SEM: Standard error of the mean. ^c Trial 1574 did not include an active comparator group.

Glycemic Control - Fasting and Postprandial Plasma Glucose

Secondary glucose related endpoints included fasting and postprandial glucose. Liraglutide provided reductions in fasting plasma glucose (FPG), which were superior to placebo. The changes were apparent at the first measured time point in the trials, i.e. at two weeks. At the liraglutide 1.8 mg dose, the differences ranged from 36 mg/dL (1.97 mmol/L) in Trial 1574 to 47 mg/dL (2.60 mmol/L) in Trial 1436. Significant differences to active comparators were also found in the monotherapy study vs. glimepiride (Trial 1573) with a difference to the liraglutide 1.8 mg dose of 20 mg/dL (1.13 mmol/L). The difference to active comparator was also significant in the SU combination trial comparing with rosiglitazone (Trial 1436), where it was 13 mg/dL (0.71 mmol/L) to the liraglutide 1.8 mg dose ([Figure 6–19](#)). Based on glucose profiles, a greater proportion of liraglutide-treated subjects remained below the target for postprandial plasma glucose of 180 mg/dL.

Other Secondary Efficacy Endpoints

Body Weight

In confirmation of weight data from earlier clinical studies, an estimated mean weight loss in Trial 1573 after 52 weeks of monotherapy with liraglutide 1.8 mg was 2.45 kg and 2.05 kg with liraglutide 1.2 mg. In four of the five long-term phase 3 trials (all except Trial 1436), 19–33% of the

subjects had a weight loss of 5% or more. In Trial 1436, the majority of subjects treated with liraglutide + glimepiride or with glimepiride alone maintained their weight whereas subjects treated with rosiglitazone + glimepiride gained weight ([Figure 6–23](#) and [Figure 6–24](#)).

Beta-cell Function

The beta-cell is one of the primary targets of GLP-1 action and increased glucose-dependent insulin release has been demonstrated for liraglutide in early clinical studies. Thus, a number of secondary endpoints assessing this action were examined. Liraglutide improved beta-cell function as assessed by a homeostasis model assessment for beta-cell function (HOMA-B) and by pro-insulin to insulin ratio. A significant improvement in insulin resistance (HOMA-IR) was observed in the 52-week monotherapy trial (Trial 1573) after treatment with liraglutide 1.2 mg and 1.8 mg compared with glimepiride ([Table 6–9](#)).

Blood Pressure

Increased blood pressure is a risk factor for cardiovascular disease in the type 2 diabetes population. Blood pressure therefore was included as a secondary endpoint in the five long-term phase 3 trials. Across the trials, treatment with liraglutide resulted in a reduction from baseline in systolic blood pressure, ranging from 0.6 to 6.7 mmHg ([Figure 7–12](#)) and treatment with liraglutide 1.8 mg decreased systolic blood pressure significantly more than the active comparators in Trials 1573, 1572 and 1697 (in the two latter, active comparators were glimepiride, glimepiride + metformin and insulin glargine + glimepiride + metformin, respectively).

Safety

Withdrawal percentages due to adverse events ranged from 2.7%–8.8% across all treatment groups of the five long-term phase 3 trials. In subjects treated with liraglutide, adverse events leading to withdrawal were mainly gastrointestinal adverse events with a percentage in the range of 1.7%–6.2% ([Table 7–8](#)).

Nine deaths occurred in the total population of more than 6,800 subjects, and seven of the deaths occurred after randomization. Four of the subjects were randomized to run-in therapy + liraglutide and three subjects were randomized to run-in therapy + placebo or run-in therapy + active comparators. The number of deaths per treatment group was consistent with the randomization of subjects and no discernible pattern in the cause of death was identified ([Table 7–6](#)).

Gastrointestinal adverse events, including nausea, diarrhea and vomiting, were the most frequently reported events during treatment with liraglutide. Nausea was reported at least once during the trials by 21.3% of the subjects treated at the highest liraglutide dose of 1.8 mg and in 4–5% in the subjects treated with placebo or active comparators in the long-term phase 3 trials ([Table 7–1](#)). The most commonly reported serious adverse events across all treatments were in the system organ classes of cardiac disorders, neoplasms, infections and infestations and gastrointestinal disorders ([Table 7–4](#)).

Hypoglycemia is an important parameter in the treatment of type 2 diabetes and improvements in glycemic control can be associated with and increased risk of hypoglycemia. Major hypoglycemic episodes in the long-term phase 3 trials were rare (nine episodes in eight subjects) and seven of these major episodes were reported when liraglutide was used in combination with glimepiride ([Table 6–18](#)).

In the late phase of the development of liraglutide, some cases of pancreatitis were reported in subjects treated with a marketed product in the GLP-1 class, exenatide. In October 2007, the FDA issued a letter about pancreatitis and exenatide which was updated in 2008, indicating that further information would be added to the labeling about the risk of pancreatitis. Nine pancreatitis cases (liraglutide rate: 2.2, non-liraglutide rate: 0.6 events per 1,000 subject years of exposure) have been reported in the liraglutide clinical development program. Several risk factors were reported in the subjects presenting with pancreatitis. Nonetheless, even though the absolute risk is low, a small increase in relative risk cannot be excluded. This information will be reflected in the labeling of liraglutide and in the guidance to the prescriber.

Liraglutide is a peptide, and therefore adverse events related to immunogenicity were of special interest. Non-serious urticaria was reported more frequently with liraglutide ([Table 7–14](#)). No association between urticaria and antibody development towards liraglutide was observed. In the five long-term phase 3 trials, 8.6% of subjects across all liraglutide doses developed anti-liraglutide antibodies at low titers, with no impact on the HbA_{1c} lowering effect of liraglutide in the clinical trials.

Treatment-related C-cell proliferative changes were reported in the 104-week rodent carcinogenicity studies. Through a series of mechanistic studies it was found that GLP-1 agonists can activate rodent C-cells causing calcitonin release. Continued activation may later be followed by C-cell proliferation in rodents. In non-human primates neither calcitonin release nor C-cell proliferation was observed in studies up to 87 weeks' duration at high exposures.

Prompted by these nonclinical rodent findings, monitoring of calcitonin, a biomarker for C-cell mass and activation, was undertaken in the five long-term phase 3 trials. The calcitonin levels were in the low end of the normal range value in all treatment groups throughout the treatment periods, with no substantive difference between liraglutide and active comparator at any point in time. Six cases of C-cell hyperplasia were reported in the liraglutide development program – four liraglutide treated and two comparator treated subjects, i.e. the distribution reflected the 2:1 randomization. In five of the six cases, baseline or calcium stimulated calcitonin levels at baseline were elevated.

Based on the mechanistic nonclinical studies and clinical data, it was substantiated that the C-cell findings occur via a mechanism to which rodents are sensitive whereas non-human primates and man are not.

Careful evaluation and analysis of neoplasms in the liraglutide development program was done. The rates of all neoplasms (benign and malignant) were comparable for subjects treated with liraglutide

and subjects treated with placebo (26.9 and 25.3 per 1,000 subject years of exposure, respectively), and higher than for subjects treated with active comparator (17.0 events per 1,000 subject years of exposure). The most frequently reported malignant neoplasm adverse events in the liraglutide development program were prostate cancer, papillary thyroid cancer, and breast cancer ([Table 7–26](#)).

This Committee recently emphasized the importance of cardiovascular safety of new agents being developed for the treatment of diabetes mellitus. Based on the outcomes from deliberations on this topic and the new FDA ‘*Guidance for Industry - Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*’¹ which was issued on 17 December 2008, the Agency requested that a major adverse cardiovascular event (MACE) analysis be performed on the intermediate and long-term controlled, randomized, double-blind, completed phase 2 and phase 3 trials. The analyses covered several different definitions of MACE outcomes, different populations derived from the liraglutide safety database and sensitivity analyses with respect to seriousness of the events.

The results of the MACE analyses were robust and consistent across a number of different populations and outcome definitions. Sensitivity analyses of all MACE and only those categorized as serious supported this. Although the clinical trials of the liraglutide clinical program were designed and executed before the publication of the recent FDA cardiovascular guidance and hence have limitations, the results document, as would be expected from GLP-1 biology, that most of the point estimates in the main analyses were below 1 with the upper end of the 95% confidence intervals <1.8.

As a follow-up to the above and to further refine the point estimate for any cardiovascular risk associated with liraglutide, the occurrence of MACE, determined as a combined endpoint of cardiovascular death or non-fatal stroke or non-fatal acute myocardial infarction, will be studied in a dedicated large long-term post-approval outcome study (see Section [8.1](#)).

Benefit Risk Profile and Risk Management

Liraglutide met its predefined primary regulatory endpoint as defined in the clinical phase 3 program, and stands out from many other therapies in terms of the degree of improvement of glycemic control combined with a low risk of hypoglycemia. This glycemic control profile encompasses lowering of HbA_{1c}, fasting plasma glucose and postprandial plasma glucose and this would be expected to translate into a long-term reduced risk of microvascular complications.^{2,3} Based on its pharmacokinetic profile, liraglutide offers a once-daily, meal-independent dosing regimen. As additional benefits, liraglutide positively addresses some of the most important factors contributing to the risks which subjects with type 2 diabetes must live with, such as being overweight.

The safety profile of liraglutide is overall comparable to other known and marketed products for the treatment of type 2 diabetes. Treatment-related gastrointestinal adverse events were common at

initiation of treatment with liraglutide but decreased over time and were generally well tolerated. The absolute risk of pancreatitis was low, however, a small increase in relative risk of pancreatitis could not be excluded and this information will be included in the labeling. A nonclinical signal of C-cell proliferation in rodents was not seen in non-human primates. Correspondingly, in man there were no liraglutide-induced changes in calcitonin, a sensitive marker of C-cell mass and activation. While recognizing the limitations of the available liraglutide clinical safety database, there are no clinical or nonclinical data suggesting a treatment-related increased risk of experiencing a MACE or in the occurrence of adverse events in the system organ class of cardiac disorders following treatment with liraglutide.

To further refine the understanding of the liraglutide product profile and to optimize focus on patient safety, Novo Nordisk has developed a Risk Management Plan to address identified and potential risks associated with liraglutide treatment. This plan includes a proposal for a large post-approval cardiovascular outcome trial to study cardiovascular risk and potentially other rare events. The activities that will be undertaken to monitor and minimize potential risks with the use of liraglutide are summarized in Section [8](#).

On balance, liraglutide offers substantial benefits to type 2 diabetes patients and has a favorable benefit/risk profile when used for the treatment of type 2 diabetes as monotherapy and in combination therapy.

2 Introduction

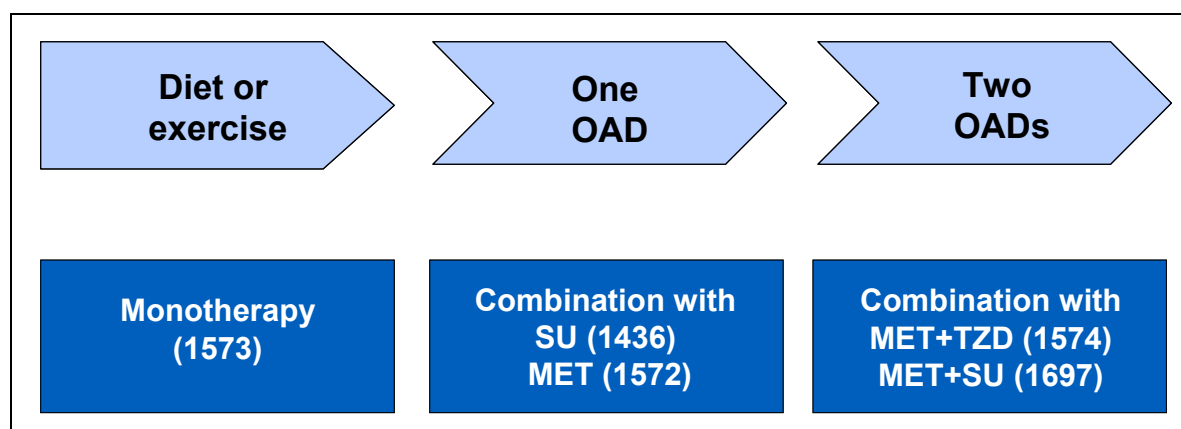
Type 2 diabetes mellitus is a metabolic disorder characterized by abnormal glucose metabolism. The pathogenesis is not fully understood but is heterogenous, involving environmental, lifestyle, and genetic factors which lead to chronic hyperglycemia caused by abnormal beta-cell function, peripheral tissue insulin resistance, and abnormal glucose metabolism in the liver.⁴

Diabetes mellitus is a leading cause of morbidity and mortality in the United States.⁵ The Center for Disease Control reported in 2007 that approximately 23.6 million people in the United States (7.8% of the population) have diabetes, and 90% to 95% of people with diabetes have type 2 diabetes.^{5,6} For most individuals with type 2 diabetes, lifestyle interventions fail to achieve or maintain metabolic goals, either because of failure to lose weight, weight regain, progressive disease or a combination of factors. Many subjects with type 2 diabetes, even with administration of one or more of the currently available medications, do not achieve glycemic control. A number of barriers to achieving glycemic control targets exist, most notable are complicated dosing regimens, risk of hypoglycemia and risk of weight gain following improved glycemic control.^{7,8}

Native GLP-1 is an important endogenous regulator of glucose homeostasis and has multiple functions in the pancreatic islets. These include glucose-dependent release of insulin and up-regulation of insulin biosynthesis, the glucokinase enzyme, and glucose transporters. Through other mechanisms, GLP-1 decreases appetite and lowers food intake leading to decreased body weight.⁹⁻¹² Finally, several nonclinical experiments and pilot clinical studies have demonstrated a positive impact of GLP-1 on the heart.¹³⁻¹⁵

The potential of exploiting these multiple characteristics of the native GLP-1 molecule led to the development of liraglutide, a slightly modified analog of human GLP-1 and a full GLP-1 receptor agonist but which, unlike native GLP-1, has a pharmacokinetic profile suitable for convenient, once-daily administration.

The five long-term phase 3 trials in the NDA were designed to evaluate the efficacy and safety of liraglutide across the continuum of care for subjects with type 2 diabetes - from the onset of type 2 diabetes with monotherapy - to combining liraglutide with one or two oral antidiabetic drugs (OADs) in subjects inadequately controlled on standard regimens ([Figure 2-1](#)).

Figure 2–1 Rationale for the Design of the Five Long-term Phase 3 Trials

SU: sulfonylurea, MET: metformin, TZD: thiazolidinedione and OAD: oral antidiabetic drug

A number of trials have documented the benefits of tight glycemic control.^{3,16,17} The epidemic nature of type 2 diabetes and the recognition that achieving specific glycemic targets can substantially reduce microvascular complications has made effective treatment of hyperglycemia a high priority.^{5,18,19}

Unfortunately, most of the blood glucose controlling agents available today produce weight gain.²⁰ Both epidemiologic and mechanistic studies have confirmed the important role that excess weight plays as a risk factor for the development of type 2 diabetes. There is increasing evidence that even modest weight loss has beneficial effects, also on parameters of glycemic control and other metabolic risk factors.²¹

The most recent glycemic target recommended by the American Diabetes Association (ADA) is an HbA_{1c} target < 7%.²² The ADA recommends that when the HbA_{1c} is >7% it is warranted to initiate or change therapy with the goal of achieving an HbA_{1c} level as close to the non-diabetic range as possible or, at a minimum, decreasing HbA_{1c} to < 7%.²³ Despite the evidence that improved glycemic control will reduce diabetes microvascular complications, almost 40% of people with diabetes fail to meet even the minimum HbA_{1c} target.²⁴

The potential clinical importance of GLP-1 receptor agonists in the treatment of type 2 diabetes was highlighted in the most recent ADA/EASD (European Association for the Study of Diabetes) consensus treatment algorithm published in Diabetes Care and Diabetologia. In this algorithm, GLP-1 receptor agonists have been introduced as 2nd tier therapy to be added to metformin in patients not achieving an HbA_{1c} of < 7% particularly when hypoglycemia is a concern with other therapies such as sulfonylureas or basal insulin or if weight loss is important.²³

Despite multiple drug classes and agents to treat type 2 diabetes, there remains a need for a type 2 diabetes treatment that can better address the multi-factorial aspects of the disease. The goal of

therapy is to achieve and maintain glycemic goals and improve other risk factors, such as excess body weight and elevated blood pressure.

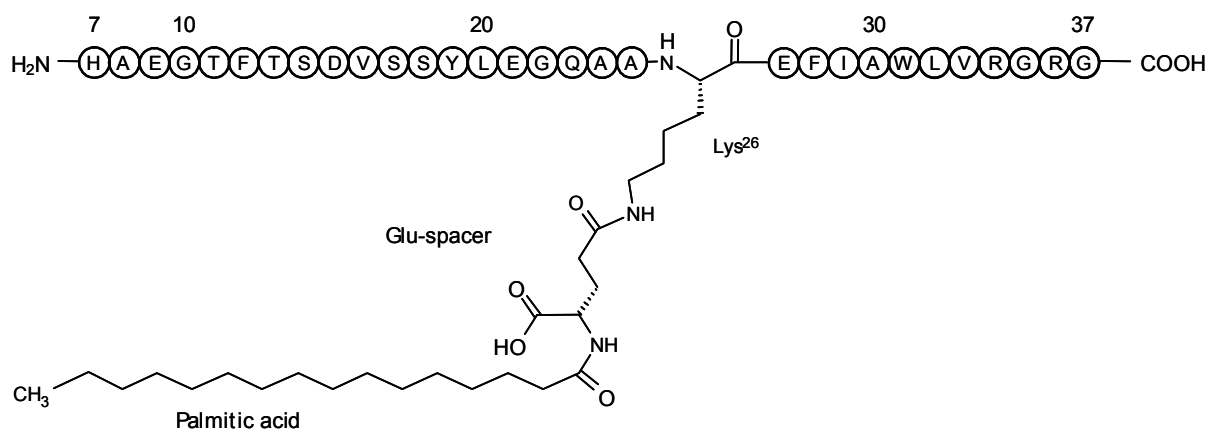
The liraglutide development program was designed to obtain the following indication as submitted in the NDA:

- Liraglutide, a human glucagon-like peptide (GLP-1) analog, is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

3 Product Description

Liraglutide is a once-daily human GLP-1 analog, classified as a GLP-1 receptor agonist. Liraglutide is a slightly modified analog of the native human Glucagon-Like-Peptide-1 (GLP-1). Liraglutide is an Arg³⁴-GLP-1 analog substituted on the ε-amino group of the lysine in position 26 with a Glu-spaced palmitic acid. Liraglutide has 97% amino acid homology with the human GLP-1 peptide and is produced by recombinant DNA technology in *Saccharomyces cerevisiae*. The structural formula ([Figure 3–1](#)) is:

Figure 3–1 Structural Formula of Liraglutide



Liraglutide is formulated as a clear, colorless solution. Each ml of liraglutide solution contains 6 mg of liraglutide. Each pre-filled pen contains a 3 ml solution of liraglutide equivalent to 18 mg salt-free anhydrous liraglutide and the following inactive ingredients: disodium phosphate dihydrate, propylene glycol, phenol, and water for injection.

4 Nonclinical Pharmacology and Toxicology

4.1 Nonclinical Pharmacology

4.1.1 Glucagon-like Peptide-1

The GLP-1 peptide hormone belongs to the superfamily of glucagon-related peptides. Physiologically, GLP-1 is processed from the preproglucagon gene. The amino acid sequence of GLP-1 is preserved in mammals and only one receptor, the GLP-1 receptor, has been identified.⁹ The GLP-1 receptor is a 7-Trans-membrane Gs-protein coupled receptor and there is close homology among the GLP-1 receptor in different mammalian species, with rat and human GLP-1 receptor having homology of 90% and monkey and human 99%.²⁵ Within the pancreas, the GLP-1 receptor is expressed in insulin-producing beta-cells, somatostatin-producing delta-cells and potentially a subset of glucagon-producing alpha-cells.

Pancreatic beta-cell stimulation following GLP-1 receptor activation is mediated by adenylate cyclase leading to cAMP accumulation and subsequently to exocytosis of insulin-containing granules. GLP-1 stimulates synthesis of insulin. GLP-1 also lowers glucose via inhibition of glucagon secretion from islet alpha-cells. The inhibition of glucagon secretion may be direct via GLP-1 receptors expressed on alpha-cells or indirect via stimulation of insulin and somatostatin secretion.¹¹

The primary pharmacological target tissues for GLP-1 agonists are the pancreatic islets (beta-cells), the gastrointestinal system and peripheral sensory vagal afferent nerves.⁹⁻¹² In animals, GLP-1 has several actions of potential pharmacological importance. Functional effects in the pancreas include glucose-dependent release of insulin as well as an up-regulation of insulin biosynthesis, glucokinase and glucose transporters. Other effects include: a) glucose-dependent growth, proliferation and antiapoptosis of pancreatic beta-cells; b) glucose-dependent lowering of glucagon secretion, which lowers hepatic glucose output; c) inhibition of gastric acid secretion and gastric emptying, the latter causing a reduction in postprandial plasma glucose excursions; and d) lowering of food intake leading to decreased body weight.⁹⁻¹²

4.1.2 Liraglutide Pharmacology

Overall, there are two approaches to enhancing GLP-1 action: inhibition of GLP-1 degradation by DPP-IV and exogenous administration of GLP-1 receptor agonists. With liraglutide, the structural changes to the GLP-1 molecule stabilize it against metabolic degradation by neutral endopeptidase (NEP) and dipeptidyl-peptidase (DPP-IV), and they facilitate its binding to plasma proteins, in particular albumin which possesses fatty acid binding sites. This leads to decreased clearance and protracted pharmacological activity. In addition, the slow absorption from the injection site, likely related to self-association, adds to prolonged action after subcutaneous administration. These features provide a compound with pharmacokinetic properties suitable for once-daily administration.

Receptor Potency and Selectivity

Liraglutide is a potent agonist *in vitro* on cloned GLP-1 receptors from human as well as mouse, rat, rabbit, pig and cynomolgus monkey and it displays only minor interspecies differences in affinity and potency. Liraglutide was tested for its receptor selectivity in *in vitro* binding and functional assays comprising more than 75 different receptors, ion-channels and drug transporters. These experiments showed that liraglutide is a highly selective GLP-1 receptor agonist without affinity to other receptors, even those belonging to the closely related glucagon receptor family. The albumin binding property of liraglutide influenced the *in vitro* EC₅₀ shifting the concentration-response curve to the right with increasing albumin concentration. This implies that only the free fraction of liraglutide is responsible for the pharmacological effect *in vitro* as well as *in vivo*.

***In vitro* Efficacy**

In vitro studies demonstrated that liraglutide exerts expected GLP-1 receptor mediated effects on the pancreatic beta-cells in the form of a dose-dependent enhancement of glucose-dependent insulin secretion and cytoprotective activity against cytokines and free fatty acids. The stimulation of insulin release was demonstrated to be additive to that induced by a sulfonylurea. Furthermore, it was demonstrated that sulfonylureas uncouple the glucose-dependency of GLP-1 induced insulin secretion.

***In vivo* Efficacy**

Animal Models of Type 2 Diabetes and Obesity

The effect of liraglutide on beta-cells was studied in normal rats and in Zucker diabetic fatty rats with established diabetes proliferation markers and stereological methods. The results demonstrated that liraglutide increases beta-cell proliferation only when hyperglycemia and/or other factors have decreased their function and mass, whereas liraglutide has minimal or no effect when normoglycemia is established. Liraglutide also was shown to increase insulin biosynthesis as measured by an increase in insulin staining intensity in beta-cells.

Liraglutide treatment of all animal models of diabetes was characterized by a consistent, acute, and dose-dependent reduction in plasma glucose. Studies demonstrated that the reduction in plasma glucose was mediated via stimulation of insulin secretion and suppression of glucagon production, both in a glucose-dependent manner. In addition, liraglutide acutely delayed gastric emptying which contributed to reduction in the peak of postprandial glucose excursion. Thus, based on animal experiments, liraglutide has similar pharmacological actions as native GLP-1.

In repeat-dose efficacy studies in diabetic mice and rats, liraglutide consistently and dose-dependently reduced HbA_{1c}. Food intake also decreased in diabetic animals (mice and rats) treated with liraglutide, an effect which translated into decreased body weight.

4.2 Overview of Nonclinical Development Program

The nonclinical program was designed in accordance with guidance given by the International Conference on Harmonization (ICH) for new chemical entities to support chronic clinical use in humans.²⁶ For general toxicology studies, the rat was chosen as the rodent species and the cynomolgus monkey as the non-rodent species because both species are known to respond pharmacologically to liraglutide and they metabolize liraglutide in a way similar to that of humans. The mouse was chosen as the second rodent species in the carcinogenicity studies. Rats and rabbits were used in reproductive toxicology studies ([Table 4–1](#)).

Table 4–1 Overview of Nonclinical Safety Pharmacology, Toxicology, and Pharmacokinetic Studies

	Mouse	Rat	Rabbit	Pig	Non-human Primates ^(a)	Other
Safety pharmacology						
No. studies	2	4	1	0	1	2
Types	CNS Exposure	Respiration CV Renal function Exposure	CV	N/A	CV	GI CV
Pharmacokinetic						
No. studies	8	23	2	2	11	17
Types	PK/TK Absorption Distribution Metabolism Excretion	PK/TK Absorption Distribution Metabolism Excretion	TK Distribution	PK Absorption	PK/TK Absorption Metabolism Excretion	<i>In vitro/in situ</i> Metabolism Plasma protein
Toxicology						
No. studies	17	29	2	3	13	9
Types	SD RD 4–13 week Carcinogenicity Mechanistic	SD RD 4–26 week Genotoxicity Carcinogenicity Reproductive/ Developmental Mechanistic (69-week)	Reproductive	Local toxicity	RD 4–52 week Mechanistic (87-week)	Genotoxicity Mechanistic

^a Cynomolgus monkeys. CNS: central nervous system; CV: cardiovascular; GI: gastrointestinal; PK: pharmacokinetic; RD: repeat dose; SD: single dose and TK: toxicokinetic.

4.3 Safety Pharmacology/Effect on Vital Organ Systems

Liraglutide was investigated in a series of safety pharmacology studies assessing its effects on cardiovascular and respiratory function, water and electrolyte metabolism, and the autonomic and central nervous system in pharmacologically responsive species (mouse, rat, rabbit, guinea-pig and cynomolgus monkey).

Liraglutide was well tolerated. The only adverse effects observed in these organ systems were confined to the rat and these were well-known GLP-1-mediated effects on the cardiovascular system and kidney function in this species.²⁷⁻²⁹ Specifically in the rat, there was an increase in diuresis and an increase in blood pressure and heart rate starting at doses of 0.2 mg/kg and higher. The cardiovascular system was not affected in a single-dose telemetry study in cynomolgus monkeys, and the renal function was not affected in the cynomolgus monkey toxicology studies at comparable or higher doses than those inducing diuresis in the rats.

When the heart weight was assessed in the rat toxicology studies, it was significantly reduced in the 4- and 26-week toxicology studies, while a smaller non-significant reduction in weight was observed in the 13-week and in the 104-week carcinogenicity study. Heart weight was not affected in mice or cynomolgus monkey with exposures more than 70-fold that in humans. These findings indicate that the acute cardiovascular effect in rats disappears during chronic treatment and that it is rat specific.

The potential of liraglutide to cause ECG abnormalities was investigated using the patch-clamp technique, isolated rabbit heart, and telemetry plus ECG monitoring in cynomolgus monkeys. Liraglutide had no effect on the ion channel (hERG) responsible for repolarization of the heart. Also, liraglutide had no effect on the ECG parameters in the isolated rabbit heart, in telemetered monkeys or in monkeys treated for 52 weeks with maximal exposure more than 70-fold that observed in trials in humans. In a closed-chest acute myocardial infarct pig model, no effect of liraglutide was seen on either infarct size or on post-infarction arrhythmias.

In conclusion, the organ-specific preclinical safety pharmacology program raised no safety concerns.

4.4 Nonclinical Pharmacokinetics and Absorption, Distribution, Metabolism and Excretion (ADME)

Pharmacokinetic properties of liraglutide were studied in the same species as those used in the efficacy, safety pharmacology and toxicology studies. There was no gender difference or time-dependency in the pharmacokinetic parameters. A correlation between body weight and clearance was observed across all species: mice, rats, rabbits, pigs and cynomolgus monkeys. The pharmacokinetic observations are consistent among species and demonstrate dose proportionality.

All species except Sprague-Dawley rats (plasma protein binding 95.8–98.2%) demonstrated a plasma protein binding of approximately 99% or higher. Liraglutide has a small volume of distribution close to the plasma volume in agreement with its high binding to albumin in all species. No special target organ was identified in the tissue distribution studies.

The metabolism and excretion pattern was highly similar across species, including humans. Liraglutide was fully degraded in the body with no single organ as a major route of elimination. No excretion of liraglutide and only very limited excretion of closely related metabolites was observed.

Metabolism by DPP-IV and NEP, although slow, resulted in similar cleavage sites in liraglutide as those reported for native GLP-1. Metabolism occurred via sequential cleavage of N- and C-terminal peptide fragments and amino acids.

No clinically relevant inhibition or induction in cytochrome P450 activity was observed.

4.5 Toxicology Findings

The majority of findings in the short-, medium- and long-term toxicity studies were related to dose-dependent primary pharmacology via GLP-1 receptor-mediated effects. These effects were a decrease in food consumption and a decrease in body weight gain. Other effects of potential interest are summarized below.

Pancreas

The pancreas was examined macro- and microscopically in all toxicology studies in mice, rats and cynomolgus monkeys. The maximal exposure levels were approximately 36 (mice), eight (rats), and 60-fold (cynomolgus monkey) more than in humans. There were no findings suggestive of inflammation in the pancreas in any of the toxicology studies, including the 104-week carcinogenicity studies and an 87-week mechanistic study in cynomolgus monkeys. No proliferative lesions, hyperplastic or neoplastic, were observed in the beta-cells or other cell types in the islets.

A significant difference in pancreas weight was identified in mid- and high-dose animals in the 52-week non-human primate study. The exposure levels in the animals at mid- and high-dose level were 8.7- and 73-fold the human exposure at maximum recommended human dose of 1.8 mg/day, based on AUC. Since the values of control females were low both when compared to concurrent male control values and historical control values it is speculated that the observed difference in weight was driven by this imbalance.

The pancreatic weight difference was not associated with any clinical signs, biochemical, macroscopic or microscopic changes related to treatment.

No changes in pancreas weight were observed in cynomolgus monkeys treated for 4, 13 or 87 weeks.

Reproductive Toxicology

The reproductive toxicity of liraglutide was investigated in standard studies covering fertility, early and late embryo-fetal development and pre- and postnatal development in rats and rabbits.

Overall, there was no effect on fertility, no major or minor malformations were recorded, and postnatal development and learning abilities were unaffected. All fetal findings in rats and rabbits, consisting of minor and reversible skeletal changes or variations, were seen at doses causing maternal toxicity or exaggerated pharmacology in the form of decreased food consumption and

body weight. It is therefore concluded that the findings were not due to a direct toxic effect on the fetus.

In rats, an increase in early embryonic deaths and an increased incidence of fetuses with minimally kinked ribs were seen at the highest dose level, corresponding to 11-fold the human exposure at the maximal recommended clinical dose. At the high dose level, maternal clinical signs of adverse reactions, decreased food consumption and body weight were observed. In rats, kinked ribs are a reversible finding occurring late in gestation and normalized within three weeks after birth.³⁰

In the embryo-fetal development study in rabbits, an increase in the incidence of fetuses with jugal connected/fused to maxilla bones just exceeding the historical background range was observed at the highest dose level. The finding is classified as a variation, i.e. a non-serious finding that is non-serious and which is known to occur in this species. The incidence of this finding generally increased with increasing dose. The incidence was 10%, 6% and 5% in the highest, mid- and low-dose groups, respectively, and 2% in the control group with a historical control range between 1 and 9%. At the mid- and high-dose levels, an increased incidence of fetuses with supernumerary ribs was observed. This finding is ascribed to the significant decrease in food consumption of the dams during the beginning of the dosing period.

In the pre- and post-natal development study in rats, pharmacological effects on food consumption and body weight were observed at all dose levels in the F0 generation (treated parent animals). The body weight effect persisted into the pre-weaning period in the F1 generation (descendants from F0 generation) at all dose levels, and during the post-weaning period in the 1.0 mg/kg dose group. Group mean litter weight was reduced in the high-dose F2 generation (descendants from F1 generation), probably due to a lower body weight of the F1 animals at this dose level.

4.6 Carcinogenicity

Liraglutide was tested in a full range of genotoxic tests consisting of Ames test, human peripheral blood lymphocyte chromosome aberration test, and *in vivo* micronucleus test in the rat. All tests were negative. Two-year carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats and results are presented below. The carcinogenicity data were peer-reviewed.

Mouse

[Table 4–2](#) summarizes the incidences of benign and malignant tumors in mice treated for two years.

Table 4–2 Tumor Incidences (%) in Mice Treated with Liraglutide for 104 Weeks

Mice	Males					Females				
Dose group, mg/kg	Vehicle ^(a)	0.03	0.2	1.0	3.0	Vehicle	0.03	0.2	1.0	3.0
Number of animals	79	67	67	67	79	79	67	67	67	79
% animals with tumors	72	72	67	58	78	72	66	85	70	75
% animals with benign tumors	59	55	45	39	53	39	39	51	37	46
% animals with malignant tumors	35	28	43	31	48	54	48	63	54	52

It should be noted that the same animal may have both benign and malignant tumors. ^a Vehicle=Liraglutide injection medium without active ingredients (placebo).

An increase in the number of uterine leiomas and leiomyosarcomas in treated mice was reported, however, there was no dose-response relationship. These tumors are reported to be among commonly occurring spontaneous tumors in female mice.³¹ This finding was not considered treatment-related.

Dorsal skin sarcomas at the injection site were significantly increased in male mice at the highest dose of 3 mg/kg/day. The percentages of male mice with dorsal skin sarcomas in controls and high-dose animals were 2.5% and 20%, respectively. The tumors were located in the area of the micro-chip implant and the injection site area. Repeated subcutaneous injections of non-genotoxic compounds and solutions as well as implantation of solid material such as micro-chips in the subcutis are known to cause development of skin sarcomas in rodents.³² The NOAEL for skin sarcomas was 1.0 mg/kg, providing a human safety ratio of 13. There have been no reports of skin sarcomas in the clinical development program. The observed increase in high-dose male mice is not considered of concern for human safety.

Rats

[Table 4–3](#) summarizes the incidences of benign and malignant tumors in rats treated for two years.

Table 4–3 Tumor Incidences (%) in Rats Treated with Liraglutide for 104 Weeks

Rats	Males				Females			
Dose group, mg/kg	Vehicle	0.075	0.25	0.75	Vehicle	0.075	0.25	0.75
Number of animals	50	50	50	50	50	50	50	50
% animals with tumors	84	90	84	86	94	94	96	98
% animals with benign tumors	80	78	80	82	94	86	90	92
% animals with malignant tumors	26	38	32	26	32	34	32	30

It should be noted that the same animal may have both benign and malignant tumors.

Pituitary anterior lobe tumors in female rats were reported at a higher incidence in treated compared to control animals. The pituitary tumors were seen in one sex only and the incidence was within the background range. Neoplasia in the anterior lobe of the pituitary gland is one of the most common tumors observed in the female Sprague-Dawley rat; the major part being adenomas. Based on this, the finding was not considered treatment-related.³³

Treatment-related proliferative changes in the C-cells (parafollicular cells) of the thyroid were observed in the mouse and rat 2-year carcinogenicity studies. Early C-cell changes were also identified in repeated dose toxicity studies. The C-cell changes ranged from focal hyperplasia to benign and malignant neoplasia and were dose-dependently increased in liraglutide-dosed animals. The C-cell changes, their mechanistic background, and an evaluation of their relevance to humans are described in detail in Section [7.7](#).

Based on the absence of genotoxic potential and on the carcinogenicity assessment conducted through two life-time rodent carcinogenicity studies, potential effects on overall tumor incidence and on the incidence of specific individual tumor types were evaluated. Due to the very high specificity of liraglutide to the GLP-1 receptor, any general effects on tumor cells would be expected to occur via the GLP-1 receptor. The liraglutide rat and mouse carcinogenicity studies showed no general overlap between tumor development and tissue GLP-1 receptor expression and there were no data suggesting carcinogenicity or growth-promoting effects of liraglutide.

5 Clinical Pharmacology

5.1 Overview of Clinical Pharmacology Trials

The clinical pharmacology program was performed to evaluate the pharmacokinetic and pharmacodynamic properties of liraglutide and included 26 trials. Of these, 19 trials were in healthy subjects (including trials in elderly subjects, subjects with renal or hepatic impairment, Japanese subjects and bioequivalence trials) and seven trials were in subjects with type 2 diabetes (including one trial in Japanese subjects). The program was supported by evidence from five phase 2 trials and a population pharmacokinetic analysis from the long-term phase 3 Trial 1573 (52-week monotherapy trial).

5.2 Pharmacokinetics

The absorption of liraglutide following s.c. administration is slow, reaching maximum concentration 8 to 12 hours post dosing. The estimated level of C_{\max} was 9.4 nmol/L for a single 0.6 mg dose of liraglutide. At the liraglutide 1.8 mg dose, the average steady state concentration was 33.7 nmol/L. Steady state was reached after about three dose administrations. Liraglutide exposure increased proportionally with dose. The accumulation ratio is 1.4–1.8, which is in agreement with the elimination pharmacokinetics and once-daily dosing of liraglutide.

The volume of distribution following s.c. administration of liraglutide was 11–17 L. This volume is small and close to the plasma volume, indicating that a high fraction of liraglutide is circulating in the blood, which is in agreement with high plasma protein binding (>98%). The clearance following s.c. administration of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours.

The combination of delayed subcutaneous absorption and a plasma half life of 13 hours provide liraglutide with 24-hour duration of action and make it appropriate for once-daily administration.

The absolute bioavailability of liraglutide following s.c. administration is approximately 55%. Minor variations in relative bioavailability after s.c. administration of liraglutide in abdomen, thigh and the upper arm were observed. Equivalence regarding AUC was demonstrated between the upper arm and abdomen, and between upper arm and thigh, but not between thigh and abdomen where a 19% lower exposure following injection in the thigh (ratio 0.81 and 90% CI [0.76; 0.86]) was observed.

Differences in bioavailability between injection sites are not unexpected, e.g. lower exposure following injection in the thigh is also observed for other injectable drugs such as insulins. The differences in exposure originating from the intra-subject variability and from differences between the proposed clinically relevant doses are expected to exceed the variability due to a difference in injection site. Furthermore, given relatively broad therapeutic dose range, the minor differences in

bioavailability between injection sites are not considered to be of clinical relevance. Therefore, all three injection sites can be used interchangeably without dose-adjustment.

The metabolite profile of liraglutide in plasma, urine and feces was investigated in healthy subjects using [³H]-liraglutide. There was no excretion of intact liraglutide in urine or feces and only low levels of metabolites were present in plasma, urine and feces. No single human metabolite contributed substantially to the radioactivity recovered. Two minor metabolites were detected in plasma ($\leq 9\%$ and $\leq 5\%$ of total plasma radioactivity exposure). The urine and feces radioactivity corresponded to three minor metabolites. Liraglutide is metabolized in a similar manner to that of native GLP-1, i.e., by DPP-IV and NEP cleavage, although at a much slower rate than native GLP-1. Liraglutide is fully degraded in the body with no single organ as a major route of elimination.

5.2.1 Special Populations and Factors Potentially Contributing to Pharmacokinetic/Pharmacodynamic Variability

Age

In Trial 1327, 16 elderly healthy subjects (65 to 83 years of age with a mean age of 69 years) and 16 young healthy subjects (21 to 45 years of age with a mean age of 33 years) received one single dose of 1 mg liraglutide. Equivalence was pre-specified as the 90% CI being fully contained within the limits of 0.80 to 1.25 demonstrated for the primary endpoint AUC_{0-t} , with the estimated ratio (elderly vs. young) being 0.94 (90% CI [0.84; 1.06]). No statistically significant differences between elderly and young subjects were observed for other pharmacokinetic endpoints. Furthermore, age had no significant effect on liraglutide pharmacokinetics in a population pharmacokinetics analysis on data from the long-term phase 3 Trial 1573.

In the long-term phase 3 trials, a total of 797 liraglutide-treated subjects were ≥ 65 years of age and 113 subjects were ≥ 75 years of age ([Table 6–4](#)). Analyses of both individual trial data and pooled data from four 26-week long-term phase 3 trials demonstrated that liraglutide had similar glycemic response in the different age groups, as measured by change in HbA_{1c} ([Table 5–1](#)).

Gender, Race and Ethnicity

The effect of gender on the pharmacokinetics of liraglutide was investigated in a single dose trial, Trial 1327, and in a population pharmacokinetics model based on data from Trial 1573.

In Trial 1327, the mean liraglutide plasma profiles indicated that female subjects had higher plasma concentrations than male subjects. No statistically significant difference between males and females was demonstrated when corrected for body weight. No statistically significant differences between females and males were observed for other pharmacokinetic endpoints.

Population pharmacokinetics in subjects with type 2 diabetes (Trial 1573) demonstrated a lower clearance in female compared to male subjects, leading to a higher liraglutide exposure in female subjects, also when adjusting for body weight. However, based on the full evaluation of the pharmacokinetic profile in male and female, this difference was not considered clinically relevant.

The clinical relevance of the above observations was evaluated for efficacy and safety across the long-term phase 3 trials. Any differences in HbA_{1c} among treatments did not depend on gender in any of the individual long-term phase 3 trials nor in the data derived across the long-term phase 3 trials.

The percentage of subjects reporting adverse events and the rate of adverse events was higher for females than for males in both the liraglutide and the comparator groups (females: 4296.3 and 3495.6 events per 1,000 subject years of exposure, respectively, and males: 3510.2 and 2820.2 events per 1,000 subject years of exposure, respectively). The most frequently reported adverse events for both genders were gastrointestinal disorders. The rate of gastrointestinal disorders with liraglutide 1.2 mg, liraglutide 1.8 mg and active comparator was higher in female (1326.7, 1639.9 and 553.4 events per 1,000 subject years of exposure) compared with male subjects (905.4, 1168.8 and 324.4 events per 1,000 subject years of exposure). The rates reported in the other treatment groups were comparable for female and male subjects.

Race and Ethnicity in Long-term Phase 3 Trials

The impact of race and ethnicity on pharmacokinetics of liraglutide was investigated in the population pharmacokinetic analysis from the 52-week monotherapy Trial 1573, where five race groups (White, Asian, Black, Hawaiian and 'Other') and two ethnic categories (Hispanic and non-Hispanic) were investigated. The effects of ethnicity and race on the clearance were not significant when adjusted for body weight and gender.

Interaction analysis of individual trial data and pooled data from the four 26-week long-term phase 3 trials did not show a significant effect of ethnicity or race, except for a significant effect of race on change in HbA_{1c} in Trials 1436 and 1697 ([Table 5-1](#)). This difference was most likely due to a difference between race groups for the placebo-treated subjects, and in Trial 1697 also due to an imbalance in the statistical analysis, as only few subjects were of other than White origin. It should be noted that while 6% of the total number of subjects in the long-term phase 3 trials were of Black/African American origin, the percentage was approximately twice as high in the two trials conducted in the US (Trials 1573 and 1574) ([Table 6-4](#)).

The percentage of subjects reporting adverse events in the long-term phase 3 trials was comparable between all race groups, while the rate of adverse events was slightly higher in the Asian / Native Hawaiian / Pacific Islander group than in the other race groups in both the liraglutide and the comparator groups. The most frequently reported adverse events for all race groups were gastrointestinal disorders and infections.

For ethnicity, the rates of adverse events were lower in Hispanic/Latino subjects compared with non Hispanic/Latino subjects. The most frequently reported adverse events were gastrointestinal disorders and infections for both ethnicity groups.

Table 5–1 Treatment Effect-by-Demographic Factor Interaction on HbA_{1c} (% points) at End of Trial

	Trial 1573		Trial 1572		Trial 1436		Trial 1574		Trial 1697	
	N	p-value	N	p-value	N	p-value	N	p-value	N	p-value
Gender	711	0.3182	1061	0.8089	1004	0.4170	518	0.7338	559	0.7634
Male	351		620		503		288		318	
Female	360		441		501		230		241	
Age	711	0.9262	1061	0.9399	1004	0.4257	518	0.3865	559	0.6587
<65 years	606		830		800		426		419	
65-75 years	85		204		179		76		120	
≥75 years	20		27		25		16		20	
Ethnicity	711	0.6360					518	0.5375		
Hispanic/Latino	250						79			
Not Hispanic/Latino	461						439			
Race	711	0.3146	1061	0.1180	1004	0.0026*	518	0.1337	559	0.0214*
White	554		928		653		431		423	
Asian/Native	26		91		317		9		82	
Hawaiian/Pacific Islander										
Black/African American	87		25		29		59		21	
Other	44		17		5		15		5	
Missing									28	
American Indian/ Alaska Native							4			
BMI at Baseline	711	0.6196	1058	0.2086	1001	0.2067	518	0.9244	557	0.0874
BMI <25 kg/m ²	50		100		174		25		79	
25≤ BMI <30 kg/m ²	187		359		378		120		199	
30≤ BMI <35 kg/m ²	229		361		288		192		173	
BMI ≥35 kg/m ²	245		238		161		181		106	
Body Weight	711	0.7930	1059	0.4878	1003	0.0105*	518	0.5719	557	0.3551
<90 kg	340		550		699		199		342	
≥90 kg	371		509		304		319		215	

For complete treatment regimens in the individual trials, see [Table 6–1](#). N: Number of subjects with data available for this analysis.

*Statistically significant interaction between treatment and demographic factor. P-value of treatment by factor interaction is calculated by following ANCOVA model. Change in HbA_{1c}: baseline HbA_{1c} + treatment + country + previous antidiabetic drug + factor + treatment x factor interaction.

Renal Impairment

Pharmacokinetics in subjects with different degrees of renal impairment were compared with subjects with normal renal function in Trial 1329. Subjects (N=5–7 per group) were administered a single s.c. dose of 0.75 mg liraglutide. Renal impairment was classified using creatinine clearance (CL_{CR}) estimated by the Cockcroft & Gault formula. Subjects were grouped as:

- ‘normal’ (CL_{CR} > 80 mL/min)
- ‘mild’ renal impairment (50 mL/min < CL_{CR} ≤ 80 mL/min)

- ‘moderate’ renal impairment ($30 \text{ mL/min} < \text{CL}_{\text{CR}} \leq 50 \text{ mL/min}$)
- ‘severe’ renal impairment ($\text{CL}_{\text{CR}} \leq 30 \text{ mL/min}$)
- end stage renal disease (ESRD) on continuous ambulatory peritoneal dialysis (CAPD)

Equivalence for $\text{AUC}_{0-\infty}$ and C_{max} was not demonstrated in the pairwise comparisons between any of the renal impairment groups and the group with normal renal function except for C_{max} between subjects with moderate renal impairment and healthy subjects (see [Table 5–2](#)). Equivalence between subjects with normal renal function and any of the groups of subjects with renal impairment was demonstrated as having been met if the 90% CI for the ratio was fully contained within the limits 0.70 to 1.43. Liraglutide exposure as assessed by AUC was lower in subjects with renal impairment compared to subjects with normal renal function, but there was no trend identified in AUC across the four degrees of renal dysfunction.

Table 5–2 Comparison of $\text{AUC}_{0-\infty}$ and C_{max} for Single Dose Liraglutide between Subjects with Different Grades of Renal Impairment (Trial 1329)

	$\text{AUC}_{0-\infty}$	C_{max}
	Ratio [90% CI]	Ratio [90% CI]
Mild/normal	0.67 [0.54; 0.85]	0.75 [0.57; 0.98]
Moderate/normal	0.86 [0.70; 1.07]	0.96 [0.74; 1.23]
Severe/normal	0.73 [0.57; 0.94]	0.77 [0.57; 1.03]
ESRD/normal	0.74 [0.56; 0.97]	0.92 [0.67; 1.27]

N: Normal=6; Mild=6; Moderate=7; Severe=5; ESRD=6. The statistical analysis was adjusted for effect of age, body weight and renal group.

A regression analysis of $\text{AUC}_{0-\infty}$ adjusted for age, body weight, and creatinine clearance demonstrated that renal function defined by creatinine clearance had no statistically significant effect on AUC. This analysis demonstrated that renal impairment was not associated with clinically relevant change in liraglutide exposure. Thus, patients with type 2 diabetes and renal impairment can be dosed with liraglutide using the proposed dosing regimen without concern for increased drug exposure. Importantly, any effect would result in decreased liraglutide exposure and would be managed by normal titration of the drug dose. However, there is limited clinical experience in patients with severe renal impairment.

Hepatic Impairment

In Trial 1328, 24 subjects (N=6 in each group) received one single s.c. dose of 0.75 mg liraglutide.

The subjects were classified according to the Child-Pugh scores of ‘mild’, ‘moderate’ and ‘severe’ hepatic impairment.³⁴

Equivalence between subjects with normal hepatic function and any of the groups of subjects with hepatic impairment was predefined as being met if the 90% CI for the ratio was fully contained within the limits 0.70 to 1.43. Overall, the exposure in subjects with hepatic impairment was lower

and equivalence between subjects with normal hepatic function and any of the groups of subjects with hepatic impairment was not demonstrated for $AUC_{0-\infty}$ or C_{max} (Table 5–3).

Table 5–3 Comparison of $AUC_{0-\infty}$ and C_{max} for Single Dose Liraglutide between Subjects with Different Grades of Hepatic Impairment (Trial 1328)

	$AUC_{0-\infty}$	C_{max}
	Ratio [90% CI]	Ratio [90% CI]
Mild/normal	0.77 [0.53; 1.11]	0.89 [0.65; 1.21]
Moderate/normal	0.87 [0.60; 1.25]	0.80 [0.59; 1.09]
Severe/normal	0.56 [0.39; 0.81]	0.71 [0.52; 0.97]

N: Normal=6; Mild=6; Moderate=6; Severe=6. The statistical analysis was adjusted for effects of age, gender and body weight.

A statistically significant positive relationship between albumin concentration and liraglutide $AUC_{0-\infty}$ ($p=0.041$) was observed. However, there was no statistically significant effect of albumin levels or hepatic impairment on liraglutide $AUC_{0-\infty}$ in an analysis where both variables were included. Therefore, it is not possible to state if the observed relationship between liraglutide $AUC_{0-\infty}$ and hepatic impairment is solely attributed to lower albumin levels or to other aspects of hepatic impairment. Nevertheless, *in vitro* studies imply that the reduced albumin concentration leads to increased clearance.

Based on PK studies, subjects with type 2 diabetes and hepatic impairment could be dosed in accordance with the proposed dose regimen for liraglutide which implies individual incremental dose titration. However, there is limited clinical experience in patients with liver impairment.

5.2.2 Drug Interactions

A study testing liraglutide for potential inhibition of cytochrome P450 (CYP) in human liver microsomes showed that liraglutide has very low potential to be involved in pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP).

The minor delay in gastric emptying shown with liraglutide could potentially influence absorption of concomitantly administered oral drugs, and thereby induce drug-drug interactions. To investigate this potential effect of liraglutide, drugs with different solubility and permeability properties were selected for investigation according to the Biopharmaceutics Classification System (BCS). Specifically, drug-drug interactions were investigated using acetaminophen, digoxin, lisinopril, griseofulvin and atorvastatin. In addition, the effect of liraglutide on ethinylestradiol and levonorgestrel administered in an oral combination contraceptive drug were investigated. The effect of liraglutide on the absorption pharmacokinetics of the oral drugs was consistent with the expected pharmacokinetics according to the absorption properties of the individual drugs and supports that liraglutide induces a minor delay in gastric emptying. Importantly, while C_{max} and t_{max} were affected by liraglutide, AUC and thus total exposure, was unaffected. Based on the drug exposure levels, the changes in absorption pharmacokinetics (Table 5–4) are considered minor and no dose adjustment is considered required.

Table 5–4 Effect of Liraglutide 1.8 mg vs. Placebo on Absorption of Orally Administered Drugs

Oral Drug	BCS Class	Dose (mg)	Trial ID	N ^(a)	AUC _{0-∞}	C _{max}	t _{max}
					Ratio [90% CI]	Ratio [90% CI]	Difference (h) [90% CI]
Acetaminophen	I	1000	1698	18	1.04 [0.97; 1.10]	0.69 [0.56; 0.85]	0.25 [0.00; 1.54]
Atorvastatin	II	40	1608	42	0.95 [0.89; 1.01]	0.62 [0.53; 0.72]	1.25 [1.00; 1.50]
Griseofulvin	II	500	1608	22	1.10 [1.01; 1.19]	1.37 [1.24; 1.51]	0.00 [-7.00; 2.00]
Lisinopril	III	20	1608	40	0.85 [0.75; 0.97]	0.73 [0.63; 0.85]	2.00 [2.00; 3.00]
Digoxin	IV	1	1608	27	0.84 [0.72; 0.98] ^(b)	0.69 [0.60; 0.79]	1.13 [0.50; 1.25]
Ethinylestradiol ^(c)	II	0.03	1330	21	1.06 [0.99; 1.13]	0.88 [0.79; 0.97]	1.50 [1.00; 2.50]
Levonorgestrel ^(c)	II	0.15	1330	14	1.18 [1.04; 1.34] ^(d)	0.87 [0.75; 1.00]	1.50 [0.50; 2.00]

^a Number of subjects included in the analysis of AUC_{0-∞}. ^b AUC_{0-72h}. ^c Ethinylestradiol and Levonorgestrel are from combination oral contraceptives. ^d Equivalence was shown for AUC_{0-t} (N=21) with similar ratio (1.15 (90% CI [1.06; 1.24])). BCS: biopharmaceutical classification system; Ratio: liraglutide/placebo; Difference: liraglutide – placebo.

5.3 Pharmacodynamics

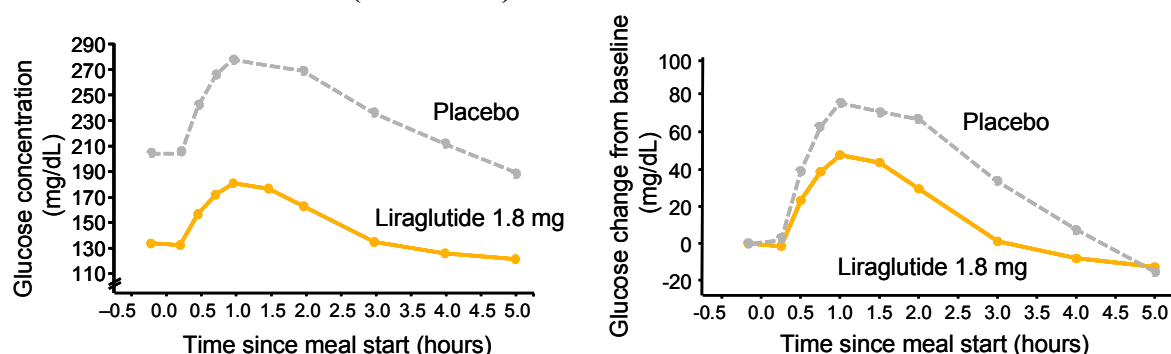
Liraglutide has a 24-hour duration of action, and improves glycemic control by lowering fasting and postprandial blood glucose in subjects with type 2 diabetes mellitus.

Trial 1698, a randomized, double-blind, placebo-controlled, two-period cross-over trial compared the effect of liraglutide 1.8 mg and placebo on postprandial glucose responses. Subjects with type 2 diabetes (N=18 males or females and age 48–70 years) were randomized to treatment with liraglutide or placebo for approximately three weeks, starting with 0.6 mg in the first week followed by 1.2 mg in the second week, and increasing to 1.8 mg in the third week. At the end of each week, 10 hours post dose administration, subjects received a standardized breakfast meal (2.0 MJ; 50 energy % (E%) carbohydrates, 35 E% fat and 15 E% protein). Postprandial glucose concentrations were measured for five hours.

Liraglutide reduced mean fasting glucose compared with placebo. The difference between liraglutide and placebo was 70 mg/dL for liraglutide 1.8 mg, 60 mg/dL for liraglutide 1.2 mg, and 52 mg/dL for liraglutide 0.6 mg. Following the standard meal, the mean 2-hour postprandial glucose concentration was 108 mg/dL lower with liraglutide 1.8 mg than with placebo ([Figure 5–1](#), left), 101 mg/dL for liraglutide 1.2 mg and 62 mg/dL for liraglutide 0.6 mg. Liraglutide 1.8 mg decreased incremental postprandial glucose excursion on average by 20 mg/dL ([Figure 5–1](#), right), 20 mg/dL for liraglutide 1.2 mg and 9 mg/dL for liraglutide 0.6 mg.

In summary, in addition to lowering fasting plasma glucose, liraglutide lowered postprandial glucose levels following a standard meal.

Figure 5–1 Mean Absolute (left) and Incremental (right) Postprandial Plasma Glucose Concentration in Subjects with Type 2 Diabetes treated with Liraglutide 1.8 mg or Placebo (Trial 1698)

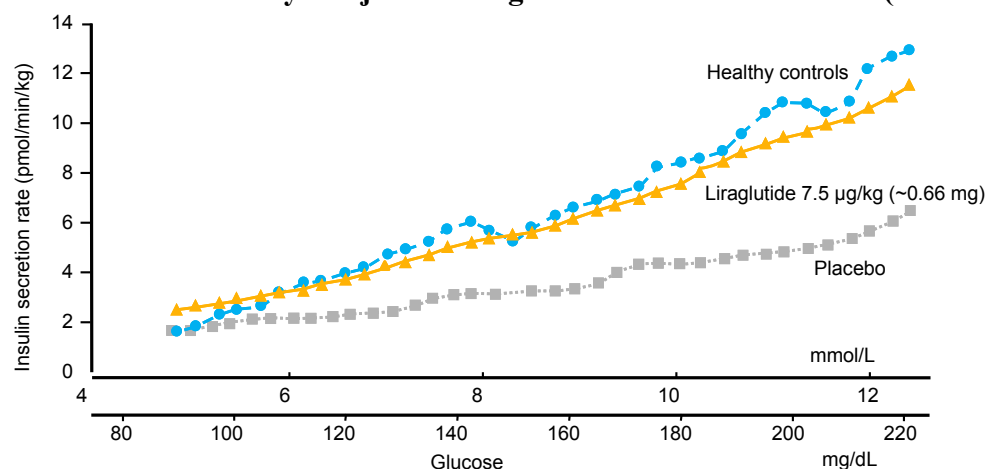


5.3.1 Glucose-Dependent Insulin Secretion

The effect of liraglutide on insulin secretion as a function of glucose concentrations was studied (Trial 2063). Using a step-wise graded glucose infusion, the insulin secretion rate progressively increased following a single dose of liraglutide administered 12 hours previously in subjects with type 2 diabetes (N=10), compared with placebo. The response in liraglutide-treated subjects with type 2 diabetes was not significantly different from that observed in untreated healthy subjects (N=10) (Figure 5–2). As illustrated in Figure 5–2, liraglutide induces insulin secretion only when blood glucose is elevated. This is consistent with data during clamp-induced hypoglycemia in the presence of liraglutide.

