Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Liraglutide (rys)

Proprietary Product Name: Victoza

Sponsor: Novo Nordisk Pharmaceuticals Pty Limited

November 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Biological Entity
Decision:	Approved
Date of Decision:	18 August 2010
Active ingredient(s):	Liraglutide (rys)
Product Name(s):	Victoza
Sponsor's Name and Address:	Novo Nordisk Pharmaceuticals Pty Limited Level 3, 21 Solent Circuit Baulkham Hills NSW 2153
Dose form(s):	Injectable solution at a concentration of 6.0 mg/ml.
Strength(s):	0.6 mg, 1.2 mg or 1.8 mg in a pen injector.
Container(s):	A pre-filled 3 mL glass cartridge contained within a disposable pen injector
Pack size(s):	1, 2, 3, 5 or 10 cartridges per pack
Approved Therapeutic use:	Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control: · in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy. · in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.
Route(s) of administration:	Subcutaneously in the abdomen, thigh or upper arm.
Dosage:	Victoza is administered once daily at any time, independent of meals. For all patients, Victoza 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 for one week. Maximum efficacy can be achieved at 1.8 mg.
ARTG Number (s):	153980

Product Background

The submission contains data in support of an application to register a new chemical entity, liraglutide. Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analog that binds to and activates the GLP-1 receptor. Activation of the GLP-1 receptor potentiates glucose-dependent insulin secretion from the pancreatic beta cells, and lowers inappropriate high glucagon secretion, also in a glucose-dependent manner.

An important and possibly primary defect in type 2 diabetes may be an impaired incretin function. Treatment with a glucagon like peptide-1 (GLP-1) can help to compensate for this defect as GLP-1 has been shown to reduce hyperglycaemia in subjects with type 2 diabetes. Studies with native GLP-1 have shown that the primary mechanisms of action are 1) to stimulate insulin secretion and decrease glucagon secretion in a glucose-dependent manner, 2) delay gastric emptying, and 3) reduce appetite.

In addition, GLP-1 might be involved in preserving beta-cell mass and function. Like native GLP-1, the mechanism of action of liraglutide is mediated via a specific action on GLP-1 receptors. Already approved drugs with GLP-1 mediated mode-of-action include the GLP-1 receptor agonist exenatide and the orally administered DPP-IV inhibitors sitagliptin and vildagliptin.

Exenatide is administered twice daily by subcutaneous (SC) injections in relation to meals, whereas liraglutide is administered once daily SC for the convenience of the patient and to improve compliance. According to the proposed product information (PI), Victoza should be initiated with a daily dose of 0.6 mg for at least one week for all patients, after which the dose should be increased to 1.2 mg for one week. Maximal efficacy can be achieved at 1.8 mg. The dose is given daily, subcutaneously in the abdomen or thigh or upper arm, without linkage to meal times. The proposed indication is as follows:

Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.

Regulatory Status

A similar application to the current Australian submission was approved in the European Union (EU) on 30 June 2009, the USA (25 January 2010), Switzerland (11 December 2009) as well as Canada, New Zealand, Norway, Iceland, Japan, Mexico, Israel and Lebanon.

The approved indication in the EU is as follows:

Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

In combination with:

• *Metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea*

In combination with:

• *Metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy*

In the US, the indication is:

Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Product Information

The approved product information current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Structure

Liraglutide is a fragment of the naturally occurring human glucagon-like peptide-1 (GLP-1) sequence position 7-37 (GLP-1[7-37]) with substitution of the naturally occurring amino acid residue in position 34 (Lys [lysine]) by Arg [arginine] and with addition of a Glu [glutamic acid]-spaced hexadecanoic acid (palmitic acid) to the ε-amino group of Lys in position 26. The analog is produced using the recombinant DNA technology in Yeast (*Saccharomyces cerevisiae*) and further chemically modified by an addition of a Glu-spaced hexadecanoic (palmitic) acid as shown below. The structural formula $Arg^{34}Lys^{26}$-(N-e-(g-Glu (N-a-hexadecanoyl)))-GLP-1[7-37] is given in Figure 1. The molecular formula of liraglutide is $C_{172}H_{265}N_{43}O_{51}$. The theoretical molecular mass of liraglutide is 3751.20 Da.

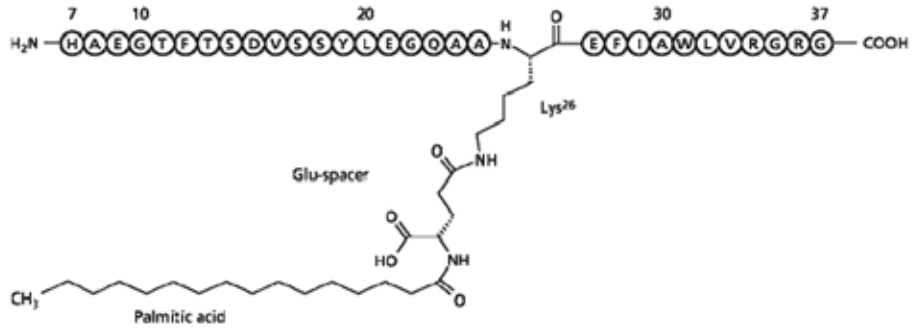


Figure 1 Structure of liraglutide

Manufacture

The liraglutide drug substance manufacturing process includes fermentation of yeast cells, recovery and purification. Purification includes precipitation, cation exchange chromatography and reverse phase chromatography. The precursor is then acylated and further purified to liraglutide drug substance through anion exchange chromatography, reverse phase chromatography, precipitation and freeze drying.

The *Saccharomyces cervisiae* strain YES2085 produces the liraglutide precursor. The strain is a transformant of *S. cervisiae* strain ME1719 containing the expression plasmid pKV308 engineered for expression of Arg^{34}-GLP-1[7-37] (the liraglutide precursor).

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and Chemical Properties

Potential product related impurities have been identified and structurally identified using N-terminal sequencing, mass spectrometry, peptide mapping, L-amino peptidase digestion and gas chromatography-mass spectrometry (GC-MS) as well as other standard analytical techniques. The impurities have been identified as truncated and extended forms, racemised and isomeric forms, glycosylated forms, aldehyde adducted forms, oxidised forms, high molecular weight forms and high molecular weight proteins. Four products are considered as liraglutide-related substances as they are structurally closely related to liraglutide and have

similar biological activity. These compounds are measured as impurities. All impurities have been safety qualified by early preclinical studies.[1]

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use, have been reviewed and are considered satisfactory. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life of 36 months at or below 18°C ± 2 °C ambient % RH for the drug substance. The real time data submitted to date support a shelf life of 36 months for the substance.

Drug Product

Formulation

Liraglutide 6.0 mg/mL, 3 mL cartridge is a clear, colourless solution containing liraglutide in a 3 mL cartridge. The pH of the product is 8.15. The excipients of liraglutide 6.0 mg/ml, 3 ml cartridge include disodium phosphate dihydrate (buffering agent), phenol (preservative), propylene glycol (tonicity agent), sodium hydroxide and hydrochloric acid (pH adjustment), Water for Injections (a solvent to make 1 mL).

The container closure system is a 3 mL glass cartridge. The closure for cartridge consists of a cap with a latex-free laminated rubber disc.

Manufacture

The excipients and liraglutide are dissolved in Water for Injections and mixed, pH is adjusted to 8.15 and the solution is sterile filtered. The finished bulk is filled aseptically into the final container.

Cartridges are washed in Water for Injections, siliconised, sterilised and depyrogenated in a tunnel at 300°C. Caps are washed in detergent and Water for Injections, sterilised by saturated steam pressure, heating to 121°C for 15 minutes. Plungers are cleaned and rinsed with Water for Injections, siliconised and sterilised by saturated steam under pressure, heating to 121°C for 15 minutes.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, were reviewed and were considered satisfactory. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data show the drug product in the primary container is sensitive to light while the pen-injector provides adequate protection of the drug product in the primary container. The proposed shelf life is 30 months when stored at 2 - 8°C. In-use stability data have also been submitted. The proposed shelf life and storage conditions

[1] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

for the opened product are 30 days when stored at or below 30°C. Liraglutide is light sensitive and needs to be protected from light and high temperatures during use.

The stability data support a shelf life of 30 months for 2-8°C and 1 month at 30°C for liraglutide drug product.

Bioavailability

In support of this submission, the company provided six bioavailability studies. Bioequivalence studies NN2211-1331, NN2211-1636 and NN2211-1693 only compared earlier formulations and did not use either the formulation proposed for supply or the other formulation used in the pivotal Phase III clinical studies as a reference treatment. For this reason they were not evaluated by the quality evaluator.

Study NN221-1149

This was a dose escalation pharmacokinetic study that also determined the absolute bioavailability of the subcutaneous (SC) injection. As it was not a cross-over study and the formulation of the product used was not that proposed for marketing, it was only summarised by the quality evaluator. It was concluded that the absolute bioavailability of SC liraglutide was 55% relative to an intravenous (IV) infusion and the liraglutide response shows linear increases in the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) with SC doses from 1.25 – 20 µg/kg to the abdomen.

Study NN2211-1745

This study compared a Formulation 4 product (concentration 6 mg/mL, drug substance Campaign 5A) at a dose of 0.60 mg administered subcutaneously into three separate sites (abdomen, thigh and upper arm). The bioavailability from the thigh was less than that from the upper arm which in turn was less than that from the abdomen. In fact the rate (C_{max}) and extent (AUC) of bioavailability from the thigh was not bioequivalent to that of the abdomen and the rate of bioavailability from the thigh was not bioequivalent to that of the upper arm (though the extents of bioavailability were equivalent). The rate and extent of bioavailability from the upper arm was bioequivalent to that of the abdomen.

Due to these results it was recommended to the Delegate that the reference to the thigh as a site of administration be removed from the PI unless there are other clinical data to support its inclusion.

Study NN2211-1692

This study compared an injection of Formulation 4 (concentration 6 mg/mL, drug substance Campaign 5A) with an injection of Formulation 4 (concentration 6 mg/mL, drug substance Campaign 6) at a dose of 120 mL[2] subcutaneously into the abdomen. Both of the products were used in the Phase III clinical trials and the second is identical to that proposed for marketing. After dose normalisation for the potency difference between the two products it was concluded that the two products were bioequivalent in terms of both rate and extent of absorption as measured by C_{max} and AUC respectively.

Consideration by PSC

Details of this submission were presented at the 126th meeting of the Pharmaceutical Subcommittee (PSC) of the Australian Drug Evaluation Committee (ADEC) in May 2009.

In relation to bioavailability, the Committee considered that the attention of the Delegate should be drawn to the fact that there is consistent lower exposure to the drug when

[2] Stated to be equivalent to 0.7044 mg of one treatment and 0.7296 mg of the other.

administered to the thigh compared to the abdomen. The PSC therefore concluded that in view of this lower drug exposure, reference to the thigh as a site of administration should either be deleted from the Product Information (PI) or a cautionary statement about the use of this site of injection be included in the PI.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

All outstanding issues regarding quality data and recommendations from the PSC have been addressed in a satisfactory manner. There were no outstanding issues regarding bioavailability, endotoxin content, pen performance, container safety or viral safety.

The absolute bioavailability of an old formulation was 55%. The two different formulations used in the clinical studies were bioequivalent and one of these can be considered identical to that proposed for registration.

However, the bioavailability from the thigh was less than that from the upper arm which in turn was less than that from the abdomen. Both the quality evaluator and the PSC wanted this fact brought to the attention of the Delegate in relation to statements in the PI about dosing in the thigh. Novo Nordisk presented data to contend that the differences in bioavailability were not of clinical significance for liraglutide, which were later accepted by the Delegate. Hence, the approved Product Information does not preclude the use of thigh as a site of administration.

As is usual for a new biological entity, it was recommended that batch release testing be a condition of registration for Victoza. The first five batches of Victoza imported into Australia may not be released for sale until: (1) samples of each batch have been tested and approved by the Office of Laboratories and Scientific Services (OLSS) of the TGA, and (2) the manufacturer's release data have been evaluated and approved by OLSS. These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The sponsor will also be required to provide evidence of satisfactory shipping conditions to Australia for every batch imported.

Three pens from each batch should be provided for testing by OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (together with their Certificates of Analysis) for method development and validation.

III. Nonclinical Findings

Introduction

This section summarises the nonclinical data that was submitted for Victoza. Following evaluation of the data originally submitted with the application for registration, Novo Nordisk submitted a supplementary data package to address the concerns that had been raised by the evaluator, primarily relating to carcinogenicity. The following pages firstly present the evaluation of the initial nonclinical data package (pages 9-23), followed by the evaluation of the supplementary nonclinical data package (pages 24-29). The reader is also referred to Section VI "Overall Conclusion and Risk/Benefit Assessment" for a more succinct description of the initial and supplementary nonclinical evaluations (pages 84-86), as well as the sponsor's reply to the supplementary evaluations (pages 97-98).

The nonclinical submission in support of liraglutide's registration as a new chemical entity was comprehensive and generally well presented, including the sponsor's written and tabulated summaries. Pivotal pharmacokinetic and toxicological studies were quality-assured and performed to contemporary standards and in compliance with Good Laboratory Practice (GLP).

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Glucagon-like peptide (GLP-1) is an incretin hormone secreted by intestinal L-cells and released into the bloodstream when food reaches the lower small intestine. Its actions (reviewed by Gautier *et al*., 2005 and Drucker, 2006) include stimulation of glucose-dependent insulin secretion by pancreatic β cells, stimulation of pancreatic β-cell proliferation, stimulation of insulin biosynthesis by pancreatic β cells, inhibition of glucagon secretion from pancreatic α cells and inhibition of gastric emptying.[3,4] GLP-1 exerts its effects by interacting with GLP-1 receptors on cell membranes. GLP-1 has a short duration of action (stemming from an *in vivo* half-life ($t_{½}$) of 1–2 minutes), making it unsuitable as a therapeutic agent.

Liraglutide is proposed as a once-daily treatment to improve glycaemic control in patients with type 2 diabetes mellitus. It exhibits 97% homology to human GLP-1, differing by substitution of lysine at position 34 with arginine, and attachment of palmitic acid via a glutamyl spacer to lysine at position 26. The therapeutic actions of liraglutide claimed by the sponsor are as follows:

- Liraglutide acts by specific interaction with GLP-1 receptors, leading to an increase in cAMP.
- The lipophilic palmitic acid substituent prolongs the duration of action of liraglutide compared with GLP-1 by binding to albumin (resulting in a longer $t_{½}$ in serum) and through oligomerisation of the molecule into heptamers (which delays absorption from the subcutis).
- Liraglutide stimulates insulin secretion and improves β-cell function (including restoration of sensitivity to glucose) in a glucose-dependent manner, thereby helping to lower blood glucose concentration.
- Liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner, resulting in lowered hepatic glucose production. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, when blood glucose is low, liraglutide does not suppress glucagon secretion and diminish insulin secretion.
- The mechanism of blood glucose lowering involves a minor delay in gastric emptying, slowing absorption of food after a meal.
- By reducing hunger and decreasing energy intake, liraglutide reduces body weight and body fat mass.

[3] Gautier JF, Fetita S, Sobngwi E, Salaün-Martin C. Biological actions of the incretins GIP and GLP-1 and therapeutic perspectives in patients with type 2 diabetes. Diabetes Metab 2005; 31: 233–242.
[4] Drucker DJ. The biology of incretin hormones. Cell Metab 2006; 3: 153–165.

Efficacy

Liraglutide displaced radiolabelled GLP-1 from human GLP-1 receptors with an median inhibitory concentration (IC_{50}) of 0.11 nM, compared with values of 0.35 nM for GLP-1 and 0.55 nM for exenatide (a peptide GLP-1 receptor agonist registered for the treatment of type 2 diabetes mellitus). Agonism of the receptor was demonstrated *in vitro* in functional assays, with liraglutide's potency at the recombinant human GLP-1 receptor about 25–100% of that of the endogenous ligand, GLP-1. Liraglutide's potency at the cynomolgus monkey and pig GLP-1 receptor was comparable to that at the human receptor; lower potency compared with humans was observed for the mouse and rabbit (both ~2-times lower) and rat (~3-times lower) receptor forms. The apparent potency of liraglutide was significantly reduced in the presence of albumin and plasma, consistent with the drug's extensive plasma protein binding (about 99% or greater). Self-association of liraglutide into heptamers, with the fatty acid moiety at the core of the complex, was shown to occur in solution at concentrations ≥1 µM. Stimulation of neonatal rat pancreatic β-cell proliferation, inhibition of neonatal rat β-cell apoptosis, and glucose-dependent stimulation of insulin secretion from mouse and rat pancreatic islets were demonstrated for liraglutide in other *in vitro* studies.

In *in vivo* studies utilising the clinical route of administration (SC), liraglutide was shown to:

Reduce blood glucose levels in animal models of diabetes
- — dose-dependent; shown in diabetic ob/ob mice (30–1000 µg/kg; 100 µg/kg twice daily [bd]), db/db mice (200 µg/kg bd), ZDF rats (660–6600 µg/kg) and gerbils (50–300 µg/kg/day);[5,6,7]
- — in diabetic mice, effects were largest on the first day of treatment (that is, 45% reductions in blood glucose area under the plasma concentration time curve from time zero to 24 hours [AUC_{0-24h}] were observed on day 1 of treatment, declining to 20–30% reductions after 8–15 days).

Improve glucose tolerance
- — reductions in blood glucose AUC following oral glucose challenge were shown in pre-diabetic ZDF rats (30–200 µg/kg twice daily [bd]; by 29–66%), diabetic ZDF rats (200 µg/kg bd; about 10%), obese Sprague Dawley (SD) rats (200 µg/kg bd; 6–21%), non-diabetic pigs (50–200 nmol/animal; about 15–50%) and diabetic mini-pigs (3.3 µg/kg/day; by about 25–40%); no effect was observed, however, in non-diabetic Zucker obese rats (150 µg/kg bd);
- — in cynomolgus monkeys, liraglutide (200 µg/kg) had little to no effect on the glycaemic excursion following IV glucose loading (bolus administration at 1 hour post-dose).

Increase plasma insulin levels
- — increases in basal insulin levels or AUC_{0-24h} were shown in diabetic ob/ob mice (100 µg/kg bd; by 60%), pre-diabetic ZDF rats (150 µg/kg bd; 3-times) and non-

[5] The ob/ob or obese mouse is a mutant mouse that eats excessively and becomes profoundly obese. It is an animal model of type II diabetes.

[6] The db/db mouse is a model of diabetes wherein leptin receptor activity is deficient because the mice are homozygous for a point mutation in the gene for the leptin receptor.

[7] The Zucker diabetic fatty (ZDF) rat is an inbred rat model that, through genetic mutation and a managed diet, will closely mimic human adult onset diabetes (Type 2) and related complications.

diabetic Zucker obese rats (150 µg/kg bd; by about 75%); no effect was observed in non-diabetic pigs (50–200 nmol/animal);
— greater increases in insulin AUC following oral glucose challenge were shown in pre-diabetic ZDF rats (30–150 µg/kg bd; by 1.8–3.5-times) and diabetic ZDF rats (200 µg/kg bd; by 32%); lower increases in insulin AUC following oral glucose challenge were observed in obese SD rats (200–300 µg/kg bd; 30–36% lower compared with controls), potentially reflecting increased insulin sensitivity.

Increase pancreatic β-cell proliferation and mass
— shown in diabetic ob/ob mice (100 µg/kg bd; 62% increase in β-cell proliferation rate and 22% increase in β-cell mass), diabetic db/db mice (200 µg/kg bd; 3-fold increase in proliferation rate and 1.5-fold increase in β-cell mass) and pre-diabetic ZDF rats (30–
150 µg/kg bd; 30–78% increase in proliferation rate and a 2-fold increase in β-cell mass).

Inhibit gastric emptying
— shown in diabetic mini-pigs (3.3 µg/kg/day; by about 20–50%).

Reduce food consumption and decrease body weight
— routinely seen in the nonclinical efficacy studies using animal models of diabetes/obesity as well as in the laboratory animal species used in the toxicology studies, with effects greatest at the onset of treatment and becoming less marked with time;
— in addition, altered food preference (a favouring of standard chow over candy) was observed in obese SD rats.

With IV administration in diabetic mini-pigs, liraglutide (15 nmol) was seen to stimulate insulin secretion, suppress glucagon production and enhance glucose utilisation during glucose infusion.