Taken together this supports the low risk of hypoglycemia associated with liraglutide.

Figure 5–2 Mean Insulin Secretion Rate vs. Glucose Concentration Following Single Dose 7.5 µg/kg (~0.66 mg) or Placebo in Subjects with Type 2 Diabetes and Untreated Healthy Subjects during Graded Glucose Infusion (Trial 2063)

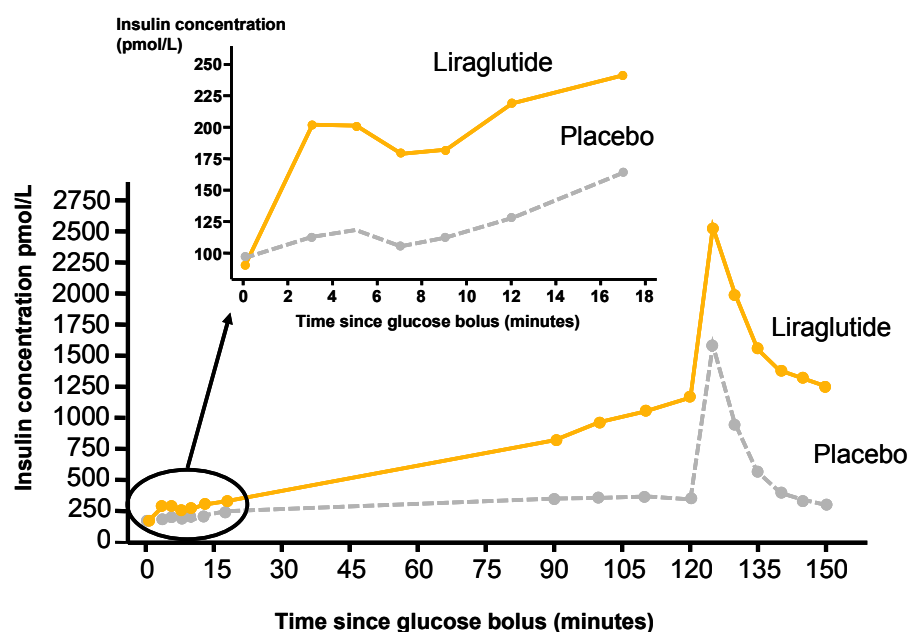


5.3.2 Beta-cell Function

Liraglutide improved beta-cell function as measured by first and second phase insulin response and maximal beta-cell secretory capacity. In one of the early trials in the development program (Trial 1332), a dose of 6 µg/kg (~0.55 mg) liraglutide per day for nine to 10 days was administered to subjects with type 2 diabetes (N=13). This demonstrated a restoration of first-phase insulin secretion (following intravenous bolus of glucose), improved second phase insulin secretion (during hyperglycemic clamp) and increased maximal insulin secretory capacity (assessed by arginine stimulation test) (Figure 5–3). Furthermore, this study also demonstrated that the pro-insulin/insulin ratio was decreased. Clinical trials of up to 52 weeks treatment with liraglutide have shown sustained improvement in beta-cell function as measured by the homeostasis model assessment for beta-cell function (HOMA-B) and the pro-insulin to insulin ratio (Section 6.9.1.5).

In Trial 1571, beta-cell function (HOMA) improved in all three liraglutide arms (liraglutide 0.65 mg, 1.25 mg and 1.90 mg) during the 14-week trial and the difference between active treatment and placebo was significant at all dose levels after 14 weeks. In contrast, insulin resistance was not affected at any dose level of liraglutide.

Figure 5–3 Mean Insulin Profiles During Glucose Bolus, Hyperglycemic Clamp and Arginine Stimulation Test Following 6 µg/kg (~0.55 mg) Liraglutide or Placebo for 10 Days in Subjects with Type 2 Diabetes (Trial 1332)



5.3.3 Glucagon Secretion

Liraglutide lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion (Trial 1332). Liraglutide did not impair the glucagon response to low glucose concentrations, thus demonstrating glucose dependence (Trial 1224).

In Trial 1332, it was shown that, with a low dose of liraglutide (6 µg/kg, corresponding to 0.55 mg per day) for 9–10 days, the fasting glucose level and the 24-hour glucose profile was decreased and also that the overall 24-hour glucagon levels and glucagon secretion after a protein rich meal were decreased.

In Trial 1224, mean glucagon secretion was measured at each of the 40-minute clamp steps with progressing hypoglycemia (78, 66, 54 and 42 mg/dL). Mean plasma glucagon increased by 1.5-fold with progressive hypoglycemia and there was no statistically significant difference between treatment with liraglutide or placebo (p=0.7590). The liraglutide dose used in this trial was 7.5 µg/kg leading to an average dose of 0.68 mg. The results from Trial 1224 led to the conclusion that liraglutide does not impair glucagon response.

6 Clinical Efficacy

6.1 Common Features of the Five Long-term Phase 3 Trials

All long-term phase 3 trials were randomized, double-blind, double-dummy, parallel-group, multi-center trials comparing liraglutide as monotherapy or combination therapy with relevant comparators ([Figure 1–1](#)). The specific design of the individual trials is presented in Section [6.8](#).

The target population for the five long-term phase 3 trials was subjects with type 2 diabetes who were not in adequate glycemic control on diet and exercise or following treatment with one or more OADs.

It is important to note that the treatment denoted ‘placebo’ in [Table 6–1](#) means that *no liraglutide* treatment was administered to this arm of the trial. However, placebo was added to the run-in treatment in that given trial. The run-in treatment was provided as study medication to create a stable baseline of therapy that would allow the comparison of liraglutide to placebo and/or another active comparator. Daily use at full doses of the run-in or background medication was required before randomization (Trial 1572: metformin 2 g for at least three weeks, Trial 1436: glimepiride 4 mg for at least two weeks, Trial 1574: metformin 2 g + rosiglitazone 8 mg for at least six weeks, and Trial 1697: glimepiride 4 mg + metformin 2 g for at least three weeks). Thus, placebo only infers that the subject did not receive liraglutide. To maintain the blinding of the trials, a double-dummy design was applied, except in Trial 1697, where insulin glargine was given unblinded.

Table 6–1 Overview of Treatment Regimens in the Five Long-term Phase 3 Trials

Trial	Number of Arms in Trial	Liraglutide Arms	Placebo Arm (=background therapy)	Active Comparator Arm		
Monotherapy (1573)	3	1.2 mg 1.8 mg	N/A	Glimepiride		
MET combination (1572)	5	0.6 mg 1.2 mg 1.8 mg	Metformin	Metformin+ Glimepiride		
SU combination (1436)	5	0.6 mg 1.2 mg 1.8 mg	Glimepiride	Glimepiride+ Rosiglitazone		
MET+TZD combination (1574)	3	1.2 mg 1.8 mg	Metformin+ Rosiglitazone	N/A		
MET+SU combination (1697)	3	1.8 mg	Metformin+ Glimepiride	Metformin+ Glimepiride+ Insulin glargine		
Drugs Details		1573	1572	1436	1574	1697
SU	Glimepiride	8 mg	4 mg	2–4 mg	N/A	2–4 mg
MET	Metformin	N/A	1.5–2.0 g	N/A	1.5–2.0 g	2.0 g
TZD	Rosiglitazone	N/A	N/A	4 mg	8 mg	N/A
Insulin glargine	Insulin glargine	N/A	N/A	N/A	N/A	Titrated
Placebo	Liraglutide placebo	N/A	+	+	+	+

Subjects were stratified with respect to previous diabetes treatment before the switch and titration to relevant background OAD study medication: diet/exercise treated vs. OAD monotherapy in Trial 1573 and OAD monotherapy vs. OAD combination therapy in Trials 1572, 1436 and 1697.

Thus, in some trials, a substantial proportion of subjects who previously had been on no pharmacological therapy (monotherapy Trial 1573) or subjects had been on one prior OAD (SU combination (Trial 1436) or MET combination (Trial 1572)). These sub-populations reflected a true 'add-on' therapy with liraglutide compared to substitution of liraglutide for a previous treatment. It is generally accepted, that adding a diabetes treatment on to prior therapy is more efficacious than substituting one therapy for another.³⁵

The liraglutide doses used were 0.6 mg, 1.2 mg and 1.8 mg s.c. for once-daily administration. To mitigate gastrointestinal symptoms related to initiation of treatment, a step-wise titration scheme was employed. All subjects initiated treatment at liraglutide 0.6 mg, increasing to 1.2 mg after one week and to 1.8 mg after one additional week, according to the dose level to which they were randomized.

Four of the trials had a primary duration of 26 weeks and one trial (Trial 1573) had a duration of 52 weeks. Two of the long-term phase 3 trials were extended by open-label treatment periods. Trial 1573 is being extended to a total of five years and Trial 1572 was extended to a total of two years. Subjects continuing in the extension phases of the trials remained on the treatment to which they were originally randomized.

6.2 Enrolment Criteria

Screening Criteria Related to Diabetes

To be eligible for participation in the trials, the subjects had to have a level of glycemic control that would prompt more aggressive therapy, according to accepted treatment guidelines as measured by HbA_{1c}. After screening, subjects discontinued their previous treatment and initiated a forced titration with the relevant oral antidiabetic treatment to be used as background therapy throughout the trial. Following this titration period, the subjects were treated with the maximum doses of the relevant OADs for two up to six weeks, depending on the trial prior to randomization. In the monotherapy Trial 1573, the subjects did not undergo a titration and maintenance treatment period prior to randomization.

Randomization Criteria Related to Diabetes

Following the maintenance period, subjects were eligible for randomization if the glycemic control was still inadequate as assessed by elevated fasting plasma glucose. The randomization criteria are presented in Section [6.8](#) along with the individual trial designs. The time of randomization and the status of the subject at that point in time are defined as the baseline of the trials.

Other Inclusion and Exclusion Criteria

Most of the inclusion and exclusion criteria were the same in all five long-term phase 3 trials and are listed in [Table 6-2](#). With respect to previous antidiabetic therapy and baseline HbA_{1c}, the inclusion criteria differed among trials, reflecting the different stages of type 2 diabetes being studied. These inclusion criteria are presented by trial in the individual trial descriptions in Section [6.8](#).

Table 6–2 Inclusion and Exclusion Criteria in the Five Long-term Phase 3 Trials

Inclusion Criteria^(a)
<ul style="list-style-type: none"> • Informed consent obtained before any trial-related activities • Diagnosed with type 2 diabetes mellitus • Age 18–80 years (both included) • Body mass index $\leq 45.0 \text{ kg/m}^2$ ($\leq 40.0 \text{ kg/m}^2$ in Trial 1572)
Exclusion Criteria
<ul style="list-style-type: none"> • Previous participation in the randomized phase of the trial • Treatment with insulin within the last three months prior to trial • Impaired liver function, defined as alanine aminotransferase or aspartate aminotransferase (the latter only included in Trials 1573 and 1574) ≥ 2.5 times upper limit of normal based on analysis from central laboratory • Impaired renal function, defined as serum creatinine $\geq 125 \text{ } \mu\text{mol/L}$ ($\geq 1.4 \text{ mg/dL}$) for males and $\geq 110 \text{ } \mu\text{mol/L}$ ($\geq 1.24 \text{ mg/dL}$) for females based on analysis from central laboratory • Clinically significant, active (over the past 12 months) disease of the gastrointestinal, pulmonary, neurological, genitourinary or hematological system that might confound the results of the study or pose additional risk in administering the study drug • Clinically significant active cardiovascular disease including history of myocardial infarction within the past six months and/or heart failure (New York Heart Association class III and IV, and for Trial 1436 NYHA class I-IV) • Proliferative retinopathy or maculopathy requiring acute treatment • Uncontrolled treated/untreated hypertension (systolic blood pressure $\geq 180 \text{ mmHg}$ and/or diastolic blood pressure $\geq 100 \text{ mmHg}$) • Subjects known to be Hepatitis B surface antigen or Hepatitis C antibody positive • Cancer (except basal cell skin cancer or squamous cell skin cancer) or any clinically significant disease or disorder, except for conditions associated to type 2 diabetes, which could interfere with the results of the trial • Recurrent major hypoglycemia or hypoglycemic unawareness (not an exclusion criterion in Trial 1572) • Known or suspected allergy to trial product(s) or related products • Use of any drug (except for OADs), which could interfere with glucose levels (e.g. systemic corticosteroids) • Receipt of any investigational drug within four weeks prior to this trial • Known or suspected abuse of alcohol or narcotics • Mental incapacity, unwillingness or language barrier precluding adequate understanding or cooperation • Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods (adequate contraceptive measures as required by local law or practice) • Any contraindications to concomitant OAD and/or insulin treatment

^a For inclusion criteria related to diabetes therapy and baseline HbA_{1c} see Section [6.2](#) and [6.8](#).

6.3 Withdrawal Criteria

In the five long-term phase 3 trials, subjects could choose to withdraw from the trial at any time. They could be withdrawn from the trial at the discretion of the investigator or the sponsor, if judged non-compliant with trial procedures or due to a safety concern. Subjects were also withdrawn if they became pregnant or intended to become pregnant.

In addition, subjects were withdrawn if the glycemic control was inadequate (based on pre-defined fasting plasma glucose levels) at defined time points during the trials, or if the subjects used less background OAD treatment than defined in the protocols.

6.4 Objectives and Endpoints

Glycosylated hemoglobin A1c (HbA_{1c}) is the most widely accepted measure of overall, long-term blood glucose control in type 1 and type 2 diabetes mellitus and a surrogate marker for microvascular complications. The **primary regulatory efficacy endpoint** for all of the long-term phase 3 trials was therefore change in HbA_{1c} from baseline to end of treatment.

Glycemic control was further investigated by assessment of secondary endpoints including fraction of subjects reaching HbA_{1c} target < 7%, fasting plasma glucose and postprandial plasma glucose.

The five trials included other secondary endpoints to evaluate the impact of liraglutide (and comparator agents) on beta-cell function over time. Examining beta-cell function and insulin resistance is important for understanding the effect of liraglutide in subjects with type 2 diabetes mellitus. In the five long-term phase 3 trials, beta-cell function and insulin resistance were assessed by fasting pro-insulin to insulin. A homeostasis model assessment (HOMA) of indices of beta-cell function and insulin resistance was derived from fasting plasma glucose and fasting insulin (HOMA-B and HOMA-IR). Elevated pro insulin to insulin ratio is a marker of abnormal beta-cell function in subjects with type 2 diabetes.

In the monotherapy Trial 1573, the slope of increase in HbA_{1c} after nadir was assessed in a subset of subjects. The slope of increase in the HbA_{1c} after nadir assesses the progressive loss of glycemic control and is assumed to reflect the long-term effect of treatment on beta-cell function.

Results from early trials demonstrated that treatment with liraglutide is not associated with weight gain but is associated with weight loss. Change in body weight was therefore a secondary efficacy endpoint in all five long-term phase 3 trials.

For a more detailed description of the power calculations, see [Appendix, Section 2](#) (Statistical Methodology).

Increased blood pressure, a well established risk factor for cardiovascular disease, and in particular increase in systolic blood pressure, is common among patients with type 2 diabetes mellitus. Changes in systolic and diastolic blood pressure from baseline to end of treatment were investigated as secondary endpoints. In the context of this Briefing Document, systolic blood pressure will be described in the Safety Section.

Effects on biochemical markers potentially associated with cardiovascular morbidity were assessed in the five long-term phase 3 trials, using a set of biomarkers for cardiovascular disease: highly sensitive C-reactive protein (hsCRP) and plasminogen activator inhibitor 1 (PAI-1), and for congestive heart failure: N terminal prohormone brain natriuretic peptide (NT-proBNP or brain natriuretic peptide, BNP).

As hyperlipidemia and dyslipidemia are linked to heart disease and other cardiovascular disorders, changes in fasting lipid profiles were investigated in all five trials. The lipids evaluated were total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), free fatty acids (FFA) and apolipoprotein B (ApoB).

As in any drug development program, safety was a key objective in all trials. The safety endpoints included adverse events, hypoglycemia, antibody development and safety laboratory assessments. All laboratory endpoints were assessed using standard methods and one central laboratory facility was used.

The design of each of the five long-term phase 3 trials is presented in Section 6.8.

6.5 Overview of Exposure

In general, all efficacy presentations are based on the individual long-term phase 3 trial database as used in the original NDA. For safety presentations, the largest possible population is generally applied, namely the 120-day Safety Update clinical database. A more detailed description of the populations referenced in this Briefing Document is found in the [Appendix, Section 1.2 \(Table 1-1\)](#). Exposure in these populations is presented in [Table 6-3](#). Tables with exposure by duration of treatment and by dose of liraglutide are presented in the [Appendix, Section 1.3](#).

Table 6-3 Exposure to Liraglutide and Comparators

	Total Liraglutide ^(a) N (Exp ^(c))	Placebo N (Exp ^(c))	Active Comparator N (Exp ^(c))	Total Comparators ^(b) N (Exp ^(c))
Population 1				
All Intermediate and Long-term Trials ^(d)	4257 (3125.9)	907 (474.4)	1474 (1118.7)	2381 (1593.1)
Population A1				
All Double-blind, Completed Intermediate and Long-term Trials	4022 (1771.8)	907 (328.2)	853 (459.4)	1760 (787.6)
Population A2				
All Completed Intermediate and Long-term Trials	4257 (1879.5)	907 (328.2)	1474 (717.6)	2381 (1045.7)
Population B				
Population A2 + open-label extensions	4257 (2882)	907 (448.8)	1474 (1037.6)	2381 (1486.4)
Population 2				
Completed Trials	4655 (2434.4)	1210 (390.6)	1297 (843.2)	2492 (1233.8)
Population 3				
Trials 1573, 1572, 1436, 1574, 1697, 1797, 1700, 1701 and NN8022-1807	3551 (2514.2)	710 (374.7)	1412 (964.7)	2122 (1339.4)
Population 4				
Completed Long-term NDA Phase 3 Trials (Blinded and Open-label Part)	2501 (1934.6)	524 (265.0)	953 (737.8)	1477 (1002.8)

For definitions of populations, see [Appendix, Table 1-1](#). ^a All doses. ^b Placebo and active comparators. ^c Exp: number of subject years of exposure is defined as duration of exposure divided by 365.25. ^d For Trials 1573, 1572 and NN8022-1807, last drug date is estimated as 30 May 2008 if not available in the clinical database.

6.6 Demographics and Baseline Characteristics in the Five Long-term Phase 3 trials

The completed trials were conducted world-wide in more than 40 countries. Based on the intermediate and long-term trials, approximately 44%, 13% and 21% of the subjects were from trials conducted in Europe, Japan and the US, respectively, and 22% of the subjects were from trials conducted in other countries. Trials 1573 and 1574 were conducted in the US and Canada and for Trial 1573, Mexico as well. Trials 1572, 1436 and 1697 were conducted in 37 countries worldwide, outside of North America.

The demographics and diabetes characteristics are presented by trial in [Table 6–4](#) and [Table 6–5](#), respectively.

The mean age across the five long-term phase 3 trials ranged between 53 and 58 years, and in the two North American trials (Trials 1573 and 1574), approximately 15% were more than 65 years of age. Average duration of type 2 diabetes was five to nine years, and approximately one third of the population was either diet/exercise treated or on monotherapy at the time of enrolment into the liraglutide clinical development program. The BMI ranged from 30 to 33 kg/m² at baseline and mean HbA_{1c} was from 8.2 to 8.5%.

In the two North American long-term phase 3 trials, Trials 1573 and 1574, the percentages of Hispanics were 35.0% and 15.3%, respectively. The percentages of African Americans in these two trials were 12.6% and 11.7%.

The demography of the study population in the five long-term phase 3 trials is comparable with the US type 2 diabetes population, as described in a recent publication from a US epidemiology study, the NHANES study.³⁶ In the NHANES study, around 45% of the studied population was between 45 and 64 years old, and approximately 35% were above 65 years of age. The Hispanic and African American percentages of the studied population were both approximately 15%. The population was split almost equally between having had type 2 diabetes for <5 years, between 5–14 years and >15 years. Approximately half of the population had a BMI <30 kg/m².

Table 6–4 Baseline Demographics in the Five Long-term Phase 3 Trials

	Trial 1573 Mono	Trial 1572 MET Combi	Trial 1436 SU Combi	Trial 1574 MET+TZD Combi	Trial 1697 MET+SU Combi	TOTAL
Safety Analysis Set	745	1087	1040	530	576	3978
Sex, N (%)						
Male	371 (49.8)	633 (58.2)	513 (49.3)	295 (55.7)	325 (56.4)	2137 (53.7)
Female	374 (50.2)	454 (41.8)	527 (50.7)	235 (44.3)	251 (43.6)	1841 (46.3)
Age (years)						
N	745	1087	1040	530	576	3978
Mean (SD)	53.0 (10.9)	56.7 (9.5)	56.1 (9.8)	55.1 (10.2)	57.6 (9.9)	55.8 (10.1)
Min ; Max	19.0 ; 79.0	25.0 ; 79.0	24.0 ; 80.0	23.0 ; 80.0	24.0 ; 80.0	19.0 ; 80.0
[18;65[638 (85.6)	847 (77.9)	828 (79.6)	438 (82.6)	430 (74.7)	3181 (80.0)
≥ 65	107 (14.4)	240 (22.1)	212 (20.4)	92 (17.4)	146 (25.3)	797 (20.0)
≥ 75	20 (2.7)	30 (2.8)	26 (2.5)	16 (3.0)	21 (3.6)	113 (2.8)
Ethnicity, N (%)						
N	745 (100.0)	N/A	N/A	530 (100.0)	N/A	1275 (100.0)
Hispanic/Latino	261 (35.0)	N/A	N/A	81 (15.3)	N/A	342 (26.8)
Not Hispanic/Latino	484 (65.0)	N/A	N/A	449 (84.7)	N/A	933 (73.2)
Race, N (%)						
White	577 (77.4)	946 (87.0)	669 (64.3)	440 (83.0)	435 (75.5)	3067 (77.1)
Native Hawaiian /Asian / Pacific Islander	28 (3.8)	98 (9.0)	337 (32.4)	9 (1.7)	87 (15.1)	559 (14.1)
Black/African American	94 (12.6)	26 (2.4)	29 (2.8)	62 (11.7)	21 (3.6)	232 (5.8)
Other	46 (6.2)	17 (1.6)	5 (0.5)	15 (2.8)	5 (0.9)	88 (2.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (4.9)	28 (0.7)
American Indian/ Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	4 (0.1)
Weight at Screening (kg)						
N	745	1085	1039	530	574	3973
Mean (SD)	92.7 (19.6)	88.6 (17.3)	81.6 (17.5)	96.3 (18.6)	85.5 (18.2)	88.1 (18.8)
Min ; Max	46.7 ;163.3	42.0 ;151.0	40.3 ;138.1	52.4 ;160.6	45.6 ;149.5	40.3 ;163.3
BMI (kg/m²)						
N	745	1084	1037	530	574	3970
Mean (SD)	33.0 (5.8)	31.0 (4.7)	29.9 (5.1)	33.3 (5.2)	30.5 (5.2)	31.3 (5.3)
Min ; Max	20.6 ; 47.8	17.0 ; 41.4	17.5 ; 45.5	19.6 ; 46.1	17.0 ; 45.2	17.0 ; 47.8
BMI <25 kg/m ²	55 (7.4)	106 (9.8)	178 (17.1)	28 (5.3)	82 (14.2)	449 (11.3)
25≤ BMI <30 kg/m ²	196 (26.3)	367 (33.8)	392 (37.7)	122 (23.0)	205 (35.6)	1282 (32.2)
30≤ BMI <35 kg/m ²	241 (32.3)	371 (34.1)	298 (28.7)	195 (36.8)	179 (31.1)	1284 (32.3)
BMI ≥35 kg/m ²	253 (34.0)	240 (22.1)	169 (16.3)	185 (34.9)	108 (18.8)	955 (24.0)

Table is based on individual trials from Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1–1](#). For complete treatment regimens in the individual trials, see [Table 6–1](#). Ethnicity is only applicable for Trials 1573 and 1574. Patients from France did not provide race which is displayed as missing. Race: Asian/Native Hawaiian/Pacific Islander refer to either Asian/Pacific Islander in 1572, 1436 and 1697 or Native Hawaiian/Pacific Islander in 1573 and 1574.

Table 6–5 Baseline Diabetes Characteristics in the Five Long-term Phase 3 Trials

	Trial 1573 Mono	Trial 1572 MET Combi	Trial 1436 SU Combi	Trial 1574 MET+TZD Combi	Trial 1697 MET+SU Combi	TOTAL
Safety Analysis Set	745	1087	1040	530	576	3978
Duration of Diabetes (years)						
N	745	1087	1040	530	576	3978
Mean (SD)	5.4 (5.3)	7.4 (5.2)	7.9 (5.4)	9.0 (5.6)	9.4 (6.2)	7.7 (5.6)
Median	3.8	6.5	6.6	7.9	8.4	6.5
Min ; Max	0.2 ; 40.3	0.3 ; 40.6	0.1 ; 32.6	0.3 ; 36.7	0.4 ; 43.5	0.1 ; 43.5
HbA_{1c} at randomization (%)						
N	745	1078	1023	530	574	3950
Mean (SD)	8.2 (1.1)	8.4 (1.0)	8.4 (1.0)	8.5 (1.2)	8.2 (0.9)	8.4 (1.0)
Median	8.0	8.3	8.4	8.3	8.2	8.2
Min ; Max	4.9 ; 11.7	4.8 ; 12.9	6.1 ; 13.2	6.1 ; 12.8	5.2 ; 10.9	4.8 ; 13.2
Previous Anti-diabetic treatment N (%)						
Diet	272 (36.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	272 (6.8)
Combination therapy	0 (0.0)	703 (64.7)	725 (69.7)	440 (83.0)	543 (94.3)	2411 (60.6)
Mono-therapy	473 (63.5)	384 (35.3)	315 (30.3)	90 (17.0)	33 (5.7)	1295 (32.6)

Table is based on individual trials from Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1–1](#). For complete treatment regimens in the individual trials, see [Table 6–1](#).

6.7 Subject Disposition

The subject disposition from the main (blinded) part of the five long-term phase 3 trials is presented in [Table 6–6](#). The table also presents the subject disposition for subjects participating in the open-label extension parts of Trials 1573 and 1572. The percentage of subjects completing the trials was comparable between liraglutide (82% for total liraglutide) and comparator treatments (78%).

For Trials 1573 and 1572, slightly more subjects treated with liraglutide completed the 12-month open-label extension (81%) as compared to total comparators (74%). The reason for withdrawal in the open-label extension was mainly ineffective therapy, and the percentage was slightly higher in subjects treated with comparators than with liraglutide. It should be noted that the fraction of subjects ‘completing’ at 18 months is the fraction of subjects having completed the 18 months visit by the 21st February 2008 cut-off date and does not take into consideration subjects being between 12 and 18 months into the studies at this time point.

The subject disposition of the intermediate and long-term trials is presented in [Table 6–7](#). The picture did not differ significantly from the numbers seen for the long-term phase 3 trials alone ([Table 6–6](#)).

Table 6–6 Subject Disposition in the Five Long-term Phase 3 Trials (Main Part and Open-label Extensions)

	Liraglutide 0.6 mg		Liraglutide 1.2 mg		Liraglutide 1.8 mg		Total Liraglutide		Placebo		Active Comparator		Total Comparators	
	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Main (Blinded) Part ^(a)														
Randomized		475		898		1133		2506		528		958		1486
Exposed		475		896		1130		2501		524		953		1477
Safety Analysis Set	100.0	475	100.0	896	100.0	1130	100.0	2501	100.0	524	100.0	953	100.0	1477
Withdrawals – Main (Blinded) Part	12.42	59	20.98	188	18.85	213	18.39	460	28.63	150	18.68	178	22.21	328
Adverse Events	3.37	16	7.70	69	8.23	93	7.12	178	2.86	15	3.67	35	3.39	50
Non-compliance	1.05	5	2.68	24	1.95	22	2.04	51	2.10	11	1.99	19	2.03	30
Ineffective Therapy	6.53	31	3.79	34	3.01	34	3.96	99	17.37	91	5.25	50	9.55	141
Other	1.47	7	6.81	61	5.66	64	5.28	132	6.30	33	7.76	74	7.24	107
Completers – Main (Blinded) Parts ^(a)	87.58	416	79.02	708	81.15	917	81.61	2041	71.37	374	81.32	775	77.79	1149
	Liraglutide 0.6 mg		Liraglutide 1.2 mg		Liraglutide 1.8 mg		Total Liraglutide		Placebo		Active Comparator		Total Comparators	
	%	N	%	N	%	N	%	N	%	N	%	N	%	N
Open-label Extension ^(b) - Safety Analysis Set	38.74	184	36.50	327	29.03	328	33.55	839	11.64	61	33.58	320	25.80	381
Withdrawals - Open-label Ext	21.74	40	14.07	46	16.46	54	16.69	140	40.98	25	21.88	70	24.93	95
Adverse Events	2.72	5	2.14	7	1.83	6	2.15	18	1.64	1	1.56	5	1.57	6
Non-compliance	2.72	5	1.83	6	1.22	4	1.79	15	0.0	0	1.56	5	1.31	5
Ineffective Therapy	11.96	22	7.65	25	7.62	25	8.58	72	31.15	19	13.44	43	16.27	62
Other	4.35	8	2.45	8	5.79	19	4.17	35	8.20	5	5.31	17	5.77	22
Total														
Completers - 12 months ^(c)	92.93	171	76.92	330	80.24	337	81.12	838	78.69	48	73.78	318	74.39	366
Completers - 18 months ^(d)	59.78	110	61.16	200	57.01	187	59.24	497	47.54	29	52.50	168	51.71	197

Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1–1](#). ^a Main refers to the blinded part of the trial (for Trials 1573 and 1572 which had an open-label extension). ^b Open-label extension of Trials 1573 and 1572 until 21st February 2008 (trials are still ongoing). ^c Trial 1573 – Main (blinded) + Trial 1572 Subjects in open-label extension treated for at least 350 days. ^d Trial 1573 and 1572: Subjects in open-label extension treated for at least 536 days. %: Proportion of subjects out of Safety Analysis Set (defined as all randomized subjects who were exposed to at least one dose of trial product(s)). Under ‘open-label extension’, % refers to proportion of exposed subjects in Trial 1573-Main + Trial 1572 open-label extension.

Table 6–7 Subject Disposition in All Intermediate and Long-Term Trials

	Total Liraglutide		Total Comparator	
	%	N	%	N
Main (Blinded) Part				
Randomized		4273		2398
Exposed		4257		2381
Safety Analysis Set	100.00	4257	100.0	2381
Withdrawals - Main Trial	15.32	652	19.87	473
Adverse Event	6.08	259	4.24	101
Ineffective Therapy	3.17	135	7.48	178
Non-compliance With Protocol	1.69	72	1.76	42
Withdrawal Criteria	0.02	1	0.04	1
Other	4.35	185	6.34	151
Completers - Main Trial	84.68	3605	80.13	1908
Open-label Extension - Safety Analysis Set	35.56	1103	29.65	706
Withdrawals - Open-label Extension	16.18	245	22.10	156
Adverse Event	2.97	45	1.98	14
Ineffective Therapy	6.67	101	12.46	88
Non-compliance With Protocol	1.25	19	1.13	8
Other	5.28	80	6.52	46
Total				
Completers - 12 months	85.66	1464	80.66	659
Completers - 18 months	46.43	703	41.08	290

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1–1](#). %: Proportion of subjects out of Safety Analysis Set (defined as all randomized subjects who were exposed to at least one dose of trial product(s)). Under ‘open-label extension’, % refers to proportion of exposed subjects in the open-label extensions of Trial 1572, 1573, NN8022-1807, 1700 and 1701.

6.8 Trial by Trial Summary of the Five Long-term Phase 3 Trials

The individual study results of the five long-term phase 3 trials are summarized in this section. Results from the trials are based on the main (blinded) part of the trials, as in the NDA.

Specifics on objectives and endpoints for each trial are presented in this section and more generally in Section [6.4](#). Demographics are summarized per trial in Section [6.6](#) and overall subject disposition is presented in Section [6.7](#).

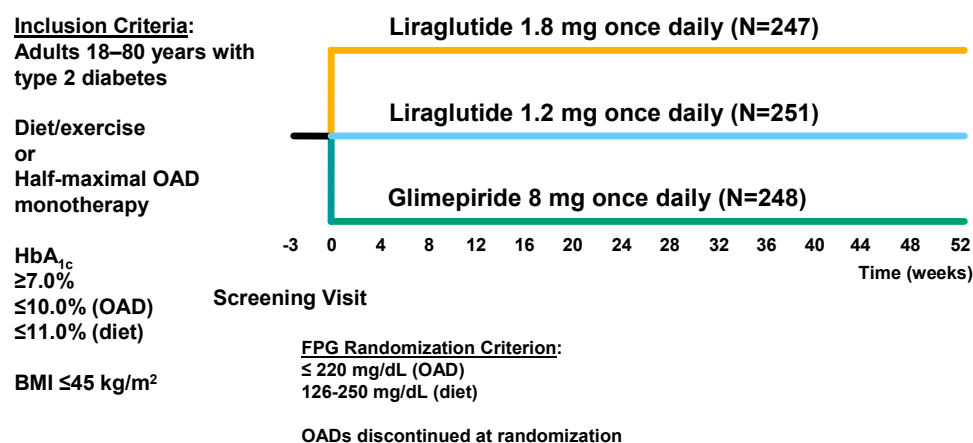
A summary of results across all of the five long-term phase 3 trials is presented in Section [6.9](#).

6.8.1 Liraglutide as Monotherapy vs. Glimepiride (Monotherapy, Trial 1573)

Study Title: Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on glycemic control of liraglutide vs. glimepiride in type 2 diabetes. A fifty-two, double-blind, multi-center, randomized, parallel study to investigate safety and efficacy, with a 48-month controlled extension period.

Study Design: For a graphical presentation of the main part (52 weeks) of the trial, see [Figure 6-1](#).

Figure 6-1 Liraglutide as Monotherapy vs. Glimepiride (Monotherapy, Trial 1573)



N=subjects randomized.

Completion rate: A total of 65%, 70% and 61% of randomized subjects completed the trial in the liraglutide 1.2 mg, liraglutide 1.8 mg and glimepiride groups, respectively. Withdrawal was slightly higher in Trial 1573, which was of 52 weeks duration as compared to the other long-term trials, which were of 26 weeks duration.

Endpoints: HbA_{1c} (primary), body weight, glycemic control (FPG, PPG profiles), beta-cell function, blood pressure, lipid profile, cardiovascular biomarkers and waist and hip circumference.

Efficacy Results: Results are presented in [Table 6-8](#) and [Table 6-9](#). A plot of mean HbA_{1c} over time is presented in [Figure 6-2](#) and a plot of mean change in body weight over time is presented [Figure 6-3](#).

Table 6–8 Summary of the Predefined Primary and Secondary Endpoints at 52 Weeks (Monotherapy, Trial 1573)

Group	ΔHbA _{1c} % points (SEM)	Percentage of subjects reaching HbA _{1c} < 7% (SEM)	ΔFPG mg/dL (SEM)	ΔPPG mg/dL (SEM)	ΔBody weight kg (SEM)
Liraglutide 1.2 mg	-0.84* (0.080)	42.80* (0.132)	-15.2* (3.498)	-30.8 (3.40)	-2.05* (0.281)
Liraglutide 1.8 mg	-1.14* (0.081)	50.85* (0.131)	-25.6* (3.499)	-37.4* (3.37)	-2.45* (0.282)
Active comparator (glimepiride)	-0.51 (0.077)	27.80 (0.144)	-5.29 (3.331)	-24.5 (3.32)	1.12 (0.269)

*Liraglutide significantly better than active comparator. SEM: standard error of the mean. Means and percentages in the table are estimated values (changes from baseline). For subjects reaching HbA_{1c} < 7% points at end of trial, the estimated mean percentage is presented.

Table 6–9 Summary of Secondary Efficacy Endpoints (Monotherapy, Trial 1573)

Group	ΔSystolic blood pressure	Beta-cell function			Lipid Profile		Cardiovascular Biomarkers	
	mmHg (SEM)	ΔHOMA- IR % (SEM)	ΔHOMA-B % (SEM)	ΔSlope of increase in HbA _{1c} after nadir	ΔHDL-C mg/dL (SEM)	ΔTG mg/dL (SEM)	ΔNT- proBNP pg/mL (SEM)	ΔhsCRP mg/L (SEM)
Liraglutide 1.2 mg	-2.12 (0.904)	-0.654* (0.519)	31.14 (53.59)	0.0053 (0.0023)	-3.827 (0.561)	-7.553 (11.349)	62.235 (23.023)	-0.866 (0.647)
Liraglutide 1.8 mg	-3.64* (0.911)	-1.354* (0.524)	30.00 (54.13)	0.0037 (0.0023)	-3.883 (0.564)	-14.402 (11.373)	21.921 (23.788)	-1.480 (0.639)
Active comparator (glimepiride)	-0.69 (0.873)	0.845 (0.497)	124.7 (51.45)	0.0054 (0.0024)	-3.943 (0.545)	2.263 (10.823)	32.428 (22.629)	-0.778 (0.621)

*Liraglutide significantly better than active comparator. SEM: standard error of the mean. Means and percentages in the table are estimated values (changes from baseline). Reduction in HOMA-IR and increase in HOMA-B are beneficial.

Figure 6–2 HbA_{1c} over Time (Mean±2SEM), ITT population (Monotherapy, Trial 1573)

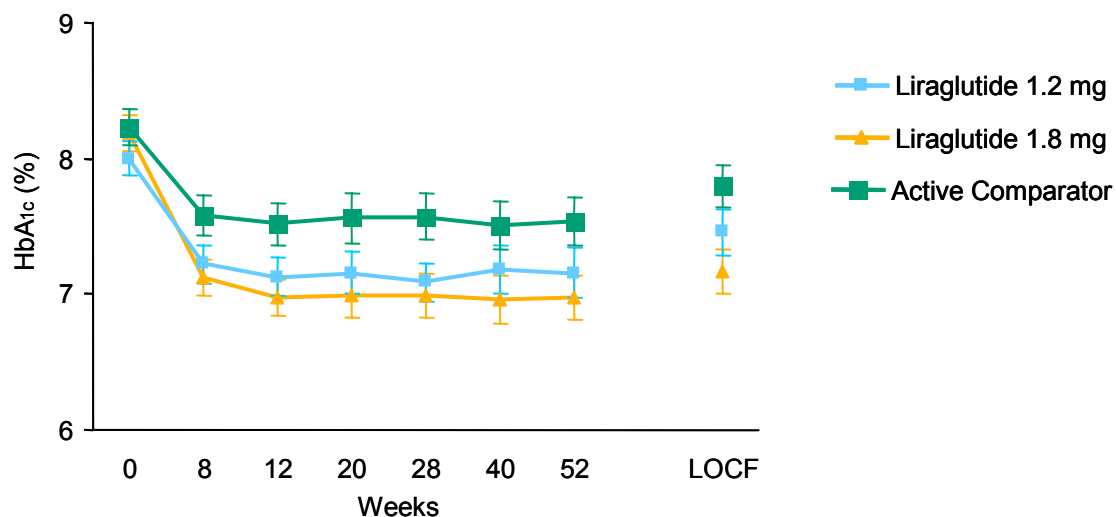
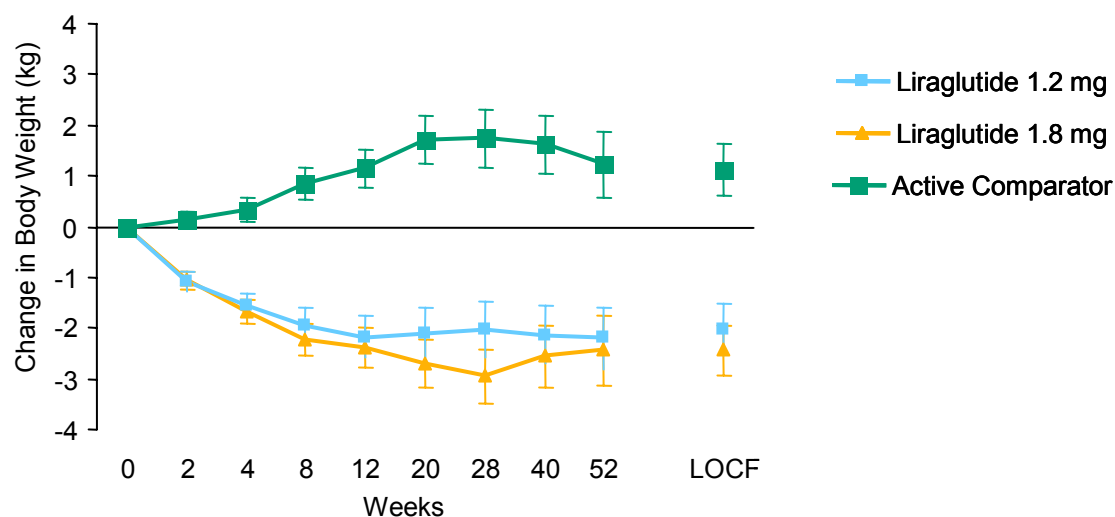


Figure 6–3 Change in Body Weight over Time (Mean±2SEM), ITT population, (Monotherapy, Trial 1573)

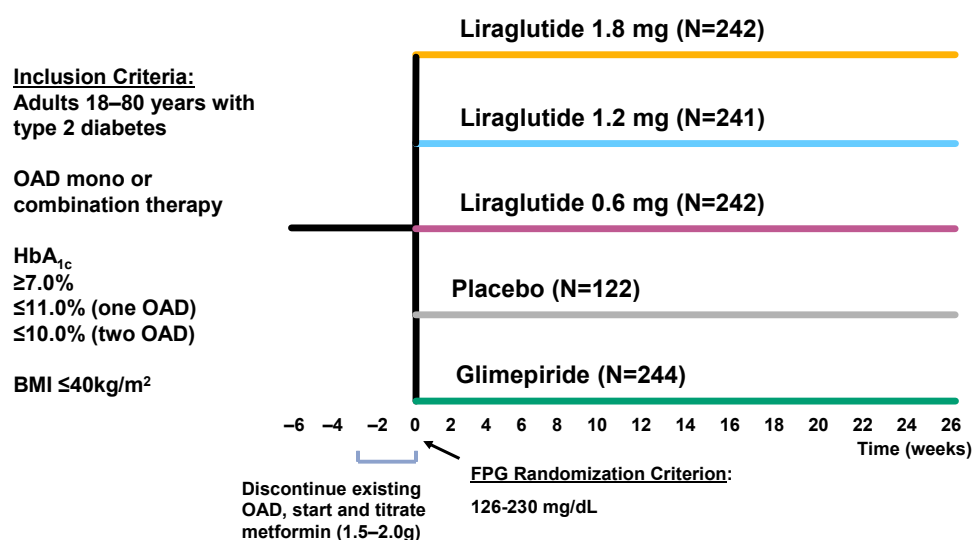


6.8.2 Liraglutide Combination with Metformin vs. Metformin and Glimepiride (MET combination, Trial 1572)

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

Study Design: For a graphical presentation of the main part (six months) of the trial, see [Figure 6-4](#).

Figure 6-4 Liraglutide in Combination with Metformin vs. Metformin and Glimepiride (MET combination, Trial 1572)



N=subjects randomized.

Completion rates: A total of 86%, 82%, 79%, 61% and 86% of randomized subjects completed the trial in the liraglutide 0.6 mg + metformin, liraglutide 1.2 mg + metformin, liraglutide 1.8 mg + metformin, placebo + metformin and glimepiride + metformin groups, respectively.

Endpoints: HbA_{1c} (primary), body weight, glycemic control (FPG, PPG profiles), beta-cell function, blood pressure, lipid profiles, cardiovascular biomarkers, waist and hip circumference, DEXA scan (sub-study) and CT scan (sub-study).

Efficacy Results: Results are presented in [Table 6-10](#) and [Table 6-11](#). A plot of mean HbA_{1c} over time is presented in [Figure 6-5](#) and a plot of mean change in body weight over time is presented in [Figure 6-6](#).

Table 6–10 Summary of the Predefined Primary and Secondary Endpoints (MET combination, Trial 1572)

Group	Δ HbA _{1c} % points (SEM)	Percentage of subjects reaching HbA _{1c} < 7% (SEM)	Δ FPG mg/dL (SEM)	Δ PPG mg/dL (SEM)	Δ Body weight kg (SEM)
Liraglutide 0.6 mg	-0.70†/** (0.067)	28.03‡/** (0.144)	-20.3** (2.789)	-30.24‡/** (2.91)	-1.78* (0.231)
Liraglutide 1.2 mg	-0.97** (0.069)	35.34** (0.137)	-29.4** (2.864)	-42.00** (3.02)	-2.58**/** (0.237)
Liraglutide 1.8 mg	-1.00** (0.066)	42.37** (0.132)	-30.3** (2.787)	-46.21** (2.97)	-2.79**/** (0.228)
Placebo (placebo+ metformin)	0.08 (0.090)	10.83 (0.294)	7.24 (3.814)	-11.09 (4.26)	-1.51 (0.313)
Active comparator (glimepiride+metformin)	-0.99 (0.068)	36.32 (0.136)	-23.5 (2.823)	-44.30 (2.95)	0.95 (0.235)

*Liraglutide significantly better than active comparator. **Liraglutide significantly better than placebo. ‡ Active comparator significantly better than liraglutide. SEM: standard error of the mean. Liraglutide 0.6, 1.2 and 1.8 mg: all given with metformin. Means and percentages in the table are estimated values (changes from baseline). For subjects reaching HbA_{1c} < 7% at end of trial, the estimated mean percentage is presented.

Table 6–11 Summary of Secondary Efficacy Endpoints (MET combination, Trial 1572)

Group	Δ Systolic blood pressure	Beta-cell function		Lipid Profile		Cardiovascular Biomarker	
	mmHg (SEM)	Δ HOMA-IR (%) (SEM)	Δ HOMA-B (%) (SEM)	Δ HDL-C mg/dL (SEM)	Δ TG mg/dL (SEM)	Δ NT- proBNP pmol/L (SEM)	Δ hsCRP mg/dL (SEM)
Liraglutide 0.6 mg	-0.58 (0.841)	-0.01 (0.26)	20.45** (5.188)	0.14 (0.51)	-19.62** (8.34)	0.30 (0.73)	0.04 (0.78)
Liraglutide 1.2 mg	-2.81* (0.863)	-0.36 (0.26)	20.33** (5.340)	0.29** (0.53)	-25.38** (8.58)	0.00 (0.76)	0.03 (0.81)
Liraglutide 1.8 mg	-2.29* (0.831)	-0.22 (0.26)	26.12** (5.198)	-0.56 (0.51)	-24.59** (8.29)	0.89 (0.73)	0.12 (0.77)
Placebo (placebo+ metformin)	-1.76 (1.139)	0.35 (0.36)	-1.63 (7.193)	-1.80 (0.71)	15.56 (11.54)	-0.13 (1.01)	2.82 (1.06)
Active comparator (glimepiride+ metformin)	0.41 (0.848)	0.36 (0.26)	24.68 (5.254)	-0.89 (0.52)	-14.52 (8.41)	1.52 (0.74)	0.48 (0.79)

*Liraglutide significantly better than active comparator. **Liraglutide significantly better than placebo. SEM: standard error of the mean. Liraglutide 0.6, 1.2 and 1.8 mg: all given with metformin. Means and percentages in the table are estimated values (changes from baseline). Reduction in HOMA-IR and increase in HOMA-B are beneficial.

Figure 6–5 HbA_{1c} over Time (Mean±2SEM), ITT population (MET combination, Trial 1572)

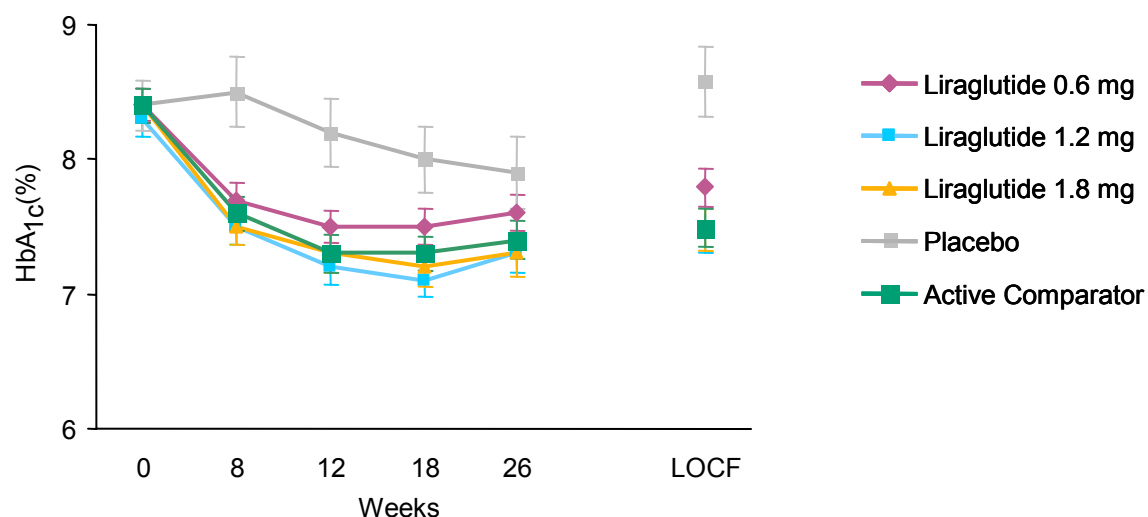
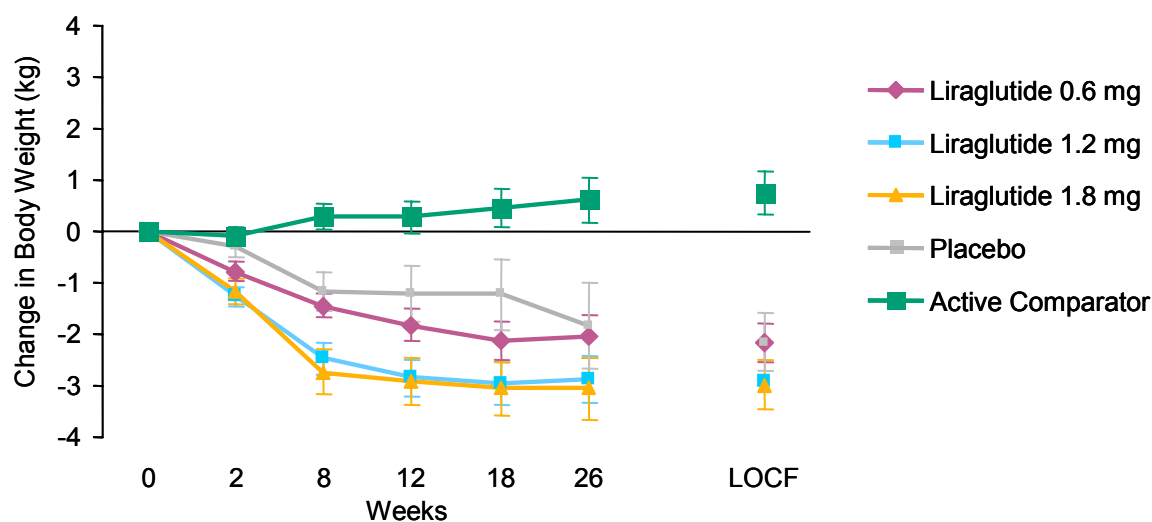


Figure 6–6 Change in Body Weight over Time (Mean±2SEM), ITT population (MET combination, Trial 1572)

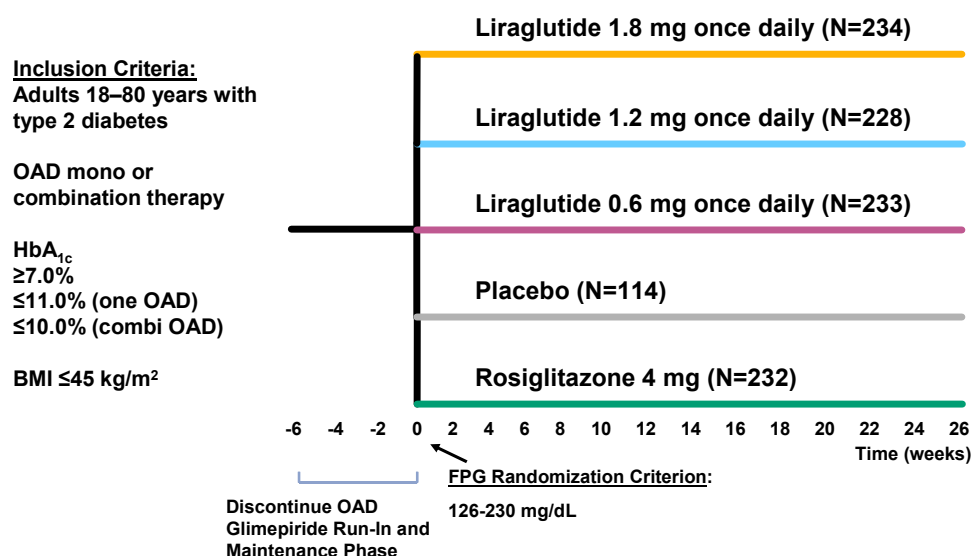


6.8.3 Liraglutide Combination with Glimepiride vs. Glimepiride and Rosiglitazone (SU combination, Trial 1436)

Study Title: Liraglutide Effect and Action in Diabetes (LEAD 1): Effect on glycemic control after once-daily administration of liraglutide in combination with glimepiride vs. glimepiride monotherapy vs. glimepiride and rosiglitazone combination therapy in subjects with type 2 diabetes. A six-month double-blind, double-dummy, randomized, active control, parallel-group, multi-center, multi-national trial.

Study Design: For a graphical presentation of the trial, see [Figure 6–7](#).

Figure 6–7 Liraglutide Combination with Glimepiride vs. Glimepiride and Rosiglitazone (SU combination, Trial 1436)



N=subjects randomized.

Completion rates: A total of 89%, 86%, 91%, 73% and 84% of randomized subjects completed the trial in the liraglutide 0.6 mg + glimepiride, liraglutide 1.2 mg + glimepiride, liraglutide 1.8 mg + glimepiride, placebo + glimepiride and rosiglitazone + glimepiride groups, respectively.

Endpoints: HbA_{1c} (primary), body weight, glycemic control (FPG, PPG profiles), beta-cell function, blood pressure, lipid profiles, cardiovascular biomarkers and waist and hip circumference.

Efficacy Results: Results are presented in [Table 6–12](#) and [Table 6–13](#). A plot of mean HbA_{1c} over time is presented in [Figure 6–8](#) and a plot of mean change in body weight over time is presented in [Figure 6–9](#).

Table 6–12 Summary of the Predefined Primary and Secondary Endpoints (SU combination, Trial 1436)

Group	Δ HbA _{1c} % points (SEM)	Percentage of subjects reaching HbA _{1c} < 7% (SEM)	Δ FPG mg/dL (SEM)	Δ PPG mg/dL (SEM)	Δ Body weight kg (SEM)
Liraglutide 0.6 mg	-0.60** (0.071)	24.11** (0.156)	-13.0** (2.855)	-33.35** (3.32)	0.72**/** (0.196)
Liraglutide 1.2 mg	-1.08**/** (0.072)	34.53**/** (0.141)	-28.3**/** (2.946)	-44.70**/** (3.43)	0.32* (0.201)
Liraglutide 1.8 mg	-1.13**/** (0.072)	41.59**/** (0.135)	-28.7**/** (2.953)	-48.89**/** (3.40)	-0.23* (0.200)
Placebo (placebo+ glimepiride)	0.23 (0.100)	7.48 (0.368)	18.14 (4.042)	-6.49 (4.91)	-0.10 (0.274)
Active comparator (rosiglitazone+ glimepiride)	-0.44 (0.071)	21.88 (0.162)	-15.8 (2.880)	-33.17 (3.41)	2.11 (0.197)

*Liraglutide significantly better than active comparator. **Liraglutide significantly better than placebo. SEM: standard error of the mean. Liraglutide 0.6, 1.2 and 1.8 mg: all given with glimepiride. Means and percentages in the table are estimated values (changes from baseline). For subjects reaching HbA_{1c} < 7% at end of trial, the estimated mean percentage is presented.

Table 6–13 Summary of Secondary Efficacy Endpoints (SU combination, Trial 1436)

Group	Δ Systolic blood pressure	Beta-cell function		Lipid Profile		Cardiovascular Biomarkers	
	mmHg (SEM)	Δ HOMA-IR (%) (SEM)	Δ HOMA-B (%) (SEM)	Δ HDL-C (mg/dL) (SEM)	Δ TG (mg/dL) (SEM)	Δ NT- proBNP pmol/L (SEM)	Δ hsCRP mg/dL (SEM)
Liraglutide 0.6 mg	-0.94 (0.837)	-0.17 (0.45)	16.84 (8.439)	-0.07 (0.48)	-6.83 (8.58)	0.04 (0.84)	-1.18 (0.62)
Liraglutide 1.2 mg	-2.56 (0.853)	-0.77 (0.46)	44.35**/** (8.676)	-0.84 (0.49)	-17.64 (8.76)	-1.02* (0.86)	-0.97 (0.64)
Liraglutide 1.8 mg	-2.81 (0.856)	-0.42 (0.47)	36.02* (8.790)	-1.57* (0.50)	-14.72 (8.78)	-0.51* (0.87)	0.86* (0.64)
Placebo (placebo+ glimepiride)	-2.32 (1.171)	0.90 (0.64)	1.87 (12.07)	-0.06 (0.69)	7.78 (12.23)	-0.32 (1.21)	-0.08 (0.89)
Active comparator (rosiglitazone+ glimepiride)	-0.93 (0.837)	-1.42 (0.46)	5.71 (8.546)	0.75 (0.49)	1.73 (8.82)	2.32 (0.86)	-1.64 (0.64)

*Liraglutide significantly better than active comparator. **Liraglutide significantly better than placebo. SEM: standard error of the mean. Means and percentages in the table are estimated values (changes from baseline). Reduction in HOMA-IR and increase in HOMA-B are beneficial.