No additive or synergistic effects on blood glucose $AUC_{0–24\,h}$ were observed for the combination of liraglutide (100 µg/kg SC bd) and metformin (125 mg/kg orally bd) in diabetic ob/ob mice. Oral glucose tolerance was further improved in liraglutide-treated diabetic ZDF rats (200 µg/kg SC bd) when combined with either pioglitazone (5 mg/kg orally bd) or atorvastatin (30 mg/kg orally bd). *In vitro*, additive stimulation of insulin secretion was shown for liraglutide combined with glipizide in the isolated rat pancreas.

Secondary pharmacodynamics and safety pharmacology

No significant secondary pharmacological activities were found for liraglutide in screening assays encompassing a wide range of receptors and ion channels.

Safety pharmacology studies assessed potential effects of liraglutide on the nervous, cardiovascular, renal, gastrointestinal and respiratory systems. Studies were designed to contemporary International Conference on Harmonization (ICH) guidelines, were GLP-compliant with the exception of a cardiovascular safety study in swine and a neurotoxicity study in rats, and were adequately conducted.

Central nervous system (CNS) function was unaffected in mice dosed at up to 2 mg/kg SC (relative exposure based on animal:human C_{max}, 13; calculated using a reference value for the clinical C_{max} of 45 nM, as obtained at the maximum recommended human dose in Clinical Study NN2211-1608). Diabetic rats treated with liraglutide at 200 µg/kg SC bid for 6 weeks

(as monotherapy or in combination with either pioglitazone or atorvastatin) displayed 7–10% reductions in caudal sensory velocity compared with untreated diabetic controls; relative exposure at this dose (based on AUC) is estimated to be about 4. F-wave latency, tibial motor amplitude, motor conduction velocity and caudal sensory amplitude were unaffected.

Liraglutide did not inhibit hERG tail current in transfected mammalian cells, or cause arrhythmia or abnormal electrocardiogram (ECG) or mean arterial pressure (MAP) waveforms in isolated perfused rabbit hearts at concentrations up to 1.4 µM (>30-times the clinical C_{max}); this concentration elicited a 6% increase in heart rate *in vitro*. *In vivo*, SC doses of 0.2 and 2 mg/kg (yielding plasma C_{max} values 1.6 and 23-times higher than the clinical C_{max}) caused a 25% increase in heart rate and similar sized increases in systolic, diastolic and mean blood pressure in rats. Heart rate and cardiac output were elevated by about 25% in pigs treated at 10 µg/kg/day for 3 days (relative exposure based on C_{max}, 0.3); blood pressure and vascular resistance were not affected. No effects on cardiovascular parameters were observed, however, in cynomolgus monkeys at SC doses of up to 2 mg/kg (estimated relative exposure based on C_{max}, >15); there were also no effects on ECG in a 12-month repeat-dose toxicity study in cynomolgus monkeys at up to 5 mg/kg/day (relative exposure, about 80).

Liraglutide caused diuresis and increased excretion of Na^+ and Cl^- ions in rats dosed at ≥0.02 mg/kg SC, together with enhanced K^+ excretion at ≥0.2 mg/kg and proteinuria and decreased urinary gamma-glutamyl transferase (GGT) activity at 2 mg/kg (estimated relative exposure based on C_{max}, 0.1, 1.6 and 23 at the respective dose levels [based on pharmacokinetic data from Study NN990268]). Diuresis and disturbances in Na^+ and K^+ excretion were also observed in a 10-day pharmacology study in rats (at 0.1 and 0.2 mg/kg/day bid). Diuresis was also observed in some of the repeat-dose toxicity studies in rodents but not in monkeys. GLP-1 is recognised to increase urine output and Na^+ excretion in rats (Tang-Christensen *et al*, 1996).[8]

Pharmacokinetics

Absorption of liraglutide following SC injection was slow, with typical time to maximal plasma concentrations (T_{max}) values of 6 hours in mice, 4–8 hours in rats, about 8 hours in rabbits and cynomolgus monkeys, 7 hours in pigs and 12 hours in humans. It is likely that the self association of liraglutide, observed *in vitro*, plays a role in slowing absorption. Bioavailability by the SC route was about 55% in both monkeys and humans, and 76% in pigs. Exposure was dose-proportional or slightly greater than dose-proportional in all species after single and repeated dosing. Sex differences were only seen in mice, with exposure tending to be lower in females compared with males. Plasma half-lives were about 5 hours in mice, 6 hours in rats, 8 hours in rabbits and monkeys, 14 hours in pigs and 12 hours in humans. Accumulation with repeat-daily dosing was not observed in mice, rats or monkeys, except for about a 45% increase in plasma $AUC_{0–24h}$ in mice at the highest dose in a 2-year carcinogenicity study. There was a 1.5-fold accumulation in humans as expected based on the longer half-life and dosing frequency. Decreased exposure was evident at the end of a 12-month study in monkeys treated at 5 mg/kg/day. This may have arisen from injection site changes (inflammation, subcutaneous thickening or swelling).

Liraglutide displayed high to very high plasma protein binding, with 95.8–99.8% of the drug bound in rat plasma, ≥99.3% bound in mouse, rabbit, pig and monkey plasma, and 98.7–

[8] Tang-Christensen M, Larsen PJ, Göke R, Fink-Jensen A, Jessop DS, Møller M, Sheikh SP. Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats. Am J Physiol 1996; 271: R848–R856.

99.8% bound in human plasma. Tissue distribution was studied in rats using ^{3}H-, ^{14}C- and ^{125}I-labelled forms of liraglutide. The pattern of distribution observed varied according to the position of radiolabelling. Peak tissue levels of radioactivity were generally observed at 4–24 hours post-dose. Highest levels of radioactivity occurred in well vascularised organs such as the liver, lung, kidneys, adrenal gland, preputial gland and ovary, consistent with high plasma protein binding. Penetration across the blood-brain barrier was poor. Microhistoautoradiography indicated that radioactivity, derived from ^{3}H-[tyrosine]-liraglutide, was not accumulated into any specific region of the thyroid or pancreas, except blood vessels. Radioactivity remained detectable in many tissues at late time-points (120–168 hours post-dose), consistent with metabolism of the parent drug into amino acid/lipid constituents that enter the general metabolic pool.

Metabolism of liraglutide involves cleavage of the peptide chain and degradation of the palmitic acid component. The drug, like GLP-1, is a substrate for dipeptidyl peptidase-IV (DPP-4) and neutral endopeptidase (NEP). These enzymes are both expressed widely, with DPP-4 also present as a circulating form in plasma. Consequently, metabolism of liraglutide *in vivo* probably involves multiple organs. *In vitro*, liraglutide was metabolised slowly but extensively when incubated with mouse, rat, cynomolgus monkey or human hepatocytes. The initial cleavage site was at the 18–19, 19–20, 27–28 or 28–29 position of the peptide chain; further cleavage gave rise to an array of shorter peptides. Liraglutide was metabolised by hepatocytes and recombinant DPP-4 and NEP significantly more slowly than was GLP-1. Intact liraglutide was the dominant circulating species in humans and the laboratory animal species. Two plasma metabolites were identified in humans. The major one, liraglutide (9–37), represents the cleavage product generated by DPP-4 and was also present in all of the experimental species; it only very weakly interacts with the GLP-1 receptor. The second one was also present in the rat. No liraglutide was excreted intact. Excretion of liraglutide degradation products involved urinary and faecal routes. A highly similar pattern of excretion was observed in humans and monkeys following dosing with ^{3}H-[palmitic acid]-liraglutide.

Pharmacokinetic drug interactions

Liraglutide displayed no significant inhibitory activity against human cytochrome P450 (CYP) isoforms 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 *in vitro* (IC_{50} values >>100 µM; that is, >2000-times the clinical C_{max}). The drug did not induce hepatic CYPs in rats treated at up to 1 mg/kg/day SC for 4 weeks (relative exposure based on AUC, 11) although CYP2A1 activity was seen to be halved in males at this dose. The extent of protein binding by liraglutide in human plasma was not significantly affected by acenocoumarol, phenprocoumon, metformin, acetylsalicylic acid, diazepam, ethanol, furosemide, glibenclamide, nicardipine, pioglitazone, rosiglitazone, repaglinide, tolbutamide, valproic acid, warfarin, myristic acid or palmitic acid.

The sponsor proposed the use of liraglutide in combination with metformin, a sulfonylurea and/or a thiazolidinedione. The potential for pharmacokinetic interactions between liraglutide and these other agents was not examined *in vivo* in laboratory animal species.

Relative exposure

Relative exposure levels in toxicology studies have been calculated based on animal:human plasma $AUC_{0–24h}$ values for liraglutide (Table 1). A human reference $AUC_{0–24h}$ of 809 nmol·h/L has been used, drawn from Clinical Study NN2211-1608 in which liraglutide was administered SC to healthy subjects at 0.6 mg/day for 7 days, 1.2 mg/day for 7 days then 1.8 mg/day (the maximum recommended human dose) for 21 days. Tabulated AUC values

are means for the sexes combined (except in mice where a sex difference in exposure exists) on the final sampling day.

Table 1: Relative Exposure

Study		Dose (mg/kg/day); SC	AUC_{0-24h} (nmol·h/L)		Relative exposure	
			M	F	M	F
NN205050	**Mouse** (CD-1); 3-day mechanistic	0.06	576	–	0.7	–
		0.25	2920	–	3.6	–
NN203261	**Mouse** (CD-1); 4-week	0.1	992	632	1.2	0.8
		0.5	5462	3411	6.8	4.2
		1	12758	6509	16	8.0
		5	71417	43801	88	54
204268	**Mouse** (CD-1); 2- & 9-week mechanistic	0.2	1876[a]	2042[a]	2.3	2.5
		5	74212[a]	62857[a]	92	78
NN204082	**Mouse** (CD-1); 3-month	0.2	1876	2042	2.3	2.5
		1	11854	18592	15	23
		5	74212	62857	92	78
NN204229	**Mouse** (CD-1); 2-year carcinogenicity	0.03	203	168	0.3	0.2
		0.2	1587	1415	2.0	1.7
		1	10090	6215	12	7.7
		3	36380	37280	45	46

Study		Dose (mg/kg/day); SC	AUC_{0-24h} (nmol·h/L)		Relative exposure	
			M	F	M	F
NN980180	**Rat** (SD); 7-day	0.125	1020		1.3	
		0.25	2603		3.2	
		1	5959		7.4	
NN980183	**Rat** (SD); 4-week	0.1	505		0.6	
		0.25	2200		2.7	
		1	9074		11	
NN205092	**Rat** (SD); 4-week [impurity]	1 (old formulation)	5100		6.3	
		1 (new formulation)	4784		5.9	
203317	**Rat** (SD); 6-week mechanistic	0.75	6600[b]		8.2	
NN980189	**Rat** (SD); 3-month	0.1	754		0.9	
		0.25	3088		3.8	
		1	10698		13	
NN200239	**Rat** (SD); 6-month	0.1	481		0.6	
		0.25	1585		2.0	
		1	6240		7.7	
NN200240	**Rat** (SD); 2-year carcinogenicity	0.075	380		0.5	
		0.25	1785		2.2	
		0.75	6225		7.7	
204163	**Rat** (SD); 16-month mechanistic	0.075	380[c]		0.5	
		0.25	1785[c]		2.2	

Study		Dose (mg/kg/day); SC	$AUC_{0\text{-}24h}$ (nmol·h/L)		Relative exposure	
			M	F	M	F
		0.75	6225[c]		7.7	
NN980186	**Rat** (SD); fertility/development [pilot]	0.1	754[d]	691	0.9	0.9
		0.25	3088[d]	2693	3.8	3.3
		1	10698[d]	9211	13	11
NN990284	**Rat** (SD); fertility/development [main]	0.1	754[d]	691[e]	0.9	0.9
		0.25	3088[d]	2693[e]	3.8	3.3
		1	10698[d]	9211[e]	13	11
NN201109	**Rat** (SD); postnatal development	0.1	–	691[e]	–	0.9
		0.25	–	2693[e]	–	3.3
		1	–	9211[e]	–	11
NN980188	**Rabbit** (NZW); embryofetal development [pilot]	0.01	–	148	–	0.2
		0.03	–	280	–	0.3
		0.1	–	766	–	0.9
NN990055	**Rabbit** (NZW); embryofetal development [main]	0.01	–	148[f]	–	0.2
		0.025	–	233[f]	–	0.3
		0.05	–	383[f]	–	0.5
NN980149	**Monkey** (Cynomolgus); 3-day	0.1	2627		3.2	
		2.5	30933		38	
		5	69158		85	
NN980181	**Monkey** (Cynomolgus); 14-day	4	57148		71	
NN980184	**Monkey** (Cynomolgus); 4-week	0.05	202		0.2	
		0.5	1858		2.3	
		5	25160		31	
NN200241	**Monkey** (Cynomolgus); 12-month	0.05	817		1	
		0.5	7020		8.7	
		5	59200		73	
203262	**Monkey** (Cynomolgus); 20-month mechanistic	0.25	7163		8.9	
		5	52120		64	

– = Not applicable [a] = From study NN204082 [b] = From study NN980183 [c] = From study NN200240
[d] = From study NN980189 [e] = Estimated from study NN980186 [f] = Extrapolated from study NN980188

Toxicology

Large multiples of the clinical AUC were obtained at the upper dose levels used in the studies, with the exception of developmental studies in rabbits (where exposure was subclinical). All repeat-dose studies were performed via the SC route; single-dose studies used the SC and IV routes. Study design and reporting were generally of an adequate standard.

Acute toxicity

No mortality occurred in the single-dose studies, conducted in mice and rats (≤20 mg/kg SC and IV) and cynomolgus monkeys (5 mg/kg SC and IV). The maximum SC doses tested would have given exposures ≥100-times greater than clinical levels, based on AUC and C_{max}. Liraglutide caused decreased body weight (in all species), decreased food consumption (mice

and rats), and postural hunching, stained fur and piloerection (rats only). No treatment-related gross pathological abnormalities were found.

Repeat-dose toxicity

Studies of up to 13 weeks duration were conducted in mice, 26 weeks in rats and 52 weeks in cynomolgus monkeys. The duration of the pivotal studies, the species used (rats and cynomolgus monkeys), group sizes and the use of both sexes were consistent with ICH guidelines.

In line with therapeutic claims made by the sponsor, decreases in food consumption and loss of body weight were seen at the beginning of all toxicity studies. Food consumption, though, tended to return fully or partially to pre-treatment values after the initial few days or weeks on-study. Bodyweight deficits compared with controls often persisted for the entire treatment phase. The high-dose levels used in the pivotal studies suppressed body weight gain by up to 19% in rats and 50% in monkeys. Following the withdrawal of treatment, food consumption and body weight gain either matched or exceeded the levels of controls.

Thyroid C-cell hyperplasia was observed in mice at all doses tested in the 3-month study (≥0.2 mg/kg/day; relative exposure, ≥2.3). Thyroid C-cell changes are discussed below under *Carcinogenicity*.

Increased incidences of hepatic centrilobular hypertrophy (in males) and Kupffer cell pigmentation (in females) occurred at≥0.03 and ≥1 mg/kg/day, respectively (relative exposure levels, 0.3 and 7.7) in the 2-year carcinogenicity study in mice. There was no No Observable Effect Level (NOEL) for hypertrophy, while abnormal cell pigmentation was not seen at 0.03 mg/kg/day. In a 4-week study in rats, there were mild increases in the severity of periportal fat vacuolation at ≥0.25 mg/kg/day (relative exposure, 2.7) and the severity of hepatic inflammatory cell infiltration at 1 mg/kg/day (relative exposure, 11), accompanied by slight increases in plasma alanine transferase (ALT), aspartate transferase (AST) and alkaline phosphatase (ALP) activities. Plasma ALP and ALT activities were also elevated in the 3-month rat study at ≥0.1 and ≥0.25 mg/kg/day, respectively (relative exposure levels, ≥0.9 and ≥3.8) but there were no associated histological abnormalities. There were no similar effects in the rat 6-month and lifetime carcinogenicity studies (highest doses of 1 and 0.75 mg/kg/day in the respective studies; relative exposure,≤7.7). Monkeys in the 12-month study showed a slight increase in total bilirubin concentration at the highest dose of 5 mg/kg/day (relative exposure, 73) but not at lower doses (relative exposure, ≤8.7), and no liver histopathological changes at any dose. The relatively high safety margin in monkeys and inconsistency of effects in rodent species suggests that liraglutide is unlikely to be hepatotoxic at the normal clinical exposure levels.

As discussed under *Safety Pharmacology* above, liraglutide caused diuresis and increased urinary excretion of electrolytes in safety and primary pharmacology studies in rats. Similar effects were also seen in some of the rodent toxicity studies, but not consistently. Rats receiving 1 mg/kg/day (relative exposure, 13) in the 3-month study displayed a decrease in urinary specific gravity. There was increased urine volume, with increased Mg^{2+} and phosphate concentrations, in mice treated at ≥1 mg/kg/day for 4 weeks (relative exposure, ≥8.0), and diuresis with increased Na^{+} concentration occurred on day 1 (but not at the end) of the 3-month mouse study. No significant effects on urinalysis parameters were observed in the pivotal rat study (relative exposure, ≤7.7), nor in any of the monkey studies (relative exposure, ≤85). Renal histopathological changes were only observed in the rat

carcinogenicity study. These comprised increases in the incidence/severity of mineralisation at ≥0.075 mg/kg/day (relative exposure, ≥0.5) and diffuse transitional cell hyperplasia at ≥0.25 mg/kg/day (relative exposure, ≥2.2) in males. These are common lesions in aging male rats and are not necessarily associated with effects on urine volume and electrolyte excretion; urinalysis was not examined in the rat carcinogenicity study. The diuretic effect of liraglutide in rodents is consistent with a pharmacological effect rather than a toxicological one.

Behavioural changes, including rolling or high-stepping gait, were observed during the initial days or weeks of treatment in many of the rat studies (general and reproductive toxicity) at 0.25 or, more usually, 1 mg/kg/day (relative exposure, 3.3–13). The effect, however, progressively diminished with time and was no longer present by termination. Histopathological changes in nervous tissue did not occur, and there were no effects on behaviour in mice or cynomolgus monkeys treated at≤5 mg/kg/day (relative exposure, ≤92 and ≤85 in the respective species). The gait disturbances in rats may represent a response to discomfort rather than neurotoxicity, a view supported by the absence of progression as well as the drug's poor penetration into the CNS.

Reductions in red blood cell (RBC) count, haematocrit and/or haemoglobin were observed in some of the repeat-dose studies in mice, rats and monkeys. Changes from controls were relatively minor and probably of little physiological significance. There were no bone marrow abnormalities nor was there evidence of haemolysis.

Although the pancreas is a principal site of liraglutide's pharmacological activity, there were few effects on this organ apparent in the repeat-dose toxicity studies. Pancreatic inflammatory cell infiltration was increased at 3 mg/kg/day in the mouse carcinogenicity study (relative exposure, 45) but not at 1 mg/kg/day (relative exposure, 7.7–12). Absolute and bodyweight-relative pancreas weight was increased in the 12-month monkey study at doses ≥0.5 mg/kg/day (relative exposure, ≥8.7), but the histological appearance and cellular structure of the tissue were normal. No pancreatic abnormalities were observed in rats treated with liraglutide (relative exposure, ≤7.7 in the pivotal repeat -dose and carcinogenicity studies).

In the 2-year rat carcinogenicity study, males displayed increases in the incidence of adrenal medullary cell focal hyperplasia and cortical cell vacuolation (at 0.75 mg/kg/day; relative exposure, 7.7) and cortical cell hypertrophy with degeneration (at≥0.075 mg/kg/day; relative exposure, ≥0.5). These abnormalities were not present with increased incidence in females and are consistent with stress. No effects on the adrenals were noted in mice (relative exposure, ≤46 in the carcinogenicity study) or cynomolgus monkeys (relative exposure, ≤73 in the 12-month study).

Toxicity in combination with other anti-diabetic agents

Potential toxic interactions between liraglutide and the other anti-diabetic agents proposed for co-therapy were not investigated in nonclinical studies.

Genotoxicity

The potential genotoxicity of liraglutide has been examined in an adequate range of validated, GLP-compliant studies. These comprised assays for gene mutation in bacteria, chromosomal aberration in cultured human lymphocytes, and chromosomal aberration in rat bone marrow and lymphocytes *in vivo*. Concentrations/doses used were appropriate, and a suitable set of *S. typhimurium* and *E. coli* strains was used in the bacterial gene mutation assay. Liraglutide was negative in all tests.

Carcinogenicity

The carcinogenic potential of liraglutide by the SC route was investigated in 2-year studies in mice and rats. The studies were appropriately designed and conducted. Exposure at the highest dose in the mouse study was a very large multiple of the clinical exposure level (46-times). A more modest exposure ratio was obtained at the high-dose level in the rat study (7.7-times), with doses being limited by excessive suppression of body weight gain.