Figure 6–8 HbA_{1c} over Time (Mean±2SEM), ITT Population (SU combination, Trial 1436)

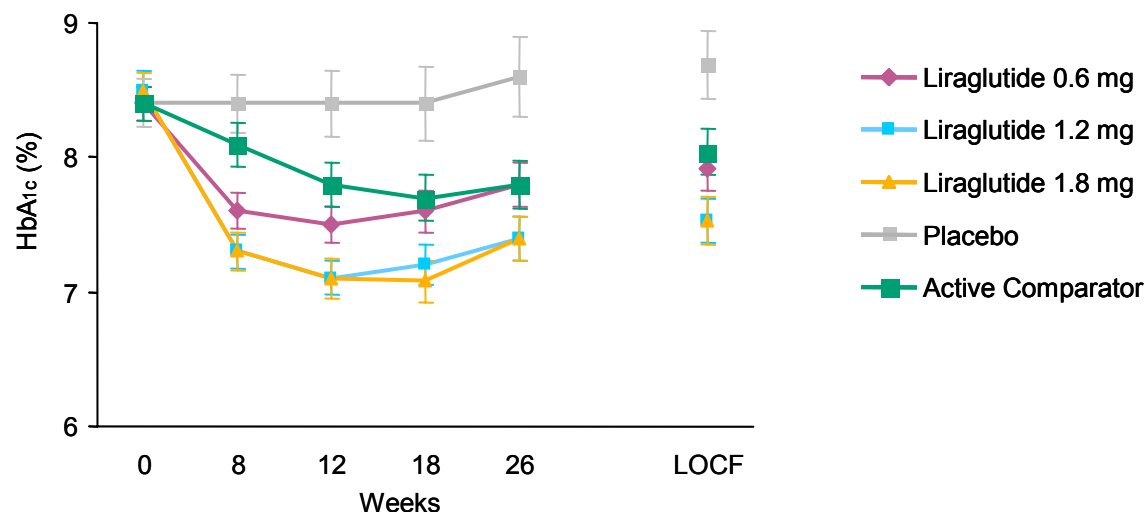
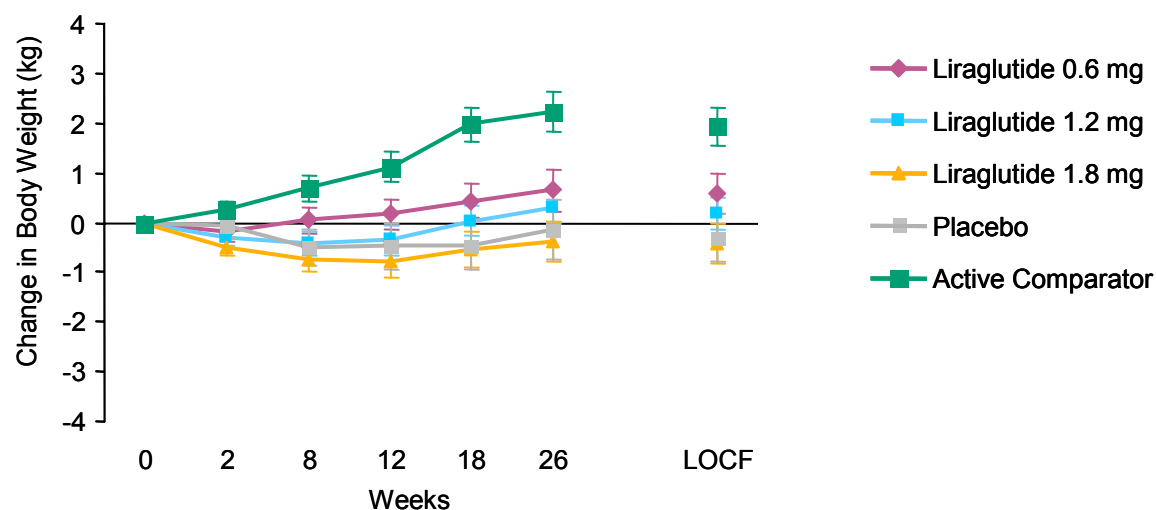


Figure 6–9 Change in Body Weight over Time (Mean±2SEM), ITT Population (SU combination, Trial 1436)

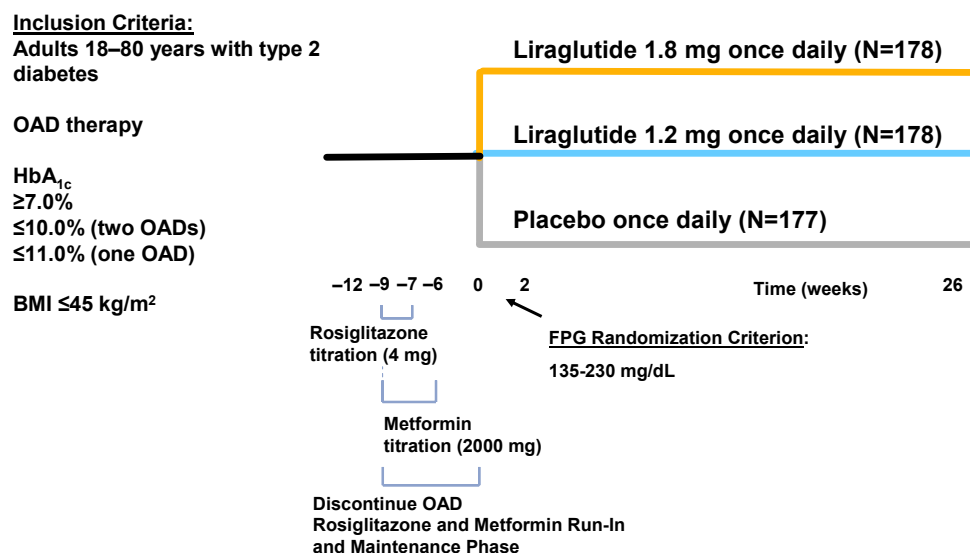


6.8.4 Liraglutide Combination with Metformin and Rosiglitazone vs. Metformin and Rosiglitazone (MET+TZD combination, Trial 1574)

Study Title: Liraglutide Effect and Action in Diabetes (LEAD 4): Effect on glycemic control of liraglutide in combination with rosiglitazone plus metformin vs. rosiglitazone plus metformin in type 2 diabetes. A twenty-six week double-blind parallel trial to investigate safety and efficacy.

Study Design: For a graphical presentation of the trial, see [Figure 6–10](#).

Figure 6–10 Liraglutide Combination with Metformin and Rosiglitazone vs. Metformin and Rosiglitazone (MET+TZD combination, Trial 1574)



N=subjects randomized.

Completion rates: A total of 86%, 75% and 68% of randomized subjects completed the trial in the liraglutide 1.2 mg + rosiglitazone + metformin, liraglutide 1.8 mg + rosiglitazone + metformin and placebo + rosiglitazone + metformin groups, respectively.

Endpoints: HbA_{1c} (primary), body weight, glycemic control (FPG, PPG profiles), beta-cell function, blood pressure, fasting lipid profile, cardiovascular biomarkers and waist and hip circumference.

Efficacy Results: Results are presented in [Table 6–14](#) and [Table 6–15](#). A plot of mean HbA_{1c} over time is presented in [Figure 6–11](#) and a plot of mean change in body weight over time is presented in [Figure 6–12](#).

Table 6–14 Summary of the Predefined Primary and Secondary Endpoints (MET+TZD combination, Trial 1574)

Group	ΔHbA_{1c} % points (SEM)	Percentage subjects reaching $\text{HbA}_{1c} < 7\%$ (SEM)	ΔFPG mg/dL (SEM)	ΔPPG mg/dL (SEM)	$\Delta\text{Body weight}$ kg (SEM)
Liraglutide 1.2 mg	-1.48** (0.078)	57.47** (0.153)	-40.0** (3.739)	-46.35** (3.56)	-1.02** (0.334)
Liraglutide 1.8 mg	-1.48** (0.075)	53.67** (0.151)	-43.6** (3.623)	-47.97** (3.45)	-2.02** (0.322)
Placebo (placebo+ rosiglitazone+metformin)	-0.54 (0.080)	28.14 (0.172)	-8.02 (3.860)	-14.50 (3.64)	0.60 (0.338)

**Liraglutide significantly better than placebo. SEM: standard error of the mean; Liraglutide 1.2 and 1.8 mg: all given with rosiglitazone + metformin. Means and percentages in the table are estimated values (changes from baseline). For subjects reaching $\text{HbA}_{1c} < 7\%$ at end of trial, the estimated mean percentage is presented.

Table 6–15 Summary of Secondary Efficacy Endpoints (MET+TZD combination, Trial 1574)

Group	$\Delta\text{Systolic blood pressure}$	Beta-cell function		Lipid Profile		Cardiovascular Biomarkers	
	mmHg (SEM)	$\Delta\text{HOMA-IR}$ (%) (SEM)	$\Delta\text{HOMA-B}$ (%) (SEM)	$\Delta\text{HDL-C}$ mg/dL (SEM)	ΔTG mg/dL (SEM)	$\Delta\text{NT-proBNP}$ pg/mL (SEM)	ΔhsCRP mg/dL (SEM)
Liraglutide 1.2 mg	-6.71** (1.141)	-0.604 (0.328)	27.36** (4.378)	-1.132 (0.601)	-33.810** (9.058)	13.419 (19.047)	1.627 (1.689)
Liraglutide 1.8 mg	-5.65** (1.101)	-0.674 (0.315)	27.19** (4.210)	-1.681 (0.581)	-28.537 (8.698)	20.080 (18.186)	-1.581 (1.628)
Placebo (placebo+ rosiglitazone+ metformin)	-1.11 (1.158)	-0.342 (0.341)	5.79 (4.546)	-1.348 (0.648)	-11.743 (9.337)	44.020 (19.472)	-0.387 (1.746)

**Liraglutide significantly better than placebo. SEM: standard error of the mean. Liraglutide 1.2 and 1.8 mg: all given with rosiglitazone + metformin. Means and percentages in the table are estimated values (changes from baseline). Reduction in HOMA-IR and increase in HOMA-B are beneficial.

Figure 6–11 HbA_{1c} over Time (Mean±2SEM), ITT Population (MET+TZD combination, Trial 1574)

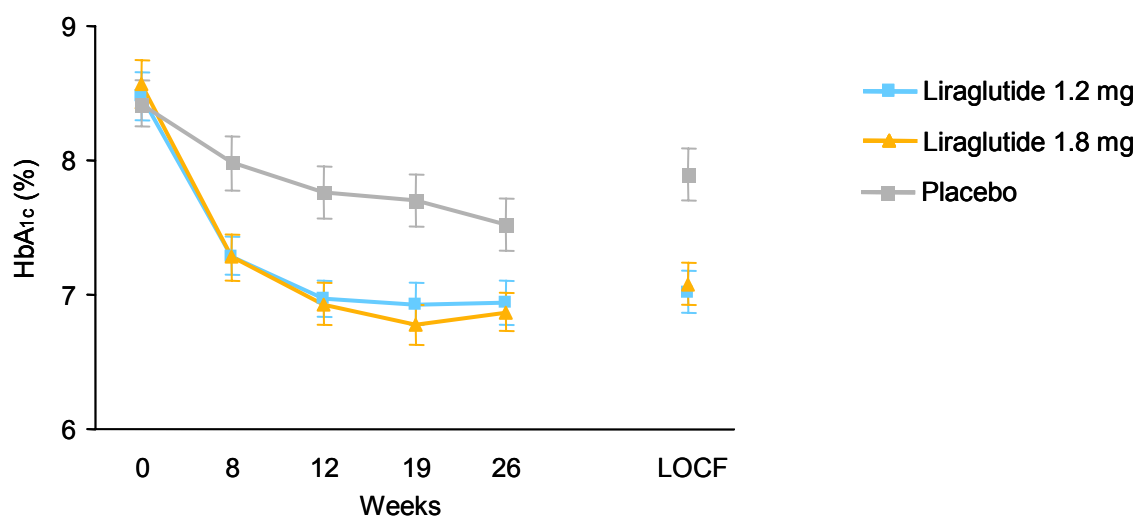
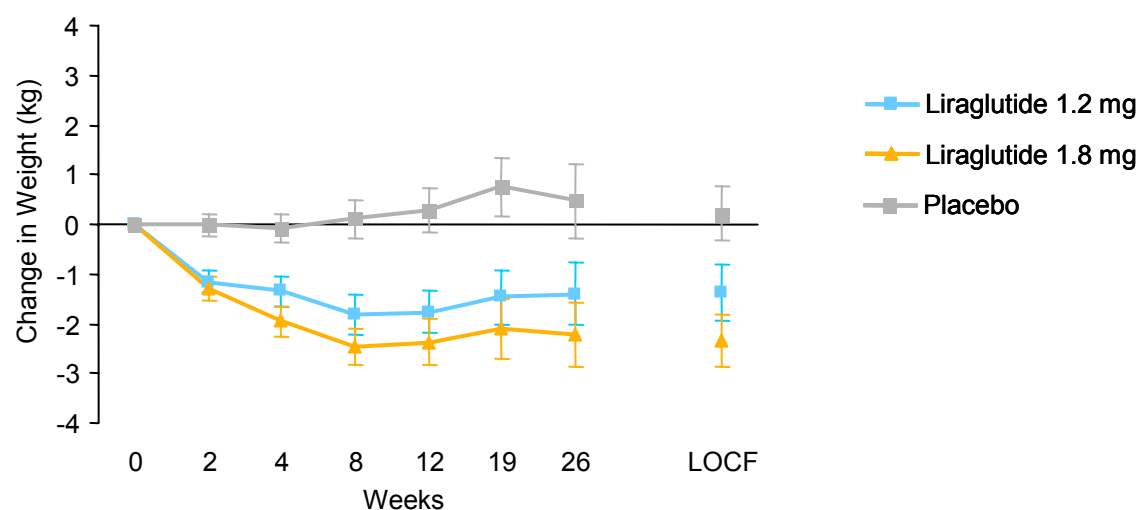


Figure 6–12 Change in Body Weight over Time (Mean±2SEM), ITT Population, (MET+TZD combination, Trial 1574)



6.8.5 Liraglutide Combination with Glimepiride and Metformin vs. Insulin Glargine with Metformin and Glimepiride (MET+SU combination Trial 1697)

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

Study Design: For a graphical presentation of the trial, see [Figure 6–13](#).

Figure 6–13 Liraglutide Combination with Glimepiride and Metformin vs. Insulin Glargine with Metformin and Glimepiride (MET+SU combination, Trial 1697)

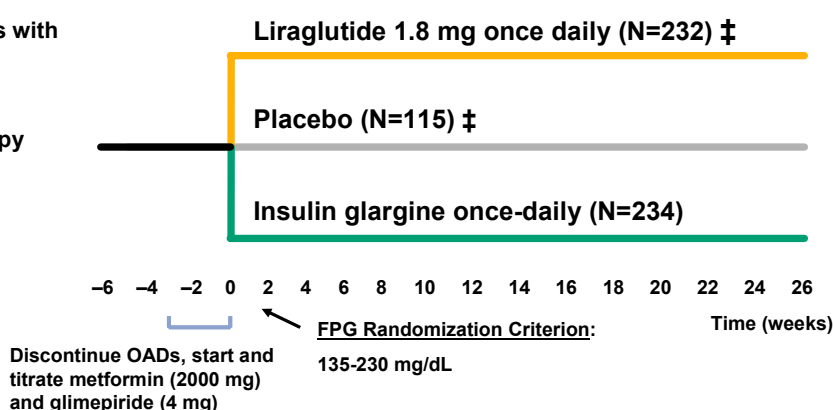
Inclusion Criteria:

Adults 18–80 years with type 2 diabetes

OAD mono or combination therapy

HbA_{1c} ≥7.0% (two OADs)
≥7.5% (one OAD)
≤10.0%

BMI ≤45 kg/m²



‡ Double-blind treatments

N=subjects randomized.

Completion rates: A total of 89%, 84% and 94% of randomized subjects completed the trial in the liraglutide 1.8 mg + glimepiride + metformin, placebo + glimepiride + metformin and insulin glargine + glimepiride + metformin groups, respectively.

Endpoints: HbA_{1c} (primary), body weight, glycemic control (FPG, PPG profiles), beta-cell function, blood pressure, lipid profiles, cardiovascular biomarkers and waist and hip circumference.

Efficacy Results: Results are presented in [Table 6–16](#) and [Table 6–17](#). A plot of mean HbA_{1c} over time is presented in [Figure 6–14](#) and a plot of mean change in body weight over time is presented in [Figure 6–15](#).

Table 6–16 Summary of the Predefined Primary and Secondary Endpoints (MET+SU combination, Trial 1697)

Group	Δ HbA _{1c} % points (SEM)	Percentage of subjects reaching HbA _{1c} < 7% (SEM)	Δ FPG mg/dL (SEM)	Δ PPG mg/dL (SEM)	Δ Body weight kg (SEM)
Liraglutide 1.8 mg	-1.33**/** (0.088)	53.12*/** (0.134)	-27.9** (3.704)	-32.67** (4.35)	-1.81*/** (0.326)
Placebo (placebo+ glimepiride+metformin)	-0.24 (0.106)	15.45 (0.264)	9.56 (4.434)	0.57 (5.20)	-0.42 (0.391)
Active comparator (insulin glargine+glimepiride+metformin)	-1.09 (0.090)	45.78 (0.134)	-32.2 (3.754)	-29.00 (4.40)	1.62 (0.331)

*Liraglutide significantly better than active comparator. **Liraglutide significantly better than placebo. SEM: standard error of the mean; Liraglutide 1.8 mg: given with glimepiride and metformin. Means and percentages in the table are estimated values (changes from baseline). For subjects reaching HbA_{1c} < 7% at end of trial, the estimated mean percentage is presented.

Table 6–17 Summary of Secondary Efficacy Endpoints (MET+SU combination, Trial 1697)

Group	Δ Systolic blood pressure	Beta-cell function		Lipid Profile		Cardiovascular Biomarkers	
	mmHg (SEM)	Δ HOMA-IR (%) (SEM)	Δ HOMA-B (%) (SEM)	Δ HDL-C mg/dL (SEM)	Δ TG mg/dL (SEM)	Δ NT- proBNP pmol/L (SEM)	Δ hsCRP mg/dL (SEM)
Liraglutide 1.8 mg	-3.97* (1.315)	-0.80 (0.41)	32.86** (6.978)	-2.32 (0.64)	-21.79 (9.97)	0.59 (4.33)	-0.77 (0.89)
Placebo (placebo+ glimepiride+metformin)	-1.44 (1.571)	-0.36 (0.48)	-1.14 (8.068)	-1.03 (0.78)	-17.45 (12.00)	-6.12 (5.26)	-0.68 (1.06)
Active comparator (insulin glargine +glimepiride+metformin)	0.54 (1.329)	N/A ^(a)	N/A ^(a)	-2.07 (0.65)	-19.52 (10.06)	-0.76 (4.40)	0.66 (0.89)

*Liraglutide significantly better than active comparator. **Liraglutide significantly better than placebo. SEM: standard error of the mean. Liraglutide 1.8 mg is given with glimepiride and metformin. Means and percentages in the table are estimated values (changes from baseline). ^a Not applicable due to cross-reactivity between insulin glargine and the insulin assay. Reduction in HOMA-IR and increase in HOMA-B are beneficial.

Figure 6–14 HbA_{1c} over Time (Mean±2SEM), ITT Population (MET+SU combination, Trial 1697)

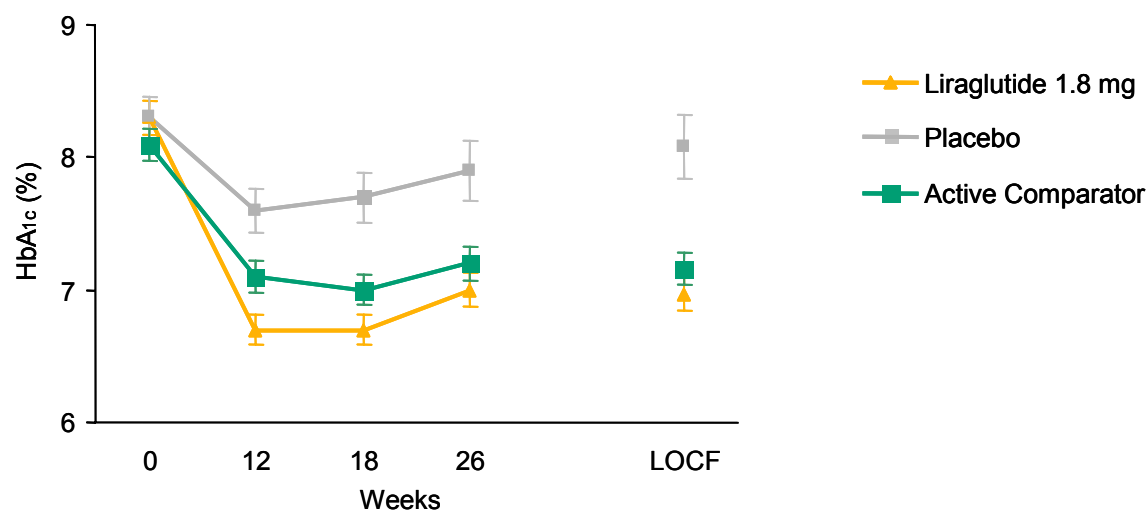
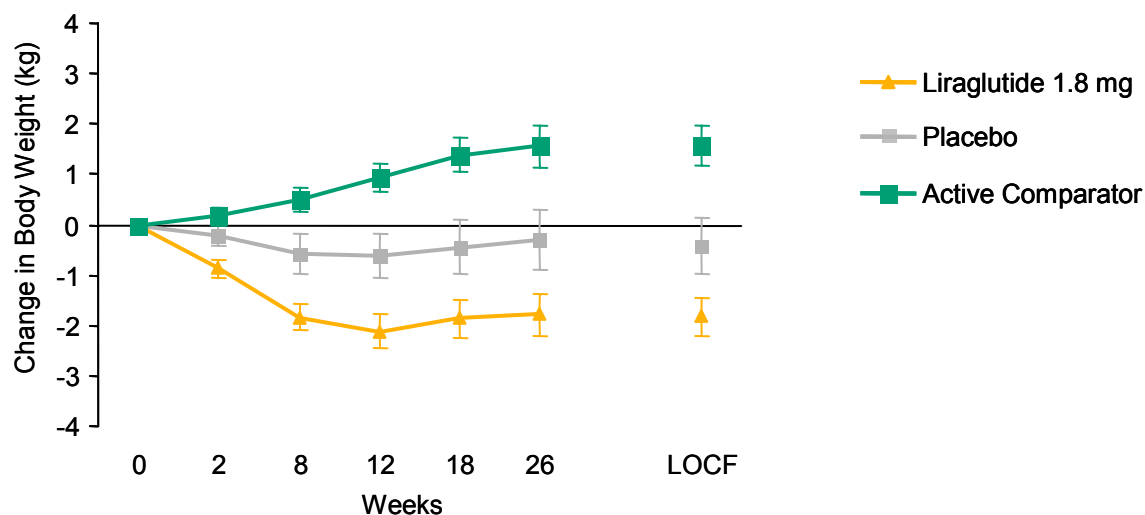


Figure 6–15 Change in Body Weight over Time (Mean±2SEM), ITT Population (MET+SU combination, Trial 1697)



6.9 Summary of Results

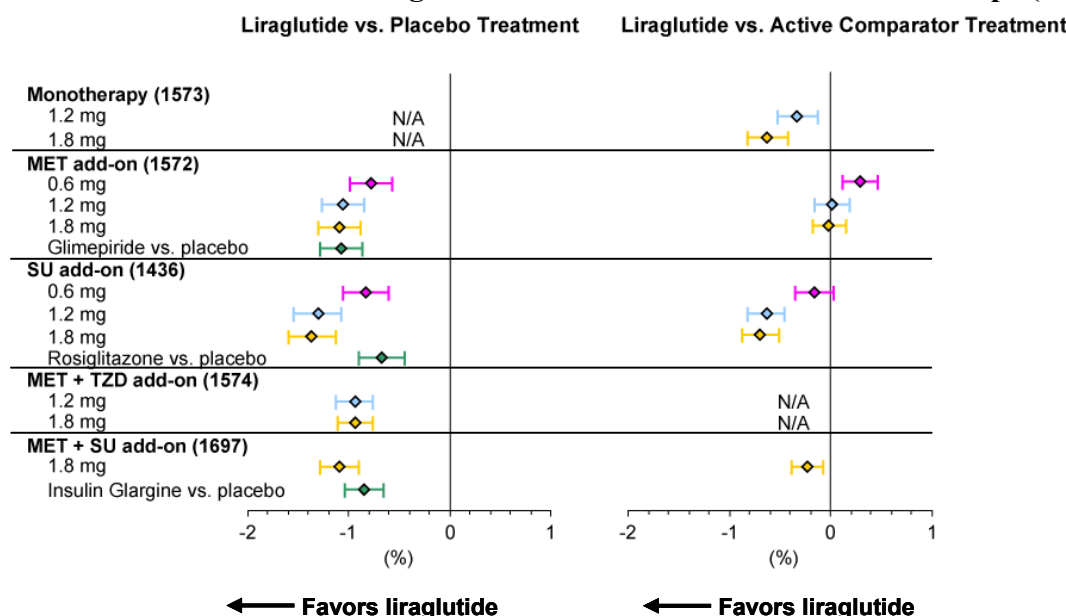
6.9.1 Glycemic Control

6.9.1.1 HbA_{1c} across the Five Long-term Phase 3 Trials

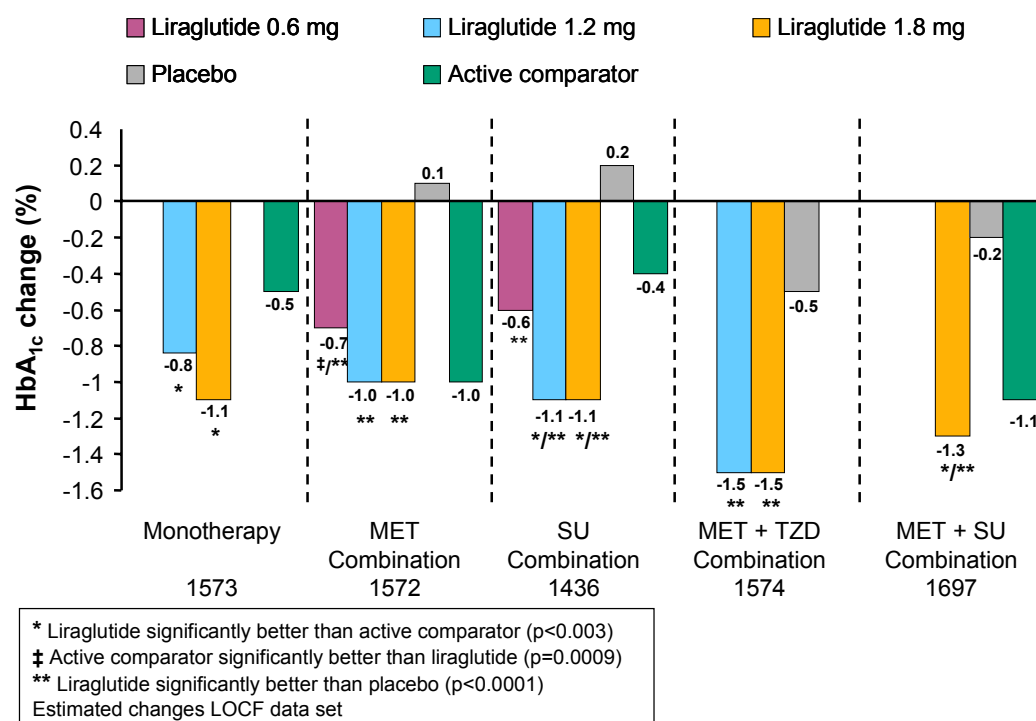
Treatment with liraglutide as monotherapy and in combination treatment resulted in a substantial, statistically significant, and clinically relevant lowering of HbA_{1c}. Treatment with liraglutide consistently reduced HbA_{1c} more than placebo. In Trials 1573, 1436, and 1697, liraglutide treatment was also statistically superior to the glucose lowering effect of the comparator treatments. The estimated mean decrease from baseline in HbA_{1c} after treatment with liraglutide ranged from 0.60% points (liraglutide 0.6 mg, Trial 1436) to 1.48% points (liraglutide 1.2 mg and 1.8 mg, Trial 1574). An overview of the results is provided in [Figure 6–16](#), and results from the individual trials are presented in [Figure 6–17](#).

The forest plot in [Figure 6–16](#) shows the estimated effects across trials and the associated confidence intervals. If the upper confidence interval limit was below 0% for the liraglutide vs. placebo or active comparators, then the treatment effect obtained with liraglutide was significantly better than placebo or active comparators. For the comparison between liraglutide and active comparator, treatment with liraglutide was non-inferior to active comparator treatment when the upper confidence interval limit was below 0.4%.

Figure 6–16 Forest Plot of HbA_{1c} (%), Comparing Estimated Mean Treatment Difference for HbA_{1c} Change from Baseline between Treatment Groups ($\pm 95\%$ CI)



Placebo treatment: Trial 1572 (metformin), Trial 1436 (glimepiride), Trial 1574 (metformin + rosiglitazone) and Trial 1697 (glimepiride + metformin). Active comparator treatment: Trial 1573 (glimepiride), Trial 1572 (glimepiride + metformin), Trial 1436 (rosiglitazone + glimepiride) and Trial 1697 (insulin glargine + glimepiride + metformin). For complete treatment regimens in the individual trials, see [Table 6–1](#).

Figure 6–17 HbA_{1c}, Change from Baseline (% points),

For complete treatment regimens in the individual trials, see [Table 6–1](#). Percentages in the figure are estimated mean percentages (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data. A hierarchical testing procedure is used ([Appendix, Section 2.2.1](#)).

In all long-term phase 3 combination trials that included a placebo group (Trials 1572, 1436, 1574 and 1697), all doses of liraglutide in combination with OAD(s) were shown to be superior to the OAD(s) treatment alone (i.e. placebo).

The glucose lowering effect of liraglutide in patients with type 2 diabetes in monotherapy (Trial 1573) showed superiority of both liraglutide 1.2 mg and 1.8 mg over the active comparator, glimepiride 8 mg.

In the metformin OAD combination study, liraglutide in combination with metformin was non-inferior to glimepiride in combination with metformin (Trial 1572). In the sulfonylurea combination study - the 1.2 mg and 1.8 g doses of liraglutide in combination with a sulfonylurea decreased HbA_{1c} levels significantly more than rosiglitazone combined with a sulfonylurea.

Finally, in dual combination therapy the combination of liraglutide to metformin and a sulfonylurea lowered HbA_{1c} significantly more than combination with the basal insulin glargine (this difference was within the pre-defined non-inferiority margin of 0.4%).

In the monotherapy trial (Trial 1573), subjects who originally (prior to enrolment) were on a diet or a single OAD were included, and in the combination therapy trials subjects who originally (prior to

enrolment) were on one or more OADs were included. Therefore, in principal, two different situations were studied: a) patients who had an increase in the number of therapies after randomization or b) subjects who had the same or lower number of therapies after randomization. To better understand the add-on effect of liraglutide, the effect in the sub-group of subjects within the trials representing an add-on situation was therefore also analyzed – representing scenario a) above. That is, the diet patient segment in the monotherapy trial, subjects on one OAD in the mono-combination trials and subjects on two OADs in the dual-combination trials (all denoted based on treatment prior to enrolment).

In Trials 1573, 1436 and 1572, these populations were approximately one third of the total populations. In contrast, in Trials 1574 and 1697 the majority of subjects were on dual OAD therapy at time of enrolment and therefore the main analysis already reflected an add-on situation.

In Trial 1573 (monotherapy), the effect on change in HbA_{1c} from baseline was 1.13 and 1.48% point for the 1.2 mg and the 1.8 mg dose, respectively. In the glimepiride treated sub-population in this trial, the decrease was 0.74% point. In Trials 1572 (MET combination trial) and 1436 (SU combination trial), the drop in HbA_{1c} was around 1.3% points and 1.4% points, respectively with no significant difference between the 1.2 mg and 1.8 mg doses. In contrast, the reduction in HbA_{1c} in the active comparator groups was between 0.8 and 1.2% points, respectively.

In other words, greater reductions from baseline were consistently seen across all groups when looking at the sub-group of add-on patients in comparison to the total population that also included subjects remaining on the same number of therapies.

Overall, under a broad array of relevant therapeutic scenarios, liraglutide consistently demonstrated a statistically significant and clinically relevant lowering effect on blood glucose, and substantially greater effect than commonly utilized diabetes treatments.

Sustainability of Effect on HbA_{1c}

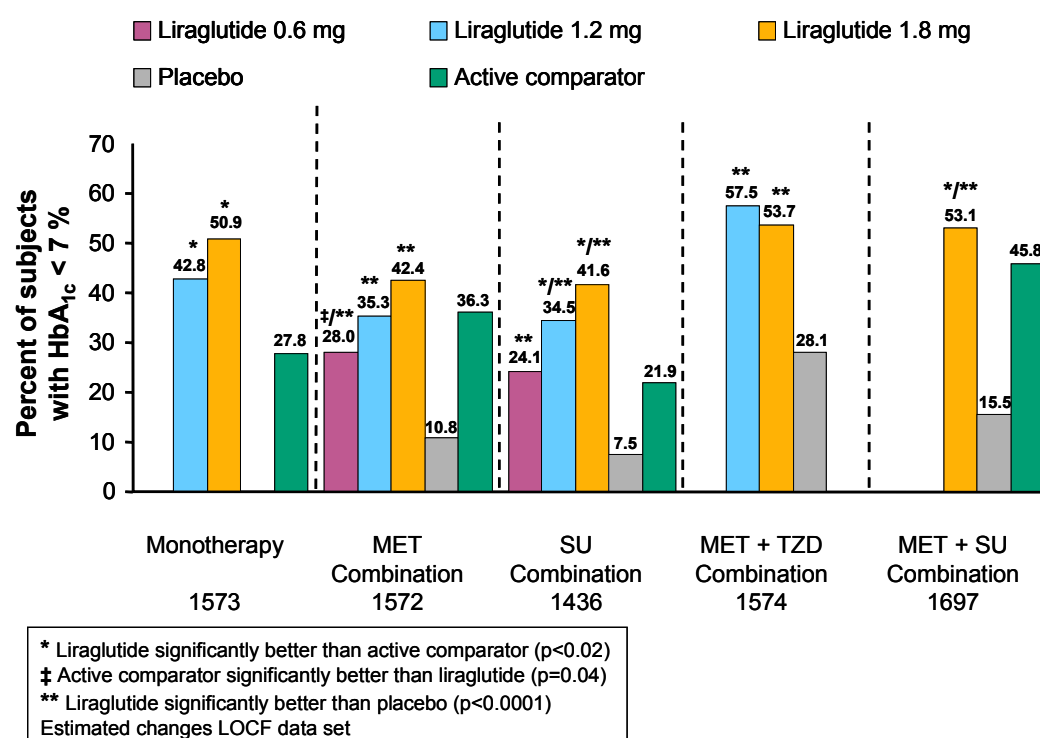
The sustained efficacy of liraglutide as assessed by HbA_{1c} was evaluated in the five long-term phase 3 trials; in Trial 1573 for 52 weeks (monotherapy) and for 26 weeks in Trials 1572, 1436, 1574 and 1697 (combination-therapy). These trials demonstrated that HbA_{1c} declined during the first 12 weeks of treatment and remained stable or increased slightly (0.1–0.2% points) for the remaining part of the treatment period for up to 26 or 52 weeks ([Figure 6–2](#)). Similarly, when liraglutide was used in combination with one or two OADs, mean HbA_{1c} levels declined within the first 12 weeks and were stable for the rest of the treatment period of 26 weeks ([Figure 6–5](#), [Figure 6–8](#), [Figure 6–11](#) and [Figure 6–14](#)).

Overall, there was no indication of reduced efficacy of liraglutide over time with regard to maintaining glycemic control as measured by HbA_{1c}. This was regardless of liraglutide dose and concomitant OAD treatment. There was no indication that antibody development affected the effect of liraglutide (Section [7.6.1](#)).

6.9.1.2 Percentage of Subjects Achieving HbA_{1c} Target

In the two trials where the 0.6 mg dose was used (Trials 1572 and 1573), a total of 24–28% of subjects on that dose reached the ADA target for HbA_{1c} < 7%. Compared to this, the more effective and clinically relevant doses of liraglutide, 1.2 mg and 1.8 mg, led to a higher percentage of subjects (ranging from 35% to 58%) who met the ADA target for HbA_{1c} < 7% ([Figure 6–18](#)).

Figure 6–18 Percentage of Subjects Achieving ADA Target (HbA_{1c} < 7%)



For complete treatment regimens in the individual trials, see [Table 6–1](#). Percentages in the figure are estimated mean percentages (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

The percentage of subjects achieving the ADA defined HbA_{1c} target of HbA_{1c} < 7% at end of trial was analyzed by logistic regression using treatment and baseline HbA_{1c} as covariates. The comparison between the liraglutide and active comparator groups showed that the 1.2 mg and 1.8 mg liraglutide doses led to a significantly larger proportion of subjects reaching the target than the active comparator treatment. The exception was in Trial 1572, where no differences were seen between liraglutide and the combination of metformin and glimepiride treatment.

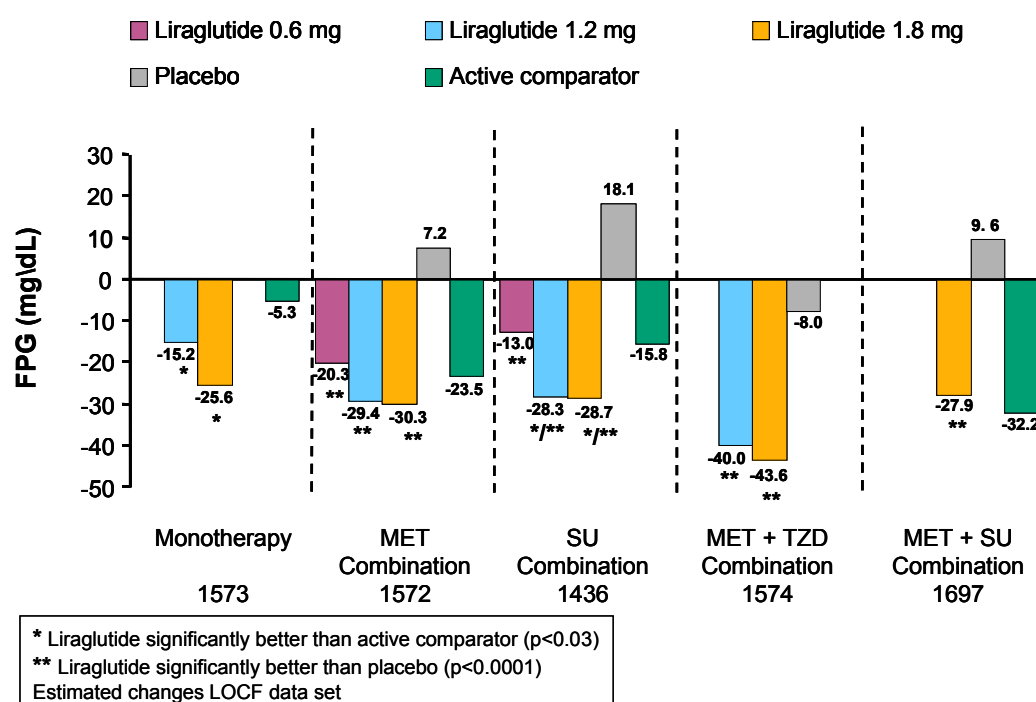
A sub-group analysis demonstrated that the most pronounced effect was seen in subjects previously treated with diet/exercise (Trial 1573) or one OAD (Trials 1572 and 1436) at entry into the trial (sub-group a) described above. In Trial 1572, the metformin combination trial, significantly more subjects reached the HbA_{1c} < 7% after liraglutide treatment with 53% and 66% for the 1.2 mg and 1.8 mg doses, respectively vs. 56% in the metformin group and 23% in the placebo group. In Trial

1436, 57% and 56% reached target in the 1.2 mg and 1.8 mg liraglutide dose groups compared with 36% in the glimepiride + rosiglitazone group and 12% in the placebo group.

6.9.1.3 Fasting Plasma Glucose (FPG)

In all five long-term phase 3 trials, treatment with liraglutide alone or in combination with one or two OADs led to a substantial lowering of FPG from baseline, ranging from 13 mg/dL (0.72 mmol/L) in Trial 1436 and 44 mg/dL (2.42 mmol/L) in Trial 1574 within the first 2–4 weeks of treatment ([Figure 6–19](#)). Mean baseline values ranged from 164–185 mg/dL (9.1–10.3 mmol/L).

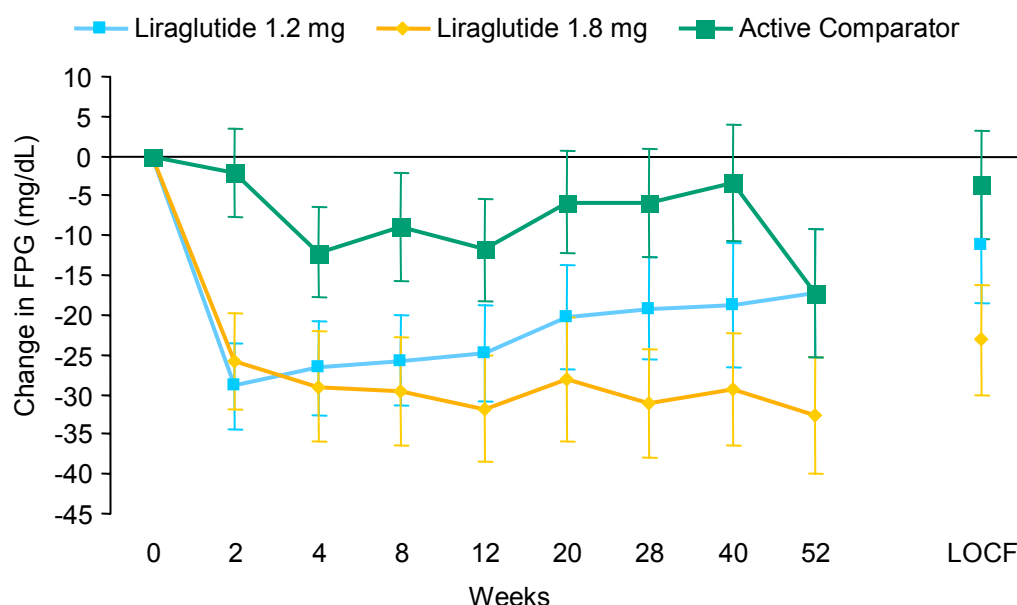
Figure 6–19 Fasting Plasma Glucose, Change from Baseline (mg/dL)



For complete treatment regimens in the individual trials, see [Table 6–1](#). Percentages in the figure are estimated mean values (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

The decrease in FPG was rapid and was seen at the first time point of evaluation and was maintained throughout the treatment period. [Figure 6–20](#) illustrates the rapid and sustained effect of liraglutide on decreasing FPG over time in the monotherapy Trial 1573, the trial with the longest duration.

Figure 6–20 Change in Fasting Plasma Glucose over Time, Mean \pm 2SEM (Monotherapy, Trial 1573)



For complete treatment regimens in the individual trials, see [Table 6–1](#).

The proportion of subjects who reached the ADA target of having FPG in the range 90–130 mg/dL (5.0–7.2 mmol/L) was analyzed by logistic regression in the five long-term phase 3 trials. This analysis demonstrated that subjects treated with liraglutide 1.2 mg or 1.8 mg in monotherapy were more likely to reach the ADA FPG target than those treated with glimepiride 8 mg (Trial 1573).

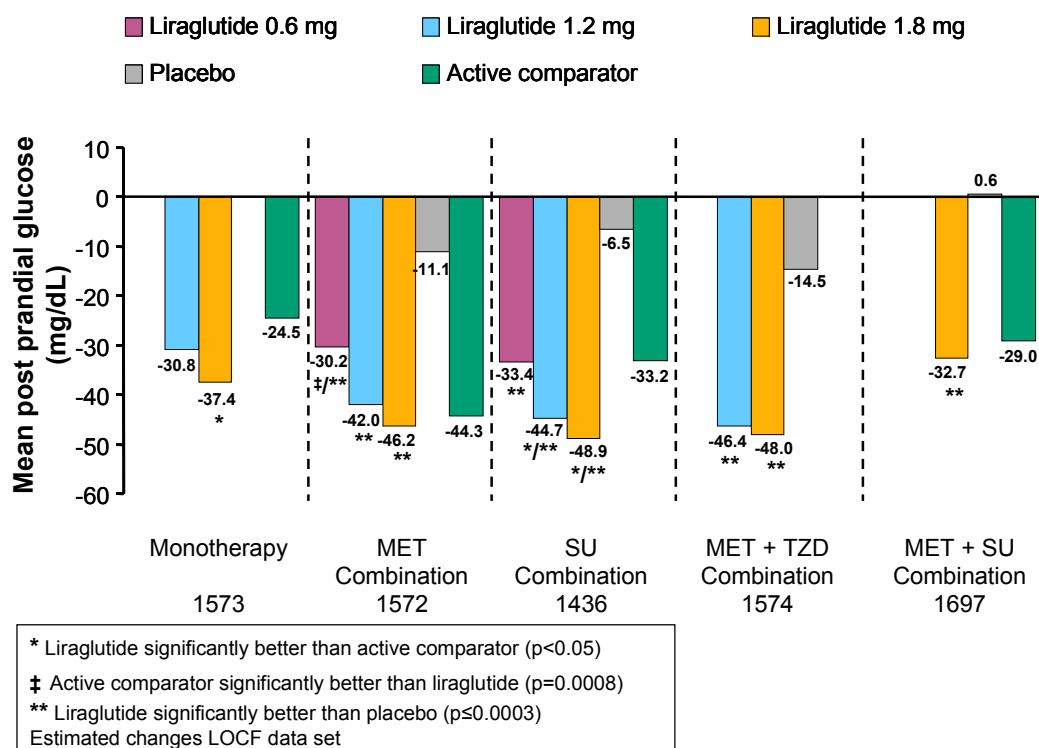
In the four combination trials (Trials 1572, 1436, 1574 and 1697), more subjects treated with liraglutide in combination with one or two OADs reached the ADA FPG target than subjects treated solely with the OAD(s) or placebo. Subjects treated with liraglutide 1.8 mg or with insulin glargine (both groups in combination with glimepiride and metformin) were equally likely to reach the ADA FPG target (Trial 1697).

Overall, the reductions in fasting plasma glucose are in line with the reductions observed in HbA_{1c}.

6.9.1.4 Postprandial Plasma Glucose

[Figure 6–21](#) illustrates the drop in postprandial plasma glucose across the five long-term phase 3 trials.

Figure 6–21 Postprandial Plasma Glucose, Change from Baseline (mg/dL)



For complete treatment regimens in the individual trials, see [Table 6–1](#). Percentages in the figure are estimated mean values (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

In the five long-term phase 3 trials, self-measured plasma glucose profiles were obtained at baseline and at end of trial. The plasma glucose profiles were 24-hour 7-point plasma glucose profiles (Trials 1572, 1436 and 1574) or 8-point plasma glucose profiles (Trials 1573 and 1697). The overall trend was that a greater proportion of liraglutide-treated subjects had values below the ADA target for postprandial glucose, 180 mg/dL (10 mmol/L), at all three meals compared with placebo or comparators. The impact on postprandial glucose was incremental to the effect on fasting; i.e., there is a direct effect on both and not just a lowering of baseline.

Overall, liraglutide was thus found to improve glycemic control by combined lowering of the fasting and postprandial glucose levels and HbA_{1c}. Thus, all measured glycemic control parameters consistently provide evidence of a robust glycemic control following treatment with liraglutide.

6.9.1.5 Beta-cell Function and Insulin Resistance

The effect of liraglutide on beta-cell function and insulin resistance was examined in the five long-term phase 3 trials and the therapeutic exploratory trials. Overall, treatment with liraglutide + OAD(s) directly improved beta-cell function as assessed by HOMA-B and the pro-insulin to insulin ratio, two approaches amenable to application in large scale trials.

Homeostasis Model Assessment Index of Beta-cell Function (HOMA-B)

In the monotherapy trial (Trial 1573), treatment with liraglutide increased beta-cell function as assessed by HOMA-B analysis, however, the effect was not significantly different from that seen with glimepiride treatment. In the liraglutide combination trials (Trials 1572, 1436, 1574, 1697), a significant difference was demonstrated for change in HOMA-B in most liraglutide dose groups in comparison to placebo. A significant difference against the active comparator was reached for liraglutide 1.2 mg and 1.8 mg in combination with glimepiride in Trial 1436. For details on changes in HOMA-B in the five individual long-term trials, see Section [6.8](#).

Pro-insulin to Insulin Ratio

In the four long-term phase 3 trials with a duration of 26 weeks (Trials 1572, 1436, 1574 and 1697), the fasting mean pro-insulin to insulin ratio decreased by 0.03 to 0.11 during treatment with all doses of liraglutide + OAD(s). The decrease was statistically different from placebo + OAD(s). The comparison against active comparators was significant for liraglutide 1.2 mg and 1.8 mg in combination with glimepiride (Trial 1436) and for liraglutide 1.8 mg in combination with metformin + glimepiride (Trial 1697).

A reduction in pro-insulin to insulin ratio means that the beta-cells produce less immature insulin, suggesting that they are subject to less stress on insulin secretion which has been interpreted as an improvement in beta-cell function. In Trial 1573 (52-week duration), the mean pro-insulin to insulin ratio increased by 0.005 and 0.006 during treatment with liraglutide 1.2 mg and 1.8 mg, but the increase was not significantly different from that found for glimepiride.

Homeostasis Model Assessment Index of Insulin Resistance (HOMA-IR)

A significant improvement in insulin resistance (HOMA-IR) was observed in the 52-week monotherapy trial (Trial 1573) after treatment with liraglutide 1.2 mg and 1.8 mg compared with glimepiride. Treatment during 52 weeks resulted in a reduction in insulin resistance of 0.65% and 1.35% with liraglutide 1.2 mg and 1.8 mg (mean baseline 6.95% and 6.87%), respectively, which was significantly different from the increase of 0.85% seen during treatment with glimepiride. The reduction is most likely secondary to the reductions in body weight. No significant effect was seen in the other trials.

For details on changes in HOMA-IR in the five individual long-term trials, see Section [6.8](#).

6.9.1.6 Hypoglycemic Episodes

Overall, the incidence of hypoglycemia with liraglutide was low across all treatments. A higher incidence was seen when liraglutide was combined with a sulfonylurea in comparison to studies with a non-sulfonylurea background. The mechanism behind this difference may reflect an uncoupling of the glucose-dependent insulin secretion of GLP-1 when combined with a sulfonylurea.³⁷

The majority of the hypoglycemic episodes were classified as ‘minor’ which was defined in the clinical trial protocols as blood glucose <56 mg/dL (3.1 mmol/L) but not requiring third party assistance. A hypoglycemic episode was defined in the clinical trial protocols as major if the subject required third-party assistance (irrespective of blood glucose levels). No episodes of major hypoglycemia were reported in the single-dose, short-term and intermediate-term trials.

The incidences of minor and major hypoglycemic episodes in the long-term phase 3 trials were highest in subjects randomized to the insulin glargine arm and in subjects treated with a sulfonylurea (glimepiride) alone or in combination with liraglutide ([Table 6–18](#)). The rate of minor hypoglycemia only exceeded one episode per subject year of exposure in the liraglutide 1.8 mg dose group of Trial 1697, where subjects were dosed in combination with glimepiride + metformin. In the comparator groups, the rate exceeded one episode per subject year in Trials 1573 and 1697, both including glimepiride in the placebo and the comparator groups. An example of this calculation is presented for minor hypoglycemic episodes in Trial 1573 where the rate (liraglutide 1.2 mg) is 241.6 events **per 1,000 subject years** of exposure, corresponding to 0.2416 minor hypoglycemic episodes **per subject year** ([Table 6–18](#)). An important factor to take into consideration is that the HbA_{1c} reductions achieved was in all cases equal or lower with liraglutide than active comparator.

Table 6–18 Major and Minor Hypoglycemic Episodes in the Five Long-term Phase 3 Trials

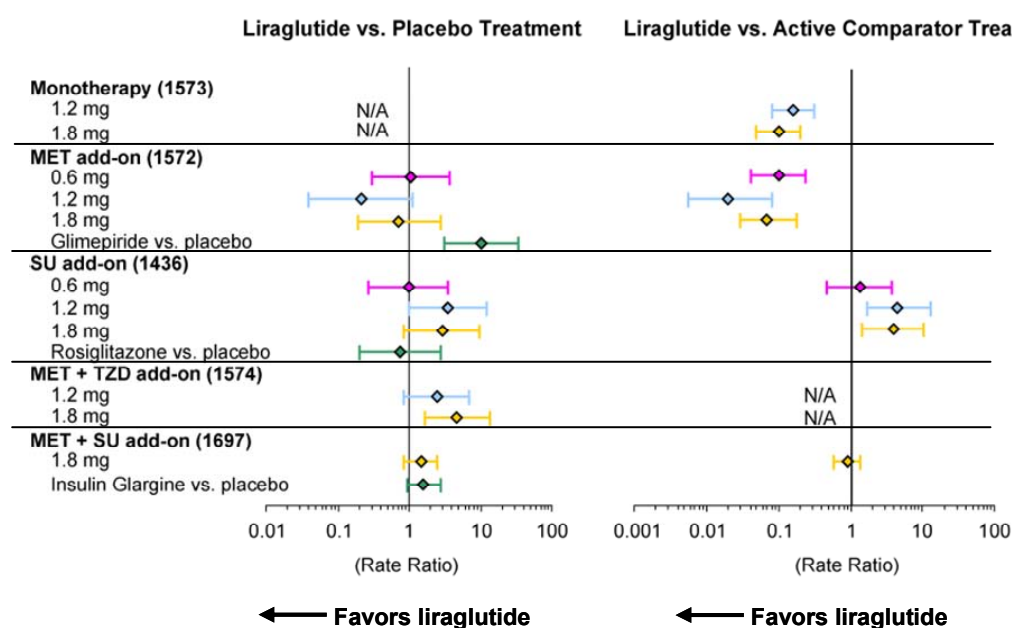
		Liraglutide 0.6 mg			Liraglutide 1.2 mg			Liraglutide 1.8 mg			Placebo			Active Comparator					
		(%) N	R	E	(%) N	R	E	(%) N	R	E	(%) N	R	E	(%) N	R	E			
Trial 1573	Major	N/A	N/A	N/A	(0.0)	0	0.0	0	(0.0)	0	0.0	0	N/A	N/A	N/A	(0.0)	0	0.0	0
	Minor	N/A	N/A	N/A	(11.6)	29	241.6	65	(7.7)	19	230.1	62	N/A	N/A	N/A	(25.0)	62	1659.2	416
Trial 1572	Major ^(a)	(0.0)	0	0.0	0	(0.4)	1	3.7	1	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0
	Minor	(4.1)	10	68.3	19	(3.3)	8	44.3	12	(3.3)	8	45.4	12	(2.5)	3	64.4	6	(22.3)	54
Trial 1436	Major	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.4)	1	9.1	1	(0.0)	0	0.0	0	(0.0)	0
	Minor	(5.2)	12	164.9	18	(9.2)	21	505.5	52	(8.1)	19	472.3	52	(2.6)	3	169.8	8	(4.3)	10
Trial 1574	Major	N/A	N/A	N/A	(0.0)	0	0.0	0	(0.0)	0	0.0	0	(0.0)	0	0.0	0	N/A	N/A	N/A
	Minor	N/A	N/A	N/A	(9.0)	16	370.1	30	(6.7)	12	614.3	45	(4.6)	8	153.2	11	N/A	N/A	N/A
Trial 1697	Major	N/A	N/A	N/A	N/A	N/A	N/A	N/A	(2.2)	5	55.9	6	(0.0)	0	0.0	0	(0.0)	0	0.0
	Minor	N/A	N/A	N/A	N/A	N/A	N/A	N/A	(27.4)	63	1156.1	124	(16.7)	19	945.9	50	(28.9)	67	1286.6

For complete treatment regimens, see [Table 6–1](#). ^a An additional major episode was reported in Trial 1572 (liraglutide 0.6 mg) but is not included in the table as it occurred the day after last drug date. N: Number of Subjects with hypoglycemic episode; %: Proportion of subjects having hypoglycemic episode; E: Number of hypoglycemic episode; Rate: Number of episodes divided by subject years of exposure multiplied by 1,000. N/A: not applicable.

The relative risks of experiencing a minor hypoglycemic episode were analyzed with a general linear model ([Figure 6–22](#)). The rate of minor hypoglycemic episodes was lower for liraglutide as

monotherapy compared with glimepiride (Trial 1573) and for liraglutide in combination with metformin vs. glimepiride + metformin (Trial 1572). When combined with a sulfonylurea, the rate was higher for liraglutide in combination with glimepiride vs. glimepiride + rosiglitazone (Trial 1436) and for liraglutide in combination with rosiglitazone and metformin vs. metformin + rosiglitazone (Trial 1574). In both Trial 1436 and 1574, the final HbA_{1c} achieved with liraglutide in combination with background therapy was lower than that achieved with background therapy or active comparator. No significant differences between treatments were seen in Trial 1697.

Figure 6–22 Forest Plot of Minor Hypoglycemic Episodes, Comparing Rate Ratios between Treatment Groups ($\pm 95\%$ CI)



Placebo treatment: Trial 1572 (metformin), Trial 1436 (glimepiride), Trial 1574 (metformin + rosiglitazone) and Trial 1697 (glimepiride + metformin). Active comparator treatment: Trial 1573 (glimepiride), Trial 1572 (glimepiride + metformin), Trial 1436 (rosiglitazone + glimepiride) and Trial 1697 (insulin glargine + glimepiride + metformin). For complete treatment regimens in the individual trials, see [Table 6–1](#).

A total of nine major hypoglycemic episodes in eight subjects were reported of which one occurred after last drug date. No episodes of major hypoglycemia were observed when administering liraglutide as monotherapy or in combination with a TZD (rosiglitazone). A total of seven of these episodes in six subjects were reported in subjects where liraglutide was administered with glimepiride (Trials 1436 and 1697) ([Table 6–18](#)). Two remaining episodes were reported in two subjects in the open-label part of Trial 1572 where the subjects were treated with liraglutide (0.6 mg and 1.2 mg) in combination with metformin.

The hypoglycemic profile of liraglutide reflects the mode of action of native GLP-1, which is dependent on the blood glucose level. The fact that liraglutide primarily exerts its effect if the blood glucose level is above the threshold to stimulate insulin release, decreases the risk of hypoglycemia. Thus, the risk of experiencing hypoglycemia is low. The risk does, however, increase when

liraglutide is administered with a sulfonylurea such as glimepiride, and this information will be reflected in the proposed label for liraglutide.

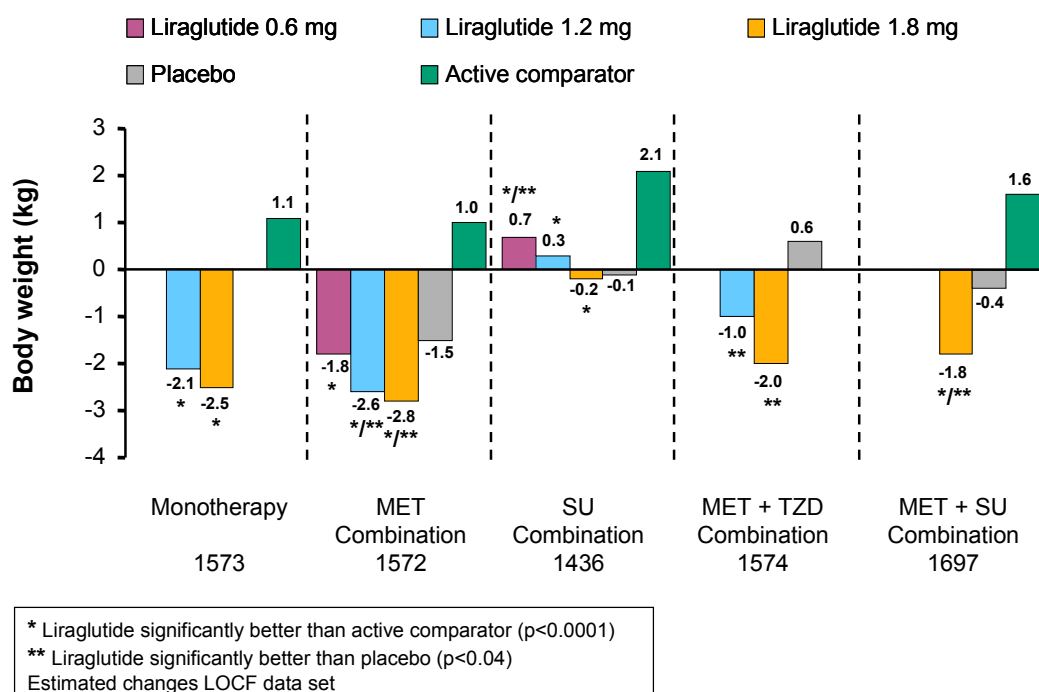
6.9.2 Weight

Change in body weight was a secondary endpoint in all five long-term phase 3 trials. Treatment with liraglutide as monotherapy or in combination with one or two OADs induced a significant weight loss in all long-term trials (except in Trial 1436) within the first eight weeks of treatment. The reduction in weight was maintained for the rest of the treatment period.

An overview of the results from the individual trials is presented in [Figure 6–23](#). In all trials with an active comparator, the difference between liraglutide and active comparators was significant and in favor of liraglutide at all liraglutide doses.

In four of the five long-term phase 3 trials (all except Trial 1436), a weight loss, ranging from 1.0 to 2.8 kg, was seen after treatment with liraglutide. In Trial 1436, only minor changes in body weight were seen with liraglutide in combination with glimepiride. Treatment with glimepiride + rosiglitazone (active comparator) led to weight gain; hence the difference to liraglutide + glimepiride was still significant, in favor of liraglutide.

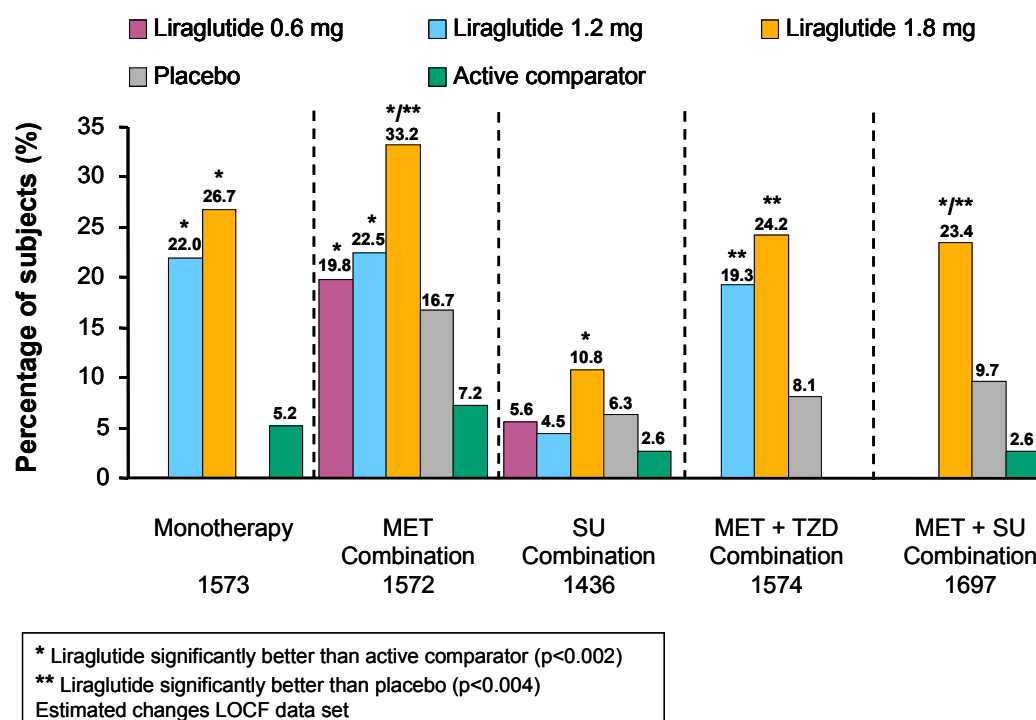
Figure 6–23 Body Weight, Change from Baseline (kg)



For complete treatment regimens in the individual trials, see [Table 6–1](#). Values are estimated mean values (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

Similarly, in four of the five trials (all except Trial 1436), approximately 19–33% of the subjects on liraglutide treatment had a weight loss of 5% or more ([Figure 6–24](#)). In Trial 1436, the majority of subjects treated with liraglutide + glimepiride or with glimepiride alone maintained their weight whereas subjects treated with rosiglitazone + glimepiride gained weight ([Figure 6–23](#)).

Figure 6–24 Fraction of Subjects with Weight Loss of 5% or More (%)



For complete treatment regimens in the individual trials, see [Table 6–1](#). Values are estimated mean values (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

Sustainability of Effect on Body Weight

Based on the results from the long-term phase 3 trials, weight declined over the first 12 weeks and remained stable thereafter. Following exposure for up to 12 months in Trial 1573, the mean body weight loss was maintained ([Figure 6–3](#)). Similarly, when liraglutide was used in combination with one or two OADs, mean body weight declined within the first 12 weeks and remained stable for the rest of the treatment period of 26 weeks ([Figure 6–6](#), [Figure 6–9](#), [Figure 6–12](#) and [Figure 6–15](#)).

6.10 Dosing Recommendations

Results from the phase 2 dose finding trials (Trials 1310, 2072, 1499, and 1571) led to the conclusion that the liraglutide 1.2 mg and 1.8 mg doses would be the relevant doses to be further studied in the long-term phase 3 trials, covering the dosing requirements of a type 2 diabetes population in monotherapy as well as in combination therapy. A step-wise dose titration beginning with liraglutide 0.6 mg was employed in the five long-term phase 3 trials for arms using liraglutide

doses of 1.2 mg or 1.8 mg. The titration was done to limit gastrointestinal intolerance which is seen with initiation on liraglutide doses of 1.2 mg or 1.8 mg.

A significant and clinically relevant difference between the liraglutide 1.2 mg and 1.8 mg doses was observed for the primary endpoint HbA_{1c} in the long-term phase 3 monotherapy Trial 1573. Importantly, in three of four long-term trials where both doses were employed, significantly more patients reached the ADA HbA_{1c} treatment target of <7.0% in the 1.8 mg group than in the 1.2 mg group. In addition, weight loss generally was greater in 1.8 mg than in the 1.2 mg dose in the trials where these were compared.

An overview of effect on glycemic control and weight in doses (liraglutide 0.6 mg, 1.2 mg and 1.8 mg) is summarized in [Table 6–19](#).

Table 6–19 Efficacy Profile of Liraglutide 0.6 mg, 1.2 mg and 1.8 mg in the Five Long-term Phase 3 Trials

Trial	1573		1572			1436			1574	
Liraglutide Dose (mg)	1.2	1.8	0.6	1.2	1.8	0.6	1.2	1.8	1.2	1.8
HbA _{1c} (% points) ^(a)	-0.84	-1.14*	-0.70	-0.97**	-1.0	-0.60	-1.08**	-1.13	-1.48	-1.48
Patients to HbA _{1c} Target (% subjects)	42.8	50.9*	28.0	35.3	42.4*	24.1	34.5**	41.6*	57.5	53.7
Weight Loss (kg) ^(a)	-2.05	-2.45	-1.78	-2.58**	-2.79	0.72	0.32	-0.23*	-1.02	-2.02*
Weight Loss ≥5% Bodyweight (% subjects)	22.0	26.7	19.8	22.5	33.2*	5.6	4.5	10.8*	19.3	24.2

*Statistically significant difference between liraglutide 1.8 mg and 1.2 mg. **Statistically significant difference between liraglutide 1.2 mg and 0.6 mg. ^a Estimated least square means.

Acknowledging that the majority of patients who would achieve target levels of HbA_{1c} would do so on the 1.2 mg dose, the data also show that a significant sub-population would achieve important and clinically relevant additional benefit from the liraglutide 1.8 mg dose. The 1.8 mg dose does provide the prescriber another safe option for increasing treatment effect of liraglutide, if clinically relevant and intensification of treatment is judged necessary. This approach is consistent with the individualization of therapy based on glycemic response used for other antidiabetic treatments.

The dosing is proposed as:

For all patients liraglutide should be initiated with a dose of 0.6 mg for at least one week, after which the dose should be increased to 1.2 mg. Based on clinical response and after at least one week the dose can be increased to 1.8 mg to achieve maximum efficacy.

6.11 Efficacy Conclusion

In summary, liraglutide was superior to placebo for the primary regulatory endpoint, change from baseline in HbA_{1c}, as defined and described in the long-term phase 3 protocols. The decrease in HbA_{1c} ranged from 0.84–1.48% points with the 1.2 mg dose and 1.0–1.48% points with the 1.8 mg dose. Furthermore, liraglutide was superior or non-inferior to a number of established therapies.

- Significant improvements in glycemic control (HbA_{1c}) were seen:
 - vs. placebo
 - in monotherapy vs. glimepiride
 - in combination with sulfonylurea vs. rosiglitazone + sulfonylurea
 - in combination with metformin + sulfonylurea vs. insulin glargine + metformin + sulfonylurea (difference within the non-inferiority margin)
- Significant and clinically relevant improvements in fasting and postprandial plasma glucose excursions were seen with liraglutide, supporting the conclusion of improved glycemic control
- Weight was a secondary endpoint and liraglutide consistently demonstrated weight reductions across the five long-term phase 3 trials
- Beta-cell function improved as assessed by secondary endpoints, HOMA-B and pro-insulin to insulin ratio

Thus, the liraglutide clinical development program has established the efficacy of liraglutide in improving glycemic control in type 2 diabetes under a spectrum of clinically relevant treatment scenarios. This efficacy is associated with low risk of hypoglycemia and weight loss.

7 Safety

This section presents results from the safety investigations with liraglutide. Adverse events, common adverse events, serious adverse events and adverse events leading to withdrawal are tabulated and presented. Specifically, the rodent C-cell findings and calcitonin monitoring in the clinical development program and major adverse cardiovascular events (MACE) are addressed in detail, but also pancreatitis immunogenicity, neoplasms, and general thyroid adverse events are discussed, as these have been identified as events of special interest.

7.1 Common Adverse Events

The adverse events described in this document, unless otherwise specified, are treatment emergent (TEAE) (see [Appendix, Section 2.3](#) for definition). Adverse events are presented by organ system class and preferred terms (e.g. gastrointestinal disorders; vomiting). This system is based on the Medical Dictionary for Regulatory Activities (MedDRA), generally used for coding and classifying adverse events for regulatory purposes.

Adverse events reported by $\geq 5\%$ of the subjects in the five blinded and open-label of the long-term phase 3 trials are presented by treatment and on a preferred term level in [Table 7-1](#). Rates as events/1,000 patient years are used for presentation of adverse events to account for differences in exposure between liraglutide, placebo, and active comparator in the development program.

Based on the pooled data from the long-term phase 3 trials, including the completed blinded part and the ongoing open-label part of extensions from Trials 1572 and 1573, 73.7–78.5% of the subjects treated with liraglutide reported adverse events ([Table 7-1](#)). For subjects treated with placebo and active comparators, the percentages were 65.8% and 66.3%, respectively.

Among those adverse events occurring in $\geq 5\%$ of subjects, the most common events reported in subjects treated with liraglutide were associated with the gastrointestinal system. From 35.4% to 44.6% of liraglutide-treated subjects had one or more gastrointestinal-related adverse event compared with 17.9% and 18.5% of the subjects treated with placebo or active comparators, respectively ([Table 7-1](#)). Gastrointestinal adverse events were reported most frequently in the early part of the treatment period with liraglutide and few subjects withdrew due to these adverse events (see Section [7.4](#) and [Figure 7-1](#) for a Kaplan-Meier Plot).

Other common adverse events across all treatment groups included headache and infections such as upper respiratory tract infections, influenza and nasopharyngitis. These events were equally distributed across all treatment groups. The most common adverse events in subjects treated with placebo and active comparators were events in the system organ class of infections and infestations. The majority of adverse events were mild, and $< 10\%$ of subjects in the five long-term phase 3 trials across treatment groups experienced adverse events of severe severity.

Novo Nordisk

Liraglutide (injection) NDA 22-341

Endocrine and Metabolic Drug Advisory Committee 2 April 2009

Table 7–1 Adverse Events in at Least 5% of the Subjects in any Treatment Group

	Liraglutide 0.6 mg				Liraglutide 1.2 mg				Liraglutide 1.8 mg				Placebo				Active Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		475				896				1130				524				953		
Total Exposure Years		387.3				724.1				824.5				265.0				738.4		
All Adverse Events	73.7	350	3075.2	1191	78.5	703	4003.4	2899	75.8	857	4142.1	3415	65.8	345	3578	948	66.3	632	2955.2	2182
GI disorders	35.4	168	712.6	276	44.1	395	1117.2	809	44.6	504	1385.2	1142	17.9	94	532.2	141	18.5	176	425.3	314
Nausea	8.2	39	113.6	44	20.8	186	324.5	235	21.3	241	402.7	332	4.8	25	109.5	29	4.1	39	73.1	54
Diarrhoea	9.3	44	131.7	51	11.2	100	209.9	152	14.0	158	245.0	202	4.6	24	98.1	26	4.6	44	82.6	61
Vomiting	3.6	17	46.5	18	8.0	72	127.0	92	8.7	98	158.9	131	2.1	11	41.5	11	1.3	12	20.3	15
Dyspepsia	3.6	17	49.1	19	3.8	34	48.3	35	6.3	71	97.0	80	1.3	7	37.7	10	2.0	19	33.9	25
Constipation	2.9	14	36.1	14	5.9	53	81.5	59	5.9	67	91.0	75	1.0	5	22.6	6	2.4	23	33.9	25
Infections and Infestations	37.5	178	741.0	287	38.4	344	820.3	594	33.5	379	773.8	638	33.8	177	958.7	254	35.5	338	777.4	574
Nasopharyngitis	10.9	52	198.8	77	8.6	77	150.5	109	8.8	99	135.8	112	6.9	36	181.2	48	10.4	99	176.1	130
Upper Respiratory Tract Infection	7.2	34	108.4	42	7.9	71	124.3	90	5.9	67	108.0	89	6.5	34	166.1	44	5.1	49	92.1	68
Nervous System Disorders	13.5	64	222.1	86	19.9	178	386.7	280	18.1	204	372.4	307	12.4	65	320.8	85	16.2	154	300.7	222
Headache	7.6	36	121.4	47	10.4	93	187.8	136	9.9	112	211.0	174	7.4	39	173.6	46	8.7	83	162.5	120
Musculoskel. and Con. Tissue Disorders	14.7	70	245.3	95	17.0	152	277.6	201	15.8	178	317.8	262	13.2	69	339.7	90	17.4	166	314.2	232
Metabolism and Nutrition Disorders	8.4	40	111.0	43	15.3	137	211.3	153	13.1	148	208.6	172	7.3	38	143.4	38	7.6	72	104.3	77
Decreased Appetite	0.8	4	10.3	4	5.1	46	73.2	53	3.8	43	55.8	46	0.6	3	11.3	3	0.1	1	1.4	1
General Disorders and Administration Site Conditions	9.5	45	129.1	50	12.9	116	200.2	145	11.9	135	212.3	175	8.8	46	234.0	62	8.8	84	143.6	106
Investigations	8.4	40	139.4	54	7.5	67	116.0	84	7.1	80	118.9	98	7.4	39	173.6	46	6.6	63	123.2	91
Respiratory, Thoracic and Mediastinal Disorders	7.2	34	103.3	40	7.8	70	138.1	100	6.6	75	118.9	98	6.9	36	158.5	42	7.1	68	128.7	95
Skin and Subcutaneous Tissue Disorders	5.7	27	74.9	29	7.7	69	109.1	79	5.9	67	89.8	74	4.6	24	101.9	27	4.9	47	74.5	55
Injury, Poisoning and Procedural Complications	6.5	31	98.1	38	6.3	56	102.2	74	5.7	64	93.4	77	4.6	24	101.9	27	8.0	76	123.2	91
Eye Disorders	6.3	30	95.5	37	6.0	54	81.5	59	5.0	56	72.8	60	5.2	27	109.5	29	5.4	51	77.2	57
Vascular Disorders	5.5	26	90.4	35	4.4	39	60.8	44	4.7	53	67.9	56	3.6	19	71.7	19	5.7	54	82.6	61
Cardiac Disorders	6.1	29	82.6	32	4.9	44	73.2	53	3.5	39	57.0	47	3.2	17	67.9	18	3.1	30	48.8	36

Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1–1](#). For complete treatment regimens in the individual trials, see [Table 6–1](#). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

[Table 7-2](#) presents adverse events occurring with liraglutide at a frequency at least 2% (absolute difference) greater than either placebo or active comparator. This table confirms the more frequent occurrence of gastrointestinal adverse events in subjects treated with liraglutide. Beyond this, an increased occurrence of events in liraglutide-treated subjects was seen in the system organ classes of infections and infestations (nasopharyngitis), nervous system disorders (headache), musculoskeletal and connective disorders (back pain and pain in extremity), metabolism and nutrition disorders (anorexia and decreased appetite), and general disorders and administration site conditions (fatigue and pyrexia).

The observed imbalance in the metabolism and nutrition disorders could be expected based on the appetite-reducing effect of liraglutide and the effect of GLP-1 to induce satiety. The remaining observed imbalances based on the defined cut-off level do not suggest a general clustering of adverse event or imbalances which would represent a safety concern.

Table 7–2 Adverse Events Occurring in at Least 2% More Subjects Treated with Liraglutide Compared with Placebo or Active Comparator

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set	2501				524				953				1477			
Total Exposure Years	1935.9				265.0				738.4				1003.3			
GI disorders	42.7	1067	1150.4	2227	17.9	94	532.2	141	18.5	176	314	425.3	18.3	270	455	453.5
Nausea	18.6	466	315.6	611	4.8	25	109.5	29	4.1	39	54	73.1	4.3	64	83	82.7
Diarrhoea	12.1	302	209.2	405	4.6	24	98.1	26	4.6	44	61	82.6	4.6	68	87	86.7
Vomiting	7.5	187	124.5	241	2.1	11	41.5	11	1.3	12	15	20.3	1.6	23	26	25.9
Constipation	5.4	134	76.5	148	1.0	5	22.6	6	2.4	23	25	33.9	1.9	28	31	30.9
Dyspepsia	4.9	122	69.2	134	1.3	7	37.7	10	2.0	19	25	33.9	1.8	26	35	34.9
Infections and Infestations	36.0	901	784.7	1519	33.8	177	958.7	254	35.5	338	574	777.4	34.9	515	828	825.3
Nasopharyngitis	9.1	228	153.9	298	6.9	36	181.2	48	10.4	99	130	176.1	9.1	135	178	177.4
Nervous System Disorders	17.8	446	347.6	673	12.4	65	320.8	85	16.2	154	222	300.7	14.8	219	307	306
Headache	9.6	241	184.4	357	7.4	39	173.6	46	8.7	83	120	162.5	8.3	122	166	165.5
Musculoskeletal and Connective Tissue Disorders	16.0	400	288.2	558	13.2	69	339.7	90	17.4	166	232	314.2	15.9	235	322	320.9
Metabolism and Nutrition Disorders	13.0	325	190.1	368	7.3	38	143.4	38	7.6	72	77	104.3	7.4	110	115	114.6
Anorexia	3.8	96	51.7	100	0.4	2	7.5	2	0.4	4	4	5.4	0.4	6	6	6.0
Decreased Appetite	3.7	93	53.2	103	0.6	3	11.3	3	0.1	1	1	1.4	0.3	4	4	4.0
General Disorders and Administration Site Conditions	11.8	296	191.1	370	8.8	46	234.0	62	8.8	84	106	143.6	8.8	130	168	167.4

Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1–1](#). For complete treatment regimens in the individual trials, see [Table 6–1](#). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events, R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

7.2 Laboratory Evaluations

Clinical laboratory parameters (standard hematology, biochemistry and urinalysis) were measured at baseline and at the end of the trial for all liraglutide trials. Additionally, long-term trials also had laboratory parameters evaluated at intervals throughout the trials.

The changes in clinical laboratory values from baseline to end of treatment as well as changes over time (weeks) were evaluated. No consistent or clinically relevant changes in hematology, biochemistry or urinalysis parameters were observed with liraglutide treatment compared to placebo or active comparator.

7.3 Serious Adverse Events

A total of 227 serious adverse events, as defined in [Appendix, Section 1.4](#), were reported by 187 liraglutide-treated subjects across all completed trials. The corresponding number for non-liraglutide-treated subjects was 129 serious adverse events reported by 104 subjects. There was no difference in the rate of serious adverse events between liraglutide and non-liraglutide exposed subjects with the rates being 93.2 in the liraglutide group and 104.6 per 1,000 subject years of exposure in the non-liraglutide group ([Table 7-3](#)). The nine deaths in the clinical development program are included in the total numbers of serious adverse events in [Table 7-3](#). For a summary of deaths experienced during the program, see [Table 7-6](#).

Table 7-3 Summary of Serious Adverse Events in All Completed Trials

	Liraglutide				Non-Liraglutide			
	%	N	R	E	%	N	R	E
Safety Analysis Set		4655				2492		
Total Exposure Years		2434.4				1233.8		
All Serious Adverse Events	4.0	187	93.2	227	4.2	104	104.6	129
Severity								
Severe	2.1	99	46.0	112	2.5	62	61.6	76
Moderate	1.5	71	32.5	79	1.5	37	34.9	43
Mild	0.6	30	14.8	36	0.4	10	8.1	10

Table is based on population 2 (all completed trials) in [Appendix, Table 1-1](#). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

Serious adverse events belonging to the system organ classes of cardiac disorders, neoplasms (benign, malignant and unspecified neoplasms including cysts and polyps), infections and infestations and gastrointestinal disorders were the most frequently reported by subjects across all treatment groups. The serious adverse events in these four system organ classes, reported at a rate of at least 0.5 events per 1,000 subject years of exposure with liraglutide, are listed in [Table 7-4](#).

Table 7–4 Serious Adverse Events in the Four Most Common System Organ Classes Reported at a Rate of at Least 0.5 Events with Liraglutide per 1,000 Subjects Years of Exposure (all Completed Trials)

	Liraglutide				Non-Liraglutide			
	%	N	R	E	%	N	R	E
Safety Analysis Set		4655				2492		
Total Exposure Years		2434.4				1233.8		
All Serious Adverse Events	4.0	187	93.2	227	4.2	104	104.6	129
Cardiac Disorders	0.8	39	16.8	41	0.7	18	15.4	19
Angina Pectoris	0.2	7	2.9	7	0.1	3	2.4	3
Acute Myocardial Infarction	0.1	6	2.5	6	0.2	4	3.2	4
Myocardial Infarction	0.1	6	2.5	6	0.2	5	4.1	5
Coronary Artery Disease	0.1	4	1.6	4	0.0	1	0.8	1
Atrial Fibrillation	0.0	2	0.8	2	0.0	1	0.8	1
Cardiac Failure Congestive	0.0	2	0.8	2				
Myocardial Ischaemia	0.0	2	0.8	2				
Supraventricular Tachycardia	0.0	2	0.8	2				
Neoplasms Benign, Malignant and Unspecified Incl Cysts and Polyps	0.6	29	12.3	30	0.4	10	8.1	10
Papillary Thyroid Cancer	0.1	5	2.1	5	0.0	1	0.8	1
Prostate Cancer	0.1	5	2.1	5	0.0	1	0.8	1
Breast Cancer	0.1	3	1.2	3	0.0	1	0.8	1
Rectal Cancer	0.0	2	0.8	2				
Infections and Infestations	0.5	24	10.7	26	0.4	11	10.5	13
Gastroenteritis	0.1	3	1.2	3	0.0	1	0.8	1
Upper Respiratory Tract Infection	0.1	3	1.2	3				
Osteomyelitis	0.0	2	1.2	3				
Appendicitis	0.0	2	0.8	2	0.0	1	0.8	1
Bronchitis	0.0	2	0.8	2				
Gastrointestinal Disorders	0.5	23	11.1	27	0.5	12	12.2	15
Vomiting	0.1	3	1.2	3	0.1	2	1.6	
Appendicitis Perforated	0.0	2	0.8	2				2
Gastritis	0.0	2	0.8	2				
Inguinal Hernia	0.0	2	0.8	2	0.1	2	1.6	2
Pancreatitis ^(a)	0.0	2	0.8	2				

Table is based on population 2 (all completed trials) in [Appendix, Table 1–1](#). ^a The two pancreatitis events tabulated here correspond to Subjects xx2009 (Trial 1572) and xx0006 (Trial 1573) in [Table 7–10](#). Subjects xx4014 (Trial 1573), xx6013 (Trial 1572) and xx6016 (Trial 1436) ([Table 7–10](#)) are not included here as the term ‘oedematous pancreatitis’ occurs at a rate lower than 0.5 with liraglutide. Subjects xx7006 (Trial 1573), xx2006 (Trial NN8022-1807), xx9001 (Trial 1797) and xx4001 (Trial 1797) ([Table 7–10](#)) are not included here, as they were reported in ongoing trials and therefore not included in population 2. N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

In [Table 7–5](#), the frequency and rate of the adverse events listed in [Table 7–4](#) are presented by dose for the five long-term phase 3 trials. As can be seen, the distribution of serious adverse events in the population in all completed trials and in the population in the long-term phase 3 trials was similar.

In the single-dose, short-term and intermediate-term trials, serious adverse events were infrequently reported with no consistent pattern across system organ classes and preferred terms.

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Table 7–5 Serious Adverse Events in the Four Most Common System Organ Classes in the Five Long-term Phase 3 Trials

	Liraglutide 0.6 mg				Liraglutide 1.2 mg				Liraglutide 1.8 mg				Placebo				Active Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		475				896				1130				524				953		
Total Exposure Years		387.3				724.1				824.5				265.0				738.4		
All Serious Adverse Events	7.6	36	111.0	43	6.1	55	95.3	69	4.6	52	76.4	63	5.5	29	135.9	36	5.7	54	86.7	64
Cardiac Disorders	2.9	14	36.1	14	1.3	12	18.0	13	0.9	10	13.3	11	1.1	6	22.6	6	1.3	12	17.6	13
Angina Pectoris	0.6	3	7.7	3	0.2	2	2.8	2	0.2	2	2.4	2	0.4	2	7.5	2	0.1	1	1.4	1
Acute Myocardial Infarction	0.4	2	5.2	2	0.2	2	2.8	2	0.1	1	1.2	1	0.2	1	3.8	1	0.3	3	4.1	3
Myocardial Infarction	0.2	1	2.6	1	0.2	2	2.8	2	0.2	2	2.4	2	0.2	1	3.8	1	0.4	4	5.4	4
Coronary Artery Disease	0.2	1	2.6	1	0.1	1	1.4	1	0.2	2	2.4	2	0.0	0	0.0	0	0.1	1	1.4	1
Atrial Fibrillation	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.1	1	1.4	1
Cardiac Failure Congestive	0.0	0	0.0	0	0.2	2	2.8	2	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
Myocardial Ischaemia	0.2	1	2.6	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
Supraventricular Tachycardia	0.0	0	0.0	0	0.1	1	1.4	1	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Neoplasms Benign, Malignant and Unspecified Incl Cysts and Polyps	0.8	4	10.3	4	0.6	5	8.3	6	0.7	8	9.7	8	0.6	3	11.3	3	0.3	3	4.1	3
Papillary Thyroid Cancer ^(a)	0.0	0	0.0	0	0.1	1	1.4	1	0.2	2	2.4	2	0.2	1	3.8	1	0.0	0	0.0	0
Prostate Cancer	0.2	1	2.6	1	0.0	0	0.0	0	0.2	2	2.4	2	0.2	1	3.8	1	0.0	0	0.0	0
Breast Cancer	0.0	0	0.0	0	0.1	1	1.4	1	0.1	1	1.2	1	0.0	0	0.0	0	0.1	1	1.4	1
Rectal Cancer	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
Infections and Infestations	0.4	2	7.7	3	1.1	10	13.8	10	0.5	6	8.5	7	1.1	6	26.4	7	0.4	4	6.8	5
Gastroenteritis	0.0	0	0.0	0	0.1	1	1.4	1	0.1	1	1.2	1	0.0	0	0.0	0	0.1	1	1.4	1
Upper Respiratory Tract Infection	0.0	0	0.0	0	0.2	2	2.8	2	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Osteomyelitis	0.0	0	0.0	0	0.1	1	1.4	1	0.1	1	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Appendicitis	0.0	0	0.0	0	0.1	1	1.4	1	0.0	0	0.0	0	0.2	1	3.8	1	0.0	0	0.0	0
Bronchitis	0.2	1	2.6	1	0.1	1	1.4	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
Gastrointestinal Disorders	0.6	3	10.3	4	0.9	8	12.4	9	0.6	7	9.7	8	0.4	2	7.5	2	0.5	5	6.8	5
Vomiting	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
Appendicitis Perforated	0.0	0	0.0	0	0.1	1	1.4	1	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Gastritis	0.2	1	2.6	1	0.1	1	1.4	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0
Inguinal Hernia	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.2	1	3.8	1	0.0	0	0.0	0
Pancreatitis ^(b)	0.0	0	0.0	0	0.2	2	2.8	2	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0

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Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1-1](#). The events presented correspond to the events presented in [Table 7-4](#) and are not sorted by a specific frequency. ^a The four papillary thyroid events tabulated here correspond to Subjects xx1006 (Trial 1573), xx6001 (Trial 1436), xx6016 and xx6008 (Trial 1574) in [Table 7-27](#). Subject xx5008 in Trial 1573 ([Table 7-27](#)) is not included here as the event of papillary thyroid cancer was reported after 21 Feb 2008 and Subject xx004 in Trial 1334 ([Table 7-27](#)) is not included here as Trial 1334 is an intermediate-term trial and therefore not included in Population 4. ^b For the two events of pancreatitis, see footnote to [Table 7-4](#). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

Deaths

Nine deaths were reported during the clinical development program (Table 7–6). Four deaths were reported for subjects randomized to liraglutide, three were reported for subjects randomized to placebo or active comparators (OADs and insulin glargine), and two deaths were reported for subjects who had not yet been randomized. The number of deaths per treatment group was consistent with the randomization ratio of subjects and there was no clustering in cause of death.

Table 7–6 All Deaths Reported in the Liraglutide Clinical Development Program

Trial ID	Subject ID	Age (years)/ Gender (M/F)	Treatment	Preferred Term [MedDRA]	Duration of Therapy at Onset of Event
Liraglutide					
1700	xx25	63/F	Liraglutide 0.9 mg	Gastroenteritis	34 days
1697	xx8004	47/M	Liraglutide 1.8 mg	Renal cell carcinoma stage IV	117 days
			+glimepiride+metformin		
1572	xx5011	63/M	Liraglutide 1.2 mg+metformin	Liver cirrhosis and hepatocellular carcinoma ^(b)	160 days
1573	xx7006 ^(a)	64/F	Liraglutide 1.8 mg	Acute pancreatitis, colon cancer	669 days
Comparators					
1697	xx9012	67/F	Glimepiride+metformin	Acute myocardial infarction	78 days
1697	xx7005	54/M	Glargine+glimepiride+metformin	Acute myocardial infarction	117 days
1573	xx4036	56/F	Glimepiride	Road traffic accident	194 days
Not randomized					
1572	xx1030	76/M	Metformin (run-in period)	Cardio-respiratory arrest	N/A
1436	xx9011	71/M	No drug given	Pancreatic carcinoma	N/A

^a This case is described in more detail in Section 7.5. ^b Exact Preferred Terms (MedDRA): Hepatic cirrhosis and Hepatic neoplasm malignant.

7.4 Withdrawals Due to Adverse Events

In the 40 completed trials, the percentage of subjects withdrawn due to adverse events was higher for subjects randomized to liraglutide (6.0%) than for subjects randomized to comparators (non-liraglutide) (3.0%). Adverse events leading to withdrawal were predominantly non-serious in all treatment groups. The number of subjects withdrawing because of serious adverse events was similar for the liraglutide and comparators (non-liraglutide) treatment groups (1.0% vs. 1.3%, respectively) ([Table 7-7](#)).

Table 7-7 Summary of Adverse Events Leading to Subject Withdrawal in All Completed Trials

	Liraglutide				Non-Liraglutide			
	%	N	R	E	%	N	R	E
Safety Analysis Set		4655				2492		
Total Exposure Years		2434.4				1233.8		
All Adverse Events Withdrawals	6.0	278	221.0	538	3.0	76	85.1	105
Serious Adverse Events Withdrawals	1.0	48	22.2	54	1.3	32	31.6	39
Severity								
Mild	1.8	86	56.7	138	0.9	23	23.5	29
Moderate	3.6	166	117.5	286	1.5	38	36.5	45
Severe	1.8	85	46.8	114	1.0	25	25.1	31

Table is based on population 2 (all completed trials) in [Appendix, Table 1-1](#). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

[Table 7-8](#) presents adverse events leading to withdrawal reported at a rate of more than five events per 1,000 subject years of exposure in the liraglutide dose 1.8 mg treated population. In addition, the table presents the three most common adverse events reported at a rate of more than two events per 1,000 subject years of exposure for liraglutide 1.8 mg. Serious adverse event withdrawals reported by more than one event per 1,000 subject years of exposure for liraglutide 1.8 mg are presented in [Table 7-9](#).

Looking across all adverse event withdrawals, the most common adverse events leading to subject withdrawal in the liraglutide group were nausea, vomiting and diarrhea. Withdrawal due to gastrointestinal adverse events was reported for 1.7–6.2% of subjects treated with liraglutide and for 0.5–0.6% of subjects treated with comparators ([Table 7-8](#)). The withdrawals due to these types of events occurred mainly during the early treatment period, as illustrated in [Figure 7-1](#). Although less frequently reported in the comparator groups, gastrointestinal adverse events were also the most common reason for subject withdrawal in these groups, followed by adverse events in the system organ classes of investigations, metabolism and nutrition disorders, and nervous system disorders.

Table 7–8 Subjects Withdrawn Due to Adverse Events in the Five Long-Term Phase 3 Trials^(a)

	Liraglutide 0.6 mg				Liraglutide 1.2 mg				Liraglutide 1.8 mg				Placebo				Active Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		475				896				1130				524				953		
Total Exposure Years		387.3				724.1				824.5				265.0				738.4		
All Adverse Events Leading to Withdrawal	4.4	21	80.0	31	8.3	74	222.3	161	8.8	100	271.7	224	2.7	14	94.4	25	3.8	36	60.9	45
GI disorders	1.7	8	31.0	12	5.4	48	106.3	77	6.2	70	154.0	127	0.6	3	15.1	4	0.5	5	8.1	6
Nausea	0.6	3	7.7	3	2.9	26	35.9	26	3.6	41	55.8	46	0.0	0	0.0	0	0.0	0	0.0	0
Vomiting	0.6	3	7.7	3	1.3	12	16.6	12	2.0	23	30.3	25	0.2	1	3.8	1	0.0	0	0.0	0
Diarrhoea	0.0	0	0.0	0	1.5	13	23.5	17	1.2	14	19.4	16	0.0	0	0.0	0	0.2	2	2.7	2
Dyspepsia	0.2	1	2.6	1	0.3	3	4.1	3	0.6	7	8.5	7	0.0	0	0.0	0	0.0	0	0.0	0
Abdominal Pain	0.0	0	0.0	0	0.0	0	0.0	0	0.5	6	7.3	6	0.2	1	3.8	1	0.1	1	1.4	1
Constipation	0.2	1	2.6	1	0.2	2	2.8	2	0.4	5	6.1	5	0.0	0	0.0	0	0.0	0	0.0	0
Metabolism and Nutrition Disorders	0.6	3	7.7	3	1.5	3	18.0	13	1.6	18	23.0	19	0.8	4	15.1	4	0.2	2	2.7	2
Anorexia ^(b)	0.2	1	2.6	1	0.8	7	9.7	7	1.0	11	13.3	11	0.0	0	0.0	0	0.1	1	1.4	1
Decreased Appetite	0.0	0	0.0	0	0.4	4	5.5	4	0.5	6	7.3	6	0.0	0	0.0	0	0.0	0	0.0	0
Nervous System Disorders	0.6	3	7.7	3	1.1	10	19.3	14	1.4	16	19.4	16	0.2	1	3.8	1	0.3	3	4.1	3
Headache	0.0	0	0.0	0	0.2	2	2.8	2	0.7	8	9.7	8	0.2	1	3.8	1	0.0	0	0.0	0
Dizziness	0.2	1	2.6	1	0.3	3	4.1	3	0.4	4	4.9	4	0.0	0	0.0	0	0.2	2	2.7	2
Lethargy	0.2	1	2.6	1	0.1	1	1.4	1	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
General Disorders and Administration Site Conditions	0.4	2	5.2	2	1.1	10	13.8	10	1.1	12	14.6	12	0.2	1	3.8	1	0.5	5	6.8	5
Fatigue	0.0	0	0.0	0	0.2	2	2.8	2	0.4	5	6.1	5	0.0	0	0.0	0	0.0	0	0.0	0
Malaise	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Investigations	0.6	3	7.7	3	1.0	9	12.4	9	0.9	10	12.1	10	0.4	2	7.5	2	0.8	8	10.8	8
Blood Calcitonin Increased	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.1	1	1.4	1
Blood Creatinine Increased	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.2	2	2.7	2
Weight Increased	0.0	0	0.0	0	0.1	1	1.4	1	0.2	2	2.4	2	0.0	0	0.0	0	0.4	4	5.4	4
Psychiatric Disorders	0.0	0	0.0	0	0.2	2	2.8	2	0.4	5	6.1	5	0.0	0	0.0	0	0.1	1	1.4	1
Insomnia	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.1	1	1.4	1
Skin and Subcutaneous Tissue Disorders	0.0	0	0.0	0	0.6	5	6.9	5	0.4	5	6.1	5	0.2	1	3.8	1	0.4	4	5.4	4

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	Liraglutide 0.6 mg				Liraglutide 1.2 mg				Liraglutide 1.8 mg				Placebo				Active Comparator			
Pruritus	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Cardiac Disorders	0.4	2	5.2	2	0.4	4	5.5	4	0.4	4	4.9	4	0.4	2	7.5	2	0.5	5	8.1	6
Myocardial Infarction	0.0	0	0.0	0	0.1	1	1.4	1	0.2	2	2.4	2	0.2	1	3.8	1	0.2	2	2.7	2
Eye Disorders	0.0	0	0.0	0	0.1	1	1.4	1	0.3	3	3.6	3	0.0	0	0.0	0	0.0	0	0.0	0
Hepatobiliary Disorders	0.0	0	0.0	0	0.1	1	1.4	1	0.3	3	3.6	3	0.0	0	0.0	0	0.0	0	0.0	0
Cholelithiasis	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Infections and Infestations	0.0	0	0.0	0	0.6	5	6.9	5	0.3	3	4.9	4	0.4	2	7.5	2	0.1	1	1.4	1
Musculoskeletal and Connective Tissue Disorders	0.4	2	5.2	2	0.4	4	6.9	5	0.3	3	3.6	3	0.2	1	11.3	3	0.0	0	0.0	0
Neoplasms Benign, Malignant and Unspecified Incl Cysts and Polyps	0.4	2	5.2	2	0.3	3	4.1	3	0.3	3	3.6	3	0.2	1	3.8	1	0.2	2	2.7	2
Ear and Labyrinth Disorders	0.0	0	0.0	0	0.1	1	1.4	1	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Vertigo	0.0	0	0.0	0	0.1	1	1.4	1	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Renal and Urinary Disorders	0.0	0	0.0	0	0.1	1	2.8	2	0.2	2	4.9	4	0.2	1	3.8	1	0.1	1	1.4	1
Urinary Retention	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Vascular Disorders	0.0	0	0.0	0	0.2	2	2.8	2	0.2	2	2.4	2	0.2	1	3.8	1	0.0	0	0.0	0
Hypertension	0.0	0	0.0	0	0.0	0	0.0	0	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0

Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1-1](#). ^a Presented adverse events: Gastrointestinal disorders: at least five events per 1,000 subject years of exposure (liraglutide 1.8 mg)/Other: three most common adverse events reported by a rate of at least two events per 1,000 subject years of exposure. ^b Anorexia as in decreased appetite. N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

Table 7–9 Percentage of Subjects Withdrawn Due to *Serious* Adverse Events in the Five Long-term Phase 3 Trials^(a)

	Liraglutide 0.6 mg				Liraglutide 1.2 mg				Liraglutide 1.8 mg				Placebo				Active Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		475				896				1130				524				953		
Total Exposure Years		387.3				724.1				824.5				265.0				738.4		
All Serious Adverse Events Leading to Withdrawal	1.3	6	20.7	8	1.6	14	22.1	16	1.1	12	17.0	14	1.3	7	37.7	10	1.7	16	25.7	19
Cardiac Disorders	0.4	2	5.2	2	0.4	4	5.5	4	0.3	3	3.6	3	0.4	2	7.5	2	0.5	5	8.1	6
Myocardial Infarction	0.0	0	0.0	0	0.1	1	1.4	1	0.2	2	2.4	2	0.2	1	3.8	1	0.2	2	2.7	2
Acute Myocardial Infarction	0.0	0	0.0	0	0.1	1	1.4	1	0.1	1	1.2	1	0.2	1	3.8	1	0.2	2	2.7	2
Neoplasms Benign, Malignant and Unspecified Incl Cysts and Polyps	0.4	2	5.2	2	0.3	3	4.1	3	0.3	3	3.6	3	0.2	1	3.8	1	0.2	2	2.7	2
Breast Cancer	0.0	0	0.0	0	0.1	1	1.4	1	0.1	1	1.2	1	0.0	0	0.0	0	0.1	1	1.4	1
Lung Carcinoma Cell Type Unspecified Recurrent	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Prostate Cancer	0.2	1	2.6	1	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Hepatobiliary Disorders	0.0	0	0.0	0	0.1	1	1.4	1	0.2	2	2.4	2	0.0	0	0.0	0	0.0	0	0.0	0
Cholecystitis	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Cholelithiasis	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Infections and Infestations	0.0	0	0.0	0	0.4	4	5.5	4	0.2	2	2.4	2	0.2	1	3.8	1	0.1	1	1.4	1
Herpes Zoster	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Spermatic Cord Funiculitis	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
GI disorders	0.0	0	0.0	0	2 0.2		2.8	2	0.1	1	1.2	1	0.2	1	3.8	1	0.3	3	4.1	3
Oedematous Pancreatitis	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Metab and Nutrition Disorders	0.2	1	2.6	1	0.0	0	0.0	0	0.1	1	1.2	1	0.4	2	7.5	2	0.0	0	0.0	0
Hypoglycaemia	0.2	1	2.6	1	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Musculoskeletal and Connective Tissue Disorders	0.2	1	2.6	1	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Collagen Disorder	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0
Nervous System Disorders	0.2	1	2.6	1	0.1	1	1.4	1	0.1	1	1.2	1	0.0	0	0.0	0	0.1	1	1.4	1
Cardiovascular Accident	0.0	0	0.0	0	0.0	0	0.0	0	0.1	1	1.2	1	0.0	0	0.0	0	0.0	0	0.0	0

Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1–1](#). ^a Withdrawal AEs reported at a rate more than one event per 1,000 subject years of exposure with liraglutide 1.8 mg are tabulated. N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

A Kaplan-Meier plot, based on pooled data from all long-term phase 3 trials, of time from randomization to withdrawal due to gastrointestinal adverse events, demonstrated that the majority of the withdrawals due to gastrointestinal adverse events happened primarily in the first eight weeks of the trials ([Figure 7-1](#)).

Figure 7-1 Kaplan-Meier Plot of Time from Randomization to Gastrointestinal Adverse Event Leading to Withdrawal

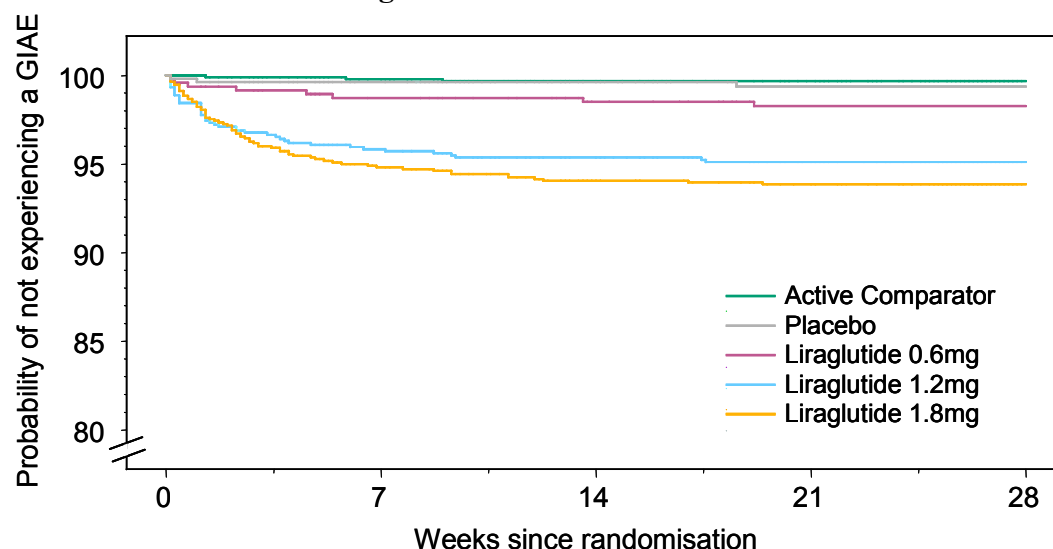


Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part) in [Appendix, Table 1-1](#). For complete treatment regimens in the individual trials, see [Table 6-1](#). GIAE: gastrointestinal adverse event.

7.5 Pancreatitis

7.5.1 Pancreatitis Adverse Events

In the late phase of the clinical development of liraglutide, cases of pancreatitis were reported in subjects treated with exenatide, a marketed product in the GLP-1 receptor agonist class.

A diagnosis of acute pancreatitis requires two of three features.³⁸ 1) abdominal pain characteristic of acute pancreatitis, 2) serum amylase and/or lipase >3 times the upper limit of normal, and 3) characteristic findings of acute pancreatitis on CT scan.^{39,40} Several well-acknowledged predisposing etiological factors are described in the literature, such as history of alcohol abuse, biliary tract disease or gall stones, abdominal surgery or family history of pancreatitis, recent abdominal trauma and weight loss.³⁸ Gall stones and alcohol abuse account for up to 80% of all cases.⁴¹ No pre-defined criteria for the diagnosis of pancreatitis were established in the liraglutide clinical trial protocols and analysis of amylase or lipase was not included as a standard assessment.

In total, nine cases of pancreatitis were reported in the liraglutide development program: liraglutide: 8 and non-liraglutide: 1. Seven cases were reported as acute and two as chronic pancreatitis. All pancreatitis events were reported in the intermediate and long-term trials. Eight of the nine cases

were reported in the 120-day Safety Update. The rates here were: 2.2, 0.0, 0.9 and 0.6 events per 1,000 subject years of exposure for total liraglutide, placebo, active comparator and total comparator, respectively. After the 120-day Safety Update, one new event of pancreatitis was reported in Trial 1797 in a subject treated with liraglutide 1.8 mg. [Table 7–10](#) provides an overview of the background of the subjects and [Table 7–11](#) provides details on the events.

The outcome of the nine pancreatitis cases was as follows: Of the seven acute cases of pancreatitis (liraglutide: 6 and non-liraglutide:1), one subject on liraglutide continued in the trial and four liraglutide subjects and the one non-liraglutide subject were withdrawn from the trial. The two subjects with chronic pancreatitis (both randomized to liraglutide) continued in the trial. In total, six of the seven subjects with pancreatitis cases reported as acute recovered. In one acute case, pancreatitis was diagnosed on the basis of autopsy findings without a concomitant clinical history. The details of this case are described later in this section. The two subjects with reported chronic pancreatitis continued on trial medication and were not withdrawn. For all nine cases of pancreatitis, the latency time varied. The range in time from onset of treatment till occurrence of pancreatitis was 50–699 days.

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Table 7–10 All Subjects with Pancreatitis in the Development Program - Background Information

Trial/ Subject ID	Treatment	Gender	Age (years)	Race/ethnicity	BMI (kg/m²)	Preferred Term (medDRA)	Identified risk factors for acute pancreatitis
Acute Pancreatitis							
1572/xx2009	Liraglutide 1.2 mg +metformin 2 g	M	49	White	31.8	Pancreatitis	N/A
1573/xx0006	Liraglutide 1.2 mg	F	46	White/not Hispanic	28.3	Pancreatitis	Regular alcohol use.
1573/xx4014	Liraglutide 1.8 mg	F	71	White/Hispanic	28.6	Oedematous pancreatitis	Cholecystitis, biliary mud, cholecystectomy performed one week after pancreatitis (cholelithiasis identified)
1573/xx7006	Liraglutide 1.8 mg	F	62	White/not Hispanic	43.4	Pancreatitis acute	Hyperlipidemia, cholelithiasis, chronic pancreatitis, treatment with lisinopril, 2x colonoscopy in general anesthesia with propofol (Diprivan), second colonoscopy three days before death (with patient maneuvering and abdominal pressure). Patient discharged with abdominal pain after procedure
NN8022-1807/xx2006	Liraglutide 3.0 mg	F	42	White	34.9	Pancreatitis acute	Cholelithiasis
1572/xx6013	Glimepiride 4 mg +metformin 2 g	F	58	White	38.7	Pancreatitis acute	Elevated triglycerides prior to the event (>1500 mg/dL)
1797/xx9001 ^(a)	Liraglutide 1.8 mg +OAD	M	64	White	31.5	Pancreatitis acute	N/A
Chronic Pancreatitis							
1436/xx6016	Liraglutide 0.6 mg +glimepiride 4 mg	M	63	White	30.02	Pancreatitis chronic	N/A
1797/xx4001	Liraglutide 1.8 mg +OAD	M	69	White	28.17	Pancreatitis chronic	N/A

^a This case was reported after the cut-off of the 120-day Safety Update and is therefore not included in tables with adverse events based on the 120-day Safety Update.

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Table 7–11 All Subjects with Pancreatitis in the Development Program - Details on Pancreatitis Event

Trial/ Subject ID	Treatment	Preferred Term (medDRA)	Diagnostic Criteria			Outcome	Withdrawn (additional details)	Latency time (days)
			Highest amylase level (normal range)	Other relevant lab tests (normal range)	Other examinations			
Acute Pancreatitis								
1572/xx2009	Liraglutide 1.2 mg +metformin 2 g	Pancreatitis	698 U/L (0–90)	CRP 50.5 mg/L (0–10) ALP and GGTP were normal	Ultrasound: normal CT scan: normal (fatty liver infiltration)	Recovered	Yes (drug not re- introduced)	50
1573/xx0006	Liraglutide 1.2 mg	Pancreatitis	519 U/L (25–115)	Lipase 1755 U/L (114–286)	ERCP: normal	Recovered	No (3 doses missed)	197
1573/xx4014	Liraglutide 1.8 mg	Oedematous pancreatitis	1651 U/L (13–53)	CRP 151 mg/L (1–3) ALT 121 U/L (7–31)	Ultrasound: signs of pancreatitis, biliary mud and possible lithiasis CT scan: pancreatitis degree C, severity index 4 points	Recovered	Yes (drug not re- introduced)	313
1573/xx7006	Liraglutide 1.8 mg	Pancreatitis acute	N/A	N/A	N/A	Fatal ^(a)	N/A	669
NN8022- 1807/xx2006	Liraglutide 3.0 mg	Pancreatitis acute	351 U/L (10–65)	ALT, ALP and bilirubin high	Ultrasound: multiple concrements in gall bladder MRCP: normal bile ducts	Recovered	Yes ^(b)	299
1572/xx6013	Glimepiride 4 mg +metformin 2 g	Pancreatitis acute	Urine >2000 U/L (<490)	ALT 19 U/L (9–43)	Ultrasound: pancreatic enlargement and augmented blood flow; CT scan: data for pancreatitis	Recovered	Yes (drug not re- introduced)	63
1797/xx9001 (c)	Liraglutide 1.8 mg g+OAD	Pancreatitis acute	538 U/L (36–128)	Lipase 1540 U/L (8–57)	CT scan: peripancreatic, inflammatory fat stranding involving distal pancreatic body and tail. No focal fluid collections. Ultrasound: minimal debris in the gallbladder but no evidence of stone, gallbladder wall	Recovered	Yes	419

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Trial/ Subject ID	Treatment	Preferred Term (medDRA)	Diagnostic Criteria			Outcome	Withdrawn (additional details)	Latency time (days)
					thickening or pericholecystic fluid. Normal common bile duct.			
Chronic Pancreatitis								
1436/xx6016	Liraglutide 0.6 mg +glimepiride 4 mg	Pancreatitis chronic	119 U/L		No signs of calcification in pancreas. CT scan: no abnormal findings besides nephrosclerosis.	Not recovered	No	157
1797/xx4001	Liraglutide 1.8 mg +OAD	Pancreatitis chronic	No levels reported	No levels reported	Unknown	Not recovered	No	88

^a See narrative of this case in text below. ^b Subject xx2006 (Trial NN8022-1807) was re-introduced to trial drug for four days, whereafter trial drug was withdrawn permanently. ^c This case was reported after the cut-off of the 120-day Safety Update and is therefore not included in tables with adverse events based on the 120-day Safety Update. ERCP: Endoscopic Retrograde Cholangiopancreatography. MRCP: Magnetic Resonance Cholangiopancreatography.

One fatality in a subject with pancreatitis occurred, and this case is reviewed in detail below.

Subject xx7006, Trial 1573 ext (liraglutide 1.8 mg), Fatal Case, Pancreatitis Acute

A 64-year-old female subject with a BMI of 43 kg/m² treated with liraglutide 1.8 mg for 669 days was reported to have acute pancreatitis based on autopsy findings and adenocarcinoma of the ascending colon (polyp). The subject died three days after having had a colonoscopy to evaluate the potential of a surgical procedure for colon cancer. Medical history was significant for hypertension, obesity, hyperlipidemia and diverticulum. An additional two events (diverticulosis and internal hemorrhoids) were reported and evaluated as non-serious.

A first colonoscopy showed a colonic polyp in the ascending colon and biopsy was performed. There was no sign of intestinal perforation during the colonoscopy as per the procedure report. No Endoscopic Retrograde Cholangiopancreatography (ERCP) was performed. Three days later, the pathology report on the biopsy was available and indicated: adenomatous polyp of ascending colon with areas of severe surface dysplasia and areas suspicious for infiltrating adenocarcinoma.

Approximately one month later, a repeat colonoscopy was performed to re-biopsy the area and to determine the extent and need for invasive surgery. After the second colonoscopy, the subject developed abdominal pain, but was described as active in the evening two days after the colonoscopy. On the third day post-colonoscopy the subject's condition deteriorated for unclear reasons and she died on the same day at home. She was not admitted to the hospital and no laboratory or imaging evaluations were conducted.

Outcome of the event adenocarcinoma of the ascending colon (polyp) was reported as unknown, as the removal of the polyp occurred only three days prior to death and there were no further pathology reports concerning invasiveness of the carcinoma.

The autopsy reported features of acute and chronic pancreatitis, cholelithiasis and fatty change of the liver. Macroscopic evaluation of the pancreas revealed that the pancreas was present in its usual location and was made up of soft tissue with mottled white, tan, and dark red to black areas with most of the lighter areas about the periphery. The gallbladder was observed to contain multiple black stones measuring up to 4 mm across. Microscopic analysis of the pancreas revealed fatty change and autolysis. Autolysis was seen in a range of organs beyond the pancreas.

The death certificate gave acute pancreatitis as the official cause of death, with cholelithiasis as a supporting condition contributing to death.

No previous medical records or amylase and lipase measurements were available. The subject had no known history of alcohol consumption. No further information concerning the three-day period between the colonoscopy and death is available.

7.5.2 Conclusion

There was a numeric imbalance in pancreatitis adverse events with a higher rate of events reported for liraglutide than for comparators. In total, nine pancreatitis adverse events were reported in the liraglutide development program. The rate was 2.2 in liraglutide-treated subjects and 0.6 in non-liraglutide subjects per 1,000 years of subject exposure. As reviewed above, a definitive role of liraglutide in any of the individual pancreatitis cases reported could not be established. Nonetheless, even though there was a low absolute risk, a small increase in relative risk could not be excluded. This information will be reflected in the labeling and in the guidance to the prescriber.

7.6 Immunogenicity and Antibody Formation

7.6.1 Presence of Antibodies

As part of the assessment of efficacy and safety of liraglutide, antibodies against liraglutide were measured in the long-term phase 3 trials. Given the methodology utilized, the most sensitive analysis of the samples for anti-liraglutide antibodies was when the subjects were off therapy and serum levels of liraglutide were negligible, reducing the risk of interference. After Week 27 (26 weeks + at least five days off drug), the proportion of samples positive for liraglutide antibodies was 9.2%, 8.2% and 8.1% with liraglutide 0.6 mg, 1.2 mg and 1.8 mg ([Table 7-12](#)). All had low titers, significantly below what is measured after treatment with other established protein therapeutics, e.g. s.c. insulin. About half of the antibody-positive samples demonstrated cross-reactivity to native GLP-1 and only a few subjects had antibodies with *in vitro* neutralizing effect on liraglutide (3, 4 and 5 subjects with liraglutide 0.6 mg, 1.2 mg and 1.8 mg, respectively) ([Table 7-12](#)).