Carcinogenic activity in the thyroid gland was evident in both species. In the mouse study, C-cell adenomas occurred at ≥1 mg/kg/day (relative exposure, ≥7.7) in both sexes, and C-cell carcinomas were observed in females at 3 mg/kg/day (relative exposure, 46). In addition, focal C-cell hyperplasia (considered a pre-neoplastic lesion) was seen at ≥0.2 mg/kg/day in both sexes (relative exposure, ≥1.7). A dose-related progression from focal hyperplasia, to adenoma and then carcinoma is clear (Table 2). Exposure ratios at the NOELs for C-cell focal hyperplasia and neoplasia are 0.3 (0.03 mg/kg/day) and 2.0 (0.2 mg/kg/day), respectively. Spontaneous proliferative C-cell lesions are uncommon in mice; none were seen in concurrent controls. Historical control data for 2-year studies in CD-1 mice indicate incidences of 0.5% for C-cell hyperplasia (Madsen *et al.*, 2008; reporting data for the study laboratory) and ≤0.07% for C-cell adenomas and carcinomas (data compiled by the animal supplier).[9]

[9] Madsen LW et al. Liraglutide. Rodent C-cell findings: Assessment of human relevance. Novo Nordisk A/S, Malov, Denmark. 28 February, 2008.

Table 2: Incidence of proliferative C-cell lesions in CD-1 mice (2-year carcinogenicity study with liraglutide SC)

Dose (mg/kg/day)	Males					Females				
	0	**0.03**	**0.2**	**1**	**3**	**0**	**0.03**	**0.2**	**1**	**3**
Focal C-cell hyperplasia	0/79 [0%]	0/66 [0%]	**1/65 [1.5%]**	**11/67 [16%]**	**30/79 [38%]**	0/75 [0%]	0/66 [0%]	**7/67 [10%]**	**10/66 [15%]**	**22/76 [28%]**
C-cell adenoma	0/79 [0%]	0/66 [0%]	0/65 [0%]	**9/67 [13%]**	**15/79 [19%]**	0/75 [0%]	0/66 [0%]	0/67 [0%]	**4/66 [6%]**	**15/76 [20%]**
C-cell carcinoma	0/79 [0%]	0/66 [0%]	0/65 [0%]	0/67 [0%]	0/79 [0%]	0/75 [0%]	0/66 [0%]	0/67 [0%]	0/66 [0%]	**2/76 [2.6%]**
Relative exposure	–	0.3	2.0	12	45	–	0.2	1.7	7.7	46

Values shown in bold represent incidences significantly greater than that of concurrent controls (p<0.05) and/or exceeding historical control levels.

Similarly, in rats, dose-related increases in the incidence and severity of focal C-cell hyperplasia, and the incidences of C-cell adenoma and carcinoma were seen at all dose levels (relative exposure, ≥0.5; Table 3). [Note that unlike the mouse, spontaneous, age-related C-cell proliferative lesions are common in the rat]. The first cases of C-cell focal hyperplasia, adenoma and carcinoma were observed in premature decedents after about 40, 47 and 86 weeks of treatment, respectively. Consistent with this, no C-cell proliferative lesions were observed in the 26-week repeat-dose toxicity study in rats, which involved dosing up to same exposure level as in the carcinogenicity study.

Table 3: Incidence of proliferative C-cell lesions in SD rats (2-year carcinogenicity study with liraglutide SC)

Dose (mg/kg/day)	Males				Females			
	0	**0.075**	**0.25**	**0.75**	**0**	**0.075**	**0.25**	**0.75**
Focal C-cell hyperplasia	11/50 [22%]	**14/49 [29%]**	**20/50 [40%]**	**24/50 [48%]**	14/50 [28%]	14/49 [29%]	**27/49 [55%]**	**24/50 [48%]**
C-cell adenoma	6/50 [12%]	**8/49 [16%]**	**21/50 [42%]**	**23/50 [46%]**	5/50 [10%]	**13/49 [27%]**	**16/49 [33%]**	**28/50 [56%]**
C-cell carcinoma	1/50 [2%]	**4/49 [8%]**	**3/50 [6%]**	**7/50 [14%]**	0/50 [0%]	0/49 [0%]	**2/49 [4%]**	**3/50 [6%]**
Relative exposure	–	0.5	2.2	7.7	–	0.5	2.2	7.7

Values shown in bold represent incidences significantly greater than that of concurrent controls (p<0.05) and/or exceeding historical control levels.

Relative exposure at the NOEL for C-cell neoplasia in exenatide-treated rats is 23; for liraglutide it is <0.5.

The sponsor conducted a large number of mechanistic studies and proposed a mode-of-action hypothesis to account for the formation of C-cell tumours in mice and rats (presented in the position paper by Madsen *et al*., 2008), concluding that the C-cell neoplasia induced by liraglutide in rodents is not relevant to humans.[8] The proposed mode of action is:

Liraglutide activates GLP-1 receptors on thyroid C-cells;

GLP-1 receptor activation induces the release of calcitonin from C-cells;

Continued calcitonin release leads to increased calcitonin synthesis;

Persistent stimulation of calcitonin synthesis gives rise to C-cell hyperplasia; and
C-cell hyperplasia leads to C-cell neoplasia.

In vitro mechanistic studies showed apparent GLP-1 receptor expression on C-cells in normal mouse, rat, cynomolgus monkey and human thyroid tissue. Levels of GLP-1 receptor mRNA were low in C-cells from mouse and rat thyroid tissue samples, and below the limit of detection in human and monkey thyroid C-cells. In experiments using thyroid C-cell carcinoma-derived cell lines, GLP-1 receptor protein and mRNA were found at higher levels in two rat cells lines compared with a human cell line. The two rat cell lines showed cAMP accumulation and release of calcitonin in response to GLP-1 receptor activation, while four human C-cell carcinoma cell lines showed low or no cAMP accumulation and no calcitonin release in response to GLP-1 receptor agonists.

In vivo, liraglutide (≥0.2 mg/kg/day) increased plasma calcitonin in a dose-dependent fashion in CD-1 mice after a single dose, 2 or 9 weeks treatment, 13 weeks treatment and persistently throughout the 2-year mouse carcinogenicity study (assessed at 26, 52 and 104 weeks). Calcitonin mRNA levels were increased in the thyroids of mice treated at 0.2 or 5 mg/kg/day for 2 weeks, and focal C-cell hyperplasia was observed after 9 weeks of treatment at these doses (relative exposure, ≥2.3). In rats, treatment at 0.75 mg/kg/day produced a significant increase in plasma calcitonin levels at 4 and 5 weeks; thyroid calcitonin mRNA was significantly reduced after a single dose (with no significant change in thyroid calcitonin peptide levels), and was not significantly different from controls after 4 weeks of treatment (observed together with a reduction in thyroid calcitonin content). A study in aged and young rats, involving dosing for up to 10 and 16 months, respectively, revealed significant, dose-dependent increases in plasma calcitonin levels after 4 weeks of treatment at 0.075–0.75 mg/kg/day; the effect did not persist, however. In young rats, no significant increases in plasma calcitonin were seen subsequently (assessed at 3 month intervals); in fact, plasma calcitonin levels were actually significantly lower than controls at 4 and 7 months. In aged rats, increases in plasma calcitonin were observed only sporadically beyond the first month of treatment (and these did not display a dose-relationship); there were no significant increases in plasma calcitonin at 10 months. The study showed that liraglutide (0.75 mg/kg/day) increased focal C-cell hyperplasia and accelerated the progression from focal C-cell hyperplasia to adenoma; adenomas were first observed after 7 months of treatment irrespective of animal age. A 20-month mechanistic study in cynomolgus monkeys showed no effect of liraglutide (≤5 mg/kg/day; relative exposure, ≤64) on plasma calcitonin levels after single or repeat dosing, and no thyroid C-cell lesions. There were also no changes in thyroid histology observed in the 12-month general repeat-dose toxicity study in cynomolgus monkeys (relative exposure, ≤73). Implicating the involvement of sustained GLP-1 receptor agonism, continuous infusion of exenatide — but not single daily bolus injection — increased the incidence of C-cell hyperplasia in mice treated at 0.25 mg/kg/day for 12–16 weeks.

As discussed below, the initial data package does not support the sponsor's proposed mechanism nor the dismissal of the findings as not relevant to humans.

No increase in *diffuse* C-cell hyperplasia was seen in rodents treated with liraglutide. C-cell proliferation in response to increased physiological demand for calcitonin would be expected to initially appear as increased diffuse hyperplasia rather than increased focal (that is, nodular) hyperplasia, as found for liraglutide. Also, therefore, the pattern of C-cell lesion development induced by liraglutide is dissimilar to the progression from diffuse hyperplasia (physiological), to focal hyperplasia (pre-neoplastic), to adenoma (benign) and then

carcinoma (malignant) that characterises spontaneous C-cell tumour development in aged rats (DeLellis *et al*., 1979; Martín-Lacave *et al*., 2002).[10,11] The absence of an increase in diffuse C-cell hyperplasia in mice and rats, the induction of focal C-cell hyperplasia in the mouse (a species with a very low background level of spontaneous C-cell hyperplasia), and the equal latencies for C-cell adenoma observed in young and aged rats (that is, the speed of their development is independent of the background level of spontaneous hyperplasia) indicate that liraglutide transforms normal (non-hyperplastic) C cells.

Liraglutide caused a persistent increase in plasma calcitonin levels in mice, but only a transient increase in calcitonin in rats. The 16-month mechanistic study in rats shows that increased focal C-cell hyperplasia and progression to adenoma with liraglutide occurred in the absence of any sustained increase in calcitonin synthesis/release (in aged rats) or an actual decrease in calcitonin (young rats).

The sponsor has argued against the human relevance of the proposed mechanism on the basis of *in vitro* data showing that GLP-1 receptor agonists do not stimulate calcitonin release from human C-cell cell lines (as opposed to rat cell lines) and *in vivo* data showing an absence of increased plasma calcitonin and C-cell lesions in monkeys treated with liraglutide for 20 months. The cell lines used were derived from C-cell carcinomas, and may not be good models for normal C cells. Increased plasma calcitonin has been observed in clinical trial participants treated with liraglutide for 26 weeks, so if the proposed mechanism is correct, it may indeed be applicable to humans. Given that treatment-related proliferative C-cell lesions were not observed until 40 weeks of treatment in rats, and that this represents a substantially longer fraction of the animals' life span than 20 months does in a cynomolgus monkey, the absence of C-cell lesions in monkeys is not fully reassuring with regard to an absence of human relevance for the C-cell tumours induced by liraglutide in rodents. The GLP-1 receptor can couple to signalling pathways that regulate cell survival and growth. The sponsor has investigated the mitogenicity of liraglutide in one human and two rat C-cell carcinoma cell lines, with no stimulation of proliferation observed; there has been no examination of the drug's mitogenicity in cultured normal thyroid C cells, however (human or other species).

The reader is referred to the evaluation of the supplementary nonclinical data package (pages 24-29) which was submitted by Novo Nordisk in response to the concerns raised above by the evaluator. The reader is also referred to Section VI "Overall Conclusion and Risk/Benefit Assessment" for a more succinct description of the initial and supplementary nonclinical evaluations (pages 84-86), as well as the Applicant's reply to the supplementary evaluations (pages 97-98).

Reproductive toxicity

The submission included reproductive toxicity studies covering all stages (fertility, embryofetal development and pre- and post-natal development). Adequate supportive toxicokinetic data were provided also. Study designs were appropriate, but exposure levels achieved in the rabbit studies did not exceed the clinical level, with doses limited by the apparently high sensitivity of rabbits to the appetite suppressing effect of the drug.

[10] DeLellis RA, Nunnemacher G, Bitman WR et al. C-cell hyperplasia and medullary thyroid carcinoma in the rat. An immunohistochemical and ultrastructural analysis. Lab Invest 1979; 40: 140–154.

[11] Martín-Lacave I, Rojas F, Bernabé R et al. Comparative immunohistochemical study of normal, hyperplastic and neoplastic C cells of the rat thyroid gland. Cell Tissue Res 2002; 309: 361–368.

Limited placental transfer of liraglutide and/or its metabolites was demonstrated in rats and rabbits. Drug and/or metabolite levels in rat fetal tissue were≤15% of the C_{max} in maternal plasma and tissues, and peak levels in rat amniotic fluid were≤3% of the maternal plasma C_{max}. In rabbits, drug concentrations in amniotic fluid and fetal plasma did not exceed 6.5% of maternal plasma levels. Excretion of liraglutide (and 5 metabolites) in milk was demonstrated in rats. A suckling pup was estimated to receive ≤3% of the maternal dose.

Male and female fertility and mating performance were unimpaired in rats treated at ≤1 mg/kg/day (relative exposure, 11 [female] and 13 [male]).

In the rat embryofetal development study, there was an approximate doubling in the level of post-implantation loss (reflecting increased early embryonic deaths) and an increased incidence of a minor skeletal abnormality (kinked ribs) with treatment at 1 mg/kg/day (relative exposure, 11); this dose was maternotoxic (based on 23% inhibition of maternal body weight gain over GD0–17 compared with controls). The NOEL for embryofetal toxicity in rats is 0.25 mg/kg/day (relative exposure, 3.3). In rabbits, embryofetal survival was not compromised, but slight retardation of fetal growth and increased incidences of several minor skeletal and visceral abnormalities (bilobed or bifurcated gall bladder, supernumerary ribs and jugals connected/fused to maxilla) were observed at all doses tested (≥0.01 mg/kg/day; relative exposure, 0.2). Connected parietal bones, a malformation, was observed in five fetuses (all from the same litter) at 0.05 mg/kg/day (relative exposure, 0.5). However, as only a single litter was affected, there is insufficient evidence to conclude that the finding is related to treatment. The effects in rabbits occurred in conjunction with significant maternotoxicity, evident as body weight losses over the treatment period and substantial reductions in food consumption (by 55–66%). The NOEL for embryofetal toxicity in rabbits is <0.01 mg/kg/day (relative exposure, <0.2).

In the postnatal development study, pups of rats treated at ≥0.1 mg/kg/day (relative exposure, ≥0.9) displayed normal weight at birth, but significantly reduced postnatal body weight gain. Pup body weight on PND21 was 11–22% lower in the treatment groups (0.1–1 mg/kg/day) compared with controls. The body weight depression persisted into adulthood, with males having 7–11% lower body weight at 16 weeks of age compared with controls, and females 4–9% lower body weight at 10 weeks of age. Maternal treatment, though, had no significant effect on postnatal survival, pup reproductive function or other developmental parameters (≤1 mg/kg/day; relative exposure, ≤11).

Local tolerance

Inflammation at SC injection sites was commonly observed in rodent studies, but effects in liraglutide-treated animals were similar to those in vehicle control animals, indicating an association with the excipients or injection trauma. In monkeys used in the 3- and 12-month toxicity studies, though, there was some evidence that liraglutide induced greater irritation/inflammation at injection sites than the vehicle alone. Injection site lesions were characterised by oedema, haemorrhage, fibrosis, eosinophilic/lymphocytic inflammatory cell infiltration and the presence of pigmented macrophages.

Three specialised local tolerance studies were conducted in pigs. None used the final formulation proposed for marketing, though one study used a formulation closely resembling it, in which liraglutide was present at a slightly higher concentration (6.25 compared with 6.0 mg/mL). Inflammatory dermal reactions were rated minimal–moderate (only slightly more intense than the reaction to saline administration) and were generally attributable to the

vehicle (containing either mannitol or propylene glycol). A propylene glycol-based formulation of pH 8.15 (as is to be marketed) was better tolerated than ones with pH 7.7 or 7.9.

Antigenicity

The development of antibodies to liraglutide was observed in cynomolgus monkeys, but not in rats or mice. With treatment at 5 mg/kg/day, 25% of monkeys in the 12-month study and 40% of monkeys in the 20-month mechanistic study (203262) developed anti-liraglutide antibodies. One monkey (of ten) treated at 0.25 mg/kg/day in the mechanistic study also developed antibodies to the drug. Antibody formation in monkeys was not seen before 52 weeks. There were no apparent adverse effects in the responding animals, and no evidence of diminished pharmacological activity or altered pharmacokinetics for the drug. Anti-liraglutide antibodies cross-reacted with GLP-1.

Immunotoxicity

No specialised immunotoxicity studies were submitted. Atrophy of the thymus was observed in male monkeys treated at 0.5 or 5 mg/kg/day in the 12-month study (relative exposure, 8.7–73). However, this was of only mild severity even at the largest exposure multiple. In addition, the other repeat-dose and carcinogenicity studies did not reveal any consistent effects on the thymus, lymph nodes, bone marrow, spleen or serum globulins suggestive of immunosuppression or enhanced activation of the immune system.

Paediatric use

No specific studies in juvenile animals were submitted by the sponsor.

Nonclinical Summary and Conclusions

Primary pharmacology studies showing favourable changes in plasma glucose and insulin, among other effects, support the drug's use for the proposed indication.

Safety pharmacology and the general repeat-dose toxicity revealed no findings considered to pose a significant risk to humans treated with liraglutide, based on their low severity, species specificity and/or the animals' margin of exposure, apart from thyroid C-cell hyperplasia (in the 3-month mouse study).

No nonclinical studies investigating pharmacokinetic or toxicological interactions between liraglutide and metformin, a thiazolidinedione or a sulfonylurea were conducted. The safety of combined use of liraglutide and these agents has to be assessed from clinical data only.

Pharmacokinetic studies indicated slow but quite extensive absorption following SC administration in all species (mice, rats, rabbits, cynomolgus monkeys, pigs and humans). Plasma half-lives were about 5–8 hours in mice, rats, rabbits and monkeys, 14 hours in pigs and 12 hours in humans. Plasma AUC was dose-proportional or slightly greater than dose-proportional in all species. Liraglutide was distributed most extensively to well vascularised organs such as the liver, lungs, kidneys and adrenal glands. Penetration across the blood-brain barrier was poor and plasma protein binding was high to very high.

Metabolism of liraglutide involved cleavage of the peptide chain and degradation of the palmitic acid component. The drug, like GLP-1, is a substrate for dipeptidyl peptidase-IV (DPP-4) and neutral endopeptidase. Metabolism was extensive, but intact liraglutide was the dominant circulating species in humans and the laboratory animal species (mouse, rat and cynomolgus monkey). Two plasma metabolites were identified in humans; the major one was present in all of the experimental species and the minor one was present in the rat. The major

metabolite represents the cleavage product generated by DPP-4; it is only very weakly pharmacologically active. Little or no liraglutide was excreted intact.

Single-dose toxicity studies in mice, rats and cynomolgus monkeys indicated a low order of acute toxicity for the drug.

Pivotal repeat-dose toxicity studies were conducted in rats (26 weeks) and cynomolgus monkeys (52 weeks). Findings in the repeat-dose studies comprised thyroid C-cell hyperplasia (observed in mice treated for 3 months), mild effects on the liver (centrilobular hypertrophy, Kupffer cell pigmentation, fatty vacuolation and inflammatory cell infiltration), transient diuresis (in mice and rats; pharmacologically mediated), behavioural changes (in rats; consistent with discomfort rather than neurotoxicity), minor changes in red blood cell indices, and adrenal medullary hyperplasia and cortical vacuolation (in rats; consistent with stress). Decreased food consumption and loss of body weight were seen at the beginning of all toxicity studies. The apparent appetite suppressing effect of treatment was temporary, however, although suppression of bodyweight gain mostly persisted with continued treatment.

Liraglutide was carcinogenic in mice and rats, causing thyroid C-cell adenomas and carcinomas. Exposure ratios at the NOELs for C-cell neoplasia are low: 2.0 in mice and <0.5 in rats. Focal (nodular) C-cell hyperplasia, a pre-neoplastic lesion, was first observed following 9 weeks of treatment in mice (a species with a very low spontaneous incidence of C-cell proliferative lesions) and 40 weeks in rats (a species with a high background level of C-cell proliferative lesions).

The sponsor's proposed mechanism for C-cell tumourigenicity—that chronic GLP-1 receptor activation on C-cells causes ongoing calcitonin release and increased calcitonin synthesis, driving hyperplasia and leading to neoplasia—is not supported by the data. C-cell neoplasia in rodents developed in a manner unlike that expected in cases where C-cell proliferation occurs in response to increased physiological demand (that is, there was no initial increase in diffuse C-cell hyperplasia) and calcitonin was not a credible biomarker for proliferative C-cell lesions in rats (that is, focal C-cell hyperplasia developed and progressed to adenoma in the absence of any sustained increased in calcitonin synthesis/release, or even a decrease in calcitonin levels). The sponsor considered that the findings were not relevant to humans as GLP-1 receptor-mediated calcitonin release could be shown in rat C-cell carcinoma cell lines but not human ones. Questions over the involvement of calcitonin aside, these cancer-derived cells may not be good models for normal C cells, and increased plasma calcitonin has been observed *in vivo* in humans treated with liraglutide. No thyroid C-cell lesions were observed in monkeys treated with liraglutide for up to 20 months. Given the variability in the time to lesion development evident in mice and rats, and considering that, as a proportion of the animals' life span, the treatment duration in monkeys is much shorter than that required for lesion development in rats, the absence of C-cell lesions in monkeys is not fully reassuring as to a lack of human relevance for the C-cell neoplasia produced by liraglutide in rodents.

Embryofetal toxicity observed with liraglutide in rats and rabbits is considered to have occurred secondary to maternal toxicity. No treatment-related teratogenicity was observed. Suppression of postnatal body weight gain, observed in rats, appears to stem from *in utero* exposure and/or reduced maternal care given the low level of excretion of the drug in milk.

Local tolerance studies in pigs revealed minimal to moderate inflammatory dermal reactions following SC dosing, principally attributable to the vehicle. There was some evidence of a liraglutide-induced inflammatory reaction at the injection site in the general repeat-dose toxicity studies in monkeys.

Registration of Victoza was not initially supported due to concerns regarding the potential for carcinogenicity in humans. This is based on findings of thyroid C-cell tumourigenicity in mice and rats and insufficient data to establish a lack of human relevance. However, please refer to the following section for review of additional data submitted by the sponsor, in response to the evaluator's concerns.

Supplementary Nonclinical Evaluation

Introduction

To address the issues raised above, the sponsor submitted supplementary nonclinical data regarding the mechanism and relevance of thyroid C-cell proliferative changes (focal hyperplasia, adenoma and carcinoma) produced by liraglutide in mice and rats, and provided a response to the nonclinical evaluation report summarised above.

The sponsor agreed that cancer-derived cell lines have limitations in relation to the interpretation of results, but reported that it was found not to be feasible to isolate and perform experiments with either rat or human thyroid C-cells in primary culture. Supplementary data, though, have been obtained from *in situ* ligand binding studies with rat and human normal thyroid tissue sections, with ligand binding to the GLP-1 receptor detected in rat (8/8) but not human tissue samples (0/13). Experiments with mouse thyroid were said not to be possible due to difficulty in obtaining material of adequate quality because of the small size of the tissue. Körner *et al.* (2007) also examined thyroid GLP-1 receptor expression in rodents and humans (by receptor autoradiography), finding high levels of receptor in the mouse and the rat in particular, and expression in only 1 of 18 normal thyroid glands from humans, though the receptor was more readily detectable in human medullary thyroid carcinoma tissue:[12]

GLP-1 receptor	Normal thyroid tissue			Human medullary thyroid carcinoma
	Mouse	Rat	Human	
Receptor-positive; incidence	3/5 (60%)	12/12 (100%)	1/18 (6%)	5/18 (28%)
Receptor density[#]; dpm/mg tissue	1982 ± 470	2289 ± 282	1193	1326 ± 264

ÿ [#] = *mean ± SEM of receptor-positive cases. Adapted from Tables 1 and 3 of Körner et al. (2007).*

The sponsor found that GLP-1 receptor binding in rat thyroid was in a pattern compatible with C-cell distribution. The absence of detectable GLP-1 receptor expression in normal human thyroid in the sponsor's study does not necessarily reflect a low level of expression of GLP-1 receptor on C-cells, but rather could be due to low C-cell density. In rats, C-cells comprise ~5–10% of thyroid cells cf. less than 1% in humans (Martín-Lacave *et al.*, 1992).[11]

The mode-of-action hypothesis proposed by the sponsor to account for the formation of C-cell tumours in mice and rodents is as follows:

- liraglutide activates GLP-1 receptors on thyroid C-cells;
- GLP-1 receptor activation induces the release of calcitonin from C-cells;
- continued calcitonin release leads to increased calcitonin synthesis;
- persistent stimulation of calcitonin synthesis gives rise to C-cell hyperplasia; and
- C-cell hyperplasia leads to C-cell neoplasia.

[12] Körner M, Stöckli M, Waser B, Reubi JC. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. J. Nucl. Med. 2007; 48:736–743.

The nonclinical evaluator questioned the validity of the sponsor's proposed mechanism for C-cell tumourigenicity on two grounds:

- there being no continued stimulation of calcitonin release/synthesis by liraglutide in rats, and
- the progression from hyperplasia to neoplasia being at odds with the pattern of C-cell proliferative changes that would be expected to occur in response to increased physiological demand for calcitonin (i.e., there was no initial increase in diffuse C-cell hyperplasia).

Continued stimulation of calcitonin release/synthesis as a cause of C-cell proliferation

The sponsor submitted two supplementary studies conducted in GLP-1-receptor knockout mice that establish that stimulation of calcitonin release in response to a single dose of liraglutide or exenatide (another GLP-1 receptor agonist) is GLP-1-receptor dependent. These new data do not address either of the evaluator's criticisms of the proposed mechanism. While both calcitonin release and C-cell proliferation are considered to be mediated by GLP-1 receptor stimulation, it does not necessarily follow that the stimulation of calcitonin release is the cause of the C-cell proliferative changes observed; as noted in the original evaluation report, the GLP-1 receptor can couple to signalling pathways that regulate cell survival and growth. The sponsor's review document ("Liraglutide. Rodent C-cell findings: Assessment of human relevance"; updated June 2009) states that: "The intracellular pathways linking GLP-1R activation and calcitonin secretion to the C-cell proliferation observed in rodents long-term were not evaluated in detail".

Newly submitted statistical analyses examined the relationship between the early change in plasma calcitonin (that is, in the first 4 weeks of treatment) and the terminal C-cell proliferative changes in a 16-month mechanistic study in rats. A significant positive correlation between the early calcitonin change and the terminal focal C-cell hyperplasia score was found, while the correlation between the early calcitonin change and the presence or absence of terminal C-cell adenoma did not reach statistical significance at the 5% level.

As noted in the original evaluation report, and indicated in the figures below, the significant increase in plasma calcitonin in liraglutide-treated cf. control animals observed in rats at 4 weeks in the study (Figure 2) was not evident at later time points (Figure 3). Thus, despite there being a correlation, the data do not support the sponsor's hypothesis that *continued* stimulation of calcitonin release/synthesis is the cause of the C-cell hyperplasia.

Figure 2: Dose-dependent increase in plasma calcitonin (at 3 hours post-dose) after 4 weeks of dosing with liraglutide in (A) young and (B) aged rats in a 16-month mechanistic study (Study 204163).
Data represent mean ln-transformed values and 95% confidence intervals (CIs).

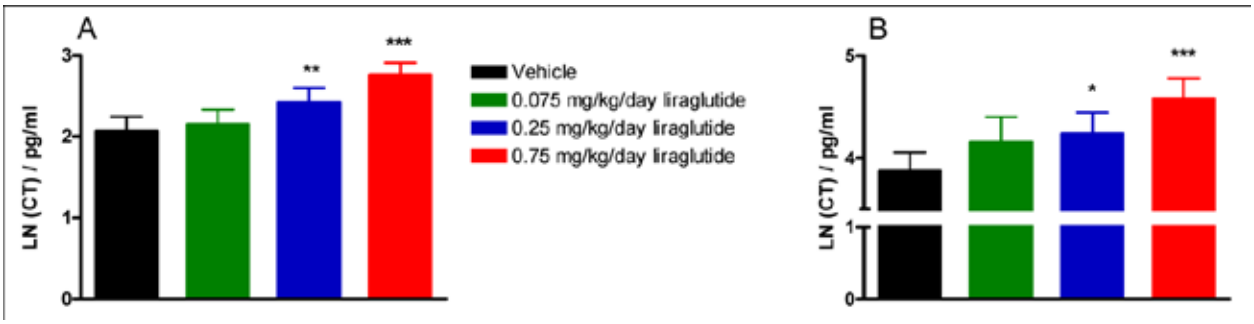
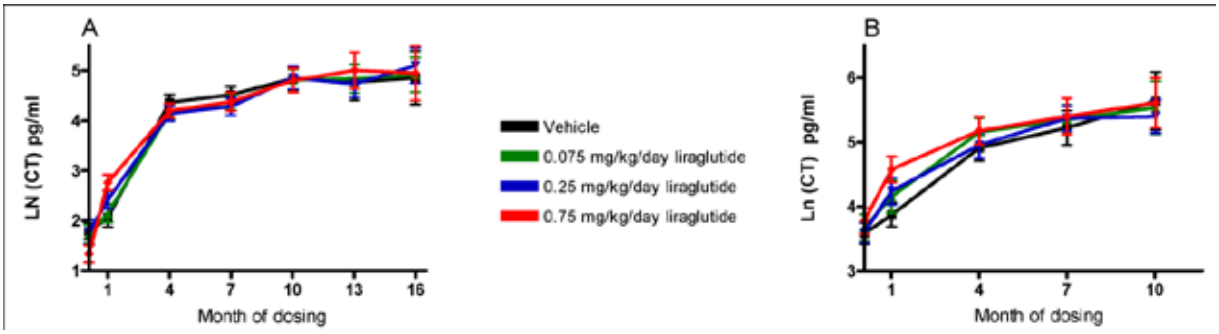


Figure 3: Plasma calcitonin (3 h post-dose) in (A) young and (B) aged rats during a 16-month mechanistic study with liraglutide (Study 204163). Data represent mean ln-transformed values and 95% CI.



The sponsor commented that: "It is conceivable that the absence of a net treatment effect on long-term plasma calcitonin is related to the underlying spontaneous increase in C-cell number along with a change in distribution pattern from diffuse to focal hyperplasia. The lack of persistency in effect of treatment on calcitonin is thus considered related to the known time-course in the development of the different types of proliferative C-cell changes also occurring spontaneously in rats". No analysis was offered by the sponsor to support this hypothesis. Table 4 compares plasma calcitonin levels in the subset of control animals without terminal focal C-cell hyperplasia (or adenoma) with levels in liraglutide-treated animals.

Table 4: Comparison of Plasma Calcitonin

Group		ln [plasma calcitonin] (pg/mL)†					
		Treatment duration (months)					
		1	4	7	10	13	16
Young rats—							
control animals without terminal focal C-cell hyperplasia/adenoma		1.61 ± 0.84 (23)	4.24 ± 0.54 (23)	4.36 ± 0.49 (23)	4.62 ± 0.66 (16)	4.54 ± 0.84 (11)	4.55 ± 0.86 (4)
liraglutide (all animals)	0.075 mg/kg/day	1.91 ± 0.87 (45)	4.15 ± 0.47 (44)	4.37 ± 0.54 (44)	4.81 ± 0.62 (35)	4.84 ± 0.68 (25)	4.91 ± 0.51 (11)
	0.25 mg/kg/day	2.36 ± 0.68* (45)	4.14 ± 0.49 (44)	4.28 ± 0.56 (41)	4.85 ± 0.64 (33)	4.73 ± 0.62 (23)	5.09 ± 0.55 (12)
	0.75 mg/kg/day	2.70 ± 0.65* (45)	4.20 ± 0.48 (44)	4.37 ± 0.60 (43)	4.80 ± 0.68 (33)	5.00 ± 0.84 (23)	4.94 ± 0.81 (11)
Aged rats—							
control animals without terminal focal C-cell hyperplasia/adenoma		3.84 ± 0.61 (38)	4.84 ± 0.55 (29)	5.21 ± 0.63 (21)	5.51 ± 0.76 (12)	–	–
liraglutide (all animals)	0.075 mg/kg/day	4.15 ± 0.83 (44)	5.15 ± 0.63 (34)	5.35 ± 0.51 (22)	5.53 ± 0.61 (11)	–	–
	0.25 mg/kg/day	4.24 ± 0.66* (41)	4.95 ± 0.57 (34)	5.37 ± 0.46 (24)	5.39 ± 0.42 (13)	–	–
	0.75 mg/kg/day	4.58 ± 0.65* (42)	5.18 ± 0.57 (31)	5.40 ± 0.63 (22)	5.61 ± 0.61 (12)	–	–

ÿ ** P < 0.05 cf. controls (One-way ANOVA with Dunnett's multiple comparison test); data are shown as mean ± SD (n);*

† *= 3 h post-dose*

Again, after excluding control animals that went on to develop focal C-cell hyperplasia/adenoma, no significant differences in plasma calcitonin levels between control and liraglutide-treated animals were observed at time points other than after one month's treatment. Moreover, the early change in plasma calcitonin was a small fraction of the normal age-related increase that occurs in rats, so it is unclear why such a relatively small and transient increase in demand for calcitonin would stimulate C-cell proliferation so dramatically.

Changes in the pharmacokinetics of calcitonin could conceivably mask a continued increase in calcitonin release. Regarding this, calcitonin is principally cleared via renal elimination by glomerular filtration (Simmons *et al.*, 1988).[13] Metabolism occurs via general protein degradation pathways, with no specific enzyme responsible for metabolism of the peptide known. Upregulation of a particular peptidase by incubation with calcitonin has been shown (Howell *et al.*, 1993).[14] Given the involvement of a large number of peptidases in the metabolism of calcitonin, though, and that glomerular filtration rate (as assessed by creatinine levels) and urine volume were unchanged in the repeat-dose toxicity studies in rats, increased clearance of calcitonin so that plasma levels appeared unchanged in the face of continued stimulation of release is considered unlikely.

Cinacalcet has also been shown to stimulate calcitonin release for C-cells in the rat, yet it reduced, rather than increased, the incidence of thyroid C-cell adenoma in rats. The disparity can be explained by the cinacalcet's additional (and dominant) actions to decrease plasma parathyroid hormone (PTH) and calcium levels.

As noted in the original nonclinical evaluation report, increased plasma calcitonin was reported to occur in clinical trial participants treated with liraglutide for 26 weeks. Based on the mechanism of action proposed by the sponsor, this finding is therefore at odds with the claimed lack of human relevance for the rodent C-cell findings. The sponsor responded, noting that "the overall conclusion from calcitonin monitoring was there were no clinically relevant treatment related effects on calcitonin". Please refer to the clinical findings for further discussion.

Together, the nonclinical data are not considered to establish increased calcitonin synthesis/release as a direct cause of the C-cell proliferative lesions in rodents.

Pattern of progression of C-cell proliferative changes

The sponsor submitted a commentary and external review of the thyroid histopathological data. The consultant pathologist reported that many of the findings of focal hyperplasia in rats represented "small aggregates of C-cells, cytologically identical in control and treated rats…an exaggeration of the normal pattern, devoid of any cytological atypia to suggest a pre-neoplastic state". For mice, it was noted that there are "no sharp histological or cytological differences that distinguish focal from diffuse hyperplasia so pathologists vary in the application of these terms. Hence, many of the changes termed focal hyperplasia in the mouse are an exaggeration of the normal pattern and the increase is likely also to be a response to physiological stimulation". Based on this and the demonstration of lesion reversibility in (most) mice that had been treated with the drug for 9 weeks, the C-cell hyperplasia induced by liraglutide in the mouse was considered to be "in accordance with

[13] Simmons RE, Hjelle JT, Mahoney C et al. Renal metabolism of calcitonin. Am J Physiol 1988; 254: F593–F600.

[14] Howell S, Caswell AM, Kenny AJ, Turner AJ. Membrane peptidases on human osteoblast-like cells in culture: hydrolysis of calcitonin and hormonal regulation of endopeptidase-24.11. Biochem J 1993, 290: 159–164.

a physiological stimulation and its cessation but incompatible with neoplastic transformation". This contention was accepted.

Absence of C-cell proliferative changes in monkeys

Liraglutide-induced C-cell proliferative lesions were first observed after 9 weeks of treatment in the mouse and 40 weeks in the rat, but were absent in cynomolgus monkeys treated for up to 20 months. As a proportion of the animals' life span, the duration of treatment required for the development of C-cell proliferative lesions in the rat was much longer than the maximum duration of the studies in monkeys (approximately 38% in rats compared with 5.4% in monkeys[15]), which may explain the absence of C-cell proliferative changes in monkeys. The sponsor provided published literature indicating that C-cell proliferation in response to receptor stimulation has been observed in macaque monkeys after as short as 10–30 days (Swarup *et al.*, 1979; in rhesus monkeys in response to hypercalcaemia induced by excess dietary calcium and administration of vitamin D).[16] Other examples of proliferation induced by endocrine stimulation in non-human primates becoming evident within months of treatment were also cited — mammary gland hyperplasia in rhesus monkeys after 7 weeks of treatment with growth hormone (Ng *et al.*, 1997), Leydig cell hyperplasia in rhesus monkeys after 53 days of treatment with gonadotrophins (Simpson and van Wagenen, 1954), and prostatic hyperplasia in cynomolgus monkeys after 3 months of treatment with an androgen (Habenicht *et al.*, 1987; cited in Jeyaraj *et al.*, 2000).[17,18,19,20]

Considering evidence that the C-cell proliferative lesions are consistent with physiological stimulation rather than neoplastic transformation, greater weight can now be placed on the absence of C-cell proliferative changes in cynomolgus monkeys treated with liraglutide in a 20-month study (≤5 mg/kg/day SC; relative exposure, ≤64). Repeat-dose toxicity studies indicate that rodents are particularly sensitive to C-cell proliferative changes in response to liraglutide compared with non-human primates.

Supplementary Nonclinical Summary and Conclusions

Liraglutide is a long-acting GLP-1 receptor agonist. The sponsor proposes that chronic GLP-1 receptor activation on C-cells causes ongoing calcitonin release and increased calcitonin synthesis, driving hyperplasia and leading to neoplasia. This was disputed based on there being no evidence of continued stimulation of calcitonin release/synthesis in rats treated with liraglutide, and the pattern of progression of C-cell proliferative changes appearing to be inconsistent with that expected to occur in response to increased physiological demand for calcitonin (that is, there was no initial increase in diffuse C-cell hyperplasia).

[15] Approximate lifespan of the cynomolgus monkey *(Macaca fascicularis)*, 31 years. <*http://pin.primate.wisc.edu/factsheets/entry/long-tailed_macaque*>

[16] Swarup K, Das S, Das VK. Thyroid calcitonin cells and parathyroid gland of the Indian rhesus monkey *Macaca mulatta* in response to experimental hypercalcaemia. Ann Endocrinol (Paris)1979; 40: 403–412.

[17] Ng ST, Zhou J, Adesanya OO, Wang J, LeRoith D, Bondy CA. Growth hormone treatment induces mammary gland hyperplasia in aging primates. Nat Med 1997; 3: 1141–1144.

[18] Simpson ME, van Wagenen G. Persistent nodules in testis of the monkey associated with Leydig cell hyperplasia induced by gonadotrophins. Cancer Res 1954; 14: 289–293.

[19] Habenicht UF, Schwarz K, Neumann F, el Etreby MF. Induction of estrogen-related hyperplastic changes in the prostate of the cynomolgus monkey *(Macaca fascicularis)* by androstenedione and its antagonization by the aromatase inhibitor 1-methyl-androsta-1,4-diene-3,17-dione. Prostate 1987; 11: 313–326.

[20] Jeyaraj DA, Udayakumar TS, Rajalakshmi M, Pal PC, Sharma RS. Effects of long-term administration of androgens and estrogen on rhesus monkey prostate: possible induction of benign prostatic hyperplasia. J Androl 2000; 21: 833–841.

A correlation between the increase in plasma calcitonin levels after 1 month of treatment with liraglutide and the terminal focal C-cell hyperplasia score in a 16-month mechanistic study in rats was demonstrated by the sponsor. While plasma calcitonin was increased by liraglutide at 1 month, no persistent treatment-related increase in plasma calcitonin levels was evident in the study, with levels between control and liraglutide-treated animals not significantly different at any subsequent time point (assessed at 3 month intervals). The sponsor proposed that this was due to underlying spontaneous changes in control animals; however, excluding control animals that went on to develop focal C-cell hyperplasia from the analysis yielded the same result.

While the data support the involvement of GLP-1 receptor activation in the development of the C-cell proliferative lesions in rodents, and the use of increased plasma calcitonin as a marker for their subsequent development, they are not considered to establish increased calcitonin release/synthesis as a direct cause. This is based on:

— the aforementioned absence of a persistent increase in plasma calcitonin in rats; and

— the initial increase in plasma calcitonin in rats treated with liraglutide being small in comparison with the normal age-related increase that occurs in the species.