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Table 7–12 Liraglutide Antibodies at End of Treatment (26 Weeks) in the Five Long-term Phase 3 Trials

	Liraglutide 0.6 mg		Liraglutide 1.2 mg		Liraglutide 1.8 mg		Placebo		Active Comparator	
	%	N	%	N	%	N	%	N	%	N
Safety Analysis Set		475		896		1130		524		953
End of Treatment (LOCF)										
N ^(a)	100.0	229	100.0	388	100.0	603	100.0	316	100.0	448
Positive Liraglutide Antibody	9.2	21	8.2	32	8.1	49	0.3	1	0.2	1
Positive <i>in vitro</i> Neutralizing Effect	1.3	3	1.0	4	0.8	5	0.0	0	0.0	0
Positive GLP-1 Cross-Reacting Effect	5.7	13	4.6	18	4.1	25	0.0	0	0.0	0

^a Number of samples taken. Subjects in open-label extensions are not included as a 5-day off-drug period is requested ensure validity of the assay.

Statistical analysis was performed to evaluate whether the presence of antibodies, *in vitro*, neutralizing effect or cross-reacting effect had an impact on the ability of liraglutide to reduce HbA_{1c}. No significant effect of the presence or absence of antibody was found in the pooled data from the four combination therapy trials (Trial 1572, 1436, 1574 and 1697). [Table 7-13](#) provides a summary of changes in mean HbA_{1c} from baseline for subjects separated by antibody status.

Table 7-13 Summary of Change in HbA_{1c} by Antibody Status ^(a)

Positive Liraglutide Antibodies	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo	Active Comparator
Negative					
N	202	337	534	311	429
Mean (SD)	-0.5 (1.0)	-1.2 (1.1)	-1.2 (1.1)	-0.2 (1.1)	-0.7 (1.0)
Positive					
N	21	32	48	1	1
Mean (SD)	-0.5 (1.1)	-1.3 (1.2)	-1.1 (0.9)	-0.8 (0.0)	-1.5 (0.0)

For an overview of treatment regimens, see [Table 6-1](#). ^a Subjects with antibody measurements at least five days off drug.

7.6.2 Immunogenicity Adverse Events

A systematic search of the clinical database was performed to find adverse events related to immunogenicity according to three Standardized MedDRA Queries (SMQs). These three groups are angioedemas, anaphylactic reactions and severe cutaneous reactions and include a large number of specific adverse event terms that can be grouped under these headings. The events are presented in [Table 7-14](#).

The rate of total immunogenicity adverse events was 12.2, 8.4, 5.4 and 6.3 events per 1,000 subject years of exposure with total liraglutide (any dose), placebo, active comparator and total comparator treatments, respectively ([Table 7-14](#)).

Table 7–14 All Immunogenicity Adverse Events Grouped by Standardized MedDRA Query

	Total Liraglutide				Placebo				Active comparator				Total comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		3125.9				474.4				1118.7				1593.1		
All Immunogenicity Adverse Events	0.8	36	12.2	38	0.4	4	8.4	4	0.4	6	5.4	6	100.4		6.3	10
Angioedema	0.8	34	11.2	35	0.2	2	4.2	2	0.3	5	4.5	5	70.3		4.4	7
Urticaria	0.4	19	6.4	20	0.2	2	4.2	2	0.2	3	2.7	3	0.2	5	3.1	5
Gingival Swelling	0.0	2	0.6	2					0.1	1	0.9	1	0.0	1	0.6	1
Pharyngeal Oedema	0.0	2	0.6	2												
Oedema Mouth	0.0	2	0.6	2												
Lip Swelling	0.0	2	0.6	2												
Eyelid Oedema	0.0	1	0.3	1					0.1	1	0.9	1	0.0	1	0.6	1
Angioedema	0.0	2	0.6	2												
Periorbital Oedema	0.0	1	0.3	1												
Face Oedema	0.0	1	0.3	1												
Eye Swelling	0.0	1	0.3	1												
Eye Oedema	0.0	1	0.3	1												
Anaphylactic Reaction	0.0	1	0.6	2	0.1	1	2.1	1	0.1	1	0.9	1	0.1	2	1.3	2
Circulatory Collapse					0.1	1	2.1	1	0.1	1	0.9	1	0.1	2	1.3	2
Anaphylactic Reaction	0.0	1	0.6	2												
Severe Cutaneous Reactions	0.0	1	0.3	1	0.1	1	2.1	1					0.0	1	0.6	1
Dermatitis Bullous	0.0	1	0.3	1	0.1	1	2.1	1					0.0	1	0.6	1

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1–1](#). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

The absolute rate for adverse events in these categories was low. The most common immunogenicity-related adverse event in all treatment groups was urticaria. These did not meet the pharmacovigilance/regulatory definitions of serious. Urticaria accounted for the majority of events in the group of angioedemas, and the remaining adverse events included various types of swelling and edemas. There was a numerical imbalance in the SMQ group of angioedemas, driven by a higher number of urticaria cases in subjects randomized to liraglutide compared to placebo and active comparators ([Table 7–14](#)). Corroborating the non-serious nature of the events – only two subjects were withdrawn, both subjects treated with liraglutide (urticaria and lip swelling).

The events in the remaining two SMQ groups included single events. One subject treated with liraglutide experienced two anaphylactic reactions. These did not meet the pharmacovigilance/regulatory definitions of serious. For the second event of anaphylaxis in this subject, the investigator reported the verbatim ‘anaphylaxis reaction (wheat)’, suggesting that the reaction was related to wheat rather than liraglutide.

Apart from one serious adverse event of angioedema, all events in [Table 7–14](#) were non-serious. The serious adverse event of angioneurotic edema occurred within minutes after the administration of the antibiotic Bioparox[®] (fusafungine) for acute laryngopharyngitis. This subject was in the

liraglutide 1.2 mg + metformin treatment group (Trial 1572), and continued treatment unchanged throughout the event and the remainder of the study. Thus, a plausible alternative aetiology is available.

A Cox proportional hazard analysis of immunogenicity adverse events identified no statistically significant difference between treatment groups ([Table 7–15](#)). The number of adverse events was low, and the imbalance observed in non-serious urticaria events contributed substantially to the observed trend. Of all subjects experiencing an immunogenicity adverse event, only two subjects were found to be positive for antibodies against liraglutide. This was a subject in a Japanese trial (Trial 1701) who reported a non-serious case of urticaria. The subject completed the study.

Table 7–15 Cox Proportional Hazard Analysis of Immunogenicity Adverse Events

Comparison	Hazard ratio	95% CI	P-value
Liraglutide vs. Placebo	1.60	[0.55 ; 4.68]	0.3916
Liraglutide vs. Active	2.14	[0.88 ; 5.22]	0.0945
Liraglutide vs. Total Comparator	1.92	[0.94 ; 3.90]	0.0717
Active vs. Placebo	0.75	[0.19 ; 2.88]	0.6724

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1–1](#). Cox regression model stratified by trial. P-value from Wald test. Intermediate-terms trials, except NN8022-1807, are grouped.

Injection site reactions also with a potential immunological background were reported in approximately 2% of subjects (30 events per 1,000 subject years of exposure). The reactions were generally reported as mild (none were serious) and comparable with what is typically seen with insulin injection. In total, six subjects were withdrawn from trial and none of these had anti-liraglutide antibodies. The most frequently reported injection site disorders in subjects treated with liraglutide were injection site bruising and injection site pain.

7.6.3 Conclusion

The percentage of subjects with antibodies was <10% and titers were low. No interaction between presence of antibodies and liraglutide effect on HbA_{1c} was found. There was a numerical imbalance in the occurrence of urticaria, all of which were non-serious. Two cases of anaphylaxis were reported in one subject, presumably related to wheat. One episode of laryngeal edema occurred following exposure to the oral spray antibiotic, Bioparox[®]. The overall rate of immunogenicity adverse events was 12.2, 8.4, 5.4 and 6.3 events per 1,000 subject years of exposure with total liraglutide, placebo, active comparator and total comparator treatments, respectively. Immune-type adverse events occurred infrequently at rates consistent with other biopharmaceutical therapeutic injectable agents.

7.7 C-cells - Nonclinical and Clinical

A treatment-related increase in thyroid C-cell proliferative changes was observed in the lifetime carcinogenicity studies in rats and mice (see also Section 4.6). This led to the conduct of more than 30 nonclinical mechanistic studies to define the underlying mechanism, identify a biomarker, and perform an assessment of human relevance.

In the clinical development program, intensive monitoring of calcitonin, the identified and validated biomarker for C-cell mass and activation was performed in more than 5,000 subjects. The rodent findings also led to an increased focus on thyroid events and additional investigations were included in several of the intermediate and long-term clinical trials compared to what is standard for clinical development programs. The following sections describe the studies and outcomes of these nonclinical and clinical activities in the liraglutide development program.

7.7.1 C-cell Findings in Toxicology Studies

Minimal to mild C-cell hyperplasia was recorded in the thyroid in a 3-month toxicity study in mice. C-cell hyperplasia was detectable at nine weeks of dosing when using sensitive sampling and identification techniques in mice. The hyperplasia was reversible and the C-cell mass was normalized following a 15-week treatment free period. The thyroid follicular cells were normal in all studies. In rats, C-cell proliferation also was observed, whereas no evidence of C-cell proliferation was observed after up to 87 weeks of dosing in cynomolgus monkeys (see Section 7.7.3.8).

7.7.2 C-cell Findings in 2-year Carcinogenicity Studies

Mice

Table 7–16 summarizes the incidence of neoplastic C-cell findings in the thyroid in the mouse study.

Table 7–16 Incidence (%) of Neoplastic C-cell Findings in Mouse 2-year Carcinogenicity Study with Liraglutide

Mouse	Males					Females				
Dose group, mg/kg/day	0	0.03	0.2	1.0	3.0	0	0.03	0.2	1.0	3.0
Exposure Ratio	N/A	0.2	1.6	13.1	36.3	N/A	0.2	1.6	13.1	36.3
C-cell carcinoma (%)	0	0	0	0	0	0	0	0	0	3
C-cell adenoma (%)	0	0	0	13***	19***	0	0	0	6*	20***

Statistically significantly different from control: *p<0.05; ***: p<0.001. Analyzed by Peto analysis.

A treatment-related increase in benign thyroid C-cell adenomas was seen in the high mid-dose (1.0 mg/kg) and the high-dose group (3.0 mg/kg) in male and female mice. The systemic exposure levels were 13 and 36 times higher than human exposure at the 1.8 mg clinical dose. There were no C-cell adenomas in the control animals and the low and low-mid dose groups, and the no observed

adverse effect level (NOAEL) was 0.2 mg/kg. C-cell carcinomas were seen in two of 76 females in the 3 mg/kg dose group. No treatment-related findings were observed in the follicular part of the thyroid.

Rats

[Table 7–17](#) summarizes the incidence of neoplastic C-cell findings in the thyroid in the rat study.

Table 7–17 Incidence (%) of Neoplastic C-cell Findings in Rat 2-year Carcinogenicity Study with Liraglutide

Rats	Males				Females			
Dose group, mg/kg/day	0	0.075	0.25	0.75	0	0.075	0.25	0.75
Exposure Ratio	N/A	0.5	2.4	8.1	N/A	0.5	2.4	8.1
C-cell carcinoma (%)	2	8	6	14**	0	0	4	6
C-cell adenoma (%)	12	16	42***	46***	10	27*	33**	56***

Significantly higher than control: * P<0.05, ** P<0.01, *** P<0.001. Analyzed by Peto analysis.

In rats, a treatment-related increase in benign thyroid C-cell adenomas was seen in the mid-dose group (0.25 mg/kg) and high-dose (0.75 mg/kg) group of male rats and in all female dose groups. An increase in thyroid C-cell carcinomas was observed in all groups of males and in the mid- and high-dose female rats. A NOAEL for occurrence of C-cell tumors was not identified in rats. No treatment-related findings were observed in the follicular part of the thyroid.

7.7.3 Rodent C-cell Proliferative Findings – Mode-of-Action

7.7.3.1 Introduction

To assess the human relevance of the increased frequency of hyper- and neoplastic lesions in C-cells in rodents, the Human Relevance Framework (HRF) was applied.^{42,43} This methodology is a stepwise approach which includes validation of a Mode-of-Action hypothesis by mapping key events and their association. The key events are compared between animals and humans on a qualitative and quantitative level. Based on the combined weight of evidence of the mechanistic information, a human safety assessment can be made.

A wide range of dedicated nonclinical *in vitro* and *in vivo* studies was conducted. The *in vitro* studies included studies, characterizing GLP-1 receptor expression and function in rodents and man, receptor screening studies and mitogenicity studies in C-cells. The *in vivo* studies provided information from C-cell studies of varying duration in rodents and in non-human primates following up to 87-weeks exposure at more than 60-fold human exposure.

The consolidated data from these studies substantiated the following sequence of events in the process leading to C-cell proliferation in rodents after long-term GLP-1 receptor agonist dosing:

- GLP-1 receptor agonists bind to and activate GLP-1 receptors on C-cells
- GLP-1 receptor activation on C-cells induces calcitonin release

- Continued calcitonin secretion is followed by increased calcitonin synthesis
- Persistent stimulation of calcitonin synthesis is followed by C-cell hyperplasia in rodents
- Long-term C-cell hyperplasia may lead to C-cell neoplasia in rodents

These identified key events in the substantiated Mode-of-Action in rodents were compared to non-human primate and human data at both the qualitative and quantitative level to establish the relevance to humans.

Key mechanistic studies and results from these are described in details in the following.

7.7.3.2 C-cell Anatomy and Physiology

Embryologically, the thyroid is derived from two distinct embryological origins. The follicular tissue is of endodermal origin whereas the C-cells are of ectodermal neural-crest origin.⁴⁴ C-cells, which constitute a minor fraction of the thyroid gland, are characterized by their exclusive production and content of the peptide hormone, calcitonin.

In rats, calcitonin secretion is closely linked to calcium homeostasis and calcitonin acts as an acute regulator of plasma calcium levels in relation to feeding.⁴⁵ The action of calcitonin is antagonistic to that of parathyroid hormone (PTH), the main calcium-mobilizing hormone. Hence, it has been suggested that calcitonin acts physiologically as an emergency hormone secreted to protect against hypercalcemia in rodents.⁴⁴

The endocrine regulation of calcium homeostasis in rats is known to be labile and feeding influences the plasma calcitonin levels.⁴⁶ A link between the gastrointestinal tract and the thyroid has been demonstrated by the stimulatory action of different gastrointestinal peptides such as cholecystokinins (CCK) on calcitonin secretion.⁴⁷ This link probably constitutes a signaling mechanism by which the influence of feeding on calcium homeostasis is endocrinologically regulated, i.e., a feed-back loop to prevent feeding-induced hypercalcemia. The existence of this link between the gastrointestinal tract and C-cells is also known from situations with increased endogenous levels of gastrointestinal hormones. For example, elevated plasma calcitonin is seen following pharmacologically induced elevation in the gastrointestinal hormone gastrin, as is seen during treatment with proton-pump inhibitors such as omeprazole.⁴⁸

In rats, serum calcium itself does not change with age but calcitonin levels increase markedly with age.^{49,50} This is paralleled by an increase in C-cell number with age. Proliferative lesions in C-cells are very frequent in rats; spontaneous incidences of up to 69% have been observed in 104-week studies.⁵¹ In comparison, the incidence of spontaneous proliferative C-cell lesions in mice is low.⁵² Therefore little is known about C-cell regulation in the mouse while the rat has been intensively characterized. Compared to both rats and mice, C-cells are very sparse in non-human primates and humans.^{53,54} Correspondingly, while calcitonin plays an important role in rodents, no major physiological role for calcitonin in humans has been established.⁵⁵

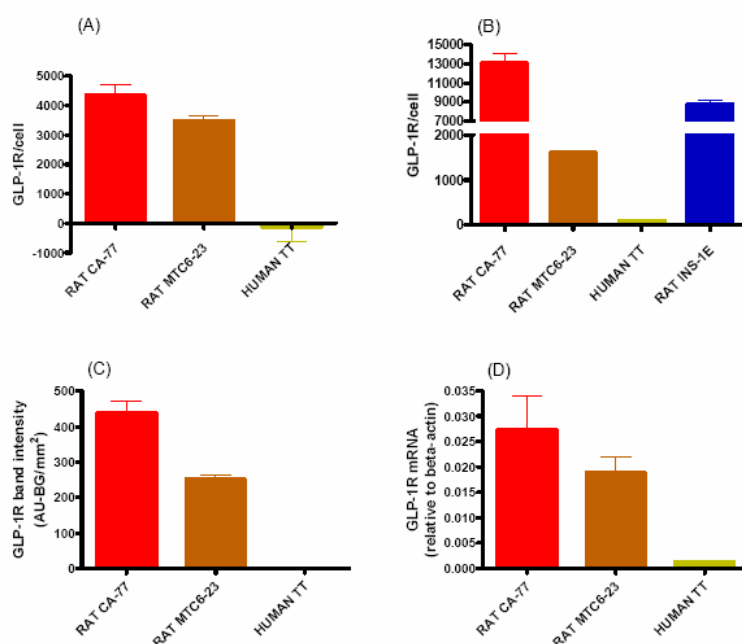
7.7.3.3 GLP-1 Receptor Expression on C-cells

The presence of the GLP-1 receptor on rodent C-cells is described in the literature^{56,57} and was confirmed by a number of techniques. At the level of mRNA, *in situ* hybridization demonstrated the presence of GLP-1 receptor mRNA in small amounts in both rat and mouse thyroid C-cells. In contrast, GLP-1 receptor mRNA could not be detected in cynomolgus monkey or human thyroid tissue. As controls, calcitonin mRNA and a general control mRNA were detected in both cynomolgus monkey and human thyroid tissue. Pancreas and intestine were used as positive controls for demonstrating GLP-1 receptor mRNA.

At the protein level, the GLP-1 receptor was probed by Western blotting and the specific localization on C-cells was visualized by immunohistochemistry. By immunohistochemistry, GLP-1 receptor expression was found to be confined to C-cells and no receptor was found on thyroid follicular cells. C-cells in all evaluated species (mice, rats, cynomolgus monkeys and humans) stained positive using a polyclonal anti-GLP-1 receptor antibody. GLP-1 receptor expression was found to be confined to C-cells. Immunohistochemistry is not a quantitative technique and does not imply functionality of the protein detected.

To evaluate species differences *in vitro*, the only available and well characterized human C-cell line, the TT cell line⁵⁸ was compared to two rat C-cell lines by a number of different techniques (Figure 7-2).

Figure 7-2 Quantitative Comparison of GLP-1 Receptor Expression Showing Marked Species Differences



(A) Saturation binding with fluorescence labeled GLP-1. (B) Saturation binding with iodinated GLP-1. (C) Western blotting. (D) Semi-quantitative PCR. Rat C-cell lines: CA-77 and MTC-23. Human C-cell line: TT. Rat beta-cell line: INS-1E

The quantitative evaluation of the available C-cell lines from rats and humans showed a marked species differences in receptor expression levels. By ligand binding, the rat cell lines expressed 1,600 to 13,000 receptors/cell compared to 105 receptors/cell in the human TT cell line.

In line with these data, a study from the literature using *in situ* ligand binding reported that, the GLP-1 receptor was only detected in one of 18 normal human thyroids.⁵⁶ In contrast, in mice three out of five thyroids were positive, while in rats all 12 thyroids evaluated were positive. This paper concluded that there are species differences between humans and rodents in GLP-1 receptor expression based on quantitative analysis. When detectable, GLP-1 receptor levels in the thyroid gland were reported to be at a remarkably lower level in humans than in rats.⁵⁶

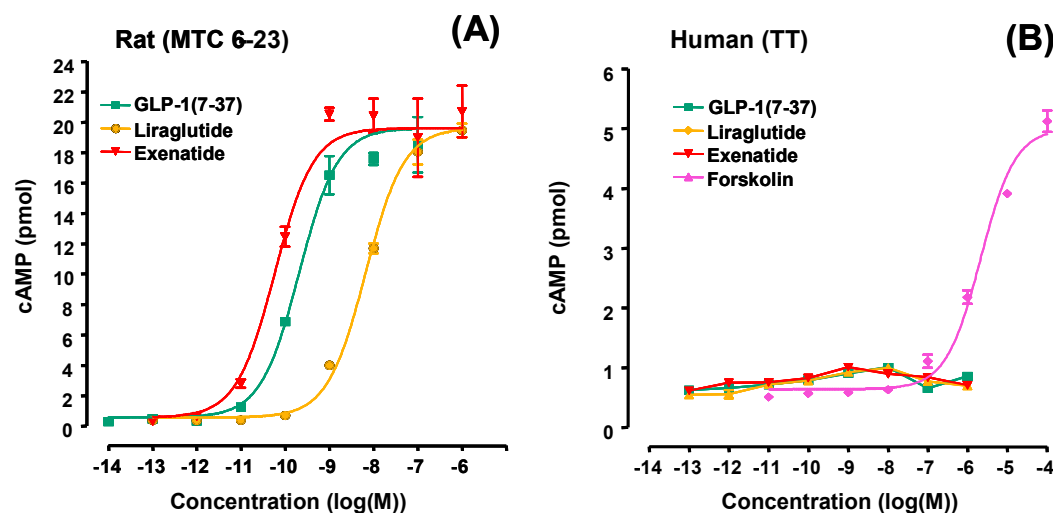
To further define human C-cell responses to GLP-1, three human cell lines thought to be of C-cell origin were screened: SINJ, MTC-SK, SHER-1.⁵⁹⁻⁶¹ In contrast to the TT-cells, these lines have not been previously reported to secrete calcitonin. Studies in the current program demonstrated no cAMP response using forskolin, a general stimulator of cAMP and a C-cell secretagogue (Section 7.7.3.4). Therefore, these cell lines were not considered functional and their C-cell origin could not be confirmed. In addition, contact was established to research groups reporting on other human cell lines potentially of C-cell origin: RG, RO-D81-1 and RO-H85-1.^{62,63} However, in these cases the cell lines were no longer available for use.

7.7.3.4 *In vitro* Findings on GLP-1 Receptor Activation and Calcitonin Release

In vitro cell line data were used to elucidate the biology of the rat C-cell GLP-1 receptor and to compare this to human data. The rat C-cell GLP-1 receptor was coupled to cAMP accumulation as expected for a functional receptor. GLP-1, exenatide and liraglutide were all full agonists on the receptor (Figure 7-3 (A)). For liraglutide, the EC₅₀ for cAMP was 5,800 pM. Consistent with previously published data, exendin(9-39) was a potent antagonist of GLP-1 and induced cAMP accumulation.^{57,64}

With the human C-cell line, TT, the cAMP response also was evaluated with GLP-1, liraglutide and exenatide (Figure 7-3 (B)). Consistent with the paucity of receptors discussed above, the response in TT-cells was profoundly weaker than that in rat C-cells, was bell-shaped, and could not be antagonized by exendin(9-39). Of note, TT-cells were responsive to the cAMP-releasing substance, forskolin, demonstrating that the intra-cellular pathways were functional. The results obtained with GLP-1 receptor agonists therefore suggest that TT-cells do not contain a functional GLP-1 receptor.

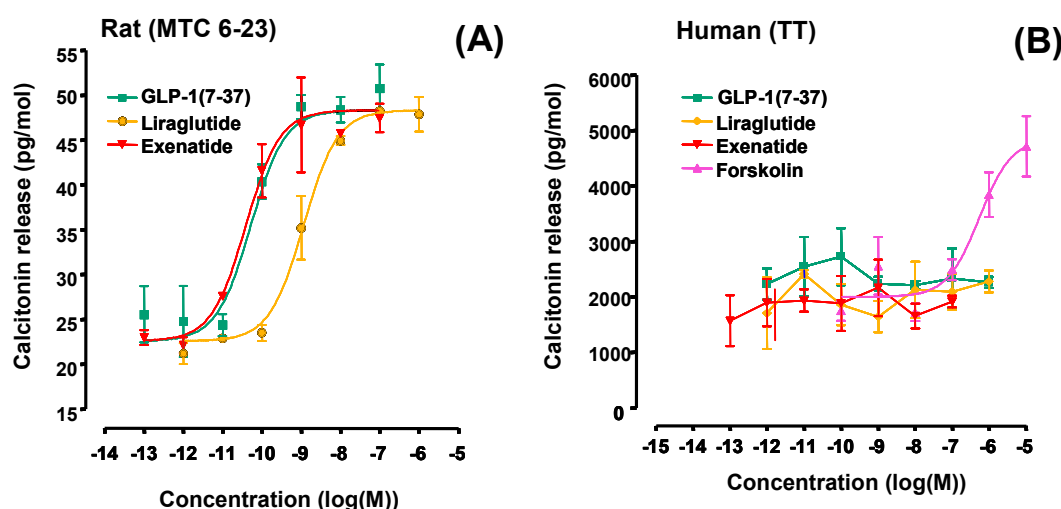
Figure 7-3 Comparison of cAMP Generation in Rat (A) and Human (B) Thyroid C-cell Lines



Calcitonin release caused by GLP-1 receptor agonists in rat C-cell lines correlated well with cAMP response. Again, GLP-1, exenatide and liraglutide all elicited calcitonin release in rat C-cell lines ([Figure 7-4 \(A\)](#)). For liraglutide, the EC_{50} for calcitonin release was 5,300 pM. A cAMP-coupled mechanism of calcitonin release was supported by demonstration that forskolin caused calcitonin release.

Corresponding to the cAMP data from the human cell line, none of the GLP-1 receptor agonists showed dose-related effects on calcitonin release in human TT-cells ([Figure 7-4 \(B\)](#)). Importantly, the cell line was able to respond to forskolin with calcitonin release.

Figure 7-4 Calcitonin Release in Rat (A) and Human (B) C-cell lines



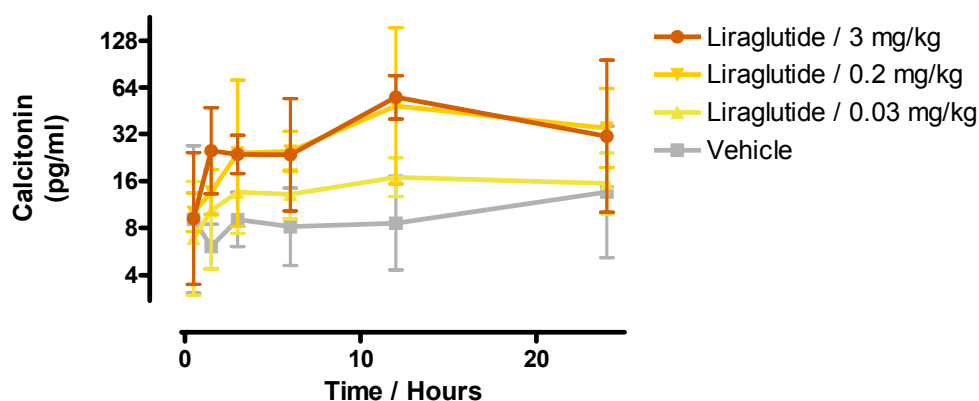
Based on these data, it was concluded that rat thyroid C-cell lines express a biologically functional GLP-1 receptor. When activated by different GLP-1 agonists, cAMP-mediated calcitonin release is seen. In the human C-cell line, no specific functional response of the GLP-1 receptor was observed.

7.7.3.5 *In vivo* Findings on Calcitonin and Relation to C-cell Proliferation in Rodents

In vivo studies in mice and rats documented early increases in plasma calcitonin in relation to dosing with GLP-1 receptor agonists.

In mice, an acute calcitonin-releasing effect of liraglutide was observed ([Figure 7–5](#)).

Figure 7–5 Calcitonin Release in Mice - Single Dose Liraglutide

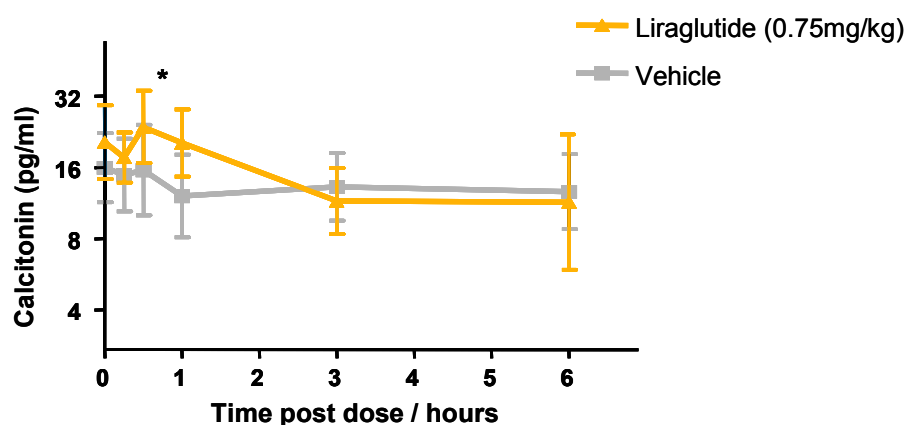


Calcitonin: Plasma calcitonin (geometric mean and 95% CI).

After a single dose of liraglutide, calcitonin was significantly elevated at doses of 0.2 mg/kg and above ($p < 0.05$). The magnitude of the calcitonin response increased with increasing dose and for the two highest doses, calcitonin levels were consistently elevated up to 8-fold over a 36-hour period.

The acute calcitonin release was further corroborated by data from short-term studies where treatment-related calcitonin release was consistently demonstrated with both liraglutide and exenatide. Significant calcitonin release was seen in studies with three days and two, four, nine and 12–13 weeks of dosing. Long-term in mice, a progressive, dose-dependent increase in plasma calcitonin was seen over two years of dosing with liraglutide. C-cell hyper- and neoplasia after two years showed dose-dependency and was only seen at dose-levels inducing an increased calcitonin response. This confirmed the correlation between a preceding increase in calcitonin and C-cell proliferation.

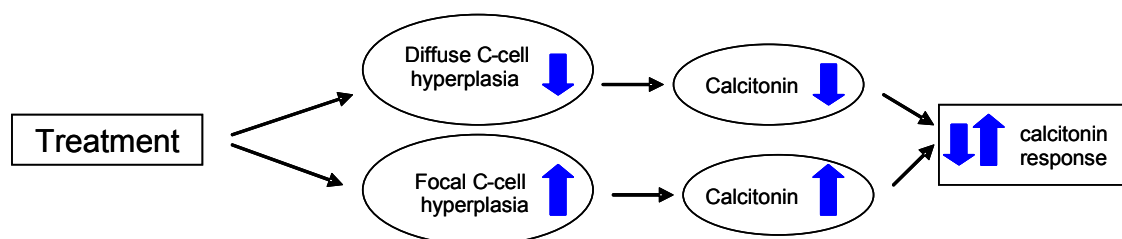
In rats, a calcitonin-releasing effect of liraglutide was also found. In a single-dose study, an initial increase in plasma calcitonin was seen ([Figure 7–6](#)).

Figure 7-6 Calcitonin Release in Rats - Single Dose Liraglutide

Calcitonin: Plasma calcitonin (geometric mean and 95% CI), * p<0.05.

However, at the same time, a massive loss of calcium in the urine occurred because of a marked diuretic effect of a single dose of liraglutide in rats (Section 4.3). The effect of decreased plasma calcium to inhibit calcitonin release may have blunted the acute stimulatory effect of liraglutide on calcitonin secretion. After two weeks of dosing, the diuretic effect had waned and plasma calcitonin concentrations were found to be increased. This treatment-related effect was confirmed after four to five weeks of dosing when an approximate two-fold increase in calcitonin concentration was sustained over 24 hours.

Calcitonin was also followed during 16 months of dosing in rats. Calcitonin increased during the first months of this study. The early increase in calcitonin levels correlated to the observed focal C-cell hyperplasia induced by treatment with liraglutide. Consistent with the literature, plasma calcitonin was also found to correlate to diffuse C-cell hyperplasia which occurs spontaneously and increases with age.⁴⁹ In the rat, when the incidence of focal C-cell hyperplasia increases, a concurrent decrease in diffuse C-cell hyperplasia is seen.^{51,65} This naturally occurring inverse association between development of diffuse C-cell hyperplasia and focal C-cell hyperplasia and the influence of treatment with liraglutide on these changes is illustrated in Figure 7-7.

Figure 7-7 Illustration of the Relationship between the Different Treatment-related C-cell Changes Occurring in Parallel and their Combined Effect on Calcitonin in Rats

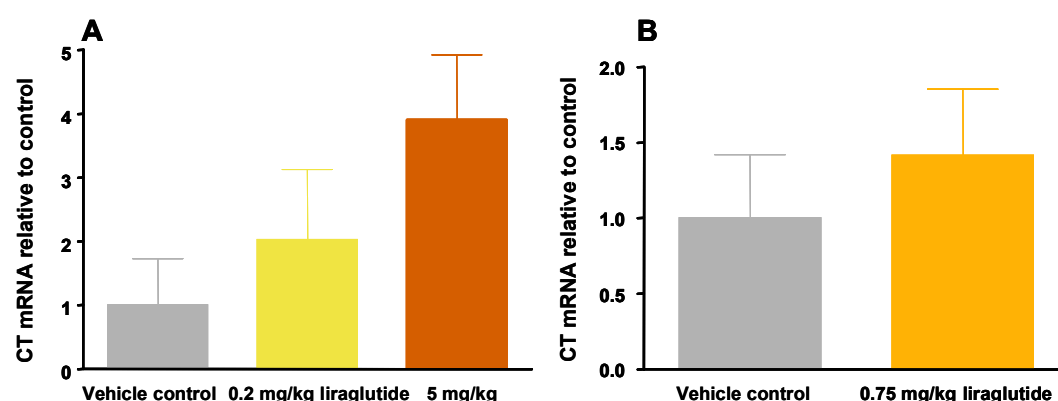
Consistent with the fact that treatment affects diffuse C-cell hyperplasia and focal hyperplasia in opposite directions, there was no consistent effect on plasma calcitonin concentrations in the late phases of the 16-months study.

In both rodent species, the calcitonin increase was consistently observed prior to any sign of C-cell proliferation. The mechanism of calcitonin release *in vivo* thereby documented the potential for using plasma calcitonin as a biomarker for the GLP-1 agonist induced C-cell stimulation. This observed direct stimulatory action of GLP-1 receptor agonists on C-cells is consistent with literature data on other intestinal hormones stimulating calcitonin release in rodents.⁴⁷ The use of calcitonin as a biomarker for the C-cell activation by GLP-1 receptor agonists is also parallel to the mechanism behind the clinical use of secretagogues such as pentagastrin, as described in more detail in Section 7.7.4.1.

7.7.3.6 Findings on Calcitonin Synthesis in Rodents

Following continued calcitonin secretion, a compensatory increase in calcitonin protein biosynthesis was seen. This was evidenced by an increase in calcitonin mRNA observed at time points after the liraglutide induced calcitonin release but before C-cell proliferation was observed in rodents. With liraglutide treatment in mice, a specific increase in thyroid calcitonin mRNA was observed after two weeks of dosing (Figure 7–8). Similar observations were made after two weeks of dosing with exenatide. In rats, a trend towards a treatment-related increase in calcitonin mRNA was observed after four weeks of dosing with liraglutide.

Figure 7–8 Up-regulated Calcitonin (CT) mRNA in Mice and Rats Treated with Liraglutide



(A) CT mRNA in mice (18–29 animals/group) dosed with liraglutide for two weeks.

(B) CT mRNA in rats (14 animals/group) dosed with liraglutide for four weeks.

Calcitonin mRNA quantified relative to housekeeping genes (beta actin/GAPDH) and normalized against mean levels in vehicle controls (mean and 95% CI).

Protein-specific mRNA is generally considered an early marker of up-regulated protein synthesis. Specifically, literature data from mice and rats support the relationship between increases in calcitonin secretion and biosynthesis as determined by mRNA levels.⁵⁰ In these published studies,

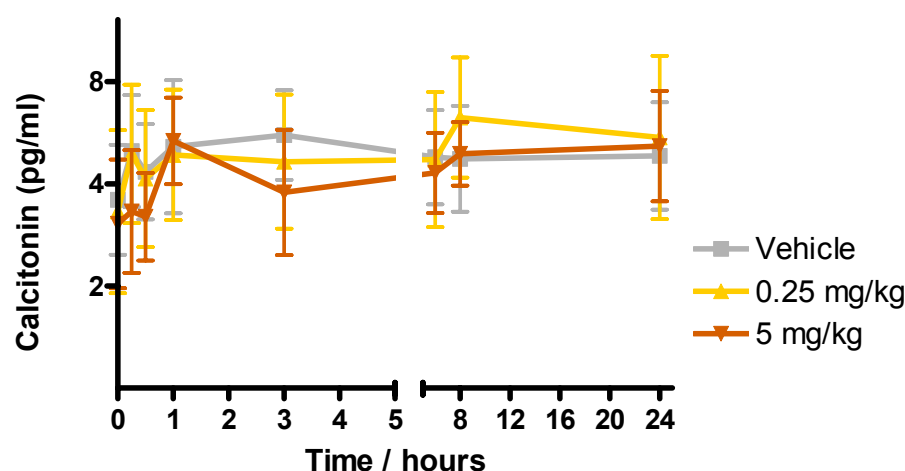
such increases also preceded hyperplastic changes. This is consistent with the observations from the GLP-1 receptor agonist studies in mice and rats where calcitonin mRNA levels increased prior to the onset of hyperplasia.

7.7.3.7 *In vivo* Calcitonin Findings in Non-human Primates

Unlike in rodents, no treatment-related calcitonin release was observed in cynomolgus monkeys acutely or following long-term dosing with liraglutide.

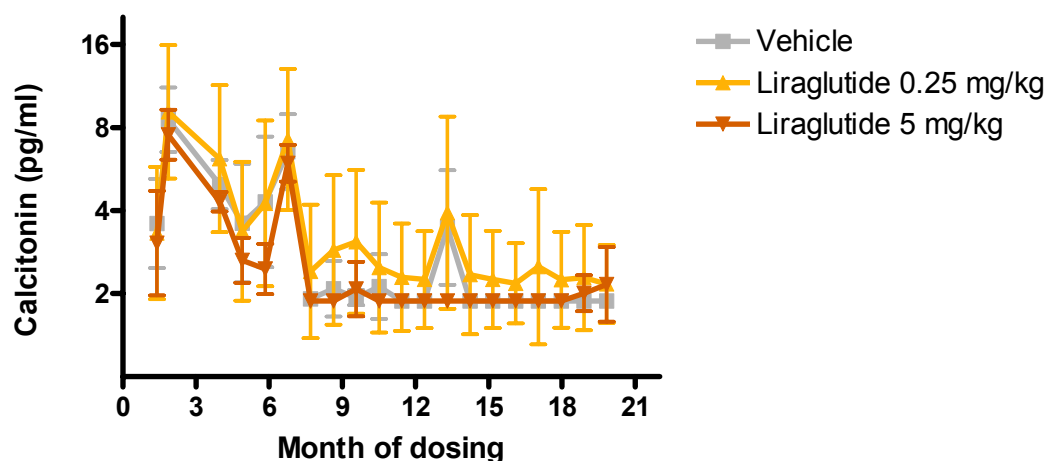
In an 87-week study in cynomolgus monkeys (N=30), the calcitonin profile was closely evaluated. The doses applied corresponded to more than 60-fold the maximal recommended human dose. In this study, calcitonin response was assessed after the animals received the first dose of liraglutide. There was no treatment-related increase in plasma calcitonin when liraglutide (up to 5 mg/kg/day) was administered ([Figure 7-9](#)).

Figure 7-9 No Acute Calcitonin Release in Non-human Primates



Calcitonin: Plasma calcitonin (geometric mean and 95% CI).

Following the single-dose phase, the animals in this study continued into a long-term phase where calcitonin was measured every four weeks. The calcitonin profile over time showed no signs of treatment-induced calcitonin release ([Figure 7-10](#)). The observed levels in calcitonin values between groups were maintained during the study. Single animals in the 0.25 mg/kg dose group and in the vehicle group had consistently high calcitonin levels also present at baseline and not increasing during treatment. Statistical analysis did not show any treatment-related effects on calcitonin values over time.

Figure 7–10 Calcitonin Profile over Time in Cynomolgus Monkeys

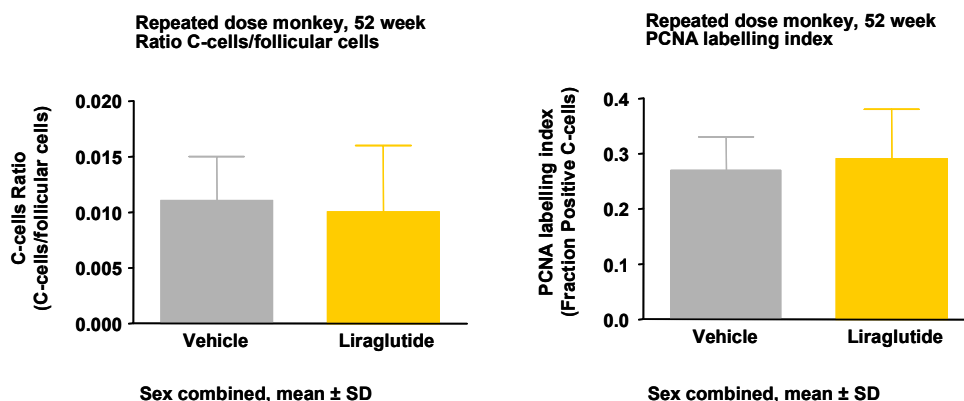
Calcitonin: Plasma calcitonin (geometric mean and 95% CI).

The absence of calcitonin response to liraglutide treatment in non-human primates was validated by calcium stimulation. Using calcium stimulation, calcitonin release can be elicited in rodents, non-human primates and humans.⁶⁶⁻⁶⁸ Calcium stimulation yields an exaggerated response under conditions of C-cell hyperplasia. Calcium stimulation in the cynomolgus monkeys in the single-dose phase and after 8 weeks of dosing caused the expected increase in plasma calcitonin with no differences in the response between vehicle and liraglutide-treated groups.

7.7.3.8 *In vivo* Data on C-cell Hyperplasia in Non-human Primates

Consistent with the plasma calcitonin measurements, no signs of C-cell hyperplasia were observed in toxicity studies of 4, 13, 52 and 87 weeks duration in cynomolgus monkeys. Quantitative analysis of the thyroids from the 52-week non-human primate study (N=6–8 per treatment group) was performed applying immunohistochemistry for C-cell detection and proliferating cell nuclear antigen (PCNA) as a proliferation marker. No changes were observed in the relative thyroid C-cell mass (C-cell to follicular cell ratio) or proliferation index as assessed by PCNA staining in the C-cells ([Figure 7–11](#)).

Figure 7–11 No Effects on C-cell Mass or C-cell PCNA Labeling Index after Daily s.c. Administration in Cynomolgus Monkeys for 52 weeks (Mean±SD)



A comprehensive C-cell evaluation was also included in the dedicated 87-week mechanistic study in cynomolgus monkeys, in which calcitonin was measured every four weeks ([Figure 7–10](#)). To enhance the sensitivity to detect C-cell effects, the study duration exceeded that of chronic non-rodent studies required to support the development of pharmaceutical agents.²⁶ The sensitivity was further increased by applying extended histopathological evaluation including immunohistochemistry and intensified sampling in the C-cell rich region of the thyroid. No treatment-related effects on C-cells were identified. The absence of proliferative effects on C-cells in this study was confirmed through peer-review by an international panel of pathology experts.

In contrast to this consistent absence of proliferation with liraglutide, C-cell proliferation was reported in non-human primates in a published study of one month dosing with vitamin D and calcium.⁵⁴ This validates that the non-human primate model is responsive to stimuli inducing C-cell proliferation and that any liraglutide-induced changes should have been evident in the studies performed.

7.7.3.9 Endocrine Induced Proliferation

Treatment-induced endocrine neoplasia in rodent carcinogenicity studies is not uncommon and rarely predictive for humans. Rodents are particularly sensitive to the development of endocrine tumors caused by stimulation of hormonal axes. Selected examples from rodents include the induction of pheochromocytomas with the beta-blocker atenolol⁶⁹, gastric enterochromaffin-like cell tumors with the proton pump inhibitor, omeprazole⁴⁸, and Leydig cell tumors with different pharmaceuticals such as histreline.⁷⁰ C-cell proliferation has been seen with vitamin D3 and with recombinant human PTH (teriparatide) in rats.^{71,72} Both of these agents are known to cause elevated calcium levels. Treatment-related C-cell tumors were also reported in a 104-week rat study with exenatide.⁷³

The lifespan of macaque monkeys such as the cynomolgus monkey is between 15 and 30 years.⁷⁴ The induction of tumor development via genetic damage after administration of chemical carcinogens in non-human primates takes up to 10–20 years.⁷⁵ In contrast, reports from the literature substantiate that non-genotoxic proliferation in endocrine organs in response to receptor stimulation can be induced within a few months in non-human primates.

In the testis, Leydig cell hyperplasia induced by gonadotrophins was observed in macaque monkeys after less than two months of treatment.⁷⁶ Similarly, prostate hyperplasia was induced after three months administration of an androgen,⁷⁷ and mammary gland hyperplasia occurred after less than two months of administration of human growth hormone.⁷⁸

Development of C-cell proliferation after excess calcium and D-vitamin intake has been observed in macaque monkeys in a one month study.⁵⁴ Here, C-cell stimulation due to hypercalcemia was induced by excess of calcium in the diet and drinking water and by D-vitamin administration. For comparison, proliferative C-cell lesions have been demonstrated in rodents after nine weeks of treatment with liraglutide. Thus, both in non-human primates and in rodents, C-cell proliferation can be observed within a few months if the C-cells are stimulated. That is, C-cell proliferation can occur and be detected in non-human primates after a similar absolute duration of stimulation as in rodents despite the significantly longer life span of non-human primates.

7.7.3.10 Nonclinical Conclusion

The assessment of human relevance of the rodent C-cell findings was done by applying the Human Relevance Framework model.⁴³

The GLP-1 receptor-mediated mechanism and the key events in the Mode-of-Action behind the rodent C-cell neoplasia were substantiated with experimental data and literature as summarized above.

Based on these studies and consistent with the relevant literature it is concluded that the rodent C-cell tumors induced by dosing of liraglutide were caused by a non-genotoxic, specific receptor-mediated mechanism to which rodents are particularly sensitive whereas non-human primates and humans are not.

7.7.4 Calcitonin Monitoring in the Liraglutide Development Program

7.7.4.1 Calcitonin as a Biomarker

Calcitonin is consistently and almost exclusively expressed in C-cells.⁷⁹ Plasma calcitonin is recognized as a specific marker for increased C-cell mass and activation.⁴⁹ In humans with C-cell hyperplasia or neoplasia, both unstimulated and stimulated plasma calcitonin levels are increased.^{80,81} In addition, calcitonin levels are elevated prior to the diagnosis of C-cell hyperplasia.⁸² Specifically in Europe, calcitonin has been utilized as a routine biomarker in patients with suspected C-cell pathology. In the United States, there is more controversy as to the value of

screening plasma calcitonin levels in evaluating thyroid disease given the very low frequency of spontaneous (nonfamilial) medullary thyroid carcinoma and the low specificity of elevated calcitonin as a marker of C-cell hyperplasia. In order to enhance the sensitivity and specificity of unstimulated plasma calcitonin levels, calcium or pentagastrin stimulation tests are often used to assist in the diagnosis.⁸¹ These tests are based on inducing direct calcitonin release via different C-cell receptors: calcium-sensing receptors responding to elevated plasma calcium levels and CCK receptors responding to pentagastrin. These direct calcitonin secretagogues cause a more pronounced increase in plasma calcitonin in subjects with increased C-cell mass than in normal subjects.

The rodent data described in Section [7.7.3](#) are consistent with a direct effect of GLP-1R activation as a calcitonin secretagogue in mice and rats; i.e. plasma calcitonin was elevated as the result of direct C-cell activation. Thus, in rodents, GLP-1 receptor mediated C-cell activation, detected by an increase in plasma calcitonin, occurred prior to any signs of cellular proliferation and served as a biomarker of the C-cell activation. Based on these observations in rodents, one would predict that if GLP-1 (liraglutide) activates C-cells in man, elevations of plasma calcitonin would serve as an early biomarker of these effects.

Thus, while the preclinical program established a rodent-specific mechanism for C-cell responses to liraglutide (Section [7.7.3](#)), the clinical program incorporated extensive C-cell monitoring based on plasma calcitonin measurements (basal and stimulated) to exclude any liraglutide-induced C-cell proliferation in humans.

7.7.4.2 Calcitonin Measurements in the Long-term Phase 3 Trials

Using validated assays with high specificity and sensitivity, calcitonin was measured every three months in more than 5,000 subjects in long-term phase 3 trials (the five long-term phase 3 trials, Japanese Trials 1700 and 1701 and Trial 1797), and also in 500 obese subjects without diabetes in the phase 2 trial (NN8022-1807) who were on doses up to 3 mg liraglutide for up to one year. Moreover, in order to increase the sensitivity of the assessment of any effect of liraglutide on calcitonin secretion, a calcium stimulation test was performed in a sub-population of subjects from long-term Trials 1573 and 1574. Calcium infusion acutely stimulates calcitonin release from C-cells and enhances the sensitivity and specificity of clinical assessment of C-cell mass in individuals at risk for medullary carcinoma of the thyroid.

The following provides an overview of changes in unstimulated calcitonin concentrations over time with particular attention on individual subjects demonstrating increases in calcitonin concentrations while on liraglutide. Finally, the stimulated calcitonin responses from the calcitonin stimulation sub-study described above are presented.

The results of a repeated measurement analysis of the fasting unstimulated calcitonin levels over time are presented in [Table 7-18](#).

Table 7–18 Repeated Measurement Analysis for Unstimulated Calcitonin^(a) at Weeks 26/28, 52 and 76/78

Treatment / Comparison	Estimates	95 % CI
Week 26 (Trials 1573, 1572, 1436, 1574 and 1696) LSMean (ng/L)		
Liraglutide 1.8 mg	1.01	[0.95 ; 1.06]
Liraglutide 1.2 mg	0.99	[0.94 ; 1.05]
Liraglutide 0.6 mg	0.96	[0.90 ; 1.04]
Active Comparator	0.97	[0.91 ; 1.02]
Placebo	0.89	[0.83 ; 0.95]
Week 52 (Trials 1573 and 1572-ext) LSMean (ng/L)		
Liraglutide 1.8 mg	0.81	[0.73 ; 0.90]
Liraglutide 1.2 mg	0.81	[0.73 ; 0.90]
Liraglutide 0.6 mg	0.73	[0.63 ; 0.83]
Active Comparator	0.78	[0.70 ; 0.86]
Placebo	0.62	[0.49 ; 0.79]
Week 76/78 (Trials 1573 ext and 1572 ext) LSMean (ng/L)		
Liraglutide 1.8 mg	0.54	[0.48 ; 0.62]
Liraglutide 1.2 mg	0.53	[0.46 ; 0.60]
Liraglutide 0.6 mg	0.26	[0.21 ; 0.32]
Active Comparator	0.58	[0.51 ; 0.66]
Placebo	0.01	[0.00 ; 13E11]

Table is based on Population 4 (completed long-term NDA phase 3 trials (blinded and open-label part)) in [Appendix, Table 1–1](#). For complete treatment regimens in the individual trials, see [Table 6–1](#). ^a Calcitonin with lower limit of quantification observations (calcitonin values below LLOQ of 0.7 ng/L); for statistical details on the calcitonin analysis, see [Appendix, Section 2.3](#).

Most mean calcitonin concentrations were 0.5–1 ng/L at all time points, which is in the lower end of the normal range for the assay used ([Table 7–18](#)). There were no significant differences between the liraglutide and active control treatment groups at any point in time, whereas both of these treatment groups differed significantly from placebo at week 26, but the absolute difference was small. At week 52, the 1.2 mg and the 1.8 mg doses were significantly different from placebo, but again, no difference was found between liraglutide treatment and active comparators. At 76 weeks, no significant differences were found between any treatment groups. In conclusion, the calcitonin levels were within the normal reference range in all treatment groups throughout the treatment period, and there was no difference between liraglutide and active comparator at any point in time. Thus, there was no evidence of a liraglutide-induced rise in calcitonin levels.

Calcitonin levels generally are higher in males than females; the upper normal range value for males was 8.4 ng/L and for females it was 5.0 ng/L. These values are lower than the 10–20 ng/L generally recommended in the literature as appropriate for further medical evaluation. A total of 44 adverse events of increased blood calcitonin ([Table 7–30](#)) were reported in the liraglutide development program. Of these, 34 events were in liraglutide-treated subjects (rate: 10.9 per 1,000 patient exposure years), and five events were in each of the placebo and the active comparator treated groups (placebo rate: 10.5 and active comparator rate: 4.5 per 1,000 patient exposure years). No predefined uniform definition was provided in the clinical protocols, so the decision to report an

increase in blood calcitonin as an adverse event was at the discretion of the investigator. Twenty (20) of these 34 adverse events in the liraglutide-treated subjects had increased calcitonin at baseline and six of the 10 adverse events in the total comparator treated subjects had increased calcitonin at baseline. That is, approximately 60% of subjects across all treatment groups with increased blood calcitonin reported as an adverse event had increased calcitonin at baseline.

As mean values may mask meaningful changes in individual patients, subjects ‘shifting’ to calcitonin concentrations above a clinically relevant cut-off of calcitonin ≥ 2 x the upper limit of the normal reference range (UNR) were tabulated. All liraglutide dose levels were combined into one liraglutide group and these data then were compared to the placebo and active groups, respectively ([Table 7–19](#) (Week 20/24/26/28), [Table 7–20](#) (Week 52) and [Table 7–21](#) (Week 76/78)). It should be noted that the number of subjects decreases over time based on the duration of individual trials and subject withdrawal rates. For clarity, in these tables ranges of calcitonin concentrations are used, and subjects baseline and subsequent calcitonin concentrations are compared based on these ranges.

Table 7–19 Percentages of Subjects Shifting Calcitonin Category from Baseline to 20/24/26/28 Weeks of Treatment

		Endpoint After 20/24/26/28 weeks ^(a)			
Baseline		<UNR ^(b) (%)	[UNR-2UNR[(%)	≥ 2 UNR (%)	MISSING (%)
Liraglutide N=3549^(d)	<UNR	86.9	2.2	0.0 ^(c)	4.3
	[UNR-2UNR[0.7	2.0	0.6	0.2
	≥ 2 UNR	0.1	0.2	0.5	— ^(e)
	Missing	1.9	0.1	0.0	0.3
Placebo N=710	<UNR	87.2	1.7	—	4.9
	[UNR-2UNR[1.0	2.3	0.1	0.3
	≥ 2 UNR	—	0.4	0.3	—
	Missing	1.8	—	—	—
Active Comparator N=1412	<UNR	86.2	1.8	—	5.5
	[UNR-2UNR[0.8	1.2	0.2	0.2
	≥ 2 UNR	0.1	0.4	0.8	0.2
	Missing	2.0	0.1	—	0.4

Table is based on population 3 (Trials 1573, 1572, 1436, 1574, 1697, 1797, 1700, 1701 and NN8022-1807) in [Appendix, Table 1–1](#) and includes all trials for data at 20/24/26/28 weeks (using LOCF). ^a The exact duration of the various studies varies from 20–28 weeks: ^b UNR: Upper Normal Range: ^c 0.0 means that the percentage is less than 0.05 and “—” means that there are no observations in that group ^d This N=3549 does not include two subjects who did not have any calcitonin values at any of the visits (xx3003 and xx5019, Trial 1573), thereby giving a discrepancy to the N=3551 stated in [Table 6–3](#).

Table 7–20 Percentages of Subjects Shifting Calcitonin Category from Baseline to 52 Weeks of Treatment

		Endpoint After 52 weeks			
	Baseline	<UNR ^(a) (%)	[UNR-2UNR[(%)	≥2UNR (%)	MISSING (%)
Liraglutide N=1295	<UNR	81.5	1.9	–	9.0
	[UNR-2UNR[0.6	1.7	0.7	0.5
	≥2UNR	–	0.3	0.2	0.3
	Missing	2.5	0.1	0.2	0.5
Placebo N=128	<UNR	93.0	1.6	–	2.3
	[UNR-2UNR[–	0.8	–	–
	≥2UNR	–	0.8	–	–
	Missing	1.6	–	–	–
Active Comparator N=498	<UNR	78.7	2.0	–	14.7
	[UNR-2UNR[0.4	0.4	0.2	0.4
	≥2UNR	0.2	–	0.8	0.6
	Missing	1.2	–	–	0.4

Table is based on population 3 (Trials 1573, 1572, 1436, 1574, 1697, 1797, 1700, 1701 and NN8022-1807) in [Appendix, Table 1–1](#) but includes only Trials 1573, 1572(ext) and NN8022- 1807(ext) for data at week 52 (using LOCF). ^a UNR: Upper Normal Range

Table 7–21 Percentages of Subjects Shifting Calcitonin Category from Baseline to 76/78 Weeks of Treatment

		Endpoint After 76/78 weeks			
	Baseline	<UNR ^(a) (%)	[UNR-2UNR[(%)	≥2UNR (%)	MISSING (%)
Liraglutide N=839	<UNR	84.3	2.1	0.1	5.2
	[UNR-2UNR[1.5	1.5	0.6	0.2
	≥2UNR	–	0.2	0.4	0.1
	Missing	3.0	0.1	0.1	0.4
Placebo N=61	<UNR	73.8	1.6	–	21.3
	[UNR-2UNR[–	–	–	–
	≥2UNR	–	–	–	–
	Missing	3.3	–	–	–
Active Comparator N=320	<UNR	84.1	3.1	0.3	7.5
	[UNR-2UNR[0.6	0.9	–	–
	≥2UNR	0.3	–	0.9	0.3
	Missing	1.9	–	–	–

Table is based on population 3 (Trials 1573, 1572, 1436, 1574, 1697, 1797, 1700, 1701 and NN8022-1807) in [Appendix, Table 1–1](#) but includes only Trials 1573 (ext), 1572(ext) for data at 76/78 weeks (using LOCF). ^a UNR: Upper Normal Range.