The GLP-1 receptor can couple to signalling pathways that regulate cell survival and growth.

Expert commentary provided by the sponsor indicates that the C-cell proliferative lesions in rodents are consistent with physiological stimulation rather than neoplastic transformation; difficulties and inconsistencies in distinguishing between diffuse and focal C-cell hyperplasia were noted. Considering this, greater weight can now be placed on the absence of C-cell proliferative changes in cynomolgus monkeys treated with liraglutide in a 20-month study (≤5 mg/kg/day SC; relative exposure, ≤64). The duration of this study is considered adequate to reveal potential proliferative lesions mediated by receptor stimulation (but not neoplastic transformation).

The repeat-dose studies evaluated in the original report indicate that rodents are particularly sensitive to C-cell proliferative changes in response to liraglutide compared with non-human primates. The rodent thyroid contains a much greater proportion of C-cells than the human thyroid does, and GLP-1 receptor is more readily detectable in mouse and rat thyroid compared with human thyroid. *In vitro* studies with C-cell carcinoma derived cell lines, while not ideal models for normal cells, also indicate greater expression and responsiveness to activation for GLP-1 receptors in rodent compared with human cells. *In vitro* studies with normal C-cells in primary culture were found not to be feasible.

Considering the original and supplementary data, a revised recommendation is in order: there are no nonclinical objections to the registration of Victoza for the proposed indication provided there is no evidence of stimulation of calcitonin release in humans treated with the drug. A pharmacovigilance program to further assess potential C-cell proliferative changes in patients is warranted.

IV. Clinical Findings

Introduction

This section summarises the clinical data that was submitted for Victoza. Following evaluation of the data originally submitted with the application for registration, Novo Nordisk submitted a supplementary data package to address the concerns that had been raised by the evaluator. The following pages firstly present the evaluation of the initial clinical data package (pages 29-72), followed by the evaluation of the supplementary clinical data package (pages 72-81). The reader is also referred to Section VI "Overall Conclusion and Risk/Benefit

Assessment" for a more succinct description of the initial and supplementary clinical evaluations (pages 86-97), as well as the sponsor's reply to the supplementary evaluations (pages 97-98).

The initial data comprised 40 studies conducted in 6269 subjects, 4233 exposed to liraglutide.

There were nine studies conducted in 284 subjects, 250 exposed to liraglutide, concerning pharmacodynamics:

- Study NN2211-1149: 72 subjects, 60 exposed to liraglutide
- Study NN2211-1189: 34 subjects, 22 exposed to liraglutide
- Study NN2211-1644: 51 subjects exposed to liraglutide
- Study NN2211-1698: 18 subjects exposed to liraglutide
- Study NN2211-1589: 46 subjects exposed to liraglutide
- Study NN2211-1332: 13 subjects exposed to liraglutide
- Study NN2211-1219: 11 subjects exposed to liraglutide
- Study NN2211-2063: 20 subjects, 10 exposed to liraglutide
- Study NN2211-1224: 19 subjects exposed to liraglutide

There were 15 studies conducted in 397 subjects, with 373 exposed to liraglutide concerning pharmacokinetics:

- Study NN2211-1699: 7 subjects exposed to liraglutide
- Study NN2211-1327:32 subjects exposed to liraglutide
- Study NN2211-1328: 24 subjects exposed to liraglutide
- Study NN2211-1329: 30 subjects exposed to liraglutide
- Study NN2211-1330: 21 subjects exposed to liraglutide
- Study NN2211-1608: 78 subjects exposed to liraglutide
- Study NN2211-1331: 22 subjects exposed to liraglutide
- Study NN2211-1636: 24 subjects exposed to liraglutide
- Study NN2211-1692: 21 subjects exposed to liraglutide
- Study NN2211-1693: 22 subjects exposed to liraglutide
- Study NN2211-1745: 21 subjects exposed to liraglutide
- Study NN2211-1694: 24 subjects, 18 exposed to liraglutide
- Study NN2211-1551: 24 subjects, 18 exposed to liraglutide
- Study NN2211-1326: 32 subjects, 24 exposed to liraglutide
- Study NN2211-1591: 15 subjects, 11 exposed to liraglutide

There were 10 studies conducted in 4947 subjects, with 3187 exposed to liraglutide in support of efficacy:

- Study NN2211-1571: 190 subjects, 123 exposed to liraglutide (Table 5)

- Study NN2211-1310: 190 subjects, 135 exposed to liraglutide (Table 7)
- Study NN2211-1499: 144 subjects, 72 exposed to liraglutide (Table 8)
- Study NN2211-1573: 746 subjects, 498 exposed to liraglutide (Table 10)
- Study NN2211-1572: 1087 subjects, 724 exposed to liraglutide (Table 12)
- Study NN2211-1436: 1040 subjects, 694 exposed to liraglutide (Table 14)
- Study NN2211-1574: 533 subjects, 355 exposed to liraglutide (Table 16)
- Study NN2211-1697: 581 subjects, 230 exposed to liraglutide (Table 18)
- Study NN2211-1334: 226 subjects, 180 exposed to liraglutide (Table 20)
- Study NN2211-2072: 210 subjects, 176 exposed to liraglutide (Table 21)

There were six studies conducted in 1861 subjects. This represented 641 new subjects with 423 exposed to liraglutide. The studies were:

- Study NN2211-1573-extension: 440 subjects (Table 27)
- Study NN2211-1572-extension: 780 subjects (Table 28)
- Study NN2211-1333: 33 subjects, 21 exposed to liraglutide
- Study NN2211-1464: 32 subjects exposed to liraglutide
- Study NN8022-1807: 564 subjects, 361 exposed to liraglutide (Table 30)
- Study NN9233-1898: 12 subjects, nine exposed to liraglutide

The studies represented a complete clinical development program. The studies were conducted according to Good Clinical Research Practice and the principles of the Declaration of Helsinki.

Pharmacodynamics

Study NN2211-1149 was a single centre, randomised, double-blind, placebo-controlled, dose escalation trial of single doses of liraglutide to assess tolerability, pharmacokinetics, pharmacodynamics and absolute bioavailability in healthy male subjects. Forty-eight hour liraglutide profiles and 24-hour glucose, insulin, glucagon, leptin and diuresis profiles were determined in all subjects and 2-hour profiles for glucose and insulin were determined in subjects undergoing an intravenous glucose tolerance test (IVGTT) between 9 and 11 hours post-dosing. All subjects were exposed to a single subcutaneous dose of increasing concentrations of liraglutide or placebo.

The absolute bioavailability for the 5 µg/kg subcutaneous dose was 55%. The statistical analysis showed a dose-proportional increase in Cmax and the area under the plasma concentration time curve for zero to infinity ($AUC_{¥}$) for doses between 2.5 and 20 µg/kg, but not when data from the 1.25 µg/kg dose level are included. In all subjects, there were no overall and within dose levels statistically significant differences between active and placebo in the area under the plasma concentration time curve from zero to 9 hours (AUC_{0-9}), glucose after 9 hours (Glucose/9), and the area under the plasma concentration time curve from 9 to 11 hours (AUC_{9-11}) and glucose after a further 2 hours (Glucose/2) except for the 20 µg/kg dose level where AUC_{0-9} and Glucose/9 were significantly lower after active: Similar results were obtained for glucagon and insulin. In subjects undergoing IVGTT, overall (p=0.0002) and within the 2.5, 5, 12.5 and 20 µg/kg dose levels average insulin was statistically significantly higher following active. The difference within the 17.5 µg/kg dose level was

not estimable due to limited data. No overall and within dose levels statistically significant differences between the two treatments in AUC_{0-24} leptin were detected. There was no overall trend towards a difference in the volume of urine excreted. However, the urine volume excreted with the 8-12 hour collection interval was statistically significantly lower for active (p=0.038) for the 20 µg/kg dose level.

Study NN2211-1189 was a single centre, randomised, double-blind, placebo-controlled, dose escalation, parallel-group, single and multiple dose trial of liraglutide in healthy volunteers and patients with type 2 diabetes to assess tolerability, pharmacokinetics and pharmacodynamics. The study treatment was an initial single, and subsequent, multiple subcutaneous doses of liraglutide to subjects at five dose levels.

There was a dose-proportional increase in C_{max} and AUCs following both single and multiple dosing of liraglutide in the dose range of 5-12.5 µg/kg. The ratios of AUC_{0-24}, Day11/$AUC_{¥}$, Day1 were not statistically significantly different from unity, p=0.096, indicating linearity in the pharmacokinetics of liraglutide following multiple once daily subcutaneous administration. However, there was accumulation of liraglutide with repeated dosing. There was no overall statistically significant trend towards a difference in active treatment and placebo in glucose AUC_{0-24}, except for the 10 µg/kg dose level where glucose AUC_{0-24} was significantly lower for active treatment with least squares-mean ratio of 0.8357, p=0.0297. There was no statistically significant trend towards a difference in active treatment and placebo in glucose AUC_{0-24} following either single or multiple dosing, except following a single dose of 12.5 µg/kg on Day 1. There were no consistent differences between treatment and placebo for plasma insulin or plasma leptin, except for the latter at12.5 µg/kg where there was a trend towards lower AUC_{0-16} following active treatment with a least squares-mean ratio of 0.8208 and p=0.0238. Within dose comparison, there was no difference between active treatment and placebo except on Day 10 for the 12.5 µg/kg dose level: AUC_{0-16} for active treatment was significantly lower than placebo with a least squares-mean ratio of 0.7808 and p=0.0361.

Study NN2211-1644 was a single-centre, randomised, double-blind, two-period crossover, placebo-controlled trial followed by an open label positive-controlled (moxifloxacin) treatment period in healthy males and females. A total of 51 subjects were included in the study: 25 male and 26 female, age range 18.1 to 44.6 years. There was no significant prolongation of QTc with liraglutide in comparison with placebo. There was prolongation of QTc with the positive control (moxifloxacin).

Study NN2211-1698 was a single centre, randomised, placebo controlled, double-blind, two-period cross-over trial comparing the effect of liraglutide and of placebo on the absorption pharmacokinetics (PK) of paracetamol (drug-drug interaction) and pharmacodynamic (PD) postprandial glucose response. Liraglutide was administered by pen injector in a three step dose escalation scheme of 0.6, 1.2 and 1.8 mg /day. Paracetamol 500 mg tablets were administered as two tablets (1 g) on the drug interaction investigation days and as three tablets (1.5 g) at the PD investigation days, in order to investigate the effects of liraglutide on gastric emptying. Liraglutide at a dose of 1.8 mg/kg increased the T_{max} of paracetamol: mean difference (90% CI) Liraglutide – Placebo: 15.00 (0.00 to 92.50) min. There was no difference in $AUC_{¥}$ mean ratio (90% CI) 1.04 (0.97 to 1.10) or AUC_{0-48} 0.95 (0.89 to 1.01). Liraglutide at steady state significantly lowered AUC_{0-5} of postprandial plasma glucose compared with placebo. Liraglutide significantly lowered the fasting plasma glucose (FPG) compared with placebo. Glucose C_{max} was 20-40% lower after liraglutide treatment at the three doses compared to placebo treatment. Fasting insulin, C_{max} and AUC_{0-5} were all significantly higher after 1.8 mg liraglutide treatment compared with placebo. There was a

decrease in the postprandial visual analogue scale for hunger, $AUC_{15\text{-}300min}$/285 (mm) for mean difference (95% CI) liraglutide - placebo -7.26 (-11.8 to -2.72) p=0.002, but this was not significant for 1.2 mg/kg or 0.6 mg/kg. There was a decrease in food intake for the 1.8 mg/kg dose compared with placebo.

Study NN2211-1589 was a double-dummy, randomised, double-blind two-centre study with balanced incomplete Latin square design comparing the effect of liraglutide (1.8 mg), glimepiride and placebo on energy intake at an ad libitum buffet meal, duration of the meal, macronutrient distribution, appetite sensations and nausea, gastric distension (assessed by ultrasound measurements of antral area), gastric emptying (assessed by paracetamol absorption) and metabolic and hormonal responses.

The mean ratio (95% CI) for energy intake with liraglutide compared with placebo was 0.91 (0.78 to 1.06) and glimepiride was 0.91 (0.78 to 1.07). There was no statistically significant difference for the energy intake between liraglutide treatment versus placebo and glimepiride at the ad libitum meal. Although not statistically significant, the estimated reductions of energy intake were 9% and 15% at the ad libitum meal after liraglutide treatment compared to both placebo and glimepiride. The duration of eating at the ad libitum buffet meal was shorter after liraglutide compared to placebo but there was no significant difference compared to glimepiride. A statistically significantly lower fasting sensation of hunger, assessed by visual analogue scale, was observed after liraglutide treatment compared to placebo. Paracetamol T_{max} occurred on average 20 minutes later after liraglutide treatment compared with placebo and glimepiride.

Liraglutide significantly lowered the mean body weight 1-2 kg after a 4-week treatment period compared to placebo or glimepiride. Liraglutide significantly lowered the mean fasting plasma glucose after a 4-week treatment period compared to placebo and glimepiride treatment. However, there were no differences regardless of treatment for insulin and glucagon levels. Mean peptide YY concentration was significantly decreased by liraglutide compared to placebo and glimepiride. There was a significant difference between liraglutide and placebo treatment in the change from baseline in mean adiponectin but not between liraglutide and glimepiride. Liraglutide significantly lowered the concentration of high sensitivity C-reactive protein (hsCRP) compared to glimepiride. There were no significant differences between liraglutide and placebo or glimepiride for concentration changes of ghrelin, leptin, gastric inhibitory polypeptide (GIP), lipids (total cholesterol[TC], low density lipoprotein cholesterol [LDL-C], very low density lipoprotein cholesterol [VLDL-C], high density lipoprotein cholesterol [HDL-C], free fatty acids [FFA]) and tumour necrosis factor (TNF)α.

Study NN2211-1332 was a single-centre, randomised, double-blind, crossover trial in subjects with type 2 diabetes. Liraglutide and placebo were each injected subcutaneously for 9 to 10 days. Oral hypoglycaemic agents (OHAs) were discontinued 2-3 weeks prior to treatment. A hyperglycaemic clamp was used to measure insulin release.

The 24 hour glucose profile was lower for liraglutide. There was no significant difference in the 24 hour insulin profile and no significant difference in C-peptide levels. There was a decrease in the 24 hour glucagon profile with liraglutide. There was no difference between treatments in free fatty acids, pro-insulin, leptin or insulin secretion rate.

During the hyperglycaemic clamp, insulin secretion was higher for liraglutide during the first phase and during steady state. Endogenous glucose release and glycogenolysis were decreased with liraglutide, but gluconeogenesis was not affected.

Study NN2211-1219 was a single-centre, randomised, double-blind, crossover trial to assess the effect of liraglutide on pulsatile secretion of insulin in subjects with Type 2 diabetes. A standard meal was served after dosing at each of the treatment visits. There was no difference between liraglutide or placebo in burst mass or AUC of insulin secretion rate as measured by C-peptide profiles. There was no difference between the treatments in burst amplitude or interpulse interval. Basal secretion of insulin was higher with liraglutide. An increase in insulin secretory capacity (as assessed using the homeostasis model assessment [HOMA] model) was observed with liraglutide. There was no difference in insulin resistance. The AUC of insulin secretory rate was higher during the basal period, AUC of glucagon was lower after treatment with liraglutide and gastric emptying (as measured by the 3-ortho-methyl-glucose test) was lower after treatment with liraglutide. Pro-insulin and C-peptide levels reflected the effects upon insulin.

Study NN2211-2063 was a double-blind, randomized, single-centre, placebo controlled, crossover study to examine beta-cell responsiveness to graded glucose infusion in patients with type 2 diabetes, and in comparison with a control group of healthy volunteers. A single dose of 7.5 µg/kg liraglutide, or placebo, was administered by subcutaneous injection, with a three to six week washout period between treatments. A control group of healthy volunteers of similar age and BMI was included, which did not receive any trial medication, and only received the graded glucose infusion. In response to a glucose infusion, the insulin secretion rate (measured using C-peptide levels) following liraglutide was higher than for placebo, and was similar to that observed in healthy volunteers. There was no significant difference between groups in glucagon secretion.

Study NN2211-1224 was a double-blind, placebo-controlled, randomised, two-period crossover study of the effect of liraglutide on hypoglycaemic counter-regulation during stepwise hypoglycaemic clamp in type 2 diabetic subjects. Each subject received one subcutaneous injection of 7.5 µg/kg liraglutide and placebo in a random sequence. Insulin was infused continuously intravenously and at a constant rate. The clamp was conducted at four different plasma glucose levels, which were achieved by variation of the glucose infusion. There was no statistically or clinically significant difference between liraglutide and placebo in glucagon levels, glucose infusion rate, mean cortisol levels, adrenaline levels, or noradrenaline levels. Mean glucose levels were slightly higher in the liraglutide group for the lower ranges of the hypoglycaemic clamp. Growth hormone secretion was decreased in the liraglutide group, $p=0.0320$. C-peptide levels were higher in the liraglutide group, $p<0.0001$. Insulin secretion rate was higher in the liraglutide group, $p=0.0026$.

Evaluators comments:

The pharmacodynamic data indicate that liraglutide increases the secretion of insulin in response to a glucose load, and decreases the secretion of glucagon. Liraglutide delayed gastric emptying and increased sensations of satiety.

Pharmacokinetics

Study NN2211-1699 was a single-centre, open label trial investigating the metabolites in plasma, urine and faeces after a single subcutaneous dose of tritiated liraglutide in healthy volunteers. Three components were detected in plasma: unchanged liraglutide (89-100%) and two metabolites P1 and P2 that were slightly more lipophilic and represented <9% and <5% (respectively) of the total exposure (2-24 hours). No unchanged liraglutide was detected in urine or faeces. Three metabolites were detected in urine. All of these had much lower retention times than the parent compound. The major component was excreted as 3% of the administered radioactivity. The third urinary metabolite was only detected in one subject. There were three metabolites detected in faeces. No quantification of the individual

components was possible, but it was estimated that these components in total comprised 3-5% of the administered radioactivity. Up to Day 14, 26.3% of the total radioactivity was excreted in urine and faeces, with 11.5% of the total radioactivity excreted as liraglutide-related and 14.8% as tritiated water. T_{max} was 11.7 hours and $t_{½}$ was 15.4 hours. The liraglutide plasma: blood ratio was 0.6.

Study NN2211-1327 was a single centre, open label, single dose trial with two groups comparing the pharmacokinetics of liraglutide in young versus elderly subjects of both sexes. The study treatment was a single dose of liraglutide, 5 mg/mL; 1 mg administered as a single subcutaneous pen injection. The young age group had an age range of 21 to 45 years. The elderly age group had an age range of 65 to 83 years. There was no significant different in AUC_{0-t} and other pharmacokinetic parameters between the age groups or between the genders.

Study NN2211-1328 was a single-centre, open-label trial investigating the pharmacokinetics and the safety profile after a single dose of liraglutide in male and female subjects aged 18 to 75 years who were either healthy or had stable hepatic impairment classified as Child-Pugh grade A (mild), B (moderate) or C (severe) as assessed by the investigator. AUC decreased and volume of distribution increased with increasing hepatic impairment. For $AUC_{¥}$ the ratio (90% CI) of mild hepatic impairment to normal was 0.77 (0.53 to 1.11), moderate hepatic impairment to normal was 0.87 (0.60 to 1.25) and severe hepatic impairment to normal was 0.56 (0.39 to 0.81). Unbound concentration decreased with hepatic impairment.

Study NN2211-1329 was a single-centre, open-label trial investigating the pharmacokinetics and the tolerability of liraglutide in subjects with normal renal function and in subjects with impaired renal function. There were no clear differences in pharmacokinetic parameters on the basis of renal function. Equivalence was not demonstrated between the group of subjects with severe renal impairment and healthy subjects with respect to the primary endpoint AUC but there was no clear association between degree of renal impairment and $AUC_{¥}$.

Bioequivalence Studies

Study NN2211-1331 was a randomised, single-blind, single-centre, two-period, cross-over trial investigating the bioequivalence between completed Phase 2 (Reference) and planned Phase 3 (Test) formulations of liraglutide in healthy subjects. The relative bioavailability of the Phase 3 formulation compared to the Phase 2 formulation was estimated at 97.63% based on AUC_{0-t} with the 90% confidence interval (CI) ranging from 92% to 104%, and at 98.03% based on $AUC_{¥}$ (CI: 93%-104%). The between-treatment ratio was 96.32% for C_{max} (CI: 89%-104%).

Study NN2211-1636 was a randomised, double-blind, single-centre, three-period, crossover trial in healthy subjects investigating the bioequivalence between each of the two new liraglutide formulations at pH 7.9 and 8.15 and the planned Phase 3 formulation at pH 7.7. The three formulations were bioequivalent.

Study NN2211-1692 was a randomised, double-blind, single-centre, two-period, cross-over trial in healthy subjects investigating the bioequivalence between the Phase 3a formulation of liraglutide (formulation 4) and the planned Phase 3b formulation (final formulation 4). . This study has also been reviewed under Section II. The estimated ratio for AUC_{0-t} was 0.99 (CI: 0.92, 1.06) and for C_{max} was 1.02 (CI: 0.91, 1.14).

It was stated that the composition and manufacturing process of liraglutide 6.0 mg/mL batch SQ50360, used in clinical trial NN2211-1692 is identical to the composition and manufacturing process of the product intended to be marketed in Australia.

Study NN2211-1693 was a randomised, double-blind, single-centre, two-period, crossover trial in healthy subjects investigating the bioequivalence between the Phase 2 formulation of liraglutide at pH 7.7 (formulation 3) and the Phase 3 formulation at pH 8.15 (formulation 4). The mean (90% CI) ratio of Formulation 4/ Formulation 3 was for AUC_{0-t} 1.06 (1.00 to 1,13) and for C_{max} 1.04 (0.95 to 1.13).

Study NN2211-1745 was a randomised, open-label, single-centre, three period, crossover bioequivalence study of liraglutide administered at different injection sites. This study has also been reviewed under Section II. The two injection sites - upper arm and abdomen - were not bioequivalent with respect to $AUC_{¥}$ for liraglutide, with a mean (90% CI) ratio of 0.90 (0.83 to 0.96). The two injection sites - upper arm and thigh - were bioequivalent with respect to $AUC_{¥}$ for liraglutide, with a mean (90% CI) ratio of 1.11 (1.03 to 1.19). The two injection sites - thigh and abdomen - were not bioequivalent with respect to $AUC_{¥}$ for liraglutide, with a mean (90% CI) ratio of 0.81 (0.76 to 0.86). Results based on the primary analysis were supported by the secondary PK endpoints based on AUC_{0-t} and C_{max}.

Additional pharmacokinetic studies performed in Japanese subjects:

Study NN2211-1694 was a randomised, double-blind within dose group, parallel group, single centre, placebo-controlled, dose escalation, multiple subcutaneous dose study to assess the safety and tolerability of liraglutide 20 μg/kg and 25 μg/kg in healthy Japanese male subjects. The pharmacokinetics of liraglutide were linear in Japanese male subjects. Blood glucose and insulin levels decreased in a dose dependent manner.

Study NN2211-1551 was a randomised, double-blind, single-centre, placebo-controlled, 21-day multiple subcutaneous doses, dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in healthy Japanese male subjects. The pharmacokinetics of liraglutide were linear. Postprandial glucose was decreased in the liraglutide groups compared with placebo, but not in a dose dependent manner.

Study NN2211-1326 was a randomised, double-blind, single-centre, placebo-controlled, ascending single subcutaneous dose, sequential group study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of liraglutide in healthy Japanese male subjects. The pharmacokinetics of liraglutide were linear. Glucose levels following the evening meal were decreased, as were the evening glucagon levels in a dose dependent manner.

Study NN2211-1591 was a randomised, double-blind within dose group, single-centre, placebo controlled, parallel 2-different dose group, 14-day multiple subcutaneous doses study to assess the safety, pharmacokinetics and pharmacodynamics of liraglutide in Japanese subjects with type 2 diabetes. The pharmacokinetics of liraglutide at steady state were linear. Postprandial glucose levels were decreased in both liraglutide groups relative to placebo. Serum insulin levels were higher in the 10 μg/kg group compared with placebo.

Summary

The pharmacokinetics of liraglutide were linear with respect to absorption and elimination. Liraglutide was completely metabolized with no parent drug present in urine or faeces. There were slight differences in absorption between injection sites, with greater absorption from the abdomen than the upper arm or thigh. The pharmacokinetic parameters of liraglutide were not affected by age or gender. The pharmacokinetics of liraglutide were similar in Japanese and Caucasian subjects. Liraglutide AUC decreased by up to 44% and volume of distribution increased with increasing hepatic impairment. The unbound concentration of liraglutide decreased with hepatic impairment. Liraglutide AUC decreased by up to 33% with renal impairment.

Drug Interactions

Study NN2211-1330 was a single centre, a double-blind, two period crossover, drug interaction study in healthy subjects investigating the influence on the pharmacokinetics of ethinyloestradiol and levonorgestrel in an oral contraceptive drug after multiple dose administration of liraglutide. The study was conducted in 21 healthy postmenopausal women aged 51 to 71 years. There was no influence on the $AUC_{¥}$ of ethinyloestradiol but there was a slight increase in the $AUC_{¥}$ of levonorgestrel: 1.182 (1.040 to 1.343). The secondary pharmacokinetic parameters for ethinyloestradiol and levonorgestrel were similar for liraglutide in steady state and for placebo.

Study NN2211-1608 was a two-centre, randomised, double-blinded, placebo-controlled, two-way crossover trial with two Parts (A and B) comparing the effect of liraglutide on the absorption PK of 40 mg atorvastatin, 20 mg lisinopril (Part A), 500 mg griseofulvin and 1 mg digoxin (Part B) and on intragastric pH (Part B). For liraglutide compared to placebo treatment equivalence was demonstrated for atorvastatin and griseofulvin but not for lisinopril and digoxin. C_{max} for atorvastatin, lisinopril and digoxin were 38%, 27% and 31% lower, respectively. The C_{max} for griseofulvin was 37% higher. For atorvastatin, lisinopril and digoxin, T_{max} was delayed by 1.25, 2.0 and 1.125 hours, respectively, compared to placebo. For griseofulvin, T_{max} was not affected by treatment. Liraglutide did not affect intragastric pH.

Summary

Liraglutide increased the T_{max}, and decreased the C_{max} for atorvastatin, lisinopril and digoxin. Liraglutide decreased the AUC for lisinopril and digoxin. Liraglutide had no effect on ethinyloestradiol exposure, and a clinically insignificant increase in exposure to levonorgestrel.

Efficacy

Study NN2211-1571 was a multicentre, multi-national, double-blind, randomised, parallel-group clinical trial of the effect on glycaemic control of three doses of liraglutide in monotherapy versus placebo in subjects with type 2 diabetes (Table 5). The study was conducted at 28 sites in four countries: Denmark (6 sites), The Netherlands (6), France (7) and Slovakia (9). The study included patients with type 2 diabetes treated for at least 3 months with OAD or diet; including males or females with an age >18 years and with an HbA1c between 7.5% and 10%. The study examined three doses of liraglutide: 0.65 mg, 1.25 mg and 1.90 mg, compared with placebo.

Table 5: Details of Study NN2211-1571

Nr. of subjects with age and sex **Duration**	**Diagnosis + criteria for incl/exclusion**	**Test Product** **Dosage Regimen** **Route of administration, Formulation**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
163 subjects, 123 treated with liraglutide 99 male, 64 female 27 to 79 years 14 weeks	Subjects with type 2 diabetes treated for at least 3 months with OAD or diet. Males or females with an age >18 years and with an HbA1c between 7.5% and 10%.	Liraglutide: 0.65 mg, 1.25 mg and 1.90 mg,	glycaemic control as assessed by HbA1c effect on overall glycaemic control parameters (fasting plasma glucose, insulin, C-peptide, pro-insulin and glucagon, fructosamine and 7-point plasma glucose profiles) β-cell function as assessed by HOMA and pro-insulin/insulin ratio, safety and tolerability, effect on body weight and formation of liraglutide antibodies, effect on lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA, apoB), compare bio-markers for cardiovascular effect (adiponectin, leptin, CRP, IL-6, TNF-α, PAI-1 and BNP)	There was a dose dependent improvement in HbA1c with liraglutide. There was a dose dependent improvement in FBG with liraglutide There was a dose dependent improvement in β-cell function with liraglutide Compared to placebo, there was a significant mean (95% CI) weight loss in the Liraglutide 1.90mg group: -1.21 [-2.36;-0.06] p=0.0390 Systolic blood pressure decreased in the liraglutide groups PAI-I and BNP were both decreased in the 1.25 mg and 1.90 mg groups There were no between group differences in CRP, IL-6 and TNFα	82 AEs were reported in 21 (51.2%) patients in the 1.90 mg/kg group, 77 in 19 (45.2%) of the 1.25 mg/kg group, 48 in 17 (42.5%) of the 0.65 mg/kg group and 52 in 20 (50.0%) of the placebo group There was one SAE in the 1.90 mg/kg group: influenza; and one in the placebo group: fall/hip pain/arthralgia There were four AEs leading to withdrawal in the liraglutide groups, and three in the placebo group There was one hypoglycaemic episode occurring in the 1.90 mg/kg group There were no significant abnormalities in laboratory safety parameters

The outcome measures were glycaemic control as assessed by glycosylated haemoglobin (HbA1c) (primary efficacy outcome measure), effect on overall glycaemic control parameters (fasting plasma glucose [FBG], insulin, C-peptide, pro-insulin and glucagon, fructosamine and 7-point plasma glucose profiles), β-cell function as assessed by HOMA and pro-insulin/insulin ratio, safety and tolerability, effect on body weight and formation of liraglutide antibodies, effect on lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA, Apoprotein B), and compared bio-markers for cardiovascular effect (adiponectin, leptin, CRP, interleuikin-6 [IL-6], TNF-α, plasminogen activator inhibitor type 1 [PAI-1] and brain natriuretic peptide [BNP]).

There was a dose dependent improvement in HbA1c with liraglutide compared with placebo (Table 6). There was a dose dependent improvement in FBG with liraglutide. There was a dose dependent improvement in β-cell function with liraglutide. Compared to placebo, there was a significant mean (95% CI) weight loss in the liraglutide 1.90mg group: -1.21 (-2.36 to -0.06) p=0.0390. Systolic blood pressure decreased in the liraglutide groups. PAI-I and BNP were both decreased in the 1.25 mg and 1.90 mg groups. There were no between group differences in CRP, IL-6 and TNFα. There was no difference between groups in insulin resistance. There was no significant difference in pre-prandial glucose. There were no consistent changes in plasma lipids, with differences between groups relating to changes in the placebo group.

Table 6: ANOVA of the Primary Endpoint, HbA1c (%) – ITT Analysis Set

Type 2 Diabetic Subjects	Comparison of change of HbA1c (%) after 14 weeks of treatment		
Treatment/comparison	Estimates	95% CI	p value
Adjusted Mean			
Liraglutide 1.90mg	-1.45	[-1.77;-1.13]	
Liraglutide 1.25mg	-1.40	[-1.72;-1.08]	
Liraglutide 0.65mg	-0.98	[-1.31;-0.66]	
Placebo	0.29	[-0.06; 0.63]	
Adjusted Difference			
Liraglutide 1.90mg vs. Placebo	-1.74	[-2.18;-1.29]	<.0001*
Liraglutide 1.25mg vs. Placebo	-1.69	[-2.13;-1.24]	<.0001*
Liraglutide 0.65mg vs. Placebo	-1.27	[-1.72;-0.82]	<.0001*

The estimates are obtained from an ANOVA with treatment and previous treatment as fixed effect and baseline value as covariate.
An asterisk indicates statistical significance on a 5% significance level.

Study NN2211-1310 was a 12-week multicentre, double-blind, randomised, parallel group study of the dose-response relationship of five dose levels of liraglutide (compared with placebo and oral hypoglycaemic agents [OHA]) on glycaemic control in type 2 diabetic patients (open labelled OHA arm) (Table 7). The study was conducted at 28 trial sites: United Kingdom (14), Denmark (6), Sweden (4), and Norway (4).

Table 7: Details of Study NN2211-1310

Nr. of subjects with age and sex **Duration**	**Diagnosis + criteria for incl/exclusion**	**Test Product** **Dosage Regimen** **Route of administration, Formulation**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
193 subjects were randomized and 190 received study treatment; 26 0.045 mg, 24 0.225 mg, 27 0.45 mg, 30 0.60 mg, 28 0.75 mg, 29 placebo and 26 glimepiride 127 males, 63 females age range 33 to 75 years 12 weeks	Patients of both sexes, with type 2 diabetes, aged 30-75 years, duration of diabetes ≥3 months, and body mass index (BMI) ≤40 kg/m2. HbA1c at screening had to be within 7.5-10.0% for diet-treated and ≤9.0% for OHA treated (raised to ≤9.5% by amendment 2 to the protocol). At randomisation, fasting blood glucose had to be within 6-11.5 mmol/L (raised to 6-13 mmol/L by amendment 2 to the protocol).	Liraglutide 0.045 mg, 0.225 mg, 0.45 mg, 0.60 mg, and 0.75 mg Once daily subcutaneous injections before breakfast	Primary efficacy outcome measure: HbA1c after 12 weeks treatment Secondary efficacy outcome measure: fasting serum glucose, fructosamine, fasting C-peptide, fasting glucagons, and fasting insulin (all after 12 weeks treatment) 7-point blood glucose profiles after 12 weeks treatment, -mean blood glucose pro-insulin/insulin ratio after 12 weeks treatment β-cell function derived from fasting insulin and glucose using a HOMA model, SecrHOMA, after 12 weeks treatment insulin resistance derived from fasting insulin and glucose using a HOMA model, IRHOMA, after 12 weeks treatment	The effect of liraglutide on HbA1c increased with increasing dose; Emax was estimate as a 1.74 percent unit decrease in HbA1c, and ED50, was estimated as 0.76 mg, but because the estimated ED50 was similar to the highest dose investigated the sponsor concluded that only the lower part of the dose-response curve had been established in this trial. For the two higher dose levels (0.60 mg and 0.75 mg) compared with placebo there were statistically significant decreases in HbA1c, fasting serum glucose, fructosamine, and mean blood glucose In the 0.75 mg group there were improvements in β-cell function ans the pro-insulin/insulin ratio	AEs were more common in the higher dose groups, particularly headache, dizziness and nausea There were two SAEs: cerebral haemorrhage in the 0.60 mg group and skin ulceration in the placebo group There was one hypoglycaemic event in the 0.60 mg group and three in the glimepiride group

The primary efficacy outcome measure was HbA1c after 12 weeks treatment. Secondary efficacy outcome measures were: fasting serum glucose, fructosamine, fasting C-peptide, fasting glucagon, and fasting insulin (all after 12 weeks treatment), 7-point blood glucose

profiles after 12 weeks treatment (mean blood glucose), pro-insulin/insulin ratio after 12 weeks treatment. Exploratory endpoints were: β-cell function derived from fasting insulin and glucose using a HOMA model (SecrHOMA) after 12 weeks treatment, insulin resistance derived from fasting insulin and glucose using a HOMA model, (IRHOMA) after 12 weeks treatment.

The effect of liraglutide on HbA1c increased with increasing dose: The maximum response (E_{max}) was estimated as a 1.74 percent unit decrease in HbA1c, and ED50 was estimated as 0.76 mg, but because the estimated median effective dose (ED_{50}) was similar to the highest dose investigated the sponsor concluded that only the lower part of the dose-response curve had been established in this trial. For the two higher dose levels (0.60 mg and 0.75 mg) compared with placebo there were statistically significant decreases in HbA1c, fasting serum glucose, fructosamine, and mean blood glucose. In the 0.75 mg group there were improvements in β-cell function and the pro-insulin/insulin ratio.

Study NN2211-1499 was a double blind, double-dummy, randomised, parallel-group, dose titration study (with an open labelled OHA arm) of the effect on glycaemic control of individual maximum effective dose of liraglutide as add on therapy to metformin compared to monotherapy: liraglutide or metformin or metformin-SU in type 2 diabetes (Table 8).

Table 8: Details of Study NN2211-1499

Nr. of subjects with age and sex **Duration**	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
260 patients were screened and 144 were randomized to treatment: 36 to each treatment group. All were included in the ITT group There were fewer completers in the liraglutide groups 91 males, 53 females Age range 27 to 69 years 5 weeks	Male or female patients with type 2 diabetes, treated with OHA (mono- or combination therapy, and receiving at least 50% of maximum dose), HbA1c between 8.0-13.0% (both inclusive), aged 18-70 years, body mass index (BMI) between 25-40 kg/m^2. At randomisation, fasting plasma glucose had to be above 9 mmol/L (162 mg/dL)	Liraglutide 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, once-daily subcutaneous injection in the abdomen or thigh (in the evening) Metformin placebo Liraglutide 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, once-daily subcutaneous injection in the abdomen or thigh (in the evening) and metformin; 1000 mg, 1500 mg, 2000 mg; 500 mg tablets oral administration (administered morning and evening)	metformin; 1000 mg, 1500 mg, 2000 mg; 500 mg tablets oral administration (administered morning and evening) Liraglutide placebo metformin; 1000 mg, 1500 mg, 2000 mg; 500 mg tablets and glimepiride; 2 mg, 3 mg, 4 mg; 1 and 2 mg tablets for oral administration (administered in the morning)	Primary efficacy endpoint: fasting serum glucose after five weeks of treatment Secondary efficacy endpoints were: dose-response relationship of liraglutide as add-on therapy to metformin dose-response relationship of liraglutide as monotherapy 7-point plasma glucose profile, fructosamine, insulin, C-peptide, HbA1c, weight, β-cell function and insulin resistance (HOMA model)	The greatest decrease in FSG was in the metformin/liraglutide group, followed by metformin-glimepiride, followed by liraglutide. There was no change in the metformin alone group For the combination of liraglutide+metformin the liraglutide ED50 was 0.51 mg and ED90 was 0.80 mg For liraglutide alone, the ED50 was 1.74 mg and the ED90 was 2.63 mg The postprandial rise in plasma glucose was less in the liraglutide groups HbA1c was lowest in the metformin/liraglutide group, followed by metformin-glimepiride, followed by liraglutide. Body weight decreased in the liraglutide and metformin groups but not for the metformin/glimepiride group B-cell function improved in the liraglutide groups Insulin resistance improved in the metformin groups	There were 84 AEs reported in 27 (25%) subjects in the liraglutide group, 94 reported in 25 (69.4%) in the liraglutide/metformin group, 57 reported in 26 (72.2%) of the metformin group and 36 reported in 18 (50.0%) of the metformin/glimepiride group There was one SAE in the liraglutide group: chest pain There were no deaths 3 hypoglycaemic events occurred in the metformin/glimepiride group and one in the metformin/liraglutide group There were 9 withdrawals due to AEs: 6 from the liraglutide alone group, 2 from metformin alone, one from liraglutide/metformin and none from metformin/glimepiride

The study was conducted at 39 trial sites in 8 countries: Australia (4), Austria (2), Czech Republic (2), Denmark (5), France (4), Germany (5), Poland (2) and the United Kingdom (15).

The primary efficacy outcome measure was fasting serum glucose after five weeks of treatment. The secondary efficacy endpoints were: dose-response relationship of liraglutide as add-on therapy to metformin, dose-response relationship of liraglutide as monotherapy, seven point plasma glucose profile - HbA1c, body weight, C-peptide, insulin, fructosamine, β-cell function and insulin resistance (HOMA model).

The greatest decrease in fasting serum glucose was in the metformin/liraglutide group, followed by metformin-glimepiride, followed by liraglutide (Table 9). There was no change in the metformin alone group. There was a similar change in fructosamine. Insulin and C-peptide levels increased in the liraglutide groups, and to a lesser degree in the metformin/glimepiride group. For the combination of liraglutide+metformin the liraglutide ED_{50} was 0.51 mg and ED_{90} was 0.80 mg. For liraglutide alone, the ED_{50} was 1.74 mg and the ED_{90} was 2.63 mg. The postprandial rise in plasma glucose was less in the liraglutide groups. HbA1c was lowest in the metformin/liraglutide group, followed by metformin-glimepiride, followed by liraglutide. Body weight decreased in the liraglutide and metformin groups but not for the metformin/glimepiride group. β -cell function improved in the liraglutide groups. Insulin resistance improved in the metformin groups.