When comparing liraglutide to active comparator, there was no statistically significant increase in the fraction of subjects increasing to ≥2xUNR or above for weeks 20–28, 52 or 76/78 ([Table 7–22](#)). At week 20–28, approximately 85% of all subjects were below the UNR (86.9%, 87.2, and 86.2% for liraglutide, placebo, and active comparator, respectively). At week 52, the percentages were 81.5%, 93.0, and 78.7%, respectively and at week 76/78, the percentages below UNR were 84.3%, 73.8%, and 84.1%, respectively. At all time points, less than 1% shifted to ≥2xUNR, however, there was a significantly higher fraction of subjects increasing to 2xUNR vs. placebo for liraglutide-

treated subjects at Week 26 but no difference to active comparator. No significant differences were seen between any treatment groups at Weeks 52 and 76/78 ([Table 7–22](#)). The total number of placebo-treated subjects decreased significantly beyond 26 weeks duration due to the duration of the individual trials. The apparent change at 26 weeks was not seen at subsequent time points and involved a small number of subjects, which suggests that this was not a clinically meaningful observation.

Table 7–22 Logistic Regression of Subjects with Calcitonin $\geq 2 \times \text{UNR}^{(a)}$ after 20 to 28, 52 and 76/78 Weeks of Treatment (LOCF)

Treatment / Comparison	Estimates	95% CI	P-value
20 to 28 Weeks of Treatment (LOCF)			
Odds Ratio			
Liraglutide - Placebo	10.67	[1.33; 85.34]	0.0077
Liraglutide - Active Comparator	1.76	[0.64; 4.84]	0.2650
Active Comparator - Placebo	6.07	[0.65; 57.01]	0.0853
52 Weeks of Treatment (LOCF)			
Odds Ratio			
Liraglutide – Placebo ^(b)	N/A	N/A	0.6207
Liraglutide - Active Comparator ^(c)	1.36	[0.22 ; 8.35]	0.7346
Active Comparator - Placebo ^(b)	N/A	N/A	0.5940
76/78 Weeks of Treatment (LOCF)			
Odds Ratio			
Liraglutide – Placebo ^(b)	N/A	N/A	1.0000
Liraglutide - Active Comparator ^(c)	1.16	[0.21 ; 6.36]	0.8618
Active Comparator - Placebo ^(b)	N/A	N/A	1.0000

Table is based on population 3 (Trials 1573, 1572, 1436, 1574, 1697, 1797, 1700, 1701 and NN8022-1807) in [Appendix, Table 1–1](#) but includes only Trials 1573, 1572(ext) and NN8022-1807(ext) for analysis at 52 weeks and Trials 1573(ext), 1572(ext) for analysis at 76/78 weeks. The model includes treatment, trial and baseline calcitonin level. ^a UNR: Upper Normal Range. ^b P-value from a Fishers exact test, due to zero cell(s) for the Placebo arm. ^c P-value from Likelihood Ratio test.

To increase the sensitivity for demonstrating alterations in C-cell mass, calcium stimulation tests were performed in a subset of subjects from two of the long-term phase 3 trials (Trials 1573 and 1574). ANCOVA comparisons between treatments using the ratio of peak to basal calcitonin concentrations during the stimulation test at the end of the trial are presented in [Table 7–23](#). The mean in [Table 7–23](#) is estimated end-of-study levels and the comparator in [Table 7–23](#) is pooled comparator from the two trials (Trials 1573 and 1574), i.e., 8 mg glimepiride/placebo. No significant differences between treatments in the ratios of peak to basal calcium concentrations were observed with stimulation testing. In [Table 7–24](#), a similar ANCOVA of comparisons between treatments using the peak value is shown.

Table 7–23 Analysis (ANCOVA) of Ratio of Calcitonin (ng/L) in Calcium Stimulation Test at End of Treatment (Trials 1573 and 1574, Sub-Study Population)

Treatment / Comparison			
Least Square Means	N	Mean	
Liraglutide 1.8 mg	28	10.5 ng/L	
Liraglutide 1.2 mg	29	10.3 ng/L	
Comparator	28	9.4 ng/L	
Estimated Treatment Ratio	LSMean	95% CI	P-value
Liraglutide 1.8 mg vs. Comparator	1.120	[0.781; 1.606]	0.5344
Liraglutide 1.2 mg vs. Comparator	1.096	[0.761; 1.580]	0.6182
Liraglutide 1.8 mg vs. Liraglutide 1.2 mg	1.021	[0.715; 1.459]	0.9063

For complete treatment regimens in the individual trials, see [Table 6–1](#). The estimates were first estimated based on ANCOVA model with log-transformed ratio of peak value to basal value at end of study as dependent variable, treatment, sex as fixed effects, and log-transformed ratio of peak value to basal value at week 0 as a covariate, then they were converted back to original scale.

Table 7–24 Analysis (ANCOVA) of Peak Value of Calcitonin (ng/L) in Calcium Stimulation Test at End of Treatment (Trials 1573 and 1574, Sub-Study Population)

Treatment / Comparison			
Least Square Means	N	Mean	
Liraglutide 1.8 mg	29	11.1 ng/L	
Liraglutide 1.2 mg	29	14.8 ng/L	
Comparator	28	12.1 ng/L	
Estimated Treatment Ratio	LSMean	95% CI	P-value
Liraglutide 1.8 mg vs. Comparator	0.924	[0.650; 1.314]	0.6559
Liraglutide 1.2 mg vs. Comparator	1.223	[0.857; 1.744]	0.2634
Liraglutide 1.8 mg vs. Liraglutide 1.2 mg	0.756	[0.532; 1.073]	0.1162

For complete treatment regimens in the individual trials, see [Table 6–1](#).

In conclusion, the geometric mean calcitonin levels were in the low end of the normal range value in all treatment groups throughout the treatment periods, with no difference between liraglutide and active comparator at any point in time. Similarly there was no difference in the fraction of outliers (defined as subjects shifting to levels $\geq 2 \times$ Upper Normal Range) between liraglutide and the active comparators. The rates of adverse events of increased blood calcitonin were similar between liraglutide and placebo, both being higher than active comparator. Based on the intensive monitoring of calcitonin in the liraglutide clinical development program, data do not support a liraglutide effect on calcitonin in humans.

7.7.4.3 Clinical Adverse Events Related to C-cells

During the course of the clinical development program, six cases of C-cell hyperplasia were reported. Five of these cases were based on pathological evaluation of thyroid tissue removed because of elevated baseline or calcium-stimulated calcitonin. Three of the cases (xx8002, xx1008 and xx0001) were reported after the 120-day Safety Update. The six cases were distributed consistent with the skewed randomization in of the trials with four subjects in the liraglutide group and two subjects in the active comparator group ([Table 7–25](#)). Importantly, in most liraglutide-

associated cases, the clinical summaries make clear that the C-cell pathology pre-dated liraglutide exposure.

Table 7–25 Human C-cell Hyperplasia Reported in the Liraglutide Clinical Development Program

Trial/ Subject ID	Gender	Reason for Thyroidectomy	Treatment	Duration of Treatment	Pathology
1572/ xx4012	Male	Elevated basal calcitonin reported approximately three months post-randomization (12.1ng/L) ^(b)	Glimepiride+ metformin	370 days	Neoplastic C-cell hyperplasia (medullary carcinoma <i>in situ</i>)
1572/ xx8002 ^(a)	Male	Elevated calcitonin (21.5 ng/L) reported at randomization	Liraglutide 0.6 mg	190 days	Bilateral nodular goiter, C-cell hyperplasia
1572/ xx1008 ^(a)	Male	Elevated calcitonin (22.3 ng/L) reported nine months post-randomization	Liraglutide 1.8 mg	363 days	Papillary microcarcinoma/physiological C-cell hyperplasia/ goiter/benign thyroid nodules
1573/ xx1006	Female	Elevated stimulation test at 12 months visit (calcitonin levels were 80.7 ng/L and 94 ng/L at 5 and 10 minutes after stimulation, respectively)	Liraglutide 1.2 mg	484 days	Diffuse C-cell hyperplasia
1573/ xx5008	Male	Elevated basal calcitonin at baseline (22.3 ng/L) ^(b)	Liraglutide 1.8 mg	28 days	Bilateral neoplastic nodular C-cell hyperplasia
1697/ xx0001 ^(a)	Male	Elevated calcitonin (1023 ng/L) reported two months pre-randomization	Glimepiride+ metformin+ insulin glargine	145 days	Medullary thyroid carcinoma/ blood calcitonin increased/ benign thyroid nodules

^a Reported after the 120-day safety Update. ^b Reference range: 0.7–8.4 ng/L. Calcium Stimulation Test (CST), upper normal range 90 ng/L for female and 130 ng/L for male subjects.

Subject xx4012 (Trial 1572 - metformin + glimepiride) had elevated unstimulated calcitonin reported approximately three months post-randomization. Following surgery, the subject was diagnosed with bilateral neoplastic C-cell hyperplasia (medullary carcinoma *in situ*). This subject had a past history of struma nodosa.

Subject xx8002 (Trial 1572 - liraglutide 0.6 mg) had a calcitonin of 21.5 ng/L at baseline. Thyroid ultrasound and cervical CT scan showed mononodular goiter. Scintigraphy showed increased activity in one nodule. A fine needle aspiration biopsy was inconclusive. A pentagastrin test showed peak calcitonin of 142 ng/L (baseline/unstimulated 39.2 ng/L). Thyroidectomy was performed seven months post-randomization. Histological diagnoses were multinodular goiter, C-cell hyperplasia.

Subject xx1008 (Trial 1572 - liraglutide 1.8 mg) had a calcitonin of 22.3 ng/L nine months post-randomization (baseline calcitonin was 15.1 ng/L). A subsequent calcium stimulation test showed calcitonin peak of 203 ng/L and ultrasound showed multinodular goiter. Total thyroidectomy was performed 13 months post-randomization. Histological diagnoses were bilateral adenomatous

nodules, papillary microcarcinoma (diameter 2 mm) and C-cell hyperplasia. The pathology report notes that C-cell hyperplasia was classified as physiological.

Subject xx1006 (Trial 1573 - liraglutide 1.2 mg) had a baseline calcium stimulation test that peaked at the 90–95th percentile for females in the sub-study. At the end of trial, the peak value was above the normal range as defined in the sub-study. A thyroidectomy was performed and the subject was diagnosed with C-cell hyperplasia and a papillary microcarcinoma. Both of these findings were in the context of a multinodular goiter.

Subject xx5008 (Trial 1573 - liraglutide 1.8 mg) had an elevated baseline calcitonin. This subject was treated with liraglutide for one month and withdrawn from the trial when the baseline calcitonin values became known. Following surgery, pathology of the thyroid gland revealed bilateral neoplastic nodular C-cell hyperplasia, adenomatoid nodules, and papillary microcarcinoma.

Subject xx0001 (Trial 1697 - glimepiride + metformin + insulin glargin) had a calcitonin of 1023 ng/L reported pre-randomization. Five months post-randomization, an ultrasound was performed, showing bilateral thyroid nodules and cysts. Trial drug was discontinued. A fine needle aspiration biopsy was inconclusive. Nine months after drug discontinuation, a total thyroidectomy was performed. Histological diagnoses were medullary thyroid carcinoma, benign thyroid adenomas and angiolipoma of the neck.

The six cases of C-cell hyperplasia (four in liraglutide and two in active comparator) in the clinical trials were all diagnosed as a consequence of the intensive monitoring in the clinical development program of unstimulated calcitonin and the calcium stimulation tests. C-cell hyperplasia in a non-nodular form as defined by an increase in overall C-cell numbers is a relatively common finding in human thyroid material. Identification requires specific staining for C-cells. C-cell hyperplasia has been found in up to 33% of autopsies of expected normal thyroid glands and the clinical consequence is unclear.^{83,84} In sporadic cases, i.e., those not attributed to a risk of familial medullary carcinoma, there is no clear evidence that C-cell hyperplasia progresses to neoplastic lesions.⁸⁵

Five of the six individuals who were found to have C-cell pathology had abnormalities of calcitonin secretion (increased baseline levels) prior to the start of liraglutide or comparator treatment and all had a background of thyroid pathology in which the frequency of C-cell hyperplasia is increased.

7.7.5 Consolidated C-cell Conclusion

The GLP-1 receptor-mediated mechanism and the key events in the Mode-of-Action behind the rodent C-cell neoplasia were substantiated with experimental data and literature as summarized above.

There were no acute or chronic changes in calcitonin levels in non-human primates.

Based on these nonclinical studies and consistent with the relevant literature, it is concluded that the rodent C-cell tumors induced by dosing of liraglutide were caused by a non-genotoxic, specific receptor-mediated mechanism, to which rodents are particularly sensitive whereas non-human primates and humans are not.

Over time, calcitonin levels were within the normal reference range in all treatment groups throughout the treatment period with no difference between liraglutide and active comparator at any point in time.

At all time points, less than 1% across treatments shifted to $\geq 2 \times \text{UNR}$. Stimulated calcitonin increments from baseline to peak were not different between liraglutide and the active control, confirming the absence of C-cell hyperplasia in humans. Thus, there was no evidence of a liraglutide-induced rise in calcitonin levels.

Six cases of C-cell hyperplasia were reported, five of these based on pathological evaluation of thyroid tissue removed because of elevated baseline or calcium-stimulation calcitonin. The six cases were distributed consistent with the skewed randomization of the trials with four subjects in the liraglutide group and two subjects in the active comparator group.

Based on the consolidated nonclinical and clinical data from this development program as well as the relevant literature, there is no signal to suggest that liraglutide induces C-cell proliferative changes in humans.

7.8 Neoplasms

7.8.1 Neoplasm Adverse Events

In the liraglutide clinical development program, a total of 116 treatment emergent neoplasm adverse events were reported. In the single-dose trial 1636, an event of benign breast neoplasm was reported, however, because of the short duration of the trial, the tabulations do not include this event. In the intermediate and long-term trials, 115 treatment emergent neoplasm adverse events were reported and of these, 45 were classified as malignant neoplasms ([Table 7-26](#)).

The rates of total neoplasm adverse events (benign and malignant) were 26.9, 25.3, 17.0, and 19.5 events per 1,000 subject years of exposure for total liraglutide, placebo, active comparator and total comparator, respectively ([Table 7-26](#)). The rates of malignant neoplasm adverse events were 10.9, 6.3, 7.2 and 6.9 events per 1,000 subject years of exposure for total liraglutide, placebo, active comparator and total comparator, respectively ([Table 7-26](#)).

Table 7–26 All Neoplasm Adverse Events (Benign and Malignant)

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		3125.9				474.4				1118.7				1593.1		
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	1.8	78 ^(a)	26.9	84	1.3	12	25.3	12	1.2	17	17.0	19	1.2	29	19.5	31
Benign Neoplasms	1.1	48	16.0	50	1.0	9	19.0	9	0.6	9	9.8	11	0.8	18	12.6	20
Thyroid Neoplasm	0.5	21	7.0	22	0.3	3	6.3	3	0.1	1	0.9	1	0.2	4	2.5	4
Uterine Leiomyoma	0.1	5	1.6	5	0.1	1	2.1	1	0.1	1	0.9	1	0.1	2	1.3	2
Melanocytic Naevus	0.0	2	0.6	2	0.1	1	2.1	1	0.1	2	1.8	2	0.1	3	1.9	3
Skin Papilloma	0.1	3	1.0	3					0.1	1	0.9	1	0.0	1	0.6	1
Lung Neoplasm	0.1	3	1.0	3					0.1	1	0.9	1	0.0	1	0.6	1
Lipoma	0.1	4	1.3	4												
Colon Adenoma	0.0	2	0.6	2	0.1	1	2.1	1	0.1	1	0.9	1	0.1	2	1.3	2
Seborrhoeic Keratosis									0.1	2	2.7	3	0.1	2	1.9	3
Benign Neoplasm Of Skin	0.0	1	0.3	1	0.1	1	2.1	1					0.0	1	0.6	1
Tongue Neoplasm Benign	0.0	1	0.3	1												
Parathyroid Tumour Benign	0.0	1	0.3	1												
Ovarian Neoplasm	0.0	1	0.3	1												
Neuroma	0.0	1	0.3	1												
Neoplasm Skin	0.0	1	0.3	1												
Morton's Neuroma	0.0	1	0.3	1												
Hair Follicle Tumour Benign									0.1	1	0.9	1	0.0	1	0.6	1
Benign Neoplasm Of Thyroid Gland	0.0	1	0.3	1												
Benign Neoplasm					0.1	1	2.1	1					0.0	1	0.6	1
Benign Breast Neoplasm	0.0	1	0.3	1												
Acrochordon					0.1	1	2.1	1					0.0	1	0.6	1
Malignant Neoplasms	0.8	34	10.9	34	0.3	3	6.3	3	0.5	8	7.2	8	0.5	11	6.9	11
Prostate Cancer	0.1	5	1.6	5	0.1	1	2.1	1					0.0	1	0.6	1
Papillary Thyroid Cancer	0.1	5	1.6	5	0.1	1	2.1	1					0.0	1	0.6	1
Breast Cancer	0.1	3	1.0	3					0.1	2	1.8	2	0.1	2	1.3	2
Colon Cancer	0.0	2	0.6	2					0.1	1	0.9	1	0.0	1	0.6	1
Renal Cell Carcinoma	0.0	1	0.3	1					0.1	1	0.9	1	0.0	1	0.6	1
Rectal Cancer	0.0	2	0.6	2												

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	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
Basal Cell Carcinoma	0.0	2	0.6	2												
Thyroid Cancer ^(b)									0.1	1	0.9	1	0.0	1	0.6	1
Squamous Cell Carcinoma	0.0	1	0.3	1												
Renal Cell Carcinoma Stage Unspecified	0.0	1	0.3	1												
Oesophageal Carcinoma	0.0	1	0.3	1												
Nasopharyngeal Cancer	0.0	1	0.3	1												
Multiple Myeloma	0.0	1	0.3	1												
Metastatic Neoplasm									0.1	1	0.9	1	0.0	1	0.6	1
Metastases To Liver	0.0	1	0.3	1												
Malignant Lymphoma	0.0	1	0.3	1												
Unclassifiable High Grade Lung Carcinoma Cell Type	0.0	1	0.3	1												
Unspecified Recurrent Lung Adenocarcinoma	0.0	1	0.3	1												
Laryngeal Cancer									0.1	1	0.9	1	0.0	1	0.6	1
Hepatic Neoplasm Malignant	0.0	1	0.3	1												
Glioblastoma Multiforme					0.1	1	2.1	1					0.0	1	0.6	1
Gastric Cancer	0.0	1	0.3	1												
Colon Cancer Stage 0	0.0	1	0.3	1												
Bowen's Disease									0.1	1	0.9	1	0.0	1	0.6	1
B-Cell Lymphoma	0.0	1	0.3	1												
Adenocarcinoma Pancreas	0.0	1	0.3	1												

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1-1](#). ^a Four subjects had both benign and malignant events, why this number is lower than the expected 82 (48+34 subjects). ^b This case is Subject xx4012 in Trial 1572. This event of thyroid cancer also included C-cell hyperplasia (see also [Table 7-25](#)). For Trial 1572, 1573 and NN8022-1807, all AEs included until 21 Feb 2008 (for Trial NN8022-1807 until 52 Weeks) while until 30 May 2008 only serious cases included. N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set.

Thyroid neoplasms were the most common neoplasm adverse events and approximately 80% of all the thyroid neoplasms were benign nodules. The rates of benign thyroid neoplasms (liraglutide: 22 events, rate: 7.0; placebo: 3 events, rate: 6.3; active comparator: 1 event, rate: 0.9) were comparable for subjects treated with liraglutide and subjects treated with placebo and higher than for subjects treated with active comparator ([Table 7–26](#)).

The reporting of thyroid neoplasms may in part represent ascertainment bias due to the intensive thyroid evaluations associated with the C-cell surveillance program. In the Japanese Trial 1334, screening procedures were introduced and baseline thyroid ultrasounds were performed on all subjects. In this Trial 1334, there was a 4:1 randomization of subjects to liraglutide vs. placebo and there was no active comparator group. This contributes significantly to the numerical imbalance in neoplasm adverse events between liraglutide, placebo and active comparators. Indeed, 3.4% of the subjects in the liraglutide development program (Trial 1334) accounted for around 50% of the thyroid neoplasms identified in the liraglutide development program population. In trials without thyroid ultrasound, half of the liraglutide-treated subjects identified with thyroid nodules had a history of thyroid disease or elevated calcitonin at baseline, the latter often prompting structural evaluation. Additional thyroid neoplasms were identified during evaluation for elevated calcitonin levels, which often were detected at the baseline laboratory.

In regard to malignant neoplasms which are of more clinical consequence, prostate cancer, papillary thyroid cancer, breast cancer, colon cancer and renal cell carcinoma were the most commonly reported malignant neoplasms across treatment groups. The rate of malignant thyroid and prostate neoplasms were similar for subjects treated with liraglutide and subjects treated with placebo ([Table 7–26](#)). The remaining malignant neoplasms occurred at low rates with no apparent pattern in type of neoplasms.

Of the five cases of thyroid papillary cancer in the liraglutide-treated group, one subject had a nodule detected at baseline by ultrasound examination in the Japanese Trial 1334 that proved to be a papillary tumor at end of trial. Three of the remaining four subjects had elevated calcitonin levels at baseline and these subjects had incidental papillary microcarcinomas diagnosed at surgical excision for other reasons. Three of the four microcarcinomas were < 4 mm. Thus, there was an imbalance in thyroidectomies due to conditions present at baseline. The thyroid papillary cancer in the active comparator group also had elevated baseline calcitonin.

Information on the six cases of papillary thyroid cancer (liraglutide: 5; rate 1.6; placebo: 1, rate 2.1 per 1,000 patient years of exposure) is presented in [Table 7–27](#). Of note, autopsy studies have identified papillary carcinomas in up to 36% of the population without any previous diagnosis of thyroid disease.⁸⁶ From a clinical perspective, micropapillary carcinoma found at incidental examination of surgically removed thyroid tissue is considered of uncertain clinical relevance and there are few data evaluating outcomes in lesions less than 5 mm in size.^{87,88}

Of the six cases of prostatic cancer identified in the liraglutide development program, four of the six had evidence of pre-existent prostate disease, either prostatic hypertrophy or an elevated prostate specific antigen (PSA) at baseline.

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Table 7–27 All Papillary Thyroid Cancer Adverse Events

Trial	Subject ID	Age (yrs)/ Gender (M/F)	Treatment	Preferred Term [MedDRA] (Outcome)	Duration of Therapy at Onset	Duration of Event	Elevated Calcitonin Baseline	Elevated Calcitonin During Trial	Papillary Thyroid Pathology
1573	xx5008	64/M	Liraglutide 1.8 mg	Papillary thyroid cancer (Recovered)	1 day	107 days	22.3 ng/L (2–3X UNR) ^(a)	26.4 ng/l 29.4 ng/l	Papillary microcarcinoma
1334	xx004	70/F	Liraglutide 0.6 mg	Papillary thyroid cancer (Recovered)	99 days ^(d)	406 days	No	No	Papillary adenocarcinoma
1573	xx1006	62/F	Liraglutide 1.2 mg	Thyroid disorder (Recovered) Papillary thyroid cancer (Recovered) Benign neoplasm of the thyroid gland (Recovered) Thyroid neoplasm (Recovered)	356 days	113 days	21.2 ng/L (CST ^(b) 90%)	94.0 ng/L Abnormal CST peak ^(c)	Papillary microcarcinoma Multiple benign adenomatous nodules
1436	xx6001	59/M	Liraglutide 1.8 mg+ glimepiride	Papillary thyroid cancer (Recovered) Autoimmune thyroiditis (Recovered) Blood calcitonin increased (Recovered)	175 days 50 days 1 day	149 days	13.0 ng/L (1–2x UNR)	23.0 ng/L 17.9 ng/L	Papillary microcarcinoma Nodular colloid goiter
1574	xx6016	53/F	Liraglutide 1.8 mg+ metformin+ rosiglitazone	Goitre (Recovered) Papillary thyroid cancer (Recovered)	22 days 50 days	30 days 63 days	10.7 ng/L (2–3X UNR)	14.5 ng/L	Papillary carcinoma
1574	xx6008	59/M	Placebo+ Metformin+ rosiglitazone	Papillary thyroid cancer (Recovered) Blood calcitonin increased (Not recovered)	1 day 1 day	91 days	19.4 ng/L (2–3X UNR)	29.6 ng/L 19.1 ng/L	Papillary microcarcinoma

^a Upper normal range (UNR) for males of 8.4 ng/L, and for females of 5.0 ng/L. ^b Peak at 90th percentile for females in the substudy. ^c Calcium Stimulation Test (CST), upper normal range 90 ng/L for female and 130 ng/L for male subjects. Gender: M=male and F=female. ^d Detected abnormal thyroid ultrasound at baseline.

A Cox proportional hazard analysis of all neoplasm adverse events is presented in [Table 7–28](#). No statistically significant difference was observed between treatment groups, neither for all neoplasms ([Table 7–28](#)) nor for malignant neoplasms alone ([Table 7–29](#)).

Table 7–28 Cox Proportional Hazard Analysis of Neoplasm Events (Benign and Malignant)

Comparison	Hazard ratio	95% CI	P-value
Liraglutide vs. Placebo	1.00	[0.52 ; 1.91]	0.9985
Liraglutide vs. Active	1.55	[0.90 ; 2.69]	0.1145
Liraglutide vs. Total Comparator	1.32	[0.85 ; 2.03]	0.2146
Active vs. Placebo	0.64	[0.28 ; 1.46]	0.2900

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1–1](#). Cox regression model stratified by trial. P-value from Wald test. For Trial 1572 and 1573 all AEs included until 21 Feb 2008 (for Trial NN8022-1807 until 52 Weeks) while until 30 May 2008 only serious cases included.

Table 7–29 Cox Proportional Hazard Analysis of Malignant Neoplasm Adverse Events

Comparison	Hazard ratio	95% CI	P-value
Liraglutide vs. Placebo	1.42	[0.41; 4.98]	0.5816
Liraglutide vs. Active	1.65	[0.75; 3.63]	0.2142
Liraglutide vs. Total Comparator	1.59	[0.80; 3.16]	0.1879
Active vs. Placebo	0.86	[0.21; 3.63]	0.8400

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1–1](#). Cox regression model stratified by trial. P-value from Wald test. For Trial 1572, 1573 and NN8022-1807, all AEs included until 21 Feb 2008 (for Trial NN8022-1807 until 52 Weeks) while until 30 May 2008 only serious cases included.

7.8.2 Conclusion

The rates of total neoplasm adverse events were 26.9, 25.3, 17.0, and 19.5 events per 1,000 subject years of exposure for total liraglutide, placebo, active comparator and total comparator, respectively. The most common benign neoplasm was thyroid nodules, the majority of which were diagnosed due to the intensified thyroid monitoring procedures included in the clinical trials and based on abnormalities detected at baseline. Papillary thyroid cancers and prostate cancers were the most frequently reported malignant neoplasms. These were reported in liraglutide and placebo treated subjects at similar rates and at a higher rate than in the active comparator group. Single cases of neoplasms from various tissues and diverse tumor types in the liraglutide-treated subjects were reported with no clustering. Neoplasms are rare events, however, based on the clinical safety database from the liraglutide development program and consistent with the nonclinical data, there is no suggestion of a link between liraglutide exposure and the development of neoplasms in humans.

7.9 Thyroid Adverse Events

7.9.1 Thyroid Adverse Events

Unlike the C-cell findings in rodents (Sections [7.7.2](#) and [7.7.3](#)), there was no evidence of thyroid follicular abnormalities in mice or rats.

In reviewing the thyroid adverse events it is important to recognize the potential for ascertainment bias in the liraglutide program resulting from the intensive calcitonin-related surveillance as described in Section [7.7.4](#). This led to increased use of imaging modalities and detection of abnormalities that would otherwise likely have been clinically silent. Thyroid adverse events were distributed in three system organ classes: investigations (predominantly laboratory tests), endocrine disorders and neoplasms (benign, malignant and unspecified). The adverse events included increased blood calcitonin, increased blood thyroid stimulating hormone, goiter, hypo- and hyperthyroidism and various neoplasms ([Table 7-30](#)).

The total number of thyroid adverse events reported across treatments in all intermediate and long-term phase 3 trials was 140 and of these, 18 were reported as serious. The rates of all thyroid adverse events in all intermediate and long-term phase 3 trials were 33.3, 29.5, 19.7 and 22.6 events per 1,000 subject years of exposure for total liraglutide, placebo, active comparator and total comparator, respectively ([Table 7-30](#)). The rates of serious thyroid adverse events were 5.1, 2.1, 0.9 and 1.3 events per 1,000 subject years of exposure for total liraglutide, placebo, active comparator and total comparator, respectively.

Overall, the rates of thyroid adverse events in the system organ class of investigations, endocrine disorders and neoplasms were similar for subjects treated with liraglutide and subjects treated with placebo but higher than for subjects treated with active comparator. The most frequently reported adverse events were increased blood calcitonin, goiter and thyroid neoplasm. The thyroid neoplasms including the cases of papillary thyroid carcinoma are described in Section [7.8](#) and calcitonin is described in Section [7.7.4](#).

There was a numeric imbalance in the number of goiter in the intermediate and long-term trials. A total of 21 cases of goiter occurred in these trials: 18 in the liraglutide, 1 in the placebo and 2 in the active comparator group. The corresponding rates were 5.8 per 1,000 patient years for liraglutide-treated subjects, 2.1 in placebo-treated subjects and 1.8 for the active comparators ([Table 7-30](#)). Of these, seven liraglutide and one non-liraglutide subject had a recorded thyroid disease or increased calcitonin at baseline. Of the totality of 21 reported goiters, nine cases were reported in Trial 1572 and of these, six cases were reported in Germany. Trial 1572 (non-US) recruited approximately one third of subjects in countries historically considered to have endemic goiter as defined by WHO (total goiter prevalence of > 5%). These included Germany, Denmark, Australia, and India.⁸⁹

Table 7–30 All Thyroid Adverse Events

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		3125.9				474.4				1118.7				1593.1		
All Thyroid Adverse Events	1.9	80	33.3	104	1.4	13	29.5	14	1.4	21	19.7	22	1.4	34	22.6	36
Investigations	0.9	40	13.8	43	0.7	6	12.6	6	0.5	7	6.3	7	0.5	13	8.2	13
Blood Calcitonin Increased	0.8	32	10.9	34	0.6	5	10.5	5	0.3	5	4.5	5	0.4	10	6.3	10
Blood Thyroid Stimul. Hormone Increased	0.1	5	1.9	6	0.1	1	2.1	1	0.1	1	0.9	1	0.1	2	1.3	2
Ultrasound Thyroid Abnormal	0.0	1	0.3	1												
Thyroxine Decreased	0.0	1	0.3	1												
Blood Thyroid Stimulating Hormone Decreased									0.1	1	0.9	1	0.0	1	0.6	1
Blood Calcitonin Abnormal	0.0	1	0.3	1												
Endocrine Disorders	0.6	27	10.2	32	0.4	4	8.4	4	0.9	13	11.6	13	0.7	17	10.7	17
Goitre	0.4	17	5.8	18	0.1	1	2.1	1	0.1	2	1.8	2	0.1	3	1.9	3
Hypothyroidism	0.1	3	1.0	3	0.1	1	2.1	1	0.3	5	4.5	5	0.3	6	3.8	6
Hyperthyroidism	0.1	3	1.0	3	0.1	1	2.1	1	0.1	2	1.8	2	0.1	3	1.9	3
Thyroid Cyst	0.1	3	1.0	3					0.1	1	0.9	1	0.0	1	0.6	1
Autoimmune Thyroiditis	0.0	2	0.6	2	0.1	1	2.1	1	0.1	1	0.9	1	0.1	2	1.3	2
Thyroid Disorder	0.0	2	0.6	2												
Toxic Nodular Goitre									1 0.1	1	0.9	1	1 0.0		0.6	1
Thyroiditis Chronic	0.0	1	0.3	1											0.6	1
Thyroid Pain									0.1	1	0.9	1	0.0	1		
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0.6	26	9.3	29	0.4	4	8.4	4	0.1	2	1.8	2	0.3	6	3.8	6
Thyroid Neoplasm	0.5	21	7.0	22	0.3	3	6.3	3	0.1	1	0.9	1	0.2	4	2.5	4
Papillary Thyroid Cancer	0.1	5	1.6	5	0.1	1	2.1	1			0.9	1	0.0	1	0.6	1
Thyroid cancer ^(a)									0.1	1			0.0	1	0.6	1
Parathyroid Tumour Benign	0.0	1	0.3	1												
Benign Neoplasm Of Thyroid Gland	0.0	1	0.3	1												

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1–1](#).^a This case is Subject xx4012 in Trial 1572. This event of thyroid cancer also included C-cell hyperplasia (see also [Table 7–25](#)). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years for Safety Analysis Set

A Cox proportional hazard analysis of all thyroid adverse events identified no statistically significant difference between treatment groups ([Table 7-31](#)).

Table 7-31 Cox Proportional Hazard Analysis of all Thyroid Adverse Events

Comparison	Hazard ratio	95% CI	P-value
Liraglutide vs. Placebo	1.04	[0.52 ; 2.09]	0.9083
Liraglutide vs. Active	1.16	[0.70 ; 1.93]	0.5618
Liraglutide vs. Total Comparator	1.12	[0.73 ; 1.73]	0.6002
Active vs. Placebo	0.90	[0.40 ; 2.03]	0.7933

Table is based on population 1 (all intermediate and long-term trials) in [Appendix, Table 1-1](#). Cox regression model, stratified by trial. P-value from Wald test.

7.9.2 Conclusion

Overall, rates for all thyroid adverse events were 33.3, 29.5 and 19.7 events per 1,000 subject years of exposure for liraglutide, placebo and active comparators, respectively. As discussed elsewhere, rates of increased blood calcitonin concentrations and thyroid neoplasms were generally comparable for subjects treated with liraglutide and subjects treated with placebo, and higher than for subjects treated with active comparator. There was no overall statistically significant treatment difference in a Cox proportional hazard analysis of all thyroid adverse events. There was, however, a numeric imbalance in reported adverse events of goiter. Part of the diagnoses was based on baseline thyroid findings where screening procedures assessed calcitonin with presence of thyroid disease, and almost 50% of all reported goiters were in a non-US trial, Trial 1572, with a high percentage of recruitment in regions with historically WHO defined endemic goiter.

7.10 Cardiovascular Safety

7.10.1 Nonclinical Observations

Cardiovascular Effects of GLP-1

The actions of native GLP-1 in the heart have been investigated extensively in nonclinical models and in some pilot clinical studies as well. Activation of cardiac GLP-1 receptors leads to increased glucose uptake in cardiomyocytes in rats.¹³ In non-ischemic heart, this is achieved through increased myocardial nitric oxide production, p38 mitogen-activated kinase (p38 MAP) activity and glucose transporter (GLUT-1) translocation, which is distinct from known insulin actions. In cardiomyocytes undergoing ischemia, mechanisms leading to increased glucose uptake are similar to those of insulin.¹³ Stimulation of cardiac GLP-1 receptors also appears to activate pro-survival pathways, and thus reduce infarct size.¹⁴ In a canine model of myocardial stunning (using 10-minute occlusion of the proximal left circumflex coronary artery), administration of GLP-1 caused earlier recovery of regional wall motion, no residual contractile dysfunction, improved isovolumic left ventricular relaxation and led to fewer episodes of ventricular tachycardia.¹⁵ Dogs with advanced dilated cardiomyopathy which was induced by rapid pacing and subsequently undergoing i.v. infusion of GLP-1 were found to have significantly increased (improved) left systolic (LV)

systolic pressure and reduced LV end-diastolic pressure. Interestingly, heart rate was reduced by 34 ± 5 beats per minute, while ejection fraction increased from $28 \pm 1\%$ to $38 \pm 5\%$. Systemic vascular resistance was lowered.⁹⁰ GLP-1 infusion also improved left ventricular ejection fraction and functional status in patients with chronic heart failure.⁹¹

In a murine model of experimental myocardial infarction (ligation of left anterior descending coronary artery), liraglutide significantly decreased infarct size, cardiac rupture, and mortality. In the same study, liraglutide was found to activate intracellular pathways known to protect the heart against injury.⁹²

No specific cardiovascular safety concerns have been identified on the basis of nonclinical studies.

7.10.2 Blood Pressure

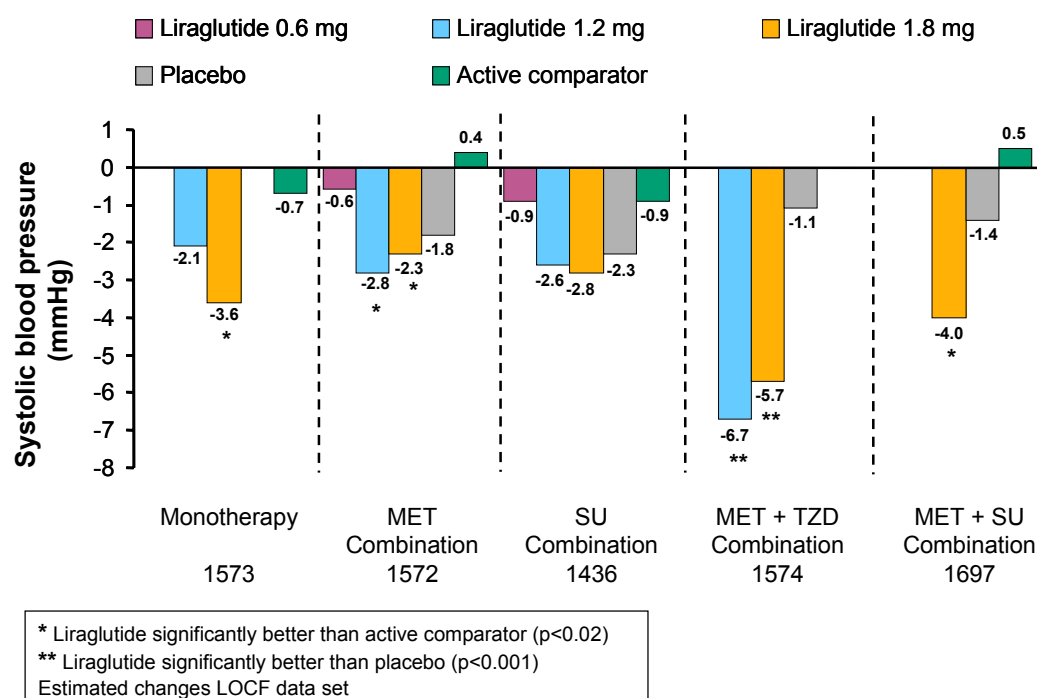
Increased blood pressure is a risk factor for cardiovascular disease, and in particular increased systolic blood pressure is common among subjects with type 2 diabetes. Based on results from phase 2 trials, changes in systolic and diastolic blood pressure were analyzed in the five long-term phase 3 trials as a secondary endpoint. A standardized procedure for the measurement of blood pressure was followed to increase consistency of the measurements.

Across the long-term phase 3 trials, liraglutide treatment resulted in a reduction from baseline in systolic blood pressure ([Figure 7-12](#)). During treatment with liraglutide, the 0.6 mg dose caused a decrease between 0.6 and 0.9 mmHg, the 1.2 mg dose led to a decrease of 2.1 to 6.7 mmHg and liraglutide 1.8 mg caused a decrease of 2.3 to 5.7 mmHg. Treatment with liraglutide 1.8 mg decreased systolic blood pressure significantly more than the active comparator in Trials 1573, 1572 and 1697. Systolic blood pressure was also significantly lower after liraglutide treatment when compared with placebo + metformin + rosiglitazone in Trial 1574. No significant differences were seen for diastolic blood pressure in any of the trials.

The mechanism behind the blood pressure lowering effect of liraglutide remains to be studied in more detail. Recent experiments with native GLP-1 suggest a lower renal sodium reabsorption and decreased sodium absorption in the gastrointestinal tract as potential mechanisms, rather than changes in cardiac autonomic functions.^{93,94} In the liraglutide clinical studies, the reduction in systolic blood pressure was associated with a minor increase in heart rate of 2–4 beats/min ([Section 7.10.4](#)).

The systolic blood pressure is a more important cardiovascular risk factor than diastolic hypertension in people over 50 years - a group well represented in the liraglutide target population. Of note and consistent with epidemiological data, a high percentage of subjects in the liraglutide development program (72%) had a concomitant diagnosis of hypertension.^{89,95}

Figure 7–12 Systolic Blood Pressure, Change from Baseline (mmHg)



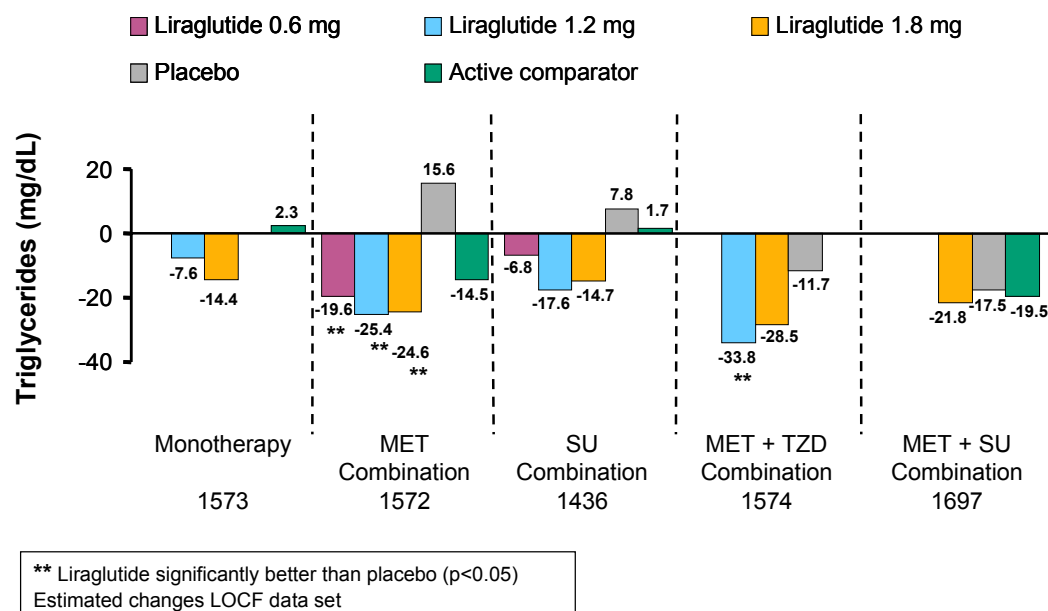
For complete treatment regimens in the individual trials, see [Table 6–1](#). Values are estimated means (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

7.10.3 Cardiovascular Biomarkers and Lipids

7.10.3.1 Fasting Lipid Profiles

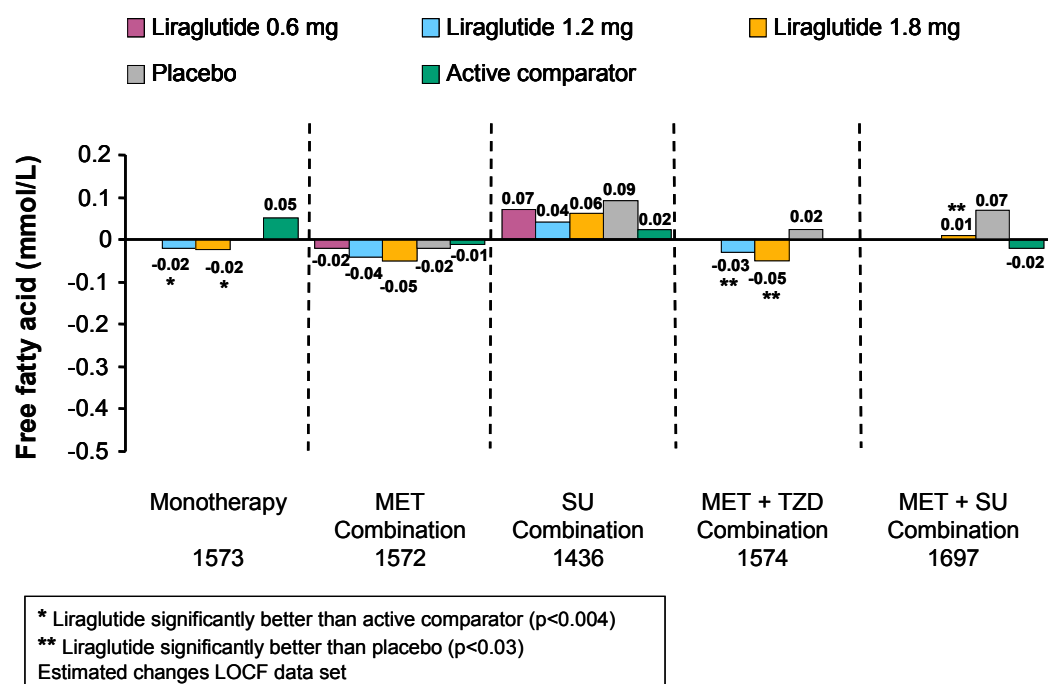
The changes in fasting lipid profiles were investigated in the five long-term phase 3 trials. There were no data suggesting an adverse impact of liraglutide treatment on the lipid profile with respect to cardiovascular risk. Overall, there were indications of positive changes in the lipid profiles as presented in [Figure 7–13](#) and [Figure 7–14](#) for triglycerides and free fatty acids. Results from each of the individual long-term phase 3 trials are presented in Section [6.8](#) for triglycerides and HDL-C.

Figure 7–13 Total Triglycerides, Change from Baseline (mg/dL)



For complete treatment regimens in the individual trials, see [Table 6–1](#). Values are estimated means (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

Figure 7–14 Free Fatty Acids, Change from Baseline (mmol/L)



For complete treatment regimens in the individual trials, see [Table 6–1](#). Values are estimated means (LOCF). Data from Trial 1573 are 52-week data and data from Trials 1572, 1436, 1574 and 1697 are 26-week data.

7.10.3.2 Biomarkers of Cardiovascular Risk

The effect of liraglutide on a set of biomarkers for cardiovascular disease was measured in all five long-term phase 3 trials. Generally, liraglutide dose, treatment duration or co-medication did not have any adverse effects on these biomarkers of PAI-1, CRP or NTproBNP.

Results on NT-proBNP and hsCRP from each of the five long-term phase 3 trials are presented in Section [6.8](#). Although not consistently significant, there was no indication of any adverse effect of liraglutide on the assessed cardiovascular biomarkers.

7.10.4 Vital Signs, ECG and QTc Assessments

No clinically relevant findings of safety concern were seen. A minor increase in pulse was consistently observed in the intermediate-term and long-term trials, as well as indicated in the single-dose and short-term trials.

In the long-term phase 3 trials, the mean increase in pulse observed with liraglutide treatment from baseline to Week 76/78 was 2.0, 2.2 and 1.4 beats per minute with increasing liraglutide dose (0.6 mg, 1.2 mg and 1.8 mg, respectively). A slight increase in mean pulse was also observed with active comparator treatment (0.2 beats per minute), whereas a minor decrease of 0.6 beats per minute was observed with placebo treatment.

The estimated treatment differences between liraglutide at any dose vs. placebo and active comparator were analyzed in a repeated measurements analysis. Statistically significant differences were observed for liraglutide at any dose vs. comparators for Weeks 26/28 and 52, whereas no significant differences were observed for liraglutide vs. comparators at Week 76/78. The mechanism behind this increase is not known, but could be a compensatory response to the observed decrease in systolic blood pressure.

Liraglutide was not, at any dose, associated with clinically significant changes in ECG during any trial. A QTc-trial (TQT) was conducted according to the ICH E14 guideline (Trial 1644) with moxifloxacin as a positive control. The primary objective was to assess the time-matched mean maximum difference between the baseline subtracted QTci (individually corrected QT) intervals for 1.8 mg/day liraglutide (treatment) versus placebo. Following randomization, subjects received liraglutide 0.6 mg daily for seven days, liraglutide 1.2 mg daily for seven days, followed by liraglutide 1.8 mg daily for seven days. Subjects came into the clinic every morning for dosing, and baseline ECG assessments were performed for 24 hours immediately prior to the first 0.6 mg dose (before each of the two crossover periods). Subjects had 24 hours of serial ECG monitoring and PK blood samplings immediately after the seventh and final doses of liraglutide 1.2 mg and 1.8 mg, respectively.

The upper bound of the 95% one-sided confidence interval for the time-matched maximum mean difference between QTc for liraglutide and placebo was less than 10 ms (less than 3 ms for QTci, QTciL and QTcF).

The categorical descriptive analysis of outliers of QTc or Δ QTc demonstrated that the number of subjects exceeding the critical values of QTc for liraglutide was not greater compared to placebo (for all methods of QT correction).

The largest time-matched mean difference between QTc for moxifloxacin and placebo was greater than 10 ms for QTci (primary comparison), QTcil, QTcF, and QTcB, and the largest difference was achieved at 2h (around the published t_{max}) for moxifloxacin.

Based on the above, the study is concluded as negative, while the design and assessments were adequate and sensitive enough to capture a potential QT prolongation.

Additional to the dedicated QTc trial (Trial 1644), recordings of PR and QT intervals and QRS duration were performed in three single-dose trials (Trials 1149, 1464 and 1219 and one short-term trial (Trial 1189)). No changes of clinical significance were noted at any liraglutide dose level in any of the trials.

Overall, no safety concerns were raised with respect to vital signs.

7.10.5 Major Adverse Cardiovascular Events (MACE)

In December 2008, the FDA issued a ‘*Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*’.¹ The guidance was issued based on the Endocrinologic and Metabolic Drugs Advisory Committee meeting of July 1–2, 2008. The guidance provides recommendations on how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

The guidance divides development programs in two categories, those whose trials had not been completed and those with completed studies at the time of the guidance’s release. Liraglutide falls in the latter category, as the liraglutide clinical development program was completed before the current FDA guidance was issued. For these programs, the guidance recommends applying an integrated analysis (meta-analysis) on controlled phase 2 and phase 3 clinical trials to 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. For a new therapeutic agent to be approved without additional pre-approval commitment for assessing cardiovascular safety, this analysis should demonstrate that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.

The results presented below are part of a comprehensive effort to be responsive to the recommendations of the Advisory Committee recommendations and the FDA guidance document. It includes analyses and populations specifically requested from the FDA in January 2009 that also defined the outcomes to make up this MACE analysis ([Appendix, Section 3](#)).

Conducting the analyses of MACE in retrospect after completion of the trials will inherently be limited, as the development program was design based on HbA_{1c} being a valid surrogate endpoint. Therefore, blinded adjudication of events was not done, pre-defined event definitions were not employed and subjects at particular high cardiovascular risk were excluded. Nonetheless, the liraglutide development program provides an extensive randomized exposure experience. Valuable additional exposure data are available from the extension studies as subjects maintained their randomized assignments during the extension allowing for meaningful comparisons. Thus, although done in retrospect, the analyses provide useful insight into the relative risk for cardiovascular events during liraglutide treatment, despite the limitations imposed by the trial designs and study population which were based on the standard for diabetes drug development at the time they were designed.

7.10.5.1 Definitions of MACE Endpoints and Populations

MACE Endpoints

MACE endpoints were defined based on Standardized MedDRA Queries (SMQ) (see [Appendix, Table 3–1](#) and [Table 3–2](#) for term listings). Different strategies were used to allow for an assessment of the robustness of the analyses. Overall sets of adverse event terms were defined for the MACE analysis requested by the FDA. These were defined based on tabulations of cardiovascular death, SMQ ‘Myocardial Infarction’ and SMQ ‘Central Nervous System Haemorrhages and Cerebrovascular Accidents’ plus a customized list of adverse event terms designated ‘Custom MACE’. Within the SMQ MACE – a predefined broader and narrower set of adverse events terms exist and for completeness, both definitions were applied for the SMQ MACE endpoint.

Therefore, in total three categories were applied and labeled as a ‘Broad’, a ‘Narrow’ and a ‘Custom’ search. The ‘Broad’ search includes the largest number of terms – the ‘Narrow’ is a subset of terms within the Broad search, and the ‘Custom’ includes the smallest number of terms and is a subset of the ‘Narrow’. An additional three sets of events were developed by limiting the previously defined events in the ‘Broad’, ‘Narrow’ and ‘Custom’ groups to only those designated as serious by the investigator. These are henceforth referred to as ‘Broad Serious’, ‘Narrow Serious’ and ‘Custom Serious’. All MedDRA preferred terms are assigned as in the 120-day Safety Update. In line with the FDA Guidance, no post-hoc adjudication of adverse events has been performed.

The clinical safety database is based on the 120-day Safety Update.

Populations

Three populations were defined – *Population A1*, *Population A2*, and *Population B*. Populations A1 and A2 include the least patient years of exposure as they do not include open-label controlled extension phases of any of the trials. The definitions of the populations are summarized below and a graphic presentation of the size and the exposure in these three populations is also provided below in [Figure 7–15](#). Population A1 is the smallest with respect to number of subjects and years of

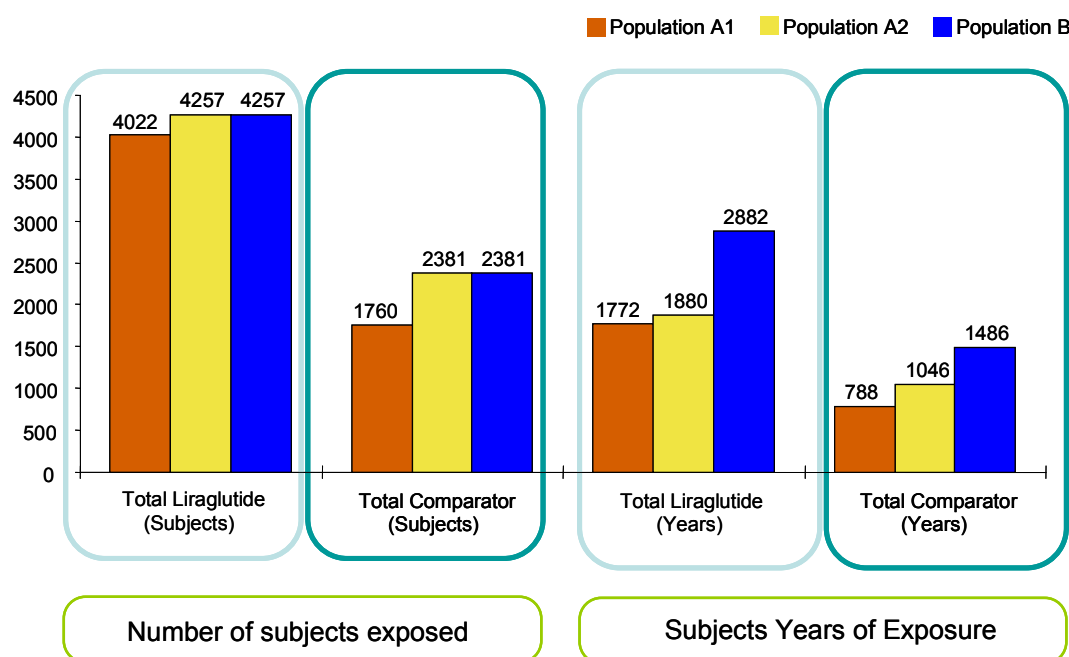
exposure. Population A2 and B contain the same number of subjects, whereas the years of exposure differ.

Population A1: Randomized, double-blind, controlled periods for all completed phase 2 and phase 3 clinical trials. This population included 5,782 subjects, of which 4,022 had been exposed to liraglutide. Total years of exposure were 2,560 and of these, 1,772 were liraglutide ([Table 6-3](#)).

Population A2: Population A1 plus open-label active control study arms and studies. This population included 6,638 subjects of which 4,257 had been exposed to liraglutide. Total years of exposure were 2,926 and of these, 1,880 were liraglutide ([Table 6-3](#)).

Population B: Population A2 plus open-label controlled extension periods. This population included 6,638 subjects of which 4,257 had been exposed to liraglutide. Total years of exposure were 4,368 and of these, 2,882 were liraglutide ([Table 6-3](#)).

Figure 7-15 Number of Subjects and Years of Exposure in Populations A1, A2, and B



Population Characteristics

Patients with type 2 diabetes are at increased risk for cardiovascular events and this risk is further increased by the presence of hypertension and hyperlipidemia. The study population in the five long-term phase 3 trials had a mean age of 55 years and approximately 800 subjects were > 65 years of age. The average BMI was in the range of 30–33 kg/m², and the typical duration of type 2 diabetes was between 5–9 years ([Table 6-4](#) and [Table 6-5](#)). Subjects in NYHA class III and IV

were excluded from enrolment in the liraglutide clinical development program, as were subjects with substantial renal impairment.

The most common concomitant illness (recorded at screening) reported in the five long-term phase 3 trials was hypertension, which was present in 62 to 68% of subjects across all treatment groups. A past medical history of myocardial infarction was reported by 2.3 to 5.0% of subjects across all treatment groups, and was most common in the placebo group and least common in the liraglutide 0.6 mg group. In accordance with the use of lipid-lowering concomitant medications taken by subjects in the five long-term phase 3 trials, concomitant hyperlipidemia (19 to 25% of subjects), hypercholesterolemia (15% of subjects), and dyslipidemia (13 to 20% of subjects) were recorded across all treatment groups.

Cardiovascular concomitant characteristics of subjects in the intermediate and long-term trials is presented in [Table 7–32](#).

Table 7–32 Concomitant Cardiovascular Disease in All Intermediate and Long-term Trials

	Liraglutide		Placebo		Active Comparator		Total Comparator	
	%	N	%	N	%	N	%	N
Any evidence of vascular disease	14.9	606	16.0	140	17.2	253	16.7	393
Ischaemic heart disease	9.1	370	10.8	94	11.9	175	11.5	269
Cerebrovascular disease	2.9	118	2.4	21	2.5	37	2.5	58
Peripheral vascular disease	4.6	186	4.2	37	4.7	70	4.6	107
Disorder of rhythm or conductivity	5.5	224	5.2	45	5.0	74	5.1	119
Heart failure or systolic/diastolic dysfunction	0.6	24	0.6	5	0.7	10	0.6	15
Valvular disease	0.6	24	1.1	10	0.8	12	0.9	22
Evidence of hypertension or hypertensive disease	57.0	2323	57.4	501	58.7	865	58.2	1366
Subjects with unclassified medical history ^(a)	4.4	181	3.9	34	0	0	1.4	34
No medical history of cardiovascular disease	37.8	1542	37.1	324	36.8	543	36.9	867

Table is based on population 1 (intermediate and long-term trials) in [Appendix, Table 1–1](#). N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events. ^a In a few studies, the preferred term was not consistently applied.