Table 9: Repeated Measures Analysis of Fasting Serum Glucose – ITT population

	Comparison of FSG (mmol/L) after 5 weeks of treatment.		
Treatment/Comparison	Adj.mean/diff	95% CI	P-value
Liraglutide+metformin	9.16	[8.44 ; 9.89]	
Liraglutide	11.69	[10.95 ; 12.44]	
Metformin	13.06	[12.27 ; 13.86]	
Metformin+glimepiride	10.41	[9.71 ; 11.12]	
Primary hypothesis:			
Liraglutide+metformin vs. metformin	-3.90	[-4.95 ; -2.85]*	<0.0001
Secondary hypotheses:			
Liraglutide+metformin vs. liraglutide	-2.53	[-3.54 ; -1.51]*	<0.0001
Liraglutide+metformin vs. metformin+glimepiride	-1.25	[-2.25 ; -0.25]*	0.0146
Liraglutide vs. metformin	-1.37	[-2.43 ; -0.32]*	0.0109
Liraglutide vs. metformin+glimepiride	1.28	[0.27 ; 2.29]*	0.0132

An asterisk indicates statistical significance.
The estimates are obtained from a repeated measurements analysis with treatment, previous OHA treatment, (mono- or combitherapy), sex, and treatment by visit as fixed effects. Subject as random effect, baseline FSG and BMI as covariate.

Study NN2211-1573 was a multicentre, double-blind, double-dummy, randomised, parallel, active-controlled clinical trial of 52 weeks treatment duration followed by a 52-week, open-label extension (reported separately) (Table 10). A substudy was conducted to assess β-cell function, body composition and a calcium stimulation test. The study was conducted at 138 sites in two countries: US (126) and Mexico (12).

Table 10: Details of Study NN2211-1573

Nr. Of subjects with age and sex **Duration**	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
746 patients were randomised to treatment: 247 to liraglutide 1.8 mg, 251 to liraglutide, and 248 to glimepiride 173 (70.0%) completed in the liraglutide 1.8 mg group, 162 (64.5%) in the liraglutide 1.2 mg group and 152 (61.3%) in the glimepiride 371 (49.7% male), 375 (50.3%) female Age range 19 to 79 years Similar demographics, prior treatment and disease severity 52 weeks	The inclusion criteria included: Subjects diagnosed with type 2 diabetes mellitus and treated with diet/exercise or not more than half-maximal oral antidiabetic drug (OAD) dose (monotherapy) for at least 2 months. OADs included sulphonylureas, meglitinides, amino acid derivatives, biguanides, alpha-glucosidase inhibitors and thiazolidinediones. Subjects treated with metformin 1500 mg or pioglitazone 30 mg were eligible for the trial At screening (Visit 1) HbA1c: - Diet/exercise treated subjects: HbA1c ≥7.0% and ≤11% and in OAD treated subjects: HbA1c ≥7.0% and ≤10% Age 18 to 80 years (inclusive) Body Mass Index (BMI) . 45.0 kg/m2	Liraglutide 1.2 mg daily Liraglutide 1.8 mg daily Dosing commenced at 0.6 mg daily then was force titrated up to the final dose injected subcutaneously in the upper arm, abdomen or thigh by use of the pen injector. The injection could be administered at any time of day that was considered to be convenient to the subject. Glimepiride placebo orally, once daily	Glimepiride orally, once daily 2 mg daily for 2 weeks then 4 mg daily for 2 weeks then 8 mg daily Centralised randomization by Interactive Voice Response System/Interactive Web Response System Stratified by baseline diabetes treatment	HbA1c, body weight, FPG, self-measured 8-point plasma glucose profiles, β-cell function (fasting insulin, fasting proinsulin, fasting C-peptide), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA, and ApoB), cardiovascular effects (hsCRP, PAI-1, and NT-proBNP), waist and hip circumference, patient-reported outcomes, In addition for the sub-study: DXA scan and FSITG	There was a dose dependent, greater reduction in HbA1c in the liraglutide groups than for glimepiride. A greater number (percentage) of patients in the liraglutide groups achieved a HbA1c < 7.0% (LOCF): 119 (50.9%) for liraglutide 1.8 mg, 101 (42.8%) for liraglutide 1.2% and 67 (27.8) for glimepiride. A greater number (percentage) of patients in the liraglutide groups achieved a HbA1c ≤6.5% (LOCF): 88 (37.6%) for liraglutide 1.8 mg, 66 (28.0%) for liraglutide 1.2% and 39 (16.2%) for glimepiride. There was a significant reduction in body weight in the liraglutide groups, and an increase in the glimepiride group. There was a dose dependent decrease in fasting plasma glucose with liraglutide compared with glimepiride. There was a greater decrease in postprandial glucose in the liraglutide 1.8 mg group compared with glimepiride	18 (7.3%) patients in the liraglutide 1.8 mg group, 25 (10.0%) in the liraglutide 1.2 mg, and 15 (6.0%) in the glimepiride group withdrew because of adverse events There were 957 AEs occurring in 195 (79.3%) patients in the liraglutide 1.8 mg group, 947 in 207 (82.5%) in the liraglutide 1.2 mg group and 705 in 177 (71.4%) of the glimepiride group. There was one death in the glimepiride group: motor vehicle accident. There were 9 SAEs reported in 8 (3.3%) patients in the liraglutide 1.8 mg group, 18 in 16 (6.4%) in the liraglutide 1.2 mg and 17 in 13 (5.2%) in the glimepiride. Gastrointestinal AEs: nausea, diarrhoea, constipation and flatulence occurred more frequently in the liraglutide groups in a dose-dependent manner

The inclusion criteria are described in Table 10. The exclusion criteria included:

- Treatment with insulin within the last three months except for short-term treatment for intercurrent illness at the discretion of the investigator
- Treatment with systemic corticosteroids or other drug (except for oral antidiabetic drugs [OADs]) which, in the investigator's opinion, could interfere with the glucose level
- Hypoglycaemia unawareness and/or recurrent severe hypoglycaemia as judged by the investigator
- Impaired liver function, defined as screening aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 2.5 times the upper normal range (ULN)
- Positive screening Hepatitis B antigen or Hepatitis C antibody

- Clinically significant, active (over the past 12 months) disease of the gastrointestinal, pulmonary, neurological, renal (impaired renal function defined as screening serum-creatinine ≥152 μmol/l), genitourinary, or haematological system that, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering study drug
- Clinically significant active cardiovascular disease, including history of myocardial infarction within the past 6 months and/or heart failure (New York Heart Association (NYHA) class III-IV).
- Cancer (except basal cell skin cancer or squamous cell skin cancer) or any clinically significant disease or disorder, except for conditions associated with type 2 diabetes, which in the investigator's opinion could interfere with the results of the trial.
- Severe uncontrolled treated or untreated hypertension (sitting diastolic blood pressure (BP) ≥100 or systolic ≥180 mmHg) or history of proliferative retinopathy or maculopathy requiring treatment
- Pregnant or positive pregnancy test at screening, nursing mother, or unwillingness to use adequate contraception
- Current addiction to alcohol or substances of abuse as determined by the investigator

There was a dose dependent, greater reduction in HbA1c in the liraglutide groups than for glimepiride (Table 11).

Table 11: ANCOVA of Primary Endpoint - Change in HbA1c (%) – ITT Population

Treatment / Comparison	Estimates			P-value
Least Square Means	N	Mean	SE	
Lira1.8mg	234	-1.136	0.081	
Lira1.2mg	236	-0.843	0.080	
Glimepiride	241	-0.513	0.077	
Estimated Treatment Differences	LSMean	95% CI		
Lira1.8mg - Glimepiride	-0.623	[-0.826 ; -0.421]		<.0001
Lira1.2mg - Glimepiride	-0.329	[-0.531 ; -0.127]		0.0014
Lira1.8mg - Lira1.2mg	-0.294	[-0.497 ; -0.091]		0.0046

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

A greater number (percentage) of patients in the liraglutide groups achieved a HbA1c < 7.0% (last observation carried forward [LOCF]): 119 (50.9%) for liraglutide 1.8 mg, 101 (42.8%) for liraglutide 1.2% and 67 (27.8) for glimepiride. A greater number (percentage) of patients in the liraglutide groups achieved a HbA1c≤6.5% (LOCF): 88 (37. 6%) for liraglutide 1.8 mg, 66 (28.0%) for liraglutide 1.2% and 39 (16.2%) for glimepiride. There was a significant reduction in body weight in the liraglutide groups, and an increase in the glimepiride group. There was a dose dependent decrease in fasting plasma glucose with liraglutide compared with glimepiride. There was a greater decrease in postprandial glucose in the liraglutide 1.8 mg group compared with glimepiride: least squares mean difference (95% CI) -0.715 (-1.199 to -0.231) mmol/L, p=0.0038. Fasting insulin and C-peptide levels decreased in all three treatment groups during the study. This decrease was greater for the liraglutide 1.8 mg group compared with the glimepiride: least squares mean difference (95% CI) -22.753 (-42.647 to -2.859) pmol/L p=0.0250. There were no differences between treatment groups in proinsulin to insulin ratio or in β-cell function. Insulin resistance decreased in the liraglutide groups compared with the glimepiride group. There was a significant fall in glucagon levels in the liraglutide group compared with glimepiride. There was a significant decrease in systolic blood pressure in the liraglutide 1.8 mg group compared with glimepiride: least squares mean difference (95% CI) -2.951 (-5.244 to -0.657) mmHg p=0.0117. There was a significant fall

in serum free fatty acids in the liraglutide group compared with glimepiride. ApoB levels increased in all three groups, but to a lesser degree in the liraglutide 1.8 mg group ($p<0.05$). There were no other significant changes in fasting serum lipid profile. There were no significant changes in urine albumin to creatinine ratio or in cardiac biomarkers. The mean waist circumference measured at baseline and Weeks 28 and 52 showed a decrease for the liraglutide treatment groups and a slight increase in the glimepiride group. At study end, the proportion of patients with metabolic syndrome was less in the liraglutide 1.8 mg group, 147 (66.5%) for than the glimepiride group, 185 (78.4%) p=0.0044. In the substudy population, there was no difference between groups in lean tissue mass, but there was a decrease in fat mass in the liraglutide groups and an increase in the glimepiride. Bone mineral mass and bone mineral density were unchanged. For overall Quality of Life scores, liraglutide 1.8 mg was superior to glimepiride.

Study NN2211-1572 was a multicentre, multinational, double-blind, double-dummy, randomised, active control, parallel-group, trial with an 18 months extension period investigating the safety and efficacy of liraglutide as add-on to metformin (Table 12). The 18 month extension period is reported separately. The study was conducted in a total of 170 centres in 21 countries: Argentina (4), Australia (19), Belgium (6), Bulgaria (1), Germany (33), Denmark (9), Spain (14), United Kingdom (11), Croatia (2), Hungary (5), Ireland (4), India (5), Italy (10), Netherlands (5), NZ (3), Norway (8), Romania (3), Russia (6), Sweden (8), Slovakia (7) and South Africa (7).

Table 12: Details of Study NN2211-1572

Nr. of subjects with age and sex **Duration of Treatment**	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration , Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
1662 patients were screened, 1091 were randomised, 242 to liraglutide 0.6 mg/metformin, 241 to liraglutide 1.2 mg/metformin, 242 to liraglutide 1.8 mg/metformin, 122 to metformin alone, and 244 to metformin/glimepiride 635 (58.2%) were male and 456 (41.8%) were female Age range was 25 to 79 years The treatment groups were similar in demographic characteristics and in disease severity 6 months with	Inclusions: Subjects diagnosed with type 2 diabetes and treated with OAD(s) for at least three months. HbA1c in the range of 7.0-10.0% (inclusive) in subjects on OAD combination therapy, or 7.0-11.0% (inclusive) in subjects on OAD monotherapy Age 18-80 years, both inclusive Body mass index (BMI) ≤40.0 kg/m2. Exclusions: Treatment with insulin within the last three months prior to trial (except for short-term treatment due to intercurrent illness at the discretion of the	Liraglutide active (0.6 mg/day) + glimepiride placebo + metformin (1.5-2.0 g/day) Liraglutide active (1.2 mg/day) + glimepiride placebo + metformin (1.5-2.0 g/day) Liraglutide active (1.8 mg/day) + glimepiride placebo + metformin (1.5-2.0 g/day) Liraglutide was injected subcutaneously in the upper arm, abdomen or thigh using a pen injector. Administered was at any time of the day but subjects were encouraged to	Liraglutide placebo + glimepiride placebo + metformin (1.5-2.0 g/day) Liraglutide placebo + glimepiride (4 mg/day) + metformin (1.5-2.0 g/day) Randomisation using Interactive Voice or Web Response System, IVRS/IWRS Stratification by previous OAD monotherapy or combination therapy	The primary efficacy measure was the change from baseline in HbA1c. Secondary efficacy outcomes included: weight, glycaemic control parameters; β-cell function; fasting glucagons, systolic and diastolic BP fasting lipid profile, cardiovascular biomarkers; urine albumin-to-creatinine ratio; waist circumference ; waist-to-hip ratio; and the proportion of subjects having metabolic syndrome. In	Liraglutide 1.8mg and 1.2 mg doses were superior to metformin alone, and non-inferior to glimepiride /metformin. There was an apparent plateau in the effect with the liraglutide 1.2 mg dose. Significant weight loss also occurred with liraglutide and this effect also had a plateau with the 1.2 mg dose. There was significant improvement in fasting plasma glucose compared with metformin alone but not in comparison with glimepiride/metformin . There was a similar finding for mean post-prandial plasma glucose, but no between treatment difference for mean prandial plasma glucose concentration. There were no between treatment differences in fasting	A total of 472 AEs were reported in 168 (69.4%) patients in the liraglutide 0.6 mg group, 516 in 169 (70.4%) in the liraglutide 1.2 mg, 556 in 178 (73.6%) in the liraglutide 1.8 mg, 180 in 74 (61.2%) in the metformin and 437 in 160 (66.1%) in the glimepiride/ metformin. A total of 8 SAEs were reported in 8 (3.35) patients in the liraglutide 0.6 mg group, 18 in 14 (5.8%) in the liraglutide 1.2 mg, 9 in 9 (3.7%) in the liraglutide 1.8 mg, 4 in 4

18 month open label extension	investigator). Impaired liver function, defined as alanine aminotransferase (ALAT) ≥ 2.5 times upper limit of normal Hepatitis B antigen or Hepatitis C antibody positive.	inject liraglutide at the same time each day		subsets of subjects: patient reported QOL; DEXA scan computerised tomography scan	insulin concentrations or fasting C-peptide concentrations. Pro-insulin to insulin ratio was lower for all liraglutide treatments in comparison with metformin but not in comparison with glimepiride/metformin.	(3.3%) in the metformin and 12 in 10 (4.1%) in the glimepiride/ metformin. There were no deaths reported during the study.

The primary efficacy outcome measure was the change from baseline in HbA1c after 26 weeks of treatment. The secondary efficacy outcome measures were: body weight, glycaemic control parameters (fasting plasma glucose; mean prandial increments of plasma glucose [based on self-measured 7-point plasma glucose profile]; mean post-prandial plasma glucose (based on self-measured 7-point plasma glucose profile); β-cell function (fasting insulin, fasting C-peptide, pro-insulin to insulin ratio, HOMA index of β-cell function, HOMA index of insulin resistance); fasting glucagons, systolic and diastolic blood pressure, fasting lipid profile (total cholesterol, LDL, VLDL, HDL, FFA and Apo-B), cardiovascular biomarkers (Highly sensitive C-reactive protein; N-terminal B-type natriuretic peptide); urine albumin-to-creatinine ratio; waist circumference; waist-to-hip ratio; the proportion of subjects having metabolic syndrome. In subsets of subjects additional outcome measures were evaluated: patient reported quality of life outcome; dual-energy X-ray absorptiometry scan (whole body fat mass; whole body lean mass; trunk fat mass; trunk lean mass; calculated whole body fat percentage; calculated trunk fat percentage); computerised tomography scan (visceral adipose tissue area, subcutaneous adipose tissue area; calculated visceral to subcutaneous adipose tissue ratio; and liver/spleen attenuation ratio). Hypothesis testing was performed using an analysis of covariance (ANCOVA) model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline measure as a covariate. A test of non-inferiority was performed between liraglutide + metformin and metformin + glimepiride with the criteria for non-inferiority being that the upper 95% CI for the difference in the change from baseline in HbA1c (liraglutide and metformin) – (metformin and glimepiride) must be <0.4%.

Liraglutide 1.8mg and 1.2 mg doses were superior to metformin alone, and non-inferior to glimepiride/metformin (Table 13). There was an apparent plateau in the effect with the liraglutide 1.2 mg dose. The effect was independent of prior treatment, gender, age or BMI. Significant weight loss also occurred with liraglutide and this effect also had a plateau with the 1.2 mg dose. There was significant improvement in fasting plasma glucose compared with metformin alone but not in comparison with glimepiride/metformin. There was a similar finding for mean post-prandial plasma glucose, but no between treatment difference for mean prandial plasma glucose concentration. There were no between treatment differences in fasting insulin concentrations or fasting C-peptide concentrations. Pro-insulin to insulin ratio was lower for all liraglutide treatments in comparison with metformin ($p<0.0001$) but not in comparison with glimepiride/metformin. HOMA measure of β-cell function significantly improved with liraglutide in comparison with metformin but not glimepiride/metformin but there was no significant difference in insulin resistance. Fasting glucagon levels decreased with liraglutide, but there was a significantly greater increase with glimepiride. Systolic blood pressure decreased significantly compared with glimepiride/metformin for liraglutide 1.2 mg and 1.8 mg: least squares mean (95% CI) -2.69

(-5.36 to -0.03) p=0.0467 for liraglutide 1.8 mg and -3.21 (-5.90 to -0.52) p=0.0128 for liraglutide 1.2 mg. There was no significant difference for diastolic blood pressure.

There were no between group differences in total cholesterol, LDL, or free fatty acids. VLDL decreased in the liraglutide groups relative to metformin. HDL decreased in the metformin group relative to liraglutide 0.6 mg and liraglutide 1.2 mg. Triglycerides decreased in the liraglutide 1.8 mg group relative to metformin: least squares mean (95% CI) -0.45 (-0.81 to -0.09) mmol/L p=0.0086; and also in the liraglutide 1.2 mg group: -0.46 (-0.82 to -0.10) mmol/L p=0.0074. ApoB decreased in the liraglutide 0.6 mg group relative to metformin: least squares mean (95% CI) -0.06 (-0.10 to -0.02) g/L p=0.0030. There were no between group differences in CRP or NT-proBNP. PAI-1 decreased in the liraglutide 1.8 mg group compared with glimepiride/metformin: least squares mean (95% CI) -3612 (-6538 to -686) U/L p=0.0093; as did that for liraglutide 1.2 mg, -4037 (-6957 to -1117) p=0.0027. There were no between group differences in urine albumin to creatinine ratio.

Table 13: ANCOVA of Primary Endpoint, Change in HbA1c (%) (LOCF), ITT

Comparison of change from baseline in HbA1c after 26 weeks of treatment

Treatment / Comparison	Estimates			Testing		
Least Square Means	N	LSMean	SE			
Lira 1.80	236	-1.00	(0.07)			
Lira 1.20	232	-0.97	(0.07)			
Lira 0.60	239	-0.69	(0.07)			
Main	234	-0.98	(0.07)			
Secondary	120	0.09	(0.09)			
Estimated Treatment Differences	LSMean	95% CI		Hypothesis	P-value	Conclusion
Lira 1.80 - Secondary	-1.09	[-1.30 ; -0.88]		Sup	<.0001*	Yes
Lira 1.80 - Main	-0.02	[-0.19 ; 0.15]		Non-inf	<.0001*	Yes
Lira 1.80 - Main	-0.02	[-0.19 ; 0.15]		Sup	0.4247	No
Lira 1.20 - Secondary	-1.06	[-1.27 ; -0.85]		Sup	<.0001*	Yes
Lira 1.20 - Main	0.01	[-0.16 ; 0.18]		Non-inf	<.0001*	Yes
Lira 1.20 - Main	0.01	[-0.16 ; 0.18]		Sup	NA	NA
Lira 0.60 - Secondary	-0.78	[-0.99 ; -0.57]		Sup	<.0001*	Yes
Lira 0.60 - Main	0.29	[0.12 ; 0.46]		Non-inf	0.1026	No
Lira 0.60 - Main	0.29	[0.12 ; 0.46]		Sup	NA	NA
Main - Secondary	-1.07	[-1.28 ; -0.86]		Sup	<.0001*	Yes

The estimates are from an ANCOVA model with treatment, country and previous treatment as fixed effects and baseline value as a covariate.
The P-values correspond to one-sided hypotheses of either Superiority or Non-inferiority.
* indicates statistical significance on a 2.5% level.
Main Comparator: Glimepiride + Metformin Secondary Comparator: Metformin

Waist circumference decreased in the liraglutide groups relative to metformin but there was no difference in waist to hip ratio. There was a decrease in lean tissue mass in the liraglutide groups relative to glimepiride/metformin and also a decrease in fat tissue. Visceral fat tissue decreased in the liraglutide 1.8 and 1.2 mg groups relative to glimepiride/metformin: least squares mean (95% CI) -25.14 (-47.33 to -2.96) cm^2 p=0.0206, and -25.33 (-47.50 to -3.16) cm^2 p=0.0193 respectively. Subcutaneous fat decreased in the liraglutide groups relative to glimepiride/metformin. There were no between group differences in overall quality of life scores. Relative to both comparators, there was a decrease in perceived hyperglycaemic episodes in the liraglutide 1.8 mg group (p<0.01). Relative to glimepiride/metformin, all the liraglutide groups had a decrease in the number of perceived hypoglycaemic episodes (p<0.01).

Study NN2211-1436 was a multicentre, multinational, randomised, double blind, double dummy, active control, parallel group clinical trial of 6 months duration comparing liraglutide in combination with glimepiride, glimepiride alone and rosiglitazone plus glimepiride (Table 14). The study was conducted in 116 centres in 21 countries: Argentina (7), Australia (9), Bulgaria (6), Croatia (3), Czech Republic (7), Finland (10), France (8), Hong Kong (1), India (4), Israel (3), Italy (5), Korea (3), Malaysia (3), Philippines (4), Poland (15), Romania (5), South Africa (5), Switzerland (5), Taiwan (4), Thailand (3) and Turkey (6).

The primary efficacy outcome measure was the change from baseline in HbA1c after 26 weeks of treatment. Secondary efficacy outcome measures were: body measurements (weight; waist and hip circumference); fasting plasma glucose; 7-point plasma glucose profiles (self-measured); β-cell function and glucagons (fasting insulin; fasting pro-insulin; fasting C-peptide and fasting glucagon); blood pressure; fasting lipid profile (total cholesterol; LDL-C; VLDL-C; HDL-C; triglyceride; free fatty acid; and apolipoprotein B); cardiovascular risk biomarkers (highly sensitive CRP; plasminogen activator inhibitor-1; N-terminal B-type natriuretic peptide). Safety outcome measures were: AEs and clinical laboratory tests. Hypothesis testing was performed using an ANCOVA model. If liraglutide/glimepiride was superior to glimepiride also then a non-inferiority test was to be performed for liraglutide/glimepiride compared with rosiglitazone/glimepiride, with the

criterion for non-inferiority being <0.4% (difference from the change from baseline in HbA1c).

Table 14: Details of Study NN2211-1436

Nr. Of subjects with age and sex **Duration of Treatment**	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
1712 subjects were screened, 1041 were randomised and 1040 received study treatment Of the randomised subjects, 514 (49.4%) were male, 527 (50.6%) were female, age range 24 to 80 years 233 were randomised to liraglutide 0.6 mg, 228 to liraglutide 1.2 mg, 234 to liraglutide 1.8 mg, 114 to glimepiride and 232 to rosiglitazone 894 (85.9%) subjects completed the entire trial period 26 weeks	Inclusions: Subjects diagnosed with type 2 diabetes and treated with OAD(s) for at least 3 months. HbA1c: 7.0-11.0 % (inclusive) in subjects on OAD monotherapy and 7.0-10.0 % (inclusive) in subjects on OAD combination therapy Age 18 – 80 years inclusive, Body mass index (BMI) ≤45.0 kg/m^2 Exclusions: Treatment with insulin within the last three months prior to the trial Impaired liver function, defined as ALAT ≥2.5 times ULN Subjects known to be Hepatitis B antigen or Hepatitis C antibody positive. Impaired renal function : serum-creatinine ≥125 µmol/L for males and ≥110 µmol/L for females Clinically significant active cardiovascular disease	Liraglutide active (0.6 mg/day) + glimepiride (2-4 mg/day) + rosiglitazone placebo Liraglutide active (1.2 mg/day) + glimepiride (2-4 mg/day) + rosiglitazone placebo Liraglutide active (1.8 mg/day) + glimepiride (2-4 mg/day) + rosiglitazone placebo Liraglutide and glimepiride were titrated up to the intended dose	Liraglutide placebo + glimepiride (2-4 mg/day) + rosiglitazone placebo Liraglutide placebo + glimepiride (2-4 mg/day) + rosiglitazone (4mg/day) Randomisation by Interactive Voice or Web Response System, Stratification by previous OAD monotherapy or combination therapy	The primary efficacy outcome measure was the change from baseline in HbA1c after 26 weeks of treatment.. Secondary efficacy outcome measures were: body measurements (weight; waist and hip circumference); fasting plasma glucose; 7-point plasma glucose profiles (self-measured); β-cell function and glucagons (fasting insulin; fasting pro-insulin; fasting C-peptide and fasting glucagons); blood pressure; fasting lipid profile; and cardiovascular risk biomarkers. Safety outcome measures were: AEs and clinical laboratory tests.	For the primary efficacy outcome measure, liraglutide 1.2 mg and 1.8 mg in combination with glimepiride were superior to both comparator groups, and liraglutide 0.6 mg in combination with glimepiride was superior to glimepiride alone and non inferior to rosiglitazone/ glimepiride. Black subjects had a better response to liraglutide. Weight and waist circumference were stable from baseline in the liraglutide/ glimepiride groups but there were increases in the rosiglitazone group. There was a greater decrease in FPG from baseline in the liraglutide 1.2 mg and 1.8 mg compared with both comparator groups. Postprandial glucose decreased in all the liraglutide/ glimepiride groups compared with glimepiride, and compared with rosiglitazone/ glimepiride for the liraglutide 1.8 mg group	425 AEs in 162 (69.5%) subjects in the liraglutide 0.6 mg-glimepiride group, 505 in 158 (69.3%) for liraglutide 1.2 mg-glimepiride, 480 in 164 (70.1%) for liraglutide 1.8 mg-glimepiride; 195 in 73 (64.0%) for glimepiride and 368 in 143 (61.9%) for rosiglitazone-glimepiride. Diarrhoea, nausea, dyspepsia and constipation were more frequent in the liraglutide groups There were 9 AEs in 7 (3.0%) subjects in the liraglutide 0.6 mg-glimepiride group, 8 in 8 (3.5%) for liraglutide 1.2 mg-glimepiride, 12 in 11 (4.7%) for liraglutide 1.8 mg-glimepiride; 4 in 3 (2.6%) for glimepiride and 6 in 6 (2.6%) for rosiglitazone-glimepiride. Hypoglycaemic episodes, including nocturnal hypoglycaemic episodes were more frequent with liraglutide-glimepiride

For the primary efficacy outcome measure, liraglutide 1.2 mg and 1.8 mg in combination with glimepiride were superior to both comparator groups, and liraglutide 0.6 mg in combination with glimepiride was superior to glimepiride alone and non inferior to rosiglitazone/ glimepiride (Table 15). Black subjects had a better response to liraglutide than White or Asian/Pacific Islander. Weight was stable from baseline in the liraglutide/ glimepiride groups but there was an increase in the rosiglitazone group. There was a significant increase in waist circumference in the rosiglitazone group in comparison with the

liraglutide 1.2 mg and 1.8 mg groups. There were no changes in waist/hip ratio. There was a greater decrease in FPG from baseline in the liraglutide 1.2 mg and 1.8 mg (in combination with glimepiride) compared with both comparator groups. Postprandial glucose decreased in all the liraglutide/ glimepiride groups compared with glimepiride, and compared with rosiglitazone/ glimepiride for the liraglutide 1.8 mg group.

Table 15: ANCOVA of Primary Endpoint - Change in HbA1c (%), ITT (LOCF)

Comparison of change from baseline in HbA1c after 26 weeks of treatment

Treatment / Comparison	Estimates			Testing		
Least Square Means	N	LSMean	SE			
Lira 1.80	226	-1.13	(0.07)			
Lira 1.20	223	-1.08	(0.07)			
Lira 0.60	224	-0.60	(0.07)			
Main	224	-0.44	(0.07)			
Secondary	107	0.23	(0.10)			
Estimated Treatment Differences	LSMean	95% CI		Hypothesis	P-value	Conclusion
Lira 1.80 - Secondary	-1.36	[-1.60 ; -1.13]		Sup	<.0001*	Yes
Lira 1.80 - Main	-0.69	[-0.88 ; -0.51]		Non-inf	<.0001*	Yes
Lira 1.80 - Main	-0.69	[-0.88 ; -0.51]		Sup	<.0001*	Yes
Lira 1.20 - Secondary	-1.31	[-1.54 ; -1.08]		Sup	<.0001*	Yes
Lira 1.20 - Main	-0.64	[-0.82 ; -0.45]		Non-inf	<.0001*	Yes
Lira 1.20 - Main	-0.64	[-0.82 ; -0.45]		Sup	<.0001*	Yes
Lira 0.60 - Secondary	-0.83	[-1.07 ; -0.60]		Sup	<.0001*	Yes
Lira 0.60 - Main	-0.16	[-0.35 ; 0.02]		Non-inf	<.0001*	Yes
Lira 0.60 - Main	-0.16	[-0.35 ; 0.02]		Sup	0.0429	No
Main - Secondary	-0.67	[-0.90 ; -0.44]		Sup	<.0001*	Yes

The estimates are from an ANCOVA model with treatment, country and previous treatment as fixed effects and baseline value as a covariate.
The P-values correspond to one-sided hypotheses of either Superiority or Non-inferiority.
An asterisk indicates statistical significance on a 2.5% level.
Main Comparator: Rosiglitazone + Glimepiride Secondary Comparator: Glimepiride

Fasting insulin was decreased in the liraglutide 1.8 mg group compared with rosiglitazone/ glimepiride: least squares mean difference (95% CI) 27.46 (2.27 to 52.65) pmol/L p=0.0273. C-peptide levels increased in the liraglutide 1.2 and 1.8 mg groups compared with both comparator groups and pro-insulin to insulin ratio decreased to reflect this change ($p<0.05$). Beta-cell function also improved in the liraglutide 1.2 mg and 1.8 mg groups relative to comparators but there was no difference in insulin resistance or fasting glucagon. There were no between group differences in blood pressure. Fasting total cholesterol, LDL-C were lower in the liraglutide group compared with rosiglitazone. VLDL-C levels were lower in the liraglutide 1.2 and 1.8 mg groups than the rosiglitazone group: least squares mean difference (95% CI) -0.10 (-0.20 to -0.00) mmol/L p=0.0476 and -0.11 (-0.21 to -0.00) mmol/L p=0.0361, respectively. HDL-C levels were lower in the liraglutide 1.8 mg group than the rosiglitazone group: least squares mean difference (95% CI) -0.06 (-0.10 to -0.02) mmol/L p=0.0018. There was no difference between the groups in fasting triglycerides, free fatty acids or apoprotein-B.

Highly selective CRP was higher in the liraglutide 1.8 mg group than the rosiglitazone group: least squares mean difference (95% CI) 2.50 (0.42 to 4.58) mg/L 0.0121.

There was no difference between the groups in PAI-1. NT-proBNP decreased in the liraglutide 1.2 mg and 1.8 mg groups in comparison with the rosiglitazone group: least squares mean difference (95% CI) -2.83 (-5.64 to -0.02) pmol/L p=0.0480 and -3.34 (-6.16 to -0.53) pmol/L p=0.0135, respectively. There was no difference between the groups in urine albumin/creatinine ratio.

Study NN2211-1574 was a multicentre, double-blind, randomised, parallel group trial of twenty-six weeks duration to assess liraglutide as add-on treatment to rosiglitazone-metformin combination in patients with type 2 diabetes (Table 16). The study was conducted at 96 trial sites in two countries: Canada (18) and US (78).

The inclusion criteria are summarised in Table 16 and the exclusion criteria included:

- Treatment with insulin within the last three months except for short-term treatment due to intercurrent illness, at the discretion of the investigator.
- Treatment with systemic corticosteroids or other drug (except for OADs) which in the investigator's opinion could interfere with the glucose level.
- Hypoglycaemia unawareness and/or recurrent severe hypoglycaemia as judged by the investigator.
- Impaired liver function, defined as screening AST or ALT≥2.5 times upper normal range
- History of hepatitis/hepatic disease within the previous two years, or has a positive Hepatitis B antigen or Hepatitis C antibody on screening laboratory results.
- Clinically significant, active (over the past 12 months) disease of the gastrointestinal, pulmonary, neurological, renal (impaired renal function defined as screening serum creatinine 125 ≥μmol/L for males and ≥115 μmol/L for females), genitourinary, or haematological system that, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering study drug.
- Clinically significant active cardiovascular disease, including a history of MI, within the past 6 months and/or heart failure (NYHA class III-IV).
- 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, in the investigator's opinion, could interfere with the results of the trial.
- Acute or chronic metabolic acidosis.
- Severe uncontrolled treated or untreated hypertension (sitting diastolic BP≥100 or systolic≥180 mmHg) or history of proliferative retinopathy or maculopathy requiring treatment.
- Pregnant or positive pregnancy test at screening, nursing mother, or unwillingness to use adequate contraception
- Any contraindication to taking metformin or rosiglitazone.
- Current addiction to alcohol or substances of abuse
- Subjects taking cardiac glycosides (e.g., digoxin) could not participate in the substudy.
- Subjects weighing greater than 250 pounds could not participate in the substudy

The primary efficacy outcome measure was the change from baseline in HbA1c. The secondary efficacy outcome measures were body weight, FPG, self-measured 7-point plasma glucose profiles, β-cell function (fasting insulin, fasting proinsulin, fasting C-peptide), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, and FFA), cardiovascular effects (hsCRP, PAI-1, and NT-proBNP), and waist and hip circumference. The safety outcome measures were: AEs, physical exam, ophthalmoscopy, hypoglycaemic episodes, laboratory safety parameters and liraglutide antibodies. Hypothesis testing was performed on the change from baseline using ANCOVA.

Table 16: Details of Study NN2211-1574

Nr. Of subjects with age and sex	Diagnosis + criteria for incl/exclusion	Test Product Dosage Regimen Route of administration, Formulation	Reference therapy Dose regimen Route of administration Duration of Treatment	Criteria for evaluation	Results (efficacy)	Adverse Reactions
533 subjects were randomized and 530 exposed to study treatment 178 were randomized to liraglutide 1.8 mg, 178 to liraglutide 1.2 mg and 177 to placebo 298 (55.9%) were male and 235 (44.1%) were female There were proportionally more females in the liraglutide 1.8 mg group The treatment groups were otherwise similar in baseline demographic characteristics and disease severity	Diagnosis of type 2 diabetes mellitus and treatment with one or more OADs for at least three months before screening. Screening HbA1c : a. ≥7.0 and ≤10.0 % in subjects on OAD combination therapy and/or exenatide b. ≤7.0 and ≥11.0 % in subjects on OAD monotherapy or exenatide therapy alone. Male or female ≥18 and ≤80 years of age Body mass index (BMI) ≤45.0 kg/m2 At randomisation: mean fasting plasma glucose reading measured three consecutive times by use of a plasma glucose meter by the investigator at the centre should be ≥7.5 mmol/L and ≤12.8 mmol/L.	Liraglutide 1.8 mg Liraglutide 1.2 mg In combination with rosiglitazone 8 mg and metformin 2000mg daily subjects in the Lira 1.2 and Lira 1.8 groups started with a 1-2 week period of forced titration with liraglutide for reaching the intended daily dose. Patients were randomised in a 1:1:1 ratio	Placebo In combination with rosiglitazone 8 mg and metformin 2000mg daily 26 week treatment period A metformin and rosiglitazone run-in period of 0-3 weeks with a maintenance period of 6 weeks followed by a 26-weeks treatment period	HbA1c, body weight, FPG, self-measured 7-point plasma glucose profiles, â-cell function (fasting insulin, fasting proinsulin, fasting C-peptide), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, and FFA), cardiovascular effects (hsCRP, PAI-1, and NT-proBNP), and waist and hip circumference. Safety: AEs, physical exam, ophthalmoscopy, hypoglycaemic episodes, lab safety parameters and liraglutide antibodies	Both liraglutide treatments were superior to placebo for the primary efficacy endpoint. There was a decrease in body weight for both liraglutide groups relative to placebo. Waist circumference decreased in the liraglutide groups relative to placebo. There was a greater decrease in FPG and post-prandial plasma glucose from baseline in both liraglutide groups relative to placebo. There was no overall difference between groups in prandial plasma glucose. There was no difference between groups in insulin levels. C-peptide levels decreased from baseline to a greater extent in the liraglutide groups. Pro-insulin to insulin ratio decreased in the liraglutide groups relative to placebo.	632 AEs reported in 148 (83.1%) subjects in the liraglutide 1.8 mg group, 498 in 149 (84.2%) in the liraglutide 1.2 mg and 362 in 123 (70.3%) in the placebo. Nausea, vomiting, diarrhoea, dyspepsia and headache were more common in the liraglutide groups, in a dose dependent manner. There were 10 SAEs reported in 7 (3.9%) subjects in the liraglutide 1.8 mg group, 8 in 8 (4.5%) in the liraglutide 1.2 mg and 13 in 12 (6.9%) in the placebo. No deaths were reported during the study. Hypoglycaemic episodes were more common to a similar extent in both liraglutide groups 27 (15.2%) in the liraglutide 1.8 mg group, 11 (6.2%) in the liraglutide 1.2 mg group and 6 (3.4%) in the placebo withdrew because of AEs

Both liraglutide treatments were superior to placebo for the primary efficacy endpoint (Table 17), and the decrease in HbA1c was similar for both liraglutide groups. There was a decrease in body weight for both liraglutide groups relative to placebo. Waist circumference decreased in the liraglutide groups relative to placebo. There was a greater decrease in FPG and post-prandial plasma glucose from baseline in both liraglutide groups relative to placebo. There was no overall difference between groups in prandial plasma glucose. There was no difference between groups in insulin levels. C-peptide levels decreased from baseline to a greater extent in the liraglutide groups. Pro-insulin to insulin ratio decreased in the liraglutide groups relative to placebo. Beta-cell function improved to a greater degree in the liraglutide groups. There was no between group difference in the change in insulin resistance or fasting glucagon levels. Systolic blood pressure decreased in the liraglutide groups relative to placebo but there was no difference in diastolic blood pressure. Total cholesterol,

VLDL-C, HDL-C was similar for the three groups. LDL-C decreased in the liraglutide 1.2 mg group relative to placebo: least squares mean difference (95% CI) -0.180 (-0.343 to -0.017) mmol/L p=0.0303. Triglycerides decreased in the liraglutide 1.2 mg group relative to placebo: least squares mean difference (95% CI) -0.249 (-0.490 to -0.009) mmol/L p=0.0424. FFA decreased to a greater extent in both liraglutide groups relative to placebo). There was no difference between treatments in urinary albumin-creatinine ratio, highly selective CRP or NT-proBNP. PAI-1 levels increased in the placebo group relative to liraglutide 1.8 mg.

Table 17: ANCOVA of Primary Endpoint - Change in HbA1c (%) – ITT

Treatment / Comparison	Estimates			P-value
Least Square Means	N	Mean	SE	
Lira1.8+OADs	177	-1.478	0.075	
Lira1.2+OADs	174	-1.482	0.078	
OADs	167	-0.541	0.080	
Estimated Treatment Differences	LSMean	95% CI		
Lira1.8+OADs - OADs	-0.936	[-1.119 ; -0.754]		<0.0001
Lira1.2+OADs - OADs	-0.941	[-1.123 ; -0.759]		<0.0001

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

Study NN2211-1697 was a multicentre, multinational, double-blind, randomised, parallel group clinical trial comparing liraglutide, glargine and placebo as add-on therapy to glimepiride and metformin in patients with type 2 diabetes (Table 18). The study was conducted at 107 centres in 17 countries: Argentina (5), Austria (7), Denmark (7), Finland (5), France (9), India (5), Italy (8), The Netherlands (8), Norway (5), Philippines (4), Poland (5), Russia (4), Serbia and Montenegro (4), Slovakia (6), South Africa (4), Spain (9) and United Kingdom (12).

The primary efficacy outcome measure was the change from baseline in HbA1c. The secondary efficacy outcome measures were: body weight, fasting plasma glucose (FPG), self-measured 8-point plasma glucose profiles, β-cell function (fasting insulin, fasting pro-insulin, fasting C-peptide), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB), cardiovascular risk biomarkers (hsCRP, PAI-1 and NT-proBNP) and waist and hip circumference. The safety outcome measures were AEs, physical examination, hypoglycaemic episodes, laboratory safety parameters and liraglutide antibodies. Hypothesis testing was performed using an ANCOVA