7.10.5.2 Statistical Analyses

Incidence Difference, Incidence Ratio, Incidence Rate Difference and Incidence Rate Ratio were estimated together with 95% CI. The analyses are based on number of subjects. Incidence does not take exposure into account, whereas Incidence Ratio does account for exposure. Note, that the statistical analyses of MACE (Incidence and Incidence Rate) are based on subjects. The MACE rates tabulated in this Briefing Document in-text and tables are calculated as events/subject years of exposure multiplied by 1,000 to make it consistent with other tables in the document. The estimations were performed for each individual trial and also for the pooled data. When more than

one comparator was available, three analyses were performed 1) liraglutide compared to placebo, 2) liraglutide compared to active comparator, and 3) liraglutide compared to placebo and active comparator groups combined (total comparators). Analysis 3) was considered the main analysis. All analyses were conducted using asymptotic methods. For the pooled data, the estimates and 95% CI were computed using a method stratified by trial (Cochran Mantel-Haenszel). Details on the analysis methods can be found in [Appendix, Section 3.2](#).

7.10.5.3 Presentation of Major Adverse Cardiovascular Events (MACE)

[Table 7–33](#) to [Table 7–35](#) provide a consolidated overview of the three search categories of all MACE adverse events in Population A1 (randomized, double-blind, controlled periods for all completed phase 2 and phase 3 clinical trials), Population A2 (A1 plus open-label active control study arms and studies), and Population B (Population A2 plus open-label controlled extension periods) by rate of occurrence, fraction of population experiencing a MACE and number of events. Further, an overview of the number of patients experiencing a MACE is tabulated for each of the three populations, A1, A2, and B ([Table 7–36](#)). Population A1 is the smallest population and Population B is the largest.

Table 7–33 Overview of all MACE, Population A1

	Broad Search						Narrow Search						Custom Search					
	Liraglutide ^(a)			Total Comparator ^(b)			Liraglutide			Total Comparator			Liraglutide			Total Comparator		
	R	%	E	R	%	E	R	%	E	R	%	E	R	%	E	R	%	E
All MACE	27.7	1.2	49	34.3	1.4	27	12.4	0.5	22	12.7	0.5	10	6.8	0.3	12	8.9	0.4	7
Serious MACE	8.5	0.4	15	10.2	0.5	8	7.9	0.3	14	10.2	0.5	8	5.6	0.2	10	7.6	0.3	6

Table is based on population A1 (double-blind, completed intermediate and long-term trials) in [Appendix, Table 1–1](#). ^a N=4022; Years of exposure=1772. ^b N=1760; Years of exposure=788 and Total Comparator=Active Comparator + Placebo. R: Number of events divided by Subject years of exposure multiplied by 1,000. %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events.

Table 7–34 Overview of all MACE, Population A2

	Broad Search						Narrow Search						Custom Search					
	Liraglutide ^(a)			Total Comparator ^(b)			Liraglutide			Total Comparator			Liraglutide			Total Comparator		
	R	%	E	R	%	E	R	%	E	R	%	E	R	%	E	R	%	E
All MACE	27.7	1.2	52	37.3	1.5	39	12.2	0.5	23	18.2	0.7	19	6.9	0.3	13	12.4	0.5	13
Serious MACE	8.5	0.4	16	15.3	0.7	16	8.0	0.4	15	15.3	0.7	16	5.9	0.3	11	11.5	0.5	12

Table is based on population A2 (completed intermediate and long-term trials) in [Appendix, Table 1–1](#). ^a N=4257; Years of exposure=1880. ^b N=2381/Years of exposure=1046 and Total Comparator=Active Comparator + Placebo. R: Number of events divided by Subject years of exposure multiplied by 1,000. %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events.

Table 7–35 Overview of all MACE, Population B

	Broad Search						Narrow Search						Custom Search					
	Liraglutide ^(a)			Total Comparator ^(b)			Liraglutide			Total Comparator			Liraglutide			Total Comparator		
	R	%	E	R	%	E	R	%	E	R	%	E	R	%	E	R	%	E
All MACE	24.6	1.6	71	33.6	1.9	50	12.5	0.8	36	18.2	1.0	27	7.3	0.5	21	11.4	0.7	17
Serious MACE	8.7	0.6	25	12.8	0.8	19	8.3	0.6	24	12.8	0.8	19	5.9	0.4	17	10.1	0.6	15

Table is based on population B (population A2 + open-label extensions) in [Appendix, Table 1–1](#).^a N=4257; Years of exposure=2882.

^b N=2381; Years of exposure=1486 and Total Comparator=Active Comparator + Placebo. R: Number of events divided by Subject years of exposure multiplied by 1,000. %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events.

As can be seen from [Table 7–33](#), [Table 7–34](#) and [Table 7–35](#), the rates for MACE in the liraglutide group are lower than or comparable to total comparator in all three MACE search categories. The tables further illustrate that, the fraction of serious MACE in all treatment groups increases as the search category narrows, suggesting greater specificity for clinically meaningful events but at the risk of excluding other relevant events. Similar results are seen in all three populations, with accrual of more events in Population B due to the larger exposure. A more detailed overview of the MACE events in Populations A1 and A2 can be seen in [Table 7–37](#) to [Table 7–42](#). Similar overview of Population B is in [Appendix, Section 3.3.1](#), [Tables 3–5](#) to [3–7](#).

Table 7–36 Number of Subjects with MACE

	Liraglutide	Total Comparator
Population A1		
All Broad	48	24
All Narrow	21	9
All Custom	12	7
Serious Broad	15	8
Serious Narrow	14	8
Serious Custom	10	6
Population A2		
All Broad	51	35
All Narrow	22	17
All Custom	13	13
Serious Broad	16	16
Serious Narrow	15	16
Serious Custom	11	12
Population B		
All Broad	69	45
All Narrow	35	24
All Custom	21	17
Serious Broad	25	19
Serious Narrow	24	19
Serious Custom	17	15

Table 7–37 Summary of SMQ MACE (Broad Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure Years		1771.8				328.2				459.4				787.6		
Serious MACE AEs	0.4	15	8.5	15	0.3	3	9.1	3	0.6	5	10.9	5	0.5	8	10.2	8
MACE Deaths	0	0	0	0	0.1	1	3.0	1	0	0	0	0	0.1	1	1.3	1
Non-Serious MACE AEs	0.8	33	19.2	34	0.7	6	18.3	6	1.3	11	28.3	13	1.0	17	24.1	19
Total MACE Adverse Events	1.2	48	27.7	49	1.0	9	27.4	9	1.8	15	39.2	18	1.4	24	34.3	27
MACE AE Withdrawals	0.2	9	5.1	9	0.3	3	9.1	3	0.4	3	6.5	3	0.3	6	7.6	6

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

Table 7–38 Summary of SMQ MACE (Broad Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
Serious MACE AEs	0.4	16	8.5	16	0.3	3	9.1	3	0.9	13	18.1	13	0.7	16	15.3	16
MACE Deaths	0.0	0	0.0	0	0.1	1	3.0	1	0.1	1	1.4	1	0.1	2	1.9	2
Non-Serious MACE AEs	0.8	35	19.2	36	0.7	6	18.3	6	1.0	15	23.7	17	0.9	21	22.0	23
Total MACE Adverse Events	1.2	51	27.7	52	1.0	9	27.4	9	1.8	26	41.8	30	1.5	35	37.3	39
MACE AE Withdrawals	0.2	10	5.3	10	0.3	3	9.1	3	0.5	7	9.8	7	0.4	10	9.6	10

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–39 Summary of SMQ MACE (Narrow Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure Years		1771.8				328.2				459.4				787.6		
Serious MACE AEs	0.3	14	7.9	14	0.3	3	9.1	3	0.6	5	10.9	5	0.5	8	10.2	8
MACE Deaths	0	0	0	0	0.1	1	3.0	1	0	0	0	0	0.1	1	1.3	1
Non-Serious MACE AEs	0.2	7	4.5	8	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
Total MACE Adverse Events	0.5	21	12.4	22	0.4	4	12.2	4	0.6	5	13.1	6	0.5	9	12.7	10
MACE AE Withdrawals	0.2	8	4.5	8	0.3	3	9.1	3	0.4	3	6.5	3	0.3	6	7.6	6

N: Number of Subjects with adverse event s; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

Table 7–40 Summary of SMQ MACE (Narrow Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
Serious MACE AEs	0.4	15	8.0	15	0.3	3	9.1	3	0.9	13	18.1	13	0.7	16	15.3	16
MACE Deaths	0.0	0	0.0	0	0.1	1	3.0	1	0.1	1	1.4	1	0.1	2	1.9	2
Non-Serious MACE AEs	0.2	7	4.3	8	0.1	1	3.0	1	0.1	2	2.8	2	0.1	3	2.9	3
Total MACE Adverse Events	0.5	22	12.2	23	0.4	4	12.2	4	0.9	13	20.9	15	0.7	17	18.2	19
MACE AE Withdrawals	0.2	9	4.8	9	0.3	3	9.1	3	0.5	7	9.8	7	0.4	10	9.6	10

N: Number of Subjects with adverse event s; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–41 Summary of MACE (Custom Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure Years		1771.8				328.2				459.4				787.6		
Serious MACE AEs	0.2	10	5.6	10	0.2	2	6.1	2	0.5	4	8.7	4	0.3	6	7.6	6
MACE Deaths	0.0	0	0.0	0	0.1	1	3.0	1	0.0	0	0.0	0	0.1	1	1.3	1
Non-Serious MACE AEs	0.0	2	1.1	2	0.1	1	3.0	1	0.0	0	0.0	0	0.1	1	1.3	1
Total MACE Adverse Events	0.3	12	6.8	12	0.3	3	9.1	3	0.5	4	8.7	4	0.4	7	8.9	7
MACE AE Withdrawals	0.2	7	4	7	0.2	2	6.1	2	0.4	3	6.5	3	0.3	5	6.3	5

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

Table 7–42 Summary of MACE (Custom Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
Serious MACE AEs	0.3	11	5.9	11	0.2	2	6.1	2	0.7	10	13.9	10	0.5	12	11.5	12
MACE Deaths	0.0	0	0.0	0	0.1	1	3.0	1	0.1	1	1.4	1	0.1	2	1.9	2
Non-Serious MACE AEs	0.0	2	1.1	2	0.1	1	3.0	1	0.0	0	0.0	0	0.0	1	1.0	1
Total MACE Adverse Events	0.3	13	6.9	13	0.3	3	9.1	3	0.7	10	13.9	10	0.5	13	12.4	13
MACE AE Withdrawals	0.2	8	4.3	8	0.2	2	6.1	2	0.5	7	9.8	7	0.4	9	8.6	9

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

Details of the MACE events by preferred term and system organ class (SOC) occurring in Populations A1 and A2 (all MACE and serious MACE, respectively) are presented in [Table 7-43](#) to [Table 7-46](#) for ‘SMQ Broad’, [Table 7-47](#) to [Table 7-50](#) for ‘SMQ Narrow’, and [Table 7-51](#) to [Table 7-54](#) for ‘Custom MACE’. Tabulations for Population B can be found in [Appendix, Sections 3.3.1](#) and [3.3.2](#)).

In all treatment groups, the most frequently reported serious MACE events were acute myocardial infarctions and myocardial infarction. These occurred at an event rate (per 1,000 subject years of exposure) of 1.7 and 2.3 for Population A1 and 2.1 and 1.6 in Population A2 in the liraglutide-treated group and 2.5 and 5.1 in Population A1 and 4.8 and 4.8 in Population A2 for total comparators. The most commonly reported term in the Nervous System Disorders group of serious MACE events was ‘Cerebrovascular Accident’ at a rate of 1.7 and 1.6 per 1,000 subject years in the liraglutide Populations A1 and A2, respectively and 0 and 1.0 in Population A1 and A2, respectively in the total comparator groups.

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Table 7–43 All SMQ MACE by SOC and Preferred Term (Broad Search) -Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure Years		1771.8				328.2				459.4				787.6		
All MACE Adverse Events	1.2	48	27.7	49	1.0	9	27.4	9	1.8	15	39.2	18	1.4	24	34.3	27
INVESTIGATIONS	0.6	26	14.7	26	0.6	5	15.2	5	1.2	10	23.9	11	0.9	15	20.3	16
Blood Creatine Phosphokinase Increased	0.6	24	13.5	24	0.4	4	12.2	4	1.2	10	23.9	11	0.8	14	19.0	15
Blood Creatine Phosphokinase Abnormal	0.0	1	0.6	1	0.1	1	3.0	1					0.1	1	1.3	1
Electrocardiogram Q Wave Abnormal	0.0	1	0.6	1												
NERVOUS SYSTEM DISORDERS	0.3	11	6.8	12	0.1	1	3.0	1	0.2	2	6.5	3	0.2	3	5.1	4
Transient Ischaemic Attack	0.1	3	1.7	3					0.1	1	2.2	1	0.1	1	1.3	1
Carotid Artery Stenosis	0.0	2	1.7	3					0.1	1	2.2	1	0.1	1	1.3	1
Cerebrovascular Accident	0.1	3	1.7	3												
Cerebrovascular Disorder	0.0	1	0.6	1	0.1	1	3.0	1					0.1	1	1.3	1
Paresis	0.0	1	0.6	1												
Paralysis									0.1	1	2.2	1	0.1	1	1.3	1
Cerebral Haemorrhage	0.0	1	0.6	1												
CARDIAC DISORDERS	0.3	11	6.2	11	0.3	3	9.1	3	0.5	4	8.7	4	0.4	7	8.9	7
Myocardial Infarction	0.1	4	2.3	4	0.2	2	6.1	2	0.4	3	6.5	3	0.3	5	6.3	5
Acute Myocardial Infarction	0.1	5	2.8	5	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
Coronary Artery Occlusion	0.0	1	0.6	1												
Acute Coronary Syndrome	0.0	1	0.6	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

Novo Nordisk

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Table 7–44 All SMQ MACE by SOC and Preferred Term (Broad Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
All MACE Adverse Events	1.2	51	27.7	52	1	9	27.4	9	1.8	26	41.8	30	1.5	35	37.3	39
INVESTIGATIONS	0.7	28	14.9	28	0.6	5	15.2	5	0.9	13	19.5	14	0.8	18	18.2	19
Blood Creatine Phosphokinase Increased	0.6	26	13.8	26	0.4	4	12.2	4	0.9	13	19.5	14	0.7	17	17.2	18
Blood Creatine Phosphokinase Abnormal	0	1	0.5	1	0.1	1	3	1					0	1	1	1
Electrocardiogram Q Wave Abnormal	0	1	0.5	1												
CARDIAC DISORDERS	0.3	11	5.9	11	0.3	3	9.1	3	0.5	8	11.1	8	0.5	11	10.5	11
Myocardial Infarction	0.1	4	2.1	4	0.2	2	6.1	2	0.3	4	5.6	4	0.3	6	5.7	6
Acute Myocardial Infarction	0.1	5	2.7	5	0.1	1	3	1	0.3	4	5.6	4	0.2	5	4.8	5
Coronary Artery Occlusion	0	1	0.5	1												
Acute Coronary Syndrome	0	1	0.5	1												
NERVOUS SYSTEM DISORDERS	0.3	12	6.9	13	0.1	1	3	1	0.4	6	11.1	8	0.3	7	8.6	9
Carotid Artery Stenosis	0	2	1.6	3					0.2	3	4.2	3	0.1	3	2.9	3
Transient Ischaemic Attack	0.1	3	1.6	3					0.1	2	2.8	2	0.1	2	1.9	2
Cerebrovascular Accident	0.1	3	1.6	3					0.1	1	1.4	1	0	1	1	1
Cerebrovascular Disorder	0	1	0.5	1	0.1	1	3	1					0	1	1	1
Paresis	0	1	0.5	1												
Paralysis									0.1	1	1.4	1	0	1	1	1
Ischaemic Stroke									0.1	1	1.4	1	0	1	1	1
Cerebral Haemorrhage	0	1	0.5	1												
Cerebellar Infarction	0	1	0.5	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

Novo Nordisk

Liraglutide (injection) NDA 22-341

Endocrine and Metabolic Drug Advisory Committee 2 April 2009

Table 7–45 Serious SMQ MACE by SOC and Preferred Term (Broad Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure Years		1771.8				328.2				459.4				787.6		
All MACE Adverse Events	0.4	15	8.5	15	0.3	3	9.1	3	0.6	5	10.9	5	0.5	8	10.2	8
CARDIAC DISORDERS	0.2	8	4.5	8	0.2	2	6.1	2	0.5	4	8.7	4	0.3	6	7.6	6
Myocardial Infarction	0.1	3	1.7	3	0.1	1	3.0	1	0.4	3	6.5	3	0.2	4	5.1	4
Acute Myocardial Infarction	0.1	4	2.3	4	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
Acute Coronary Syndrome	0.0	1	0.6	1												
NERVOUS SYSTEM DISORDERS	0.1	6	3.4	6	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
Cerebrovascular Accident	0.1	3	1.7	3												
Cerebrovascular Disorder	0.0	1	0.6	1	0.1	1	3.0	1					0.1	1	1.3	1
Transient Ischaemic Attack	0.0	1	0.6	1												
Cerebral Haemorrhage	0.0	1	0.6	1												
Carotid Artery Stenosis									0.1	1	2.2	1	0.1	1	1.3	1
INVESTIGATIONS	0.0	1	0.6	1												
Blood Creatine Phosphokinase Increased	0.0	1	0.6	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Liraglutide (injection) NDA 22-341

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Table 7–46 Serious SMQ MACE by SOC and Preferred Term (Broad Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
All MACE Adverse Events	0.4	16	8.5	16	0.3	3	9.1	3	0.9	13	18.1	13	0.7	16	15.3	16
CARDIAC DISORDERS	0.2	8	4.3	8	0.2	2	6.1	2	0.5	8	11.1	8	0.4	10	9.6	10
Acute Myocardial Infarction	0.1	4	2.1	4	0.1	1	3.0	1	0.3	4	5.6	4	0.2	5	4.8	5
Myocardial Infarction	0.1	3	1.6	3	0.1	1	3.0	1	0.3	4	5.6	4	0.2	5	4.8	5
Acute Coronary Syndrome	0.0	1	0.5	1												
NERVOUS SYSTEM DISORDERS	0.2	7	3.7	7	0.1	1	3.0	1	0.3	5	7.0	5	0.3	6	5.7	6
Cerebrovascular Accident	0.1	3	1.6	3					0.1	1	1.4	1	0.0	1	1.0	1
Transient Ischaemic Attack	0.0	1	0.5	1					0.1	1	1.4	1	0.0	1	1.0	1
Cerebrovascular Disorder	0.0	1	0.5	1	0.1	1	3.0	1					0.0	1	1.0	1
Carotid Artery Stenosis									0.1	2	2.8	2	0.1	2	1.9	2
Ischaemic Stroke									0.1	1	1.4	1	0.0	1	1.0	1
Cerebral Haemorrhage	0.0	1	0.5	1												
Cerebellar Infarction	0.0	1	0.5	1												
INVESTIGATIONS	0.0	1	0.5	1												
Blood Creatine Phosphokinase Increased	0.0	1	0.5	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–47 All SMQ MACE by SOC and Preferred Term (Narrow Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure (Years)		1771.8				328.2				459.4				787.6		
All MACE Adverse Events	0.5	21	12.4	22	0.4	4	12.2	4	0.6	5	13.1	6	0.5	9	12.7	10
CARDIAC DISORDERS	0.3	11	6.2	11	0.3	3	9.1	3	0.5	4	8.7	4	0.4	7	8.9	7
Myocardial Infarction	0.1	4	2.3	4	0.2	2	6.1	2	0.4	3	6.5	3	0.3	5	6.3	5
Acute Myocardial Infarction	0.1	5	2.8	5	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
Coronary Artery Occlusion	0.0	1	0.6	1												
Acute Coronary Syndrome	0.0	1	0.6	1												
NERVOUS SYSTEM DISORDERS	0.2	10	6.2	11	0.1	1	3.0	1	0.1	1	4.4	2	0.1	2	3.8	3
Transient Ischaemic Attack	0.1	3	1.7	3					0.1	1	2.2	1	0.1	1	1.3	1
Carotid Artery Stenosis	0.0	2	1.7	3					0.1	1	2.2	1	0.1	1	1.3	1
Cerebrovascular Accident	0.1	3	1.7	3												
Cerebrovascular Disorder	0.0	1	0.6	1	0.1	1	3.0	1					0.1	1	1.3	1
Cerebral Haemorrhage	0.0	1	0.6	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–48 All SMQ MACE by SOC and Preferred Term (Narrow Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
All MACE Adverse Events	0.5	22	12.2	23	0.4	4	12.2	4	0.9	13	20.9	15	0.7	17	18.2	19
CARDIAC DISORDERS	0.3	11	5.9	11	0.3	3	9.1	3	0.5	8	11.1	8	0.5	11	10.5	11
Myocardial Infarction	0.1	4	2.1	4	0.2	2	6.1	2	0.3	4	5.6	4	0.3	6	5.7	6
Acute Myocardial Infarction	0.1	5	2.7	5	0.1	1	3	1	0.3	4	5.6	4	0.2	5	4.8	5
Coronary Artery Occlusion	0	1	0.5	1												
Acute Coronary Syndrome	0	1	0.5	1												
NERVOUS SYSTEM DISORDERS	0.3	11	6.4	12	0.1	1	3	1	0.3	5	9.8	7	0.3	6	7.7	8
Carotid Artery Stenosis	0	2	1.6	3					0.2	3	4.2	3	0.1	3	2.9	3
Transient Ischaemic Attack	0.1	3	1.6	3					0.1	2	2.8	2	0.1	2	1.9	2
Cerebrovascular Accident	0.1	3	1.6	3					0.1	1	1.4	1	0	1	1	1
Cerebrovascular Disorder	0	1	0.5	1	0.1	1	3	1					0	1	1	1
Ischaemic Stroke									0.1	1	1.4	1	0	1	1	1
Cerebral Haemorrhage	0	1	0.5	1												
Cerebellar Infarction	0	1	0.5	1												

Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–49 Serious SMQ MACE by SOC and Preferred Term (Narrow Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure Years		1771.8				328.2				459.4				787.6		
All MACE Adverse Events	0.3	14	7.9	14	0.3	3	9.1	3	0.6	5	10.9	5	0.5	8	10.2	8
CARDIAC DISORDERS	0.2	8	4.5	8	0.2	2	6.1	2	0.5	4	8.7	4	0.3	6	7.6	6
Myocardial Infarction	0.1	3	1.7	3	0.1	1	3.0	1	0.4	3	6.5	3	0.2	4	5.1	4
Acute Myocardial Infarction	0.1	4	2.3	4	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
Acute Coronary Syndrome	0.0	1	0.6	1												
NERVOUS SYSTEM DISORDERS	0.1	6	3.4	6	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
Cerebrovascular Accident	0.1	3	1.7	3												
Cerebrovascular Disorder	0.0	1	0.6	1	0.1	1	3.0	1					0.1	1	1.3	1
Transient Ischaemic Attack	0.0	1	0.6	1												
Cerebral Haemorrhage	0.0	1	0.6	1												
Carotid Artery Stenosis									0.1	1	2.2	1	0.1	1	1.3	1

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–50 Serious SMQ MACE by SOC and Preferred Term (Narrow Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
All MACE Adverse Events	0.4	15	8	15	0.3	3	9.1	3	0.9	13	18.1	13	0.7	16	15.3	16
CARDIAC DISORDERS	0.2	8	4.3	8	0.2	2	6.1	2	0.5	8	11.1	8	0.4	10	9.6	10
Acute Myocardial Infarction	0.1	4	2.1	4	0.1	1	3	1	0.3	4	5.6	4	0.2	5	4.8	5
Myocardial Infarction	0.1	3	1.6	3	0.1	1	3	1	0.3	4	5.6	4	0.2	5	4.8	5
Acute Coronary Syndrome	0	1	0.5	1												
NERVOUS SYSTEM DISORDERS	0.2	7	3.7	7	0.1	1	3	1	0.3	5	7	5	0.3	6	5.7	6
Cerebrovascular Accident	0.1	3	1.6	3					0.1	1	1.4	1	0	1	1	1
Transient Ischaemic Attack	0	1	0.5	1					0.1	1	1.4	1	0	1	1	1
Cerebrovascular Disorder	0	1	0.5	1	0.1	1	3	1					0	1	1	1
Carotid Artery Stenosis									0.1	2	2.8	2	0.1	2	1.9	2
Ischaemic Stroke									0.1	1	1.4	1	0	1	1	1
Cerebral Haemorrhage	0	1	0.5	1												
Cerebellar Infarction	0	1	0.5	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–51 All MACE by SOC and Preferred Term (Custom Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure (Years)		1771.8				328.2				459.4				787.6		
All MACE Adverse Events	0.3	12	6.8	12	0.3	3	9.1	3	0.5	4	8.7	4	0.4	7	8.9	7
CARDIAC DISORDERS	0.2	9	5.1	9	0.3	3	9.1	3	0.5	4	8.7	4	0.4	7	8.9	7
Myocardial Infarction	0.1	4	2.3	4	0.2	2	6.1	2	0.4	3	6.5	3	0.3	5	6.3	5
Acute Myocardial Infarction	0.1	5	2.8	5	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
NERVOUS SYSTEM DISORDERS	0.1	3	1.7	3												
Cerebrovascular Accident	0.1	3	1.7	3												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

Table 7–52 All MACE by SOC and Preferred Term (Custom Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
All MACE Adverse Events	0.3	13	6.9	13	0.3	3	9.1	3	0.7	10	13.9	10	0.5	13	12.4	13
CARDIAC DISORDERS	0.2	9	4.8	9	0.3	3	9.1	3	0.5	8	11.1	8	0.5	11	10.5	11
Myocardial Infarction	0.1	4	2.1	4	0.2	2	6.1	2	0.3	4	5.6	4	0.3	6	5.7	6
Acute Myocardial Infarction	0.1	5	2.7	5	0.1	1	3	1	0.3	4	5.6	4	0.2	5	4.8	5
NERVOUS SYSTEM DISORDERS	0.1	4	2.1	4					0.1	2	2.8	2	0.1	2	1.9	2
Cerebrovascular Accident	0.1	3	1.6	3					0.1	1	1.4	1	0.0	1	1.0	1
Ischaemic stroke									0.1	1	1.4	1	0.0	1	1.0	1
Cerebellar Infarction	0	1	0.5	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 7–53 Serious MACE by SOC and Preferred Term (Custom Search) - Population A1

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4022				907				853				1760		
Total Exposure Years		1771.8				328.2				459.4				787.6		
All MACE Adverse Events	0.2	10	5.6	10	0.2	2	6.1	2	0.5	4	8.7	4	0.3	6	7.6	6
CARDIAC DISORDERS	0.2	7	4.0	7	0.2	2	6.1	2	0.5	4	8.7	4	0.3	6	7.6	6
Myocardial Infarction	0.1	3	1.7	3	0.1	1	3.0	1	0.4	3	6.5	3	0.2	4	5.1	4
Acute Myocardial Infarction	0.1	4	2.3	4	0.1	1	3.0	1	0.1	1	2.2	1	0.1	2	2.5	2
NERVOUS SYSTEM DISORDERS	0.1	3	1.7	3												
Cerebrovascular Accident	0.1	3	1.7	3												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

Table 7–54 Serious MACE by SOC and Preferred Term (Custom Search) - Population A2

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		1879.5				328.2				717.6				1045.7		
All MACE Adverse Events	0.3	11	5.9	11	0.2	2	6.1	2	0.7	10	13.9	10	0.5	12	11.5	12
CARDIAC DISORDERS	0.2	7	3.7	7	0.2	2	6.1	2	0.5	8	11.1	8	0.4	10	9.6	10
Acute Myocardial Infarction	0.1	4	2.1	4	0.1	1	3	1	0.3	4	5.6	4	0.2	5	4.8	5
Myocardial Infarction	0.1	3	1.6	3	0.1	1	3	1	0.3	4	5.6	4	0.2	5	4.8	5
NERVOUS SYSTEM DISORDERS	0.1	4	2.1	4					0.1	2	2.8	2	0.1	2	1.9	2
Cerebrovascular Accident	0.1	3	1.6	3					0.1	1	1.4	1	0	1	1	1
Ischaemic stroke									0.1	1	1.4	1	0.0	1	1.0	1
Cerebellar Infarction	0	1	0.5	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

7.10.5.4 Results of Statistical Analyses

The results from the main analyses (liraglutide vs. total comparator) in Populations A1, A2, and B are summarized in [Table 7–55](#).

The results were consistent across the range of outcome definitions and populations used. The majority of all point estimates for the Incidence Ratio for liraglutide vs. total comparator in Populations A1, A2 and B, representing the pool of data in these populations, was below 1 with the upper end of the 95% confidence intervals <1.8. This was the case for all MACE adverse events and for those reported as serious MACE when these were analyzed separately.

Table 7–55 Incidence Ratio - Pooled data - Population A1, A2, and B - Liraglutide vs. Total Comparator (Placebo + Active Comparator) - Stratified analysis

MACE Endpoints			Adverse Event Type		Population			Liraglutide Relative to Total Comparator
<u>SMQ</u>		<u>Custom</u>	<u>All MACE</u>	<u>Serious MACE</u>	<u>A1</u>	<u>A2</u>	<u>B</u>	
Broad	Narrow							(Point estimate [95% CI])
X			X		X			0.92 [0.56; 1.50]
	X		X		X			1.04 [0.48; 2.26]
		X	X		X			0.83 [0.32; 2.11]
X				X	X			0.80 [0.34; 1.90]
	X			X	X			0.74 [0.31; 1.78]
		X		X	X			0.80 [0.29; 2.22]
X			X			X		0.87 [0.57; 1.34]
	X		X			X		0.87 [0.45; 1.69]
		X	X			X		0.72 [0.32; 1.61]
X				X		X		0.67 [0.32; 1.41]
	X			X		X		0.64 [0.30; 1.34]
		X		X		X		0.69 [0.29; 1.62]
X			X				X	0.88 [0.61; 1.28]
	X		X				X	0.89 [0.52; 1.52]
		X	X				X	0.79 [0.41; 1.54]
X				X			X	0.83 [0.44; 1.56]
	X			X			X	0.80 [0.42; 1.51]
		X		X			X	0.76 [0.37; 1.57]

Only the first MACE event for each subject is counted in this analysis.

7.10.5.5 Summary of MACE Analyses

Analyses of Major Adverse Cardiovascular Events based on the July 2008 Committee recommendations and on input from the FDA have been performed. The analyses reflect the current thinking in the FDA ‘*Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*’ on completed studies which was issued on 17 December 2008.

The clinical development program for liraglutide was designed, executed and completed prior to the development of the recent FDA guidance for the assessment of cardiovascular risk associated with new therapies for the treatment of type 2 diabetes. Liraglutide therefore falls in the category of completed trials in the FDA guidance. Acknowledging the limitations this may cause, the liraglutide development program included a large number of patient exposure years. The opportunity to accrue a substantial number of MACE allowed a retrospect assessment of cardiovascular risk during the development program.

The results of the MACE analyses were robust and consistent across a number of different populations and outcome definitions. Sensitivity analyses of all MACE and only those categorized as serious supported this. The results from the MACE liraglutide analyses documented that, based on the available liraglutide clinical safety database, most of the point estimates in the main analyses were below 1 with the upper end of the 95% confidence intervals <1.8.

As a follow-up on the results from the MACE analyses, Novo Nordisk will study MACE in a large, controlled, long-term post-approval outcome study designed specifically to assess cardiovascular risk. This will refine the point estimates of MACE, determined as a combined endpoint of cardiovascular death or non-fatal stroke or non-fatal acute myocardial infarction (see Section [8.1](#)).

7.11 Safety Conclusion

- Liraglutide was generally well tolerated and the most common adverse events were related to the gastrointestinal organ system
 - Gastrointestinal adverse events were most frequent in the early part of the treatment period
 - Limited withdrawal rate due to adverse events
- Pancreatitis
 - Absolute risk is low but a small increase in relative risk could not be excluded – this information will be reflected in the labeling
- Immunogenicity
 - Imbalance observed in non-serious urticaria observed with more events in liraglutide-treated subjects
 - No relationship between efficacy and antibody development
- C-cells
 - Based on the available clinical and nonclinical data, the proliferative C-cell findings represent a rodent specific phenomenon
- Neoplasms
 - Data and analyses do not suggest any treatment-related effect of liraglutide
- Major Adverse Cardiovascular Events (MACE)
 - No nonclinical signal for cardiovascular risk
 - The MACE analyses provided consistent results across trials. While these analyses are not definitive given the design of the liraglutide development program, they do not indicate a signal of increased cardiovascular risk associated with the treatment with liraglutide.

8 Benefit-Risk Profile and Risk Management

Benefit-Risk Profile

Type 2 diabetes is a complex and multi-factorial disease. Several complicating factors increase the challenges of achieving optimal control. These include hyper- and hypoglycemia, decreased insulin sensitivity related to obesity, increased blood pressure, dyslipidemia, and a gradual deterioration in beta-cell function.

Patients with type 2 diabetes are at increased risk of developing a number of co-morbidities as long-term complications to diabetes. A number of these are caused by microvascular disease such as impaired vision or blindness, foot ulcers, amputations, and kidney failure. Effective control of blood glucose early in the course of disease has been well-documented to prevent late diabetes complications caused by microvascular damages.^{[5,18,19](#)}

Multiple classes of drugs for the treatment of type 2 diabetes are available. However, available therapies often are limited by suboptimal effect on glycemic control, difficult treatment regimens, and side effects, including the risk of hypoglycemia and weight gain. Available treatments typically only target control of blood glucose. Many available treatments induce weight gain related to the improvement in blood glucose control and others do not provide sustainable effect on blood glucose control.

In type 2 diabetes, the major defects include peripheral and hepatic resistance to insulin action and defective beta-cell function. It is, however, increasingly recognized that early defects in glucose-dependent insulin secretion deteriorate over time leading to a need for continued intensification of treatment. Liraglutide was tested in a range of clinically relevant settings, covering the span of progression of type 2 diabetes mellitus. The design of the liraglutide development program was consistent with the most recent ADA/EASD consensus treatment algorithm as published in *Diabetes Care and Diabetologia*.^{[23](#)} This algorithm suggests metformin as first line therapy, and when this fails to provide adequate glycemic control, additional therapies should be added. Among treatment options mentioned are sulfonylureas, basal insulin, thiazolidinediones, and GLP-1 agonists as 2nd tier therapy. These all have a place in treatment choices to be individualized for the specific needs of the patient. Liraglutide was tested and proven effective as monotherapy, as well as in double- and triple-combination therapy, in line with the proposal for intensification of treatment of type 2 diabetes.

Liraglutide met its primary regulatory endpoint in all trials, and treatment with liraglutide consistently led to a clinically relevant, sustainable decrease in HbA_{1c}. At the suggested therapeutic doses of 1.2 mg and 1.8 mg, liraglutide lowered HbA_{1c} by 1.0–1.5% points in spite of liraglutide replacing one existing OAD in approximately two thirds of patients in several trials. The magnitude of the HbA_{1c} decrease was significantly greater than a number of currently available type 2 diabetes treatments, which served as active comparators in this program. Superiority of liraglutide vs. comparators was proven based on change in baseline HbA_{1c} and in the number of subjects reaching

the ADA defined targets for good control. Between 40 and 60% of patients treated with the 1.8 mg dose of liraglutide met these targets. This was associated with a low risk of hypoglycemia, particularly in the absence of concomitant sulfonylurea therapy. A significant reduction in weight and some decrease in systolic blood pressure were documented across a number of the long-term phase 3 trials. Weight loss would be anticipated to provide a positive impact on insulin resistance.

Liraglutide was generally well tolerated. The most common adverse events with liraglutide treatment were related to the gastrointestinal system and the most frequently reported side effect was nausea. These adverse events were mostly mild and occurred during the initial period of treatment. When combining data from early clinical studies, gastrointestinal side effects were reduced when the dose of liraglutide was gradually titrated. Other commonly reported adverse events included upper respiratory tract infections and headache. These were reported at similar rates across treatment groups.

An increased incidence of treatment-related thyroid C-cell tumors was identified in rodents and this led to a focus on the C-cell during the development program. The mechanism behind the C-cell findings was identified and the comprehensive program of preclinical and clinical data supported that the findings are a rodent-specific phenomenon. The mean human calcitonin levels were in the normal range in all treatment groups throughout the treatment period, and the intensive monitoring of calcitonin in the clinical development program did not reveal a liraglutide treatment-related effect in humans on either basal or stimulated calcitonin. Based on the consolidated available nonclinical and clinical data, there is no signal to suggest that liraglutide induces C-cell proliferative changes in humans.

In October 2007, the FDA issued a letter about pancreatitis and another GLP-1 analog (exenatide) which was updated in 2008, indicating that further warnings would be added to the labeling about the risk of pancreatitis. The occurrence of pancreatitis in the liraglutide development program was low, and the rate in the liraglutide-treated group was 2.2 compared with 0.6 in total comparator-treated subjects. As reviewed, a definitive role of liraglutide in any of the individual pancreatitis cases reported could not be established. However, a small increase in relative risk could not be excluded, and this information will be included in the labeling.

Recently, a number of cardiovascular outcome trials within diabetes have published results (ACCORD and ADVANCE studies).^{[96,97](#)} The results of these trials have led to debate about the rationale for aggressive HbA_{1c} lowering to decrease the risk of macrovascular complications in diabetes. In addition, there have been suggestions that some diabetes drugs may increase the risk of cardiovascular complications, and there are recommendations that this should be studied more carefully for future diabetes therapies. The liraglutide development program was designed and completed before the recent FDA guidance on the matter. However, the program did include considerable patient exposure. Based on the available data and the retrospect MACE analyses, no indication of unacceptable increased risk vs. comparators was found. However, recognizing the limitations of the liraglutide clinical development safety database and in response to the specific

recommendations from the FDA Endocrine and Metabolism Advisory Committee meeting on 1–2 July 2008 and the FDA guidance issued in December 2008, Novo Nordisk is committed to performing a large, post-approval, controlled cardiovascular risk assessment clinical study to further refine the risk estimates (see Section [8.1](#)).

The clinical benefits and utility of liraglutide differ from available marketed type 2 diabetes treatments in a number of ways. Liraglutide offers a once-daily dosing regimen independent of food intake. Liraglutide addresses a number of the most important issues relevant to the treatment of type 2 diabetes: convenience of administration and weight gain. Liraglutide stands out in terms of effective glycemic control combined with a low risk of experiencing hypoglycemia. It reduces fasting plasma glucose and postprandial glucose rapidly and these effects are sustained. This unique glycemic control profile demonstrated based on HbA_{1c}, FPG and PPG is expected to translate into a reduced risk of microvascular complications, based on current understanding of diabetes pathophysiology.^{[2,3](#)}

On balance, the clinical development program provides consistent and robust evidence demonstrating that liraglutide has substantial benefit in improving glycemic control in type 2 diabetes and has a favorable benefit/risk profile when used as monotherapy or in combination therapy.

Risk Management Plan

To further refine the understanding of the liraglutide product profile and to optimize focus on patient safety, Novo Nordisk has developed a risk management plan to address identified and potential risks associated with liraglutide treatment. Different methodologies will be applied in the risk management plan for liraglutide and as part of this, routine pharmacovigilance will be performed.

A phase 3b clinical program is currently ongoing, and parts are being planned. A pharmacokinetic study in adolescents and a safety and efficacy study in a pediatric population aged 10–17 years will be conducted. Beyond this, a number of clinical trials, including more than 1,800 subjects, further investigating the clinical profile of liraglutide will be undertaken or are already ongoing. This phase 3b clinical program will contribute with continued collection of safety data from randomized and controlled clinical trials.

A large post-approval proactive claims safety surveillance database study will be undertaken, applying the i3 Aperio drug safety surveillance system. The study will focus on neoplasms, pancreatitis and cardiovascular events. Reporting to regulatory authorities will be done at 6-month intervals and the study will run for 3–5 years.

A large controlled post-approval outcome trial to further study cardiovascular events is in the planning phase. A draft study synopsis has been submitted to the FDA and the EMEA. Finalization

of the protocol will take place after the discussions with Endocrine and Metabolic Advisory Committee and a subsequent dialogue with regulatory authorities.

Finally, the labeling will clearly reflect the use of liraglutide. This will include areas with missing information, such as use of liraglutide during pregnancy and lactation, in children, and in patients with severe renal or hepatic impairment.

The activities are briefly summarized in [Table 8-1](#) and the cardiovascular study is further described in Section [8.1](#).

Table 8–1 Activities to Monitor and Minimize Risk

	Activities to Minimize Risk		Ongoing/Planned Studies	
	Labeling text	Routine Pharmacovigilance Activities	Data Capture Aid ^(a)	Clinical Trials
Identified risks				
Hypoglycemia	X ^(f)	X (MESI) ^(b)	X	(X) ^(c)
Gastrointestinal events	X	X	N/A	(X) ^(c)
Important potential risks				
Medullary Thyroid Cancer	N/A	X (MESI)	X	X ^(e)
Neoplasms	N/A	X (MESI)	X	X ^(e)
Pancreatitis	X	X (MESI)	X	X ^(e)
Severe cardiac co-morbidity	X ^(d)	X	N/A	X ^(e)
Renal and hepatic impairment		X		X ^(e)
Immungencity (antibodies)	N/A	X	X	X ^(e)
Important missing information				
Children	X	X	N/A	X (PIP ^(f))
Adolescents	X	X	N/A	X (PIP)
Pregnant/lactating women	X	X	N/A	N/A
Overdose	X	X	N/A	N/A
Abuse due to weight lowering potential	N/A	X	N/A	N/A

^a Questionnaire for collecting detailed event specific information or specific case report forms. ^b MESI: Medical Event of Special Interest, which means a targeted surveillance of all events reported as hypoglycemia, both serious and non-serious. ^c The study design does not have the event type as primary endpoint, however, event reports will be collected and analyzed. ^d In European labeling. ^e These events will be monitored in the large cardiovascular outcome study. ^f PIP: Pediatric Investigational Plan. ^f Liraglutide can be added to existing sulfonylurea or combined metformin and sulfonylurea therapy. During clinical trials physicians, at their discretion, were advised to lower the dose of the sulfonylurea by approximately half to minimize the risk of unacceptable hypoglycemia.

8.1 Cardiovascular Outcome Trial

Study Synopsis

A draft study synopsis has been submitted to the FDA and the EMEA. It is planned that finalization of the study protocol will take place second quarter 2009 following discussions at the Endocrine and Metabolic Drug Advisory Committee meeting on 2 April 2009 and subsequent dialogue with regulatory authorities.

A number of activities are currently ongoing. These include contract negotiations with key vendors, set-up of an International Steering Committee and an Independent Cardiovascular Endpoints Committee, and packaging of trial medication. Likewise, Investigator meetings are being planned.

These activities will allow for submission of clinical trial applications during third and fourth quarter 2009 and subsequent trial initiation first quarter 2010.

The cardiovascular outcome trial will be a multi-center, international, randomized double-blind, placebo-controlled trial with the addition of liraglutide or placebo to participants for who background diabetes therapy is determined by the participant's physician and/or investigator.

The population to be studied will include subjects at particular risk for cardiovascular events, such as patients with relatively advanced disease, elderly patients and patients with some degree of renal impairment. Subjects will receive standard of care background therapies for lipids and blood pressure. Glycemic control should be maintained within acceptable boundaries of HbA_{1c} based on treatment guidelines and recommendations contained in the protocol.

Trial Outcomes

The primary and secondary outcome variables to be measured are listed below. Primary and secondary outcomes will undergo adjudication by an Independent Cardiovascular Endpoints Committee. This Committee will be blinded to trial treatment and will provide final definitions of cardiovascular, microvascular and selected safety variables.

Primary Outcome

The composite primary outcome is the first occurrence of either cardiovascular (CV) death or non-fatal myocardial infarction (MI) or non-fatal stroke.

Secondary Outcomes

1. A composite microvascular outcome defined as new or worsening retinopathy (development of proliferative retinopathy, macular edema, need for photocoagulation or vitrectomy) or diabetes-related blindness or nephropathy (macroalbuminuria, or doubling of serum creatinine level to at least 200 μ mol/l, the need for renal-replacement therapy (in the absence of an acute reversible cause, or death due to renal disease)).

2. An expanded composite of cardiovascular events that includes the primary outcome plus any revascularization, unstable angina or hospitalization for congestive heart failure.
3. All-cause mortality
4. Individual components of the primary and secondary composite outcomes

Study Size and Statistical Analysis

Study size

The sample size calculation is based on the definition of non-inferiority of the cardiovascular event rates for treatment vs. placebo pre-specified by the upper limit value for the relative risk (hazard ratio denoted by Relative Risk). It is assumed that this upper Relative Risk limit of non-inferiority = 1.3. The sample size of the study will depend on event rate in the population assumed to be 1–3% and the power and the hazard ratio identified as the optimal choice for sizing the study. It is expected that the number of patients in the study will be 6,000–10,000 patients, and the duration of the study will be up to five years.

Statistical analysis

The primary endpoint is the time-to-event. A Cox proportional hazards regression model with baseline age and other covariates will be used for estimation of the hazards ratio (Relative Risk and its 95% confidence interval). If the upper 95% confidence limit for the hazards ratio is less than or equal to 1.3, then the non-inferiority of the drug in comparison with placebo will be declared.

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1 Definitions, Populations, Exposure and Methodology

1.1 Grouping of Trials

An overview of all trials is presented in [Figure 1–1](#), where trials are grouped according to development phase and with regard to planned duration of exposure to liraglutide as follows:

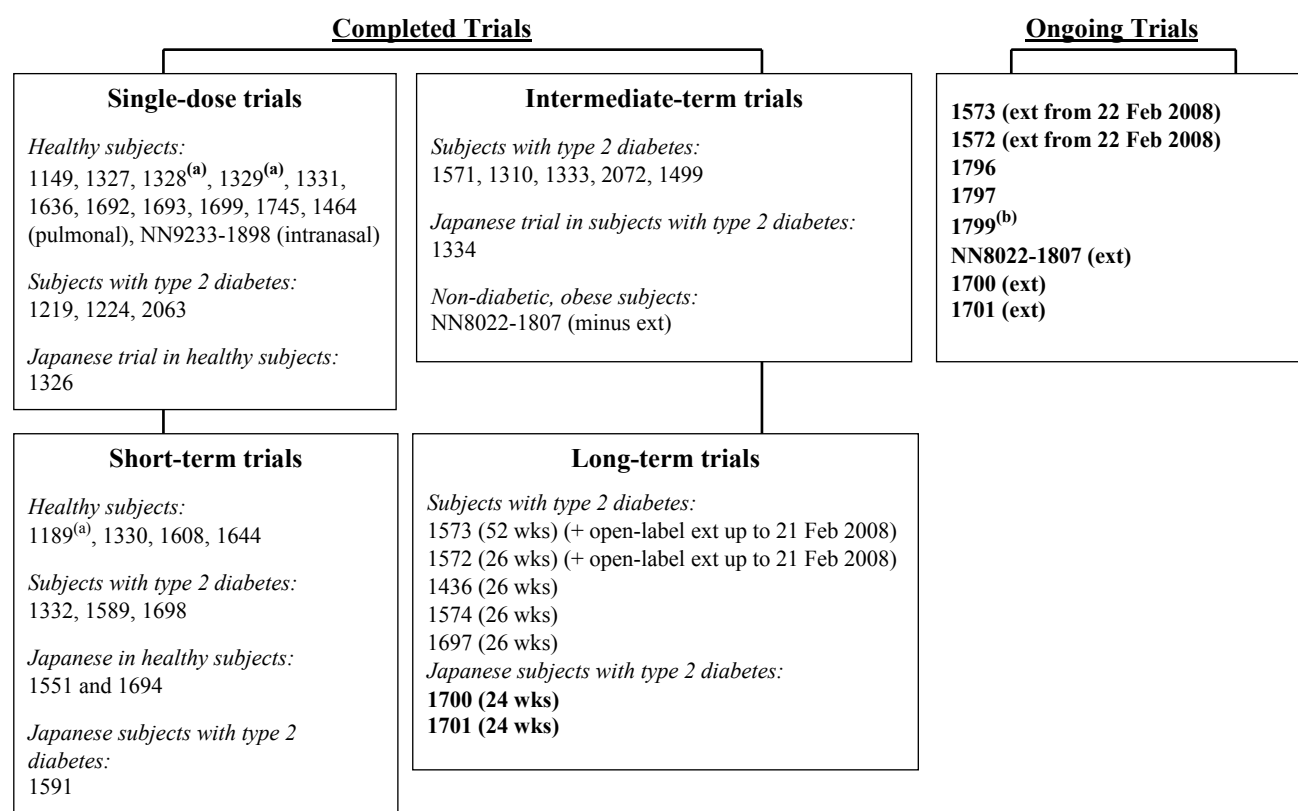
- Single-dose Trials (phase 1 Trials)
- Short-term Trials (phase 1 Trials): ≤ 5 weeks of exposure
- Intermediate-term Trials (phase 2 Trials): Exposure $> 5 < 24$ weeks
- Long-term Trials (phase 3 Trials): Exposure ≥ 24 weeks
- Ongoing trials (phase 2, 3a and 3b)

With respect to safety data included in the 120-day Safety Update, trials were grouped as completed or ongoing (see [Figure 1–1](#)) as follows:

- Completed: clinical trials with final statistical analyses available by 30 May 2008 (40 completed trials)
- Ongoing: clinical trials with no final statistical analyses available by 30 May 2008 (8 ongoing trials).

‘Main’ used in this document refers to the blinded and controlled part of phase 3 trials. ‘Extension’ (abbreviated as ‘-ext’) refers to the open-label part of the trials having an extension.

Figure 1–1 Grouping of Trials Included in the Liraglutide Clinical Development Program



Trials in **bold** are new trials which in the 120-day safety update added data since the NDA. Ext: extension.

^a Trials 1328, 1329 and 1189 included 5, 3 and 4 subjects with type 2 diabetes, respectively.

^b Trial 1799 did not contribute safety or exposure data in the 120-day Safety Update.

1.2 Populations, Exposure and Definitions

For presentation of efficacy, the five long-term phase 3 trials were used as in the NDA. For safety presentations, the data as submitted with the regulatory 120-day Safety Update submitted to the FDA in September 2008 was generally used. The 120-day Safety Update database provides the largest possible dataset for presentation of safety data. A detailed overview of the populations (datasets) used in this document, the rationale for use and the origin (NDA, 120-day Safety Update and answer to the FDA) is provided in [Table 1–1](#).

Population 1 includes all intermediate and long-term trials with blinded and open-label, randomized and controlled phases.

Population 1 was further subdivided into Populations A1, A2 and B for the MACE analyses (see also [Briefing Document, Section 7.10.5](#)).

Population 2 includes all data as available for the 120-day Safety Update. This population is the largest and used for describing overall adverse events and withdrawals.

Population 3 includes all trials with duration of > 24 weeks. This population was specifically used for the description of the calcitonin assessment program during the liraglutide development program.

Population 4 includes the five double-blind, randomized controlled phase 3 trials with the controlled open-label extensions up to the cut-off date 21 February 2008.

Table 1–1 Overview of Populations Used for Presentation of Safety Data

	Name ^(a)	Dataset Definition and Purpose	Section Where Used	Origin of Population
Population 1	All Intermediate and Long-term Trials	All completed phase 2 and phase 3 trials and their ongoing extensions, i.e. data from the blinded and non-blinded randomized and controlled phases of the intermediate-term phase 2 and long-term phase 3 trials + Trial 1797. Cut-off date 30 May 2008. Purpose: To investigate safety in all completed and ongoing phase 2 and 3 trials.	<ul style="list-style-type: none"> Demography and subject disposition (Briefing Document, Section 6.6 and 6.7). Pancreatitis, immunogenicity, neoplasms and thyroid (Briefing Document, Sections 7.5, 7.6, 7.8 and 7.9) 	120-day Safety Update
Population A1	All Double-blind, Completed Intermediate and Long-term Trials	Randomized, double-blind, controlled periods for all completed phase 2 and phase 3 clinical trials. Purpose: FDA requested MACE analysis	<ul style="list-style-type: none"> MACE (population A1) (Briefing Document, Section 7.10.5) 	FDA MACE response
Population A2	A1 plus open-label active control study arms and studies	Population A1 plus open-label active control study arms and studies. Purpose: FDA requested MACE analysis	<ul style="list-style-type: none"> MACE (population A2) (Briefing Document, Section 7.10.5) 	FDA MACE response
Population B	A2 plus open-label extensions	Population A2 plus open-label controlled extension periods. Purpose: FDA requested MACE analysis	<ul style="list-style-type: none"> MACE (population B) (Briefing Document, Section 7.10.5) 	FDA MACE response
Population 2	All Completed Trials	All randomized and exposed subjects in the 40 completed clinical trials and 2 open-label, controlled, randomized extensions to long-term Trials 1573 and 1572 with data up to the cut-off date of 21 February 2008. Purpose: To investigate serious adverse events and withdrawals in the largest possible population.	<ul style="list-style-type: none"> Serious adverse events and adverse event withdrawals (Briefing Document, Sections 7.3 and 7.4) 	120-day Safety Update
Population 3	Trials 1573, 1572, 1436, 1574, 1697, 1797, 1700, 1701 and NN8022-1807	All clinical studies with at least 24 weeks' exposure and calcitonin assessment: NN2211-1573 (main+ext ^(b)), 1572 (main+ext), 1436, 1574, 1697, 1797 (main), 1700 (main), and 1797 (main), and NN8022-1807 (main+ext). Purpose: To assess the calcitonin data >2xUNR.	<ul style="list-style-type: none"> Calcitonin (Briefing Document, Section 7.7.4). 	120-day Safety Update

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	Name ^(a)	Dataset Definition and Purpose	Section Where Used	Origin of Population
Population 4	Completed Long-term NDA Phase 3 Trials (Blinded and Open-label Part)	All randomized and exposed subjects in the five long-term phase 3 trials (Trials 1573, 1572, 1436, 1574 and 1697) and 2 open-label, controlled, randomized extensions to long-term Trials 1573 and 1572 with data up to the cut-off date of 21 February 2008. Purpose: To investigate safety in the five long-term phase 3 trials.	<ul style="list-style-type: none">• Demography and subject disposition (Briefing Document, Section 6.6 and Section 6.7).• Overall adverse event profile (Briefing Document, Section 7.1).• Serious adverse events and adverse event withdrawals (Briefing Document, Sections 7.3 and 7.4)• Vital signs (ECG, pulse and blood pressure (Briefing Document, Sections 7.10.2 and Section 7.10.4))	NDA

^a Refers to the name of the population used in tables and figures in this briefing document . ^b Main refers to the blinded part of the trial and ext refers to the open-label extension part of the trial.

1.3 Overview of Exposure

Subject exposure within each of the five individual populations presented in [Table 1–1](#) is presented in the [Briefing Document, Table 6–3](#).

Below, exposure is presented in a more detailed breakdown by trial group ([Table 1–2](#)), by duration of treatment with liraglutide (for completed trials in [Table 1–3](#) and for completed and ongoing trials in [Table 1–4](#)) and by liraglutide dose ([Table 1–5](#)).

In the 40 completed trials, 4,655 subjects were exposed to liraglutide, 1,210 subjects were exposed to placebo, and 1,297 subjects to an active comparator in completed trials ([Table 1–2](#)). In total, 81% (3,772) of the subjects exposed to liraglutide had type 2 diabetes.

Based on [Table 1–4](#) it can be seen that more than 700 subjects were exposed to liraglutide for 76 weeks or more at the time of the cut-off for the 120-day Safety Update. All data beyond 52 weeks are exclusively from open-label, but controlled extension studies. Importantly, all subjects continuing in the open-label extensions remained on the treatments assignments to which they were originally randomized.

Table 1–2 Subjects Exposed to Liraglutide and Comparators in all Completed Trials

	Liraglutide ^(a)	Placebo ^(b)	Active comparator
	N	N	N
Single-dose trials			
Healthy Subjects	312	31	24
Subjects with Type 2 Diabetes	47	40	N/A
Short-term trials (≤ 5 weeks of exposure)			
Healthy Subjects	200	167	N/A
Subjects with Type 2 Diabetes	74	65	31
Intermediate-term trials (exposure > 5 < 24 weeks)			
Subjects with Type 2 Diabetes	706	197	62
Non-diabetics, Obese Subjects	371	98	95
Long-term trials (exposure ≥ 24 weeks)			
Subjects with Type 2 Diabetes	2945	612	1085
Total	4655	1210	1297

Table is based on population 2 (all completed trials) in [Table 1–1](#) and presented by trial groups as defined in [Figure 1–1](#). Subjects receiving more than one treatment were counted in each treatment group. ^a All liraglutide doses. ^b +/- OAD combination

Table 1–3 Duration of Exposure to Liraglutide in all Completed Trials

	1 day N	> 1 day N	≥ 5 wks N	≥ 12 wks N	≥ 24 wks N	≥50 wks N	≥76 wks N
Single-dose trials							
Healthy Subjects	165	147					
Subjects with Type 2 Diabetes	47						
Short-term trials (≤ 5 weeks of exposure)							
Healthy Subjects	2	198	32				
Subjects with Type 2 Diabetes	1	73	1				
Intermediate-term trials c							
Subjects with Type 2 Diabetes		706	652	507			
Non-diabetics, Obese Subjects	2	369	349	329	1		
Long-term trials (exposure ≥ 24 weeks)							
Subjects with Type 2 Diabetes	8	2937	2766	2641	2411	840	495
Total	225	4430	3800	3477	2412	840	495
Sum of Exposure (years)	0.6	2433.8	2406.0	2356.6	2015.3	1224.2	780.2

Table is based on population 2 (all completed trials) in [Table 1–1](#) and presented by trial groups as defined in [Figure 1–1](#).

Table 1–4 Duration of Exposure to Liraglutide in all Completed and Ongoing Trials

	1 day N	> 1 day N	≥ 5 wks N	≥ 12 wks N	≥ 24 wks N	≥50 wks N	≥76 wks N	≥102 wks N
Single-dose trials								
Healthy Subjects	165	147						
Subjects with Type 2 Diabetes	47							
Short-term trials (≤ 5 weeks of exposure)								
Healthy Subjects	2	198	32					
Subjects with Type 2 Diabetes	1	73	1					
Intermediate-term trials (≤ 5 weeks of exposure)								
Subjects with Type 2 Diabetes		706	652	507				
Non-diabetics, Obese Subjects	2	369	349	329	262	240		
Long-term trials (exposure ≥ 24 weeks)								
Subjects with Type 2 Diabetes	8	3172	2987	2846	2702	1229	703	46
Total	225	4665	4021	3682	2964	1469	703	46
Sum of Exposure (years)	0.6	3144.9	3116.4	3062.7	2861.0	2089.2	1248.1	91.8

Table is based on population 2 but including the ongoing parts of the trials as well.

Table 1–5 Exposure by Liraglutide Dose in Population 4 and by Trial

	Liraglutide 0.6 mg N (Exp^(a))	Liraglutide 1.2 mg N (Exp^(a))	Liraglutide 1.8 mg N (Exp^(a))	Placebo N (Exp^(a))	Active Comparator N (Exp^(a))
Population 4					
Completed Long-term NDA Phase 3 Trials (Blinded and Open-label Part)	475 (387.3)	896 (723.9)	1130 (823.5)	524 (265.0)	953 (737.8)
Long-term Trial 1573 (Blinded Part)	N/A	251 (192.2)	246 (194.8)	N/A	248 (185.9)
Long-term Trial 1572 (Blinded Part)	242 (110.8)	240 (106.2)	242 (103.9)	121 (46.8)	242 (110.8)
Long-term Trial 1436 (Blinded Part)	233 (109.2)	228 (102.9)	234 (110.1)	114 (47.1)	231 (104.6)
Long-term Trial 1574 (Blinded Part)	N/A	177 (81.1)	178 (73.3)	175 (71.8)	N/A
Long-term Trial 1697 (Blinded Part)	N/A	N/A	230 (107.3)	114 (52.9)	232 (111.9)

For definitions of populations, see [Table 1–1](#). ^a Exp: number of subject years of exposure is defined as duration of exposure divided by 365.25 for data from open-label extension from 21 Feb-2008 and up-to 30 May-2008.

1.4 Adverse Event Definitions

An adverse event (AE) was defined as any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This included events from the first trial-related activity after the subject signed the informed consent form and until end of the post-treatment follow-up period as defined in the protocol.

The adverse events described in this document are treatment emergent (TEAE) unless otherwise specified. For a definition of treatment emergent, see Section [2.3](#).

A serious adverse event (SAE) was defined according to guidelines, as an experience that at any dose results in any of the following:

- Death
- A life-threatening¹ experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

¹The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

A non-serious adverse event was any adverse event that did not fulfill the definition of a serious adverse event.

Below are the definitions and classifications of causal relationship and outcome used by the investigators in the long-term trials. In general, these were comparable for all trials in the clinical development program.

Relationship to Trial Product Assessment Definitions

- Probable: Good reasons and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial product

Outcome Categories and Definitions

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent
- Recovering: The condition is improving and the subject is expected to recover from the event
This term should only be used when the subject has completed the trial
- Recovered with sequelae: As a result of the adverse event, the subject suffered persistent and significant disability/incapacity (e.g., became blind, deaf, paralyzed). Any adverse event recovered with sequelae should be rated as a serious adverse event
- Not recovered
- Fatal
- Unknown

Adverse events that occurred during the trials were treated by established standards of care. All serious adverse events were followed until the subject had recovered, had recovered with sequelae, or died and until all queries had been resolved.

2 Statistical Methodology

All two-sided statistical tests were performed at a 5% significance level, and one-sided tests at a 2.5% significance level, unless otherwise specified.

2.1 Analysis Sets

The **ITT** analysis set was defined as all subjects randomized and exposed to at least one dose of trial product.

The **safety analysis set** was defined as all randomized subjects who were exposed to at least one dose of trial product(s). Subjects were analyzed according to the actual treatment taken.

2.2 Clinical Efficacy

This section describes the statistical methodology used in the five long-term phase 3 trials: 1573, 1572, 1436, 1574 and 1697. All trials used pre-specified methodologies that were identical in key aspects to facilitate integration of all trial conclusions.

The statistical analyses of efficacy in all five trials were based on trial by trial assessments on the intention-to-treat (ITT) analysis set.

The secondary endpoints body weight (and HbA_{1c} trend after nadir for Trial 1573), were defined as key secondary endpoints, meaning that they were included in the sample size calculations and tested hierarchically. For the hierarchy of testing, see below for handling of multiplicity.

2.2.1 Primary Endpoint, HbA_{1c}

The primary objective of the trials was to assess and compare the effect of liraglutide to placebo and/or specific active comparator drugs on glycemic control, as measured by change in HbA_{1c}.

The hypotheses for the trials were that liraglutide was superior to (better than) placebo treatment (H₀₁) and non-inferior to (not worse than) active comparator treatment (H₀₂). If non-inferiority was demonstrated, superiority would be evaluated (H₀₃).

The hypothesis can be written:

(1) H^d₀₁: $\mu^d_{\text{liraglutide}} \geq \mu_{\text{placebo}}$ against the alternative H^d_{A1}: $\mu^d_{\text{liraglutide}} < \mu_{\text{placebo}}$

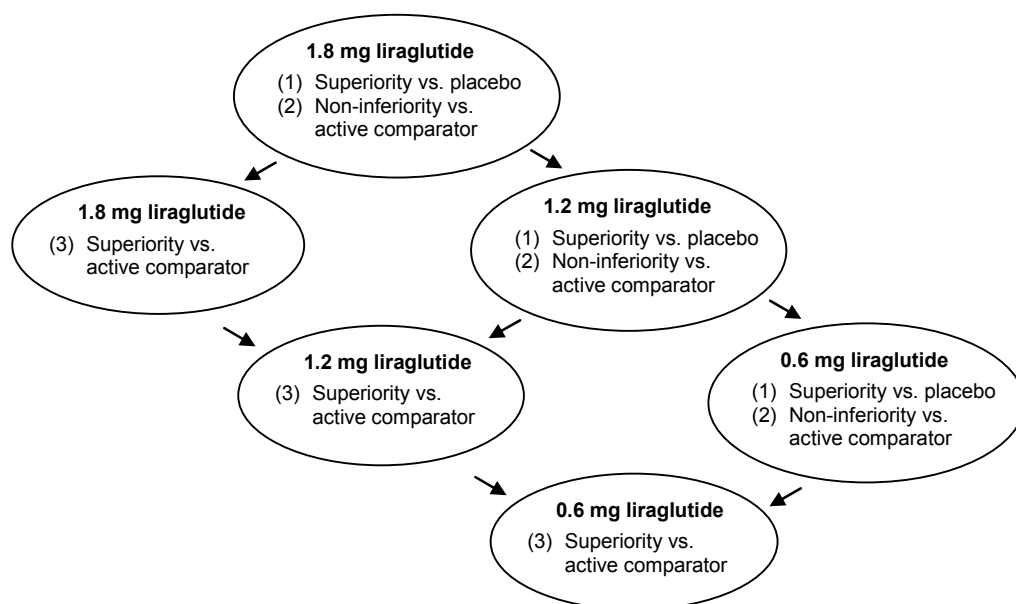
(2) H^d₀₂: $\mu^d_{\text{liraglutide}} \geq \Delta + \mu_{\text{comparator}}$ against the alternative H^d_{A2}: $\mu^d_{\text{liraglutide}} < \Delta + \mu_{\text{comparator}}$

(3) H^d₀₃: $\mu^d_{\text{liraglutide}} \geq \mu_{\text{comparator}}$ against the alternative H^d_{A3}: $\mu^d_{\text{liraglutide}} < \mu_{\text{comparator}}$

Where $\mu^d_{\text{liraglutide}}$, μ_{placebo} and $\mu_{\text{comparator}}$ denotes the change in mean HbA_{1c} after treatment with liraglutide (doses, d = 1.8, 1.2 and 0.6 mg), placebo or comparator, respectively, and Δ denotes the non-inferiority margin. For Trials 1436, 1572, 1574 and 1697, a non-inferiority margin of 0.4% was accepted based on FDA regulatory guidelines and discussions with the Agency. For Trial 1573, the non-inferiority margin was based on data from Amaryl[®] (glimepiride). Results from several randomized, ≥ 12 weeks of duration, double-blind, placebo-controlled trials, which investigated the effect of glimepiride monotherapy on glycemic control were summarized in the Summary Basis of Approval for Amaryl[®] (NDA 20-496, approved 11/30/95). The mean decreases in HbA_{1c}, relative to placebo, were 2.0%. A typical approach for determination of the non-inferiority margin is to use 50% of this effect size, however a more conservative approach of 20% was taken, i.e. approximately 0.4%, is considered to be a meaningful margin for non-inferiority.

A **hierarchical testing procedure** was employed in order to protect the overall type I error. Hypothesis testing was invoked sequentially for descending doses of liraglutide as outlined in [Figure 2-1](#).

Figure 2-1 Overview of the Hierarchical Testing Procedure Used in the Five Long-term Phase 3 Trials



For each trial, testing follows the hierarchy outlined above, but includes only the tests relevant for that trial (see [Briefing Document, Section 6.8](#) for specific trial design). Refer to the text for a detailed description of the hierarchical testing procedure.

- Superiority of a given dose of liraglutide compared to placebo (1) was concluded if the upper limit of the 95% confidence interval (CI) for the estimated treatment difference between liraglutide and placebo was below 0% (not applicable for Trial 1573).
- If superiority (1) was demonstrated, non-inferiority of the given dose of liraglutide to active comparator was evaluated (2). Non-inferiority was concluded if the upper limit of the 95% CI for the estimated treatment difference was below 0.4% (not applicable for Trial 1574).

- If non-inferiority (2) for a given dose was demonstrated, superiority for the given dose to active comparator (3) was assessed and superiority to placebo for the following dose level of liraglutide was tested. Note that a lower dose level of liraglutide would only be tested if non-inferiority to active comparator was demonstrated for the higher dose level(s) of liraglutide.

In addition, superiority of the active comparator versus placebo was assessed for Trials 1572, 1436 and 1697 to confirm the ability to detect responses in the trial.

By performing the testing sequence as described above [Figure 2–1](#), the family-wise error rate, i.e. the probability of rejecting at least one true null hypothesis (making at least one false claim) is at most 5%.

In all trials, the primary endpoint of change from baseline (at randomization) in HbA_{1c}, was analyzed in an analysis of covariance model (ANCOVA) with treatment, country and previous antidiabetic treatment as fixed effects, and baseline HbA_{1c}, value as a covariate.

2.2.2 Secondary Endpoints

Key Secondary Endpoints

The first pre-specified key secondary endpoint, **change in body weight**, was analyzed in an ANCOVA model with treatment, country and previous antidiabetic treatment as fixed effects and baseline body weight as a covariate.

For the second key secondary endpoint, **HbA_{1c} trend after nadir** (only applicable for Trial 1573), the slope of the HbA_{1c} curve after nadir was determined. The analysis was done by an ANOVA of the slope of increase in HbA_{1c} after nadir (for individual subjects) with treatment as a fixed effect. Eighteen weeks of treatment were determined to be near the nadir, and was selected before database release.

Secondary Endpoints

The percentage of subjects reaching the recommended ADA target (HbA_{1c} < 7% at end of trial) was analyzed using a logistic regression model including treatment as a fixed factor and baseline HbA_{1c} as covariate.

In addition, the secondary endpoints in the five pivotal studies were

- Glycemic control (FPG, 7 or 8-point home measured plasma glucose)
- Beta-cell function (HOMA-B, HOMA-IR, pro-insulin to insulin ratio, fasting C-peptide, FSIGT)
- Body composition (waist circumference, waist to hip circumference, DEXA, CT scan)
- Blood pressure (systolic and diastolic)
- Glucagon
- Lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB)

- Other cardiovascular biomarkers (PAI-1, hsCRP, NT-proBNP)
- Albumin to creatinine ratio

The objective of the analyses of the secondary endpoints was to investigate if change from baseline after treatment with liraglutide (monotherapy or combination therapy) was different from the comparator treatment (active or placebo).

The secondary endpoints were analyzed using the same ANCOVA described for HbA_{1c}.

Handling Multiplicity

For the primary endpoint, the factors contributing to multiple testing, multiple doses of liraglutide treatment and two comparators (Trials 1572, 1436 and 1697) were dealt with by using a hierarchical testing procedure (see Section [2.2.1](#)).

For Trials 1572, 1436 and 1697 that included both placebo and active comparator, the comparison with the active comparator was considered the primary analysis.

In order to keep the rate of false positive conclusions at the 0.05 level, key secondary endpoints were tested according to the following testing hierarchy:

- HbA_{1c} (primary analyses)
- Body weight
- HbA_{1c} trend after nadir (Trial 1573)

Following the above hierarchy, no testing was done unless the previous hypothesis was rejected for a specific dose of liraglutide. Thus, for change in body weight, no statistical testing was done unless the analogous claim could be done for change in HbA_{1c}. For HbA_{1c} trend after nadir (Trial 1573), no statistical testing was done unless the analogous claim could be done for change in body weight.

Because the rest of the secondary endpoints provided supportive evidence to the primary and key secondary endpoint(s), adjustment for multiplicity was not done.

Imputation of Missing Data

For Trials 1572, 1436, 1574 and 1697, missing baseline values were not imputed due to the run-in period with change in OAD treatment.

In Trial 1573, missing baseline values were imputed using the screening value as there was no change in OAD medication between screening and randomization.

In all analyses based on the ITT analysis set, post-baseline missing values were replaced using last observation carried forward (LOCF).

2.3 Clinical Safety

In general, statistical analysis was not performed for routine safety analysis. Adverse events were evaluated by summarizing number and percentage of subjects with adverse events (N), number of adverse events (E), and incidence rate per 1,000 subject years (R) by system organ class and preferred term. Adverse events of special interest were analyzed with Cox proportional hazards models (described in detail below).

In this document, a treatment emergent adverse event (TEAE) was defined as an adverse event that either:

- Occurred before randomization **and** increased in severity during the treatment period
- Had an onset date on or after the first day of randomized treatment and no later than X days after the last day of randomized treatment². The cut-off employed in all the long-term trials was 7 days.

The adverse events described in this document are treatment emergent unless otherwise specified.

The safety of liraglutide was assessed both on a trial by trial basis and pooled with respect to liraglutide (by dose and by total liraglutide) and comparator (placebo, active comparator and total comparator). Refer to [Briefing Document, Section 7](#) for details on pooled data.

Analysis of Adverse Events of Special Interest

Statistical analysis of adverse events related to the thyroid gland, immunogenicity and neoplasms adverse events was conducted. The hazard ratio for liraglutide versus the comparator arms (placebo or active comparator) was calculated using Cox proportional hazard models with treatment group as a covariate and stratified by trial.

Hypoglycemia

Hypoglycemic episodes were defined as treatment emergent if the onset of the episode was on or after the first day of randomized treatment and no later than the last day of the randomized treatment.

Treatment emergent hypoglycaemic episodes were analyzed using a generalised linear model assuming that the number of hypoglycemic episodes per subject follows a negative binomial distribution. The model included treatment and country as fixed effects and duration of treatment was used as an offset variable in the model.

Calcitonin

Calcitonin was assessed by evaluating the basal levels (fasting calcitonin), stimulated levels (obtained from a calcium stimulation test) and outliers of the basal levels.

² The cut-off days for treatment emergent adverse events specified in the individual trials were applied.

Basal Levels of Calcitonin

A large percentage of the fasting calcitonin levels were below the lower limit of quantification (LLOQ) of 0.7 ng/L. To accommodate this, the statistical evaluation of treatment differences in calcitonin was conducted by a repeated measurement analysis for normal censored (calcitonin values below LLOQ of 0.7 ng/L) data, where the logarithm of calcitonin was the (censored) response and trial, time, treatment, gender and treatment by time interaction were fixed effects. Subjects were entered as random effects. Separate estimation and pairwise comparisons of treatment effect were made at all visits where calcitonin was measured to enable an evaluation of the trends over time.

Stimulated Levels of Calcitonin

The increments between basal and peak plasma calcitonin concentrations were analyzed with an ANCOVA, with treatment and gender as fixed effects and baseline increment as a covariate. The substudy was prospectively powered to detect a 50% difference in stimulated plasma calcitonin (Standard deviation = 0.60) levels at a significance level of 5%. This required that 27 subjects completed the trial in each group to achieve 85% power.

Outliers Defined as Unstimulated Calcitonin Above 2xUNR

Outliers were defined as fasting calcitonin values $\geq 2xUNR$ (gender-specific upper normal range was used, as females have lower basal calcitonin levels than males).

The trials included in the analysis are NN2211-1573 (main+ext), 1572 (main+ext), 1436, 1574, 1697, 1797 (main), 1700 (main), and 1701 (main), and NN8022-1807 (main+ext) (population 3, [Table 1–1](#)). Treatment groups are pooled into groups: liraglutide (any dose), placebo and active comparator.

The data were analyzed at weeks 26, 52 and 78 using a logistic regression with treatment and trial as fixed effects and baseline calcitonin as a covariate. A Fisher's exact test was used to compare liraglutide to placebo at Weeks 52 and 76/78, because very few subjects in the placebo group had a calcitonin value $\geq 2xUNR$. The analyses are based on the number of subjects at each time point.

3 Analysis of Adverse Events of Special Interest – Major Adverse Cardiovascular Events (MACE)

3.1 MACE Analyses

The investigation and presentation of MACE events is based on the reply to a request from the FDA of 11 January 2008.

The three categories of preferred terms (also including cardiovascular death as requested) were as follows:

- SMQ MACE (Narrow)
- SMQ MACE (Broad)
- Custom MACE

The standardized MedDRA Query SMQ MACE included a composite endpoint of cardiovascular death and two SMQs: for 'Myocardial Infarction' and 'Central Nervous System Haemorrhages and Cerebrovascular Accidents'. The terms included in these SMQs are presented in [Table 3–1](#) and [Table 3–2](#), subgrouped by 'narrow' and 'broad'.

The last category, custom MACE, includes a composite endpoint of cardiovascular death and the preferred terms presented in [Table 3–1](#) and [Table 3–2](#).

In addition to presenting all treatment emergent adverse events (TEAE), serious TEAEs are presented separately.

Table 3–1 SMQ (Narrow and Broad) and Custom, Myocardial Infarction

Preferred Term	Broad	Narrow	Custom
Acute coronary syndrome	X	X	
Acute myocardial infarction	X	X	X
Coronary artery embolism	X	X	
Coronary artery occlusion	X	X	
Coronary artery thrombosis	X	X	X
Myocardial infarction	X	X	X
Papillary muscle infarction	X	X	X
Post procedural myocardial infarction	X	X	X
Postinfarction angina	X	X	
Silent myocardial infarction	X	X	X
Blood creatine phosphokinase abnormal	X		
Blood creatine phosphokinase increased	X		
Blood creatine phosphokinase MB abnormal	X		
Blood creatine phosphokinase MB increased	X		
Cardiac enzymes increased	X		
Coronary artery reocclusion	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 reperfusion injury	X		
Scan myocardial perfusion abnormal	X		
Troponin I increased	X		
Troponin increased	X		
Troponin T increased	X		
Vascular graft occlusion	X		

Table 3–2 SMQ (Narrow and Broad) and Custom, Central Nervous System Haemorrhages and Cerebrovascular Accidents

Preferred Term	Broad	Narrow	Custom
Basal ganglia haemorrhage	X	X	
Brain stem haemorrhage	X	X	
Brain stem stroke	X	X	X
Carotid aneurysm rupture	X	X	
Cerebellar haematoma	X	X	
Cerebellar haemorrhage	X	X	
Cerebral arteriovenous malformation haemorrhagic	X	X	
Cerebral haematoma	X	X	
Cerebral haemorrhage	X	X	
Cerebral haemorrhage foetal	X	X	
Cerebral haemorrhage neonatal	X	X	
Cerebrovascular accident	X	X	X
Cerebrovascular disorder	X	X	
Haematomyelia	X	X	
Haemorrhage intracranial	X	X	
Haemorrhagic cerebral infarction	X	X	X
Haemorrhagic stroke	X	X	X
Haemorrhagic transformation stroke	X	X	X
Intracerebral haematoma evacuation	X	X	
Intracranial haematoma	X	X	
Intraventricular haemorrhage	X	X	
Intraventricular haemorrhage neonatal	X	X	
Meningorrhagia	X	X	
Putamen haemorrhage	X	X	
Ruptured cerebral aneurysm	X	X	
Spinal cord haemorrhage	X	X	
Spinal epidural haemorrhage	X	X	
Spinal haematoma	X	X	
Stroke in evolution	X	X	X
Subarachnoid haemorrhage	X	X	
Subarachnoid haemorrhage neonatal	X	X	
Subdural haemorrhage	X	X	
Subdural haemorrhage neonatal	X	X	
Thalamus haemorrhage	X	X	
Basilar artery occlusion	X	X	
Basilar artery stenosis	X	X	
Basilar artery thrombosis	X	X	X
Brain stem infarction	X	X	X
Brain stem ischaemia	X	X	
Brain stem thrombosis	X	X	X
Capsular warning syndrome	X	X	
Carotid arterial embolus	X	X	X
Carotid arteriosclerosis	X	X	
Carotid artery bypass	X	X	

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Preferred Term	Broad	Narrow	Custom
Carotid artery disease	X	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	
Cerebellar artery occlusion	X	X	
Cerebellar artery thrombosis	X	X	
Cerebellar embolism	X	X	
Cerebellar infarction	X	X	X
Cerebellar ischaemia	X	X	
Cerebral arteriosclerosis	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 infarction	X	X	X
Cerebral infarction foetal	X	X	
Cerebral ischaemia	X	X	
Cerebral thrombosis	X	X	X
Cerebral vasoconstriction	X	X	
Cerebral venous thrombosis	X	X	
Cerebrovascular accident	X	X	X
Cerebrovascular disorder	X	X	
Cerebrovascular insufficiency	X	X	
Cerebrovascular spasm	X	X	
Cerebrovascular stenosis	X	X	
Embolic cerebral infarction	X	X	X
Embolic stroke	X	X	X
Ischaemic cerebral infarction	X	X	X
Ischaemic stroke	X	X	X
Lacunar infarction	X	X	X
Lateral medullary syndrome	X	X	X
Millard-Gubler syndrome	X	X	
Moyamoya disease	X	X	X
Post procedural stroke	X	X	X
Precerebral artery occlusion	X	X	
Reversible ischaemic neurological deficit	X	X	
Spinal artery embolism	X	X	
Stroke in evolution	X	X	X
Thalamic infarction	X	X	X
Thrombotic cerebral infarction	X	X	X
Thrombotic stroke	X	X	X
Transient ischaemic attack	X	X	
Vascular encephalopathy	X	X	
Vertebral artery occlusion	X	X	

Preferred Term	Broad	Narrow	Custom
Vertebral artery stenosis	X	X	
Vertebral artery thrombosis	X	X	
Vertebrobasilar insufficiency	X	X	
Wallenberg syndrome	X	X	X
Agnosia	X		
Amaurosis fugax	X		
Angiogram cerebral abnormal	X		
Aphasia	X		
Balint's syndrome	X		
Carotid artery aneurysm	X		
Carotid artery dissection	X		
Central pain syndrome	X		
Cerebral aneurysm ruptured syphilitic	X		
Cerebrovascular accident prophylaxis	X		
Charcot-Bouchard microaneurysms	X		
Diplegia	X		
Dysarthria	X		
Hemiparesis	X		
Hemiplegia	X		
Intra-cerebral aneurysm operation	X		
Intracranial aneurysm	X		
Monoparesis	X		
Monoplegia	X		
Paralysis	X		
Paralysis flaccid	X		
Paraparesis	X		
Paraplegia	X		
Paresis	X		
Quadriparesis	X		
Quadriplegia	X		
Red blood cells CSF positive	X		
Spastic paralysis	X		
Spastic paraplegia	X		
Visual midline shift syndrome	X		

3.2 Statistical Analysis

For the three categories of events, Incidence Difference, Incidence Ratio, Incidence Rate Difference and Incidence Rate Ratio were estimated together with 95% CI. These were calculated as follows (only the first MACE event for each patient was counted in the analyses):

- Incidence: Events/N, where N is number of subjects in a given treatment group
- Incidence Difference: The difference between incidences of two treatment groups
- Incidence Ratio: The ratio between incidences of two treatment groups
- Incidence Rate: Events/1,000 subject years of exposure in a given treatment group

- Incidence Rate Difference: The difference between incidence rates of two treatment groups
- Incidence Rate Ratio: The ratio between incidence rates of two treatment groups

The estimations were done for the individual trials and also for the overall results (pooled data). When more than one comparator was available, three comparisons were made:

- a) liraglutide compared to placebo
- b) liraglutide compared to active comparator
- c) liraglutide compared to placebo and active comparator groups combined (total comparator).

All analyses were conducted using asymptotic methods.

For the overall results (pooled data), the estimates and 95% CI were computed using a Cochran Mantel-Haenszel estimation with stratification by trial.

The MACE analyses are presented in the [Briefing Document, Section 7.10.5](#).

3.3 MACE Tabulations Population A1 and A2

In the following, tabulations of MACE incidence analyses on individual studies and across trials for Population A1 and A2 are presented.

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Table 3–3 Incidence of Treatment Emergent Adverse Events - SMQ MACE (Broad Search) - Population A1 - Combined Across Doses of Study Drug Reported Separately by Study

Study	Group	N	Exposure (Pt-Yrs)	Events	Incidence (% = (100* events/N)	Incidence ratio: 95% CI	Incidence difference: 95%CI ^(a)
NN2211_1571	Liraglutide	123	30.5	0	0.00	-	-
	Placebo	40	8.3	0	0.00		
	Total Comparators	40	8.3	0	0.00		
NN2211_1310	Liraglutide	135	29.8	1	0.74	-	-
	Placebo	29	5.9	0	0.00		0.01 [-0.01; 0.02]
	Total Comparators	29	5.9	0	0.00		0.01 [-0.01; 0.02]
NN2211_1333	Liraglutide	21	3.3	0	0.00	-	-
	Placebo	12	1.9	0	0.00		
	Total Comparators	12	1.9	0	0.00		
NN2211_2072	Liraglutide	175	38.0	1	0.57	-	-
	Placebo	34	7.8	1	2.94	0.19 [0.01; 3.03]	-0.02 [-0.08; 0.03]
	Total Comparators	34	7.8	1	2.94	0.19 [0.01; 3.03]	-0.02 [-0.08; 0.03]
NN2211_1499	Liraglutide	72	6.4	0	0.00	-	-
	Placebo	36	3.0	0	0.00		
	Total Comparators	36	3.0	0	0.00		
NN2211_1334	Liraglutide	180	47.1	0	0.00	-	-
	Placebo	46	11.1	0	0.00		
	Total Comparators	46	11.1	0	0.00		
NN8022_1807	Liraglutide	371	130.9	6	1.62	-	-
	Placebo	98	33.9	0	0.00		0.02 [0.00; 0.03]
	Total Comparators	98	33.9	0	0.00		0.02 [0.00; 0.03]
NN2211_1573	Liraglutide	497	387.0	8	1.61	-	-
	Active Comparator	248	185.9	3	1.21	1.33 [0.36; 4.97]	0.00 [-0.01; 0.02]
	Total Comparators	248	185.9	3	1.21	1.33 [0.36; 4.97]	0.00 [-0.01; 0.02]
NN2211_1572	Liraglutide	724	320.9	11	1.52	-	-
	Placebo	121	46.8	1	0.83	1.84 [0.24;14.11]	0.01 [-0.01; 0.03]
	Active Comparator	242	110.8	7	2.89	0.53 [0.21; 1.34]	-0.01 [-0.04; 0.01]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence difference, the incidence is given as 100*events/N.

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Study	Group	Incidence rate: (1000*events/Pt –yrs)	Incidence rate ratio: 95% CI	Incidence rate difference: 95% CI ^(a)
NN2211_1571	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
NN2211_1310	Liraglutide	33.55	-	-
	Placebo	0.00		0.03 [-0.03; 0.10]
	Total Comparators	0.00		0.03 [-0.03; 0.10]
NN2211_1333	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
NN2211_2072	Liraglutide	26.35	-	-
	Placebo	128.6	0.21 [0.01; 3.02]	-0.10 [-0.33; 0.14]
	Total Comparators	128.6	0.21 [0.01; 3.02]	-0.10 [-0.33; 0.14]
NN2211_1499	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
NN2211_1334	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
NN8022_1807	Liraglutide	45.85	-	-
	Placebo	0.00		0.05 [0.01; 0.08]
	Total Comparators	0.00		0.05 [0.01; 0.08]
NN2211_1573	Liraglutide	20.67	-	-
	Active Comparator	16.14	1.28 [0.34; 4.78]	0.00 [-0.02; 0.03]
	Total Comparators	16.14	1.28 [0.34; 4.78]	0.00 [-0.02; 0.03]
NN2211_1572	Liraglutide	34.28	-	-
	Placebo	21.36	1.61 [0.21;12.19]	0.01 [-0.03; 0.06]
	Active Comparator	63.15	0.54 [0.22; 1.37]	-0.03 [-0.08; 0.02]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence rate difference, the incidence rate is given as 1000*events/N.

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Study	Group	N	Exposure (Pt-Yrs)	Events	Incidence (% = (100* events/N)	Incidence ratio: 95% CI	Incidence difference: 95% CI ^(a)
NN2211_1572	Total Comparators	363	157.7	8	2.20	0.69 [0.28; 1.70]	-0.01 [-0.02; 0.01]
NN2211_1436	Liraglutide	695	322.2	10	1.44	-	-
	Placebo	114	47.1	3	2.63	0.55 [0.15; 1.96]	-0.01 [-0.04; 0.02]
	Active Comparator	231	104.6	5	2.16	0.66 [0.23; 1.92]	-0.01 [-0.03; 0.01]
	Total Comparators	345	151.7	8	2.32	0.62 [0.25; 1.56]	-0.01 [-0.03; 0.01]
NN2211_1574	Liraglutide	355	154.3	3	0.85	-	-
	Placebo	175	71.8	3	1.71	0.49 [0.10; 2.42]	-0.01 [-0.03; 0.01]
	Total Comparators	175	71.8	3	1.71	0.49 [0.10; 2.42]	-0.01 [-0.03; 0.01]
NN2211_1697	Liraglutide	230	107.3	5	2.17	-	-
	Placebo	114	52.9	1	0.88	2.48 [0.29;20.96]	0.01 [-0.01; 0.04]
	Total Comparators	114	52.9	1	0.88	2.48 [0.29;20.96]	0.01 [-0.01; 0.04]
NN2211_1700	Liraglutide	268	116.1	3	1.12	-	-
	Active Comparator	132	58.1	0	0.00		0.01 [-0.00; 0.02]
	Total Comparators	132	58.1	0	0.00		0.01 [-0.00; 0.02]
NN2211_1701	Liraglutide	176	78.1	0	0.00	-	-
	Placebo	88	37.7	0	0.00		
	Total Comparators	88	37.7	0	0.00		
Pooled	Liraglutide	4022	1772	48	1.19	-	-
	Placebo	907	328.2	9	0.99	1.04 [0.50; 2.16]	0.00 [-0.01; 0.01]
	Active Comparator	853	459.4	15	1.76	0.81 [0.44; 1.47]	-0.01 [-0.02; 0.00]
	Total Comparators	1760	787.6	24	1.36	0.92 [0.56; 1.50]	-0.00 [-0.01; 0.00]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence difference, the incidence is given as 100*events/N.

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Study	Group	Incidence rate: (1000*events/Pt –yrs)	Incidence rate ratio: 95% CI	Incidence rate difference: 95% CI ^(a)
NN2211_1572	Total Comparators	50.74	0.68 [0.28; 1.65]	-0.02 [-0.06; 0.02]
NN2211_1436	Liraglutide	31.04	-	-
	Placebo	63.67	0.49 [0.14; 1.70]	-0.03 [-0.11; 0.04]
	Active Comparator	47.79	0.65 [0.23; 1.86]	-0.02 [-0.06; 0.03]
	Total Comparators	52.72	0.59 [0.24; 1.47]	-0.02 [-0.06; 0.02]
NN2211_1574	Liraglutide	19.44	-	-
	Placebo	41.79	0.47 [0.10; 2.26]	-0.02 [-0.07; 0.03]
	Total Comparators	41.79	0.47 [0.10; 2.26]	-0.02 [-0.07; 0.03]
NN2211_1697	Liraglutide	46.62	-	-
	Placebo	18.92	2.48 [0.30;20.67]	0.03 [-0.03; 0.08]
	Total Comparators	18.92	2.48 [0.30;20.67]	0.03 [-0.03; 0.08]
NN2211_1700	Liraglutide	25.83	-	-
	Active Comparator	0.00		0.03 [-0.00; 0.05]
	Total Comparators	0.00		0.03 [-0.00; 0.05]
NN2211_1701	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
Pooled	Liraglutide	27.09	-	-
	Placebo	27.43	0.98 [0.47; 2.02]	-0.00 [-0.02; 0.02]
	Active Comparator	32.65	0.81 [0.45; 1.46]	-0.01 [-0.02; 0.01]
	Total Comparators	30.47	0.89 [0.55; 1.45]	-0.00 [-0.02; 0.01]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence rate difference, the incidence rate is given as 1000*events/N.

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Table 3–4 Incidence of TEAE - SMQ MACE (Broad Search) - Population A2 - Combined across doses of study drug reported separately by study

Study	Group	N	Exposure (Pt-Yrs)	Events	Incidence (% = (100* events/N)	Incidence ratio: 95% CI	Incidence difference: 95% CI ^(a)
NN2211_1571	Liraglutide	123	30.5	0	0.00	-	-
	Placebo	40	8.3	0	0.00		
	Total Comparators	40	8.3	0	0.00		
NN2211_1310	Liraglutide	135	29.8	1	0.74	-	-
	Placebo	29	5.9	0	0.00		0.01 [-0.01; 0.02]
	Active Comparator	26	6.0	0	0.00		0.01 [-0.01; 0.02]
	Total Comparators	55	11.9	0	0.00		0.01 [-0.01; 0.02]
NN2211_1333	Liraglutide	21	3.3	0	0.00	-	-
	Placebo	12	1.9	0	0.00		
	Total Comparators	12	1.9	0	0.00		
NN2211_2072	Liraglutide	175	38.0	1	0.57	-	-
	Placebo	34	7.8	1	2.94	0.19 [0.01; 3.03]	-0.02 [-0.08; 0.03]
	Total Comparators	34	7.8	1	2.94	0.19 [0.01; 3.03]	-0.02 [-0.08; 0.03]
NN2211_1499	Liraglutide	72	6.4	0	0.00	-	-
	Placebo	36	3.0	0	0.00		
	Active Comparator	36	5.2	0	0.00		
	Total Comparators	72	8.2	0	0.00		
NN2211_1334	Liraglutide	180	47.1	0	0.00	-	-
	Placebo	46	11.1	0	0.00		
	Total Comparators	46	11.1	0	0.00		
NN8022_1807	Liraglutide	371	130.9	6	1.62	-	-
	Placebo	98	33.9	0	0.00		0.02 [0.00; 0.03]
	Active Comparator	95	33.4	3	3.16	0.51 [0.13; 2.01]	-0.02 [-0.05; 0.02]
	Total Comparators	193	67.4	3	1.55	1.04 [0.26; 4.11]	0.00 [-0.02; 0.02]
NN2211_1573	Liraglutide	497	387.0	8	1.61	-	-
	Active Comparator	248	185.9	3	1.21	1.33 [0.36; 4.97]	0.00 [-0.01; 0.02]
	Total Comparators	248	185.9	3	1.21	1.33 [0.36; 4.97]	0.00 [-0.01; 0.02]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence difference, the incidence is given as 100*events/N.

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Study	Group	Incidence rate: (1000*events/Pt –yrs)	Incidence rate ratio: 95% CI	Incidence rate difference: 95% CI ^(a)
NN2211_1571	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
NN2211_1310	Liraglutide	33.55	-	-
	Placebo	0.00		0.03 [-0.03; 0.10]
	Active Comparator	0.00		0.03 [-0.03; 0.10]
	Total Comparators	0.00		0.03 [-0.03; 0.10]
NN2211_1333	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
NN2211_2072	Liraglutide	26.35	-	-
	Placebo	128.6	0.21 [0.01; 3.02]	-0.10 [-0.33; 0.14]
	Total Comparators	128.6	0.21 [0.01; 3.02]	-0.10 [-0.33; 0.14]
NN2211_1499	Liraglutide	0.00	-	-
	Placebo	0.00		
	Active Comparator	0.00		
	Total Comparators	0.00		
NN2211_1334	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
NN8022_1807	Liraglutide	45.85	-	-
	Placebo	0.00		0.05 [0.01; 0.08]
	Active Comparator	89.71	0.50 [0.13; 1.91]	-0.05 [-0.15; 0.06]
	Total Comparators	44.52	1.02 [0.26; 3.96]	0.00 [-0.06; 0.06]
NN2211_1573	Liraglutide	20.67	-	-
	Active Comparator	16.14	1.28 [0.34; 4.78]	0.00 [-0.02; 0.03]
	Total Comparators	16.14	1.28 [0.34; 4.78]	0.00 [-0.02; 0.03]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence rate difference, the incidence rate is given as 1000*events/N.

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Study	Group	N	Exposure (Pt-Yrs)	Events	Incidence (% = (100* events/N)	Incidence ratio: 95% CI	Incidence difference: 95% CI ^(a)
NN2211_1572	Liraglutide	724	320.9	11	1.52	-	-
	Placebo	121	46.8	1	0.83	1.84 [0.24;14.11]	0.01 [-0.01; 0.03]
	Active Comparator	242	110.8	7	2.89	0.53 [0.21; 1.34]	-0.01 [-0.04; 0.01]
	Total Comparators	363	157.7	8	2.20	0.69 [0.28; 1.70]	-0.01 [-0.02; 0.01]
NN2211_1436	Liraglutide	695	322.2	10	1.44	-	-
	Placebo	114	47.1	3	2.63	0.55 [0.15; 1.96]	-0.01 [-0.04; 0.02]
	Active Comparator	231	104.6	5	2.16	0.66 [0.23; 1.92]	-0.01 [-0.03; 0.01]
	Total Comparators	345	151.7	8	2.32	0.62 [0.25; 1.56]	-0.01 [-0.03; 0.01]
NN2211_1574	Liraglutide	355	154.3	3	0.85	-	-
	Placebo	175	71.8	3	1.71	0.49 [0.10; 2.42]	-0.01 [-0.03; 0.01]
	Total Comparators	175	71.8	3	1.71	0.49 [0.10; 2.42]	-0.01 [-0.03; 0.01]
NN2211_1697	Liraglutide	230	107.3	5	2.17	-	-
	Placebo	114	52.9	1	0.88	2.48 [0.29;20.96]	0.01 [-0.01; 0.04]
	Active Comparator	232	111.9	6	2.59	0.84 [0.26; 2.72]	-0.00 [-0.03; 0.02]
	Total Comparators	346	164.8	7	2.02	1.07 [0.35; 3.34]	0.00 [-0.02; 0.03]
NN2211_1797	Liraglutide	235	107.7	3	1.28	-	-
	Active Comparator	232	101.5	2	0.86	1.48 [0.25; 8.78]	0.00 [-0.01; 0.02]
	Total Comparators	232	101.5	2	0.86	1.48 [0.25; 8.78]	0.00 [-0.01; 0.02]
NN2211_1700	Liraglutide	268	116.1	3	1.12	-	-
	Active Comparator	132	58.1	0	0.00		0.01 [-0.00; 0.02]
	Total Comparators	132	58.1	0	0.00		0.01 [-0.00; 0.02]
NN2211_1701	Liraglutide	176	78.1	0	0.00	-	-
	Placebo	88	37.7	0	0.00		
	Total Comparators	88	37.7	0	0.00		
Pooled	Liraglutide	4257	1880	51	1.20	-	-
	Placebo	907	328.2	9	0.99	1.04 [0.50; 2.16]	0.00 [-0.01; 0.01]
	Active Comparator	1474	717.6	26	1.76	0.82 [0.51; 1.32]	-0.01 [-0.01; 0.00]
	Total Comparators	2381	1046	35	1.47	0.87 [0.57; 1.34]	-0.00 [-0.01; 0.00]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence difference, the incidence is given as 100*events/N.

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Study	Group	Incidence rate: (1000*events/Pt –yrs)	Incidence rate ratio: 95% CI	Incidence rate difference: 95% CI ^(a)
NN2211_1572	Liraglutide	34.28	-	-
	Placebo	21.36	1.61 [0.21;12.19]	0.01 [-0.03; 0.06]
	Active Comparator	63.15	0.54 [0.22; 1.37]	-0.03 [-0.08; 0.02]
	Total Comparators	50.74	0.68 [0.28; 1.65]	-0.02 [-0.06; 0.02]
NN2211_1436	Liraglutide	31.04	-	-
	Placebo	63.67	0.49 [0.14; 1.70]	-0.03 [-0.11; 0.04]
	Active Comparator	47.79	0.65 [0.23; 1.86]	-0.02 [-0.06; 0.03]
	Total Comparators	52.72	0.59 [0.24; 1.47]	-0.02 [-0.06; 0.02]
NN2211_1574	Liraglutide	19.44	-	-
	Placebo	41.79	0.47 [0.10; 2.26]	-0.02 [-0.07; 0.03]
	Total Comparators	41.79	0.47 [0.10; 2.26]	-0.02 [-0.07; 0.03]
NN2211_1697	Liraglutide	46.62	-	-
	Placebo	18.92	2.48 [0.30;20.67]	0.03 [-0.03; 0.08]
	Active Comparator	53.61	0.87 [0.27; 2.77]	-0.01 [-0.06; 0.05]
	Total Comparators	42.48	1.10 [0.36; 3.38]	0.00 [-0.05; 0.05]
NN2211_1797	Liraglutide	27.86	-	-
	Active Comparator	19.70	1.42 [0.24; 8.31]	0.01 [-0.03; 0.05]
	Total Comparators	19.70	1.42 [0.24; 8.31]	0.01 [-0.03; 0.05]
NN2211_1700	Liraglutide	25.83	-	-
	Active Comparator	0.00		0.03 [-0.00; 0.05]
	Total Comparators	0.00		0.03 [-0.00; 0.05]
NN2211_1701	Liraglutide	0.00	-	-
	Placebo	0.00		
	Total Comparators	0.00		
Pooled	Liraglutide	27.13	-	-
	Placebo	27.43	0.98 [0.47; 2.02]	-0.00 [-0.02; 0.02]
	Active Comparator	36.23	0.82 [0.51; 1.32]	-0.01 [-0.02; 0.01]
	Total Comparators	33.47	0.86 [0.56; 1.31]	-0.01 [-0.02; 0.01]

Only the first MACE event for each subject is counted in these analyses. ^a Note that in contrast to the incidence rate difference, the incidence rate is given as 1000*events/N.

3.3.1 All MACE Tabulations on Population B

See following pages.

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Table 3–5 Summary of SMQ MACE (Broad Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882.0				448.8				1037.6				1486.4		
Serious MACE AEs	0.6	25	8.7	25	0.3	3	6.7	3	1.1	16	15.4	16	0.8	19	12.8	19
MACE Deaths	0.0	0	0.0	0	0.1	1	2.2	1	0.1	1	1.0	1	0.1	2	1.3	2
Non-Serious MACE AEs	1.1	45	16.0	46	1.1	10	22.3	10	1.3	19	20.2	21	1.2	29	20.9	31
Total MACE Adverse Events	1.6	69	24.6	71	1.4	13	29.0	13	2.2	32	35.7	37	1.9	45	33.6	50
MACE AE Withdrawals	0.3	14	4.9	14	0.3	3	6.7	3	0.6	9	8.7	9	0.5	12	8.1	12

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

Table 3–6 Summary of SMQ MACE (Narrow Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882.0				448.8				1037.6				1486.4		
Serious MACE AEs	0.6	24	8.3	24	0.3	3	6.7	3	1.1	16	15.4	16	0.8	19	12.8	19
MACE Deaths	0.0	0	0.0	0	0.1	1	2.2	1	0.1	1	1.0	1	0.1	2	1.3	2
Non-Serious MACE AEs	0.3	11	4.2	12	0.3	3	6.7	3	0.3	5	4.8	5	0.3	8	5.4	8
Total MACE Adverse Events	0.8	35	12.5	36	0.7	6	13.4	6	1.2	18	20.2	21	1.0	24	18.2	27
MACE AE Withdrawals	0.3	12	4.2	12	0.3	3	6.7	3	0.6	9	8.7	9	0.5	12	8.1	12

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

Table 3–7 Summary of MACE (Custom Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882.0				448.8				1037.6				1486.4		
Serious MACE AEs	0.4	17	5.9	17	0.2	2	4.5	2	0.9	13	12.5	13	0.6	15	10.1	15
MACE Deaths	0.0	0	0.0	0	0.1	1	2.2	1	0.1	1	1.0	1	0.1	2	1.3	2
Non-Serious MACE AEs	0.1	4	1.4	4	0.2	2	4.5	2	0.0	0	0.0	0	0.1	2	1.3	2
Total MACE Adverse Events	0.5	21	7.3	21	0.4	4	8.9	4	0.9	13	12.5	13	0.7	17	11.4	17
MACE AE Withdrawals	0.2	10	3.5	10	0.2	2	4.5	2	0.6	9	8.7	9	0.5	11	7.4	11

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

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Table 3–8 All SMQ MACE by SOC and Preferred Term (Broad Search) – Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882				448.8				1037.6				1486.4		
All MACE Adverse Events	1.6	69	24.6	71	1.4	13	29.0	13	2.2	32	35.7	37	1.9	45	33.6	50
INVESTIGATIONS	0.8	33	11.8	34	0.8	7	15.6	7	0.9	14	14.5	15	0.9	21	14.8	22
Blood Creatine Phosphokinase Increased	0.7	31	11.1	32	0.7	6	13.4	6	0.9	14	14.5	15	0.8	20	14.1	21
Blood Creatine Phosphokinase Abnormal	0.0	1	0.3	1	0.1	1	2.2	1					0.0	1	0.7	1
Electrocardiogram Q Wave Abnormal	0.0	1	0.3	1												
NERVOUS SYSTEM DISORDERS	0.4	18	6.6	19	0.3	3	6.7	3	0.7	10	12.5	13	0.5	13	10.8	16
Carotid Artery Stenosis	0.0	2	1.0	3	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
Transient Ischaemic Attack	0.1	4	1.4	4					0.1	2	1.9	2	0.1	2	1.3	2
Cerebrovascular Accident	0.1	3	1.0	3					0.1	1	1.0	1	0.0	1	0.7	1
Cerebral Infarction	0.0	2	0.7	2					0.1	2	1.9	2	0.1	2	1.3	2
Cerebrovascular Disorder	0.0	1	0.3	1	0.1	1	2.2	1					0.0	1	0.7	1
Thalamus Haemorrhage									0.1	1	1.0	1	0.0	1	0.7	1
Subarachnoid Haemorrhage	0.0	1	0.3	1												
Paresis	0.0	1	0.3	1												
Paralysis									0.1	1	1.0	1	0.0	1	0.7	1
Ischaemic Stroke									0.1	1	1.0	1	0.0	1	0.7	1
Haemorrhage Intracranial	0.0	1	0.3	1												
Cerebral Haemorrhage	0.0	1	0.3	1												
Cerebral Arteriosclerosis	0.0	1	0.3	1												
Cerebellar Infarction	0.0	1	0.3	1												
Carotid Arteriosclerosis									0.1	1	1.0	1	0.0	1	0.7	1
Brain Stem Infarction					0.1	1	2.2	1					0.0	1	0.7	1
CARDIAC DISORDERS	0.4	18	6.2	18	0.3	3	6.7	3	0.6	9	8.7	9	0.5	12	8.1	12
Myocardial Infarction	0.2	8	2.8	8	0.2	2	4.5	2	0.3	5	4.8	5	0.3	7	4.7	7
Acute Myocardial Infarction	0.2	7	2.4	7	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
Coronary Artery Occlusion	0.0	2	0.7	2												
Acute Coronary Syndrome	0.0	1	0.3	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 3–9 All SMQ MACE by SOC and Preferred Term (Narrow Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882				448.8				1037.6				1486.4		
All MACE Adverse Events	0.8	35	12.5	36	0.7	6	13.4	6	1.2	18	20.2	21	1.0	24	18.2	27
NERVOUS SYSTEM DISORDERS	0.4	17	6.2	18	0.3	3	6.7	3	0.6	9	11.6	12	0.5	12	10.1	15
Carotid Artery Stenosis	0.0	2	1.0	3	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
Transient Ischaemic Attack	0.1	4	1.4	4					0.1	2	1.9	2	0.1	2	1.3	2
Cerebrovascular Accident	0.1	3	1.0	3					0.1	1	1.0	1	0.0	1	0.7	1
Cerebral Infarction	0.0	2	0.7	2					0.1	2	1.9	2	0.1	2	1.3	2
Cerebrovascular Disorder	0.0	1	0.3	1	0.1	1	2.2	1					0.0	1	0.7	1
Thalamus Haemorrhage									0.1	1	1.0	1	0.0	1	0.7	1
Subarachnoid Haemorrhage	0.0	1	0.3	1												
Ischaemic Stroke									0.1	1	1.0	1	0.0	1	0.7	1
Haemorrhage Intracranial	0.0	1	0.3	1												
Cerebral Haemorrhage	0.0	1	0.3	1												
Cerebral Arteriosclerosis	0.0	1	0.3	1												
Cerebellar Infarction	0.0	1	0.3	1												
Carotid Arteriosclerosis									0.1	1	1.0	1	0.0	1	0.7	1
Brain Stem Infarction					0.1	1	2.2	1					0.0	1	0.7	1
CARDIAC DISORDERS	0.4	18	6.2	18	0.3	3	6.7	3	0.6	9	8.7	9	0.5	12	8.1	12
Myocardial Infarction	0.2	8	2.8	8	0.2	2	4.5	2	0.3	5	4.8	5	0.3	7	4.7	7
Acute Myocardial Infarction	0.2	7	2.4	7	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
Coronary Artery Occlusion	0.0	2	0.7	2												
Acute Coronary Syndrome	0.0	1	0.3	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years.

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Table 3–10 All MACE by SOC and Preferred Term (Custom Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882				448.8				1037.6				1486.4		
All MACE Adverse Events	0.5	21	7.3	21	0.4	4	8.9	4	0.9	13	12.5	13	0.7	17	11.4	17
CARDIAC DISORDERS	0.4	15	5.2	15	0.3	3	6.7	3	0.6	9	8.7	9	0.5	12	8.1	12
Myocardial Infarction	0.2	8	2.8	8	0.2	2	4.5	2	0.3	5	4.8	5	0.3	7	4.7	7
Acute Myocardial Infarction	0.2	7	2.4	7	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
NERVOUS SYSTEM DISORDERS	0.1	6	2.1	6	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
Cerebrovascular Accident	0.1	3	1	3					0.1	1	1	1	0	1	0.7	1
Cerebral Infarction	0	2	0.7	2					0.1	2	1.9	2	0.1	2	1.3	2
Ischaemic stroke									0.1	1	1.0	1	0	1	0.7	1
Cerebellar Infarction	0	1	0.3	1												
Brain Stem Infarction					0.1	1	2.2	1					0	1	0.7	1

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

3.3.2 Serious MACE Tabulations on Population B

See following pages.

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Table 3–11 Serious SMQ MACE by SOC and Preferred Term (Broad Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882				448.8				1037.6				1486.4		
All MACE Adverse Events	0.6	25	8.7	25	0.3	3	6.7	0.3	1.1	16	15.4	16	0.8	19	12.8	19
CARDIAC DISORDERS	0.4	15	5.2	15	0.2	2	4.5	0.2	0.6	9	8.7	9	0.5	11	7.4	11
Myocardial Infarction	0.2	7	2.4	7	0.1	1	2.2	0.1	0.3	5	4.8	5	0.3	6	4.0	6
Acute Myocardial Infarction	0.1	6	2.1	6	0.1	1	2.2	0.1	0.3	4	3.9	4	0.2	5	3.4	5
Coronary Artery Occlusion	0.0	1	0.3	1												
Acute Coronary Syndrome	0.0	1	0.3	1												
NERVOUS SYSTEM DISORDERS	0.2	9	3.1	9	0.1	1	2.2	0.1	0.5	7	6.7	7	0.3	8	5.4	8
Cerebrovascular Accident	0.1	3	1.0	3					0.1	1	1.0	1	0.0	1	0.7	1
Transient Ischaemic Attack	0.0	1	0.3	1					0.1	1	1.0	1	0.0	1	0.7	1
Cerebrovascular Disorder	0.0	1	0.3	1	0.1	1	2.2	0.1					0.0	1	0.7	1
Cerebral Infarction									0.1	2	1.9	2	0.1	2	1.3	2
Carotid Artery Stenosis									0.1	2	1.9	2	0.1	2	1.3	2
Subarachnoid Haemorrhage	0.0	1	0.3	1												
Ischaemic Stroke									0.1	1	1.0	1	0.0	1	0.7	1
Haemorrhage Intracranial	0.0	1	0.3	1												
Cerebral Haemorrhage	0.0	1	0.3	1												
Cerebellar Infarction	0.0	1	0.3	1												
INVESTIGATIONS	0.0	1	0.3	1												
Blood Creatine Phosphokinase Increased	0.0	1	0.3	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

Table 3–12 Serious SMQ MACE by SOC and Preferred Term (Narrow Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882				448.8				1037.6				1486.4		
All MACE Adverse Events	0.6	24	8.3	24	0.3	3	6.7	3	1.1	16	15.4	16	0.8	19	12.8	19
CARDIAC DISORDERS	0.4	15	5.2	15	0.2	2	4.5	2	0.6	9	8.7	9	0.5	11	7.4	11
Myocardial Infarction	0.2	7	2.4	7	0.1	1	2.2	1	0.3	5	4.8	5	0.3	6	4	6
Acute Myocardial Infarction	0.1	6	2.1	6	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
Coronary Artery Occlusion	0	1	0.3	1												
Acute Coronary Syndrome	0	1	0.3	1												
NERVOUS SYSTEM DISORDERS	0.2	9	3.1	9	0.1	1	2.2	1	0.5	7	6.7	7	0.3	8	5.4	8
Cerebrovascular Accident	0.1	3	1	3					0.1	1	1	1	0	1	0.7	1
Transient Ischaemic Attack	0	1	0.3	1					0.1	1	1	1	0	1	0.7	1
Cerebrovascular Disorder	0	1	0.3	1	0.1	1	2.2	1					0	1	0.7	1
Cerebral Infarction									0.1	2	1.9	2	0.1	2	1.3	2
Carotid Artery Stenosis									0.1	2	1.9	2	0.1	2	1.3	2
Subarachnoid Haemorrhage	0	1	0.3	1												
Ischaemic Stroke									0.1	1	1	1	0	1	0.7	1
Haemorrhage Intracranial	0	1	0.3	1												
Cerebral Haemorrhage	0	1	0.3	1												
Cerebellar Infarction	0	1	0.3	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

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Table 3–13 Serious MACE by SOC and Preferred Term (Custom Search) - Population B

	Total Liraglutide				Placebo				Active Comparator				Total Comparator			
	%	N	R	E	%	N	R	E	%	N	R	E	%	N	R	E
Safety Analysis Set		4257				907				1474				2381		
Total Exposure Years		2882				448.8				1037.6				1486.4		
All MACE Adverse Events	0.4	17	5.9	17	0.2	2	4.5	2	0.9	13	12.5	13	0.6	15	10.1	15
CARDIAC DISORDERS	0.3	13	4.5	13	0.2	2	4.5	2	0.6	9	8.7	9	0.5	11	7.4	11
Myocardial Infarction	0.2	7	2.4	7	0.1	1	2.2	1	0.3	5	4.8	5	0.3	6	4	6
Acute Myocardial Infarction	0.1	6	2.1	6	0.1	1	2.2	1	0.3	4	3.9	4	0.2	5	3.4	5
NERVOUS SYSTEM DISORDERS	0.1	4	1.4	4					0.3	4	3.9	4	0.2	4	2.7	4
Cerebrovascular Accident	0.1	3	1	3					0.1	1	1	1	0	1	0.7	1
Cerebral Infarction									0.1	2	1.9	2	0.1	2	1.3	2
Ischaemic stroke									0.1	1	1.0	1	0	1	0.7	1
Cerebellar Infarction	0	1	0.3	1												

N: Number of Subjects with adverse events; %: Proportion of subjects in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Subject years of exposure multiplied by 1,000; Total Exposure Years: Total Exposure in years

List of Abbreviations and Definitions

ADA	American Diabetes Association
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoB	apolipoprotein B
AUC _{0-∞}	area under the curve from time zero to infinity
AUC _{0-t}	area under the curve from dosing up to time t hours after dosing
BCS	Biopharmaceutic Classification System
BMI	body mass index
cAMP	cyclic adenosine monophosphate
CAPD	continuous ambulatory peritoneal dialysis
CI	confidence interval
CL/F	total apparent clearance
CL _{CR}	creatinine clearance
C _{max}	maximal concentration
CNS	central nervous system
CRP	C-reactive protein
CT	computerized tomography
CV	cardiovascular
CYP	cytochrome P450
DEXA	dual energy X-ray absorptiometry
DPP-IV	dipeptidyl-peptidase
E	number of events
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
ESRD	end stage renal disease
FFA	free fatty acid
FSIGT	frequently-sampled intravenous glucose tolerance tests
FPG	fasting blood glucose
GI	gastrointestinal
GLP-1	glucagon like peptide-1
HbA _{1c}	glycosylated hemoglobin
HDL-C	high density lipoprotein cholesterol
HOMA-B	homeostasis model assessment for beta-cell function
HOMA-IR	homeostatic model assessment of insulin resistance
hsCRP	highly sensitive C-reactive protein
ICH	International Conference on Harmonization

ITT	intent-to-treat
i.v.	intravenous(ly)
LDL-C	low density lipoprotein cholesterol
LEAD	liraglutide effect and action in diabetes
LLOQ	lower level of quantification
LOCF	last observation carried forward
LSmean	least squares mean
LV	left ventricular
MACE	major adverse cardiovascular events
MESI	medical event of special interest
MedDRA	medical dictionary for regulatory activities
MET	metformin
N	number of subjects
N/A	not applicable
NDA	New Drug Application
NEP	neutral endopeptidase
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PAI-1	plasminogen activator inhibitor 1
PCNA	proliferating cell nuclear antigen
PIP	pediatric investigational plan
PK	pharmacokinetic
PPG	postprandial plasma glucose
PR	time from the beginning of the P wave to the beginning of the QRS complex
PT	preferred term (MedDRA)
PTH	parathyroid hormone
P wave	atrial contractions (both right and left) shown in an ECG
QT	time between the start of the Q wave and the end of the T wave shown in an ECG
QTc	QTc interval corrected for rate
QRS complex	ventricular contractions (both right and left) shown as a series of three waves on an ECG: Q-R-S
R	rate of events
RD	repeat dose
RMP	risk management plan
SAE	serious adverse event
s.c.	subcutaneous drug administration
SD	standard deviation
SEM	standard error of the mean
SMQ	Standardized MedDRA queries

SOC	system organ class (MedDRA)
SU	sulfonylurea
TC	total cholesterol
TEAE	treatment emergent adverse event
TG	triglycerides
TK	toxicokinetic
t _{max}	time to reach maximum concentration of drug in plasma
TQT	thorough QT (trial)
T wave	reflects the electrical activity produced when the ventricles are recharging for the next contraction (repolarizing) shown in an ECG
TZD	thiazolidinedione
UNR	upper normal range
VLDL-C	very low density lipoprotein cholesterol
WHO	World Health Organization

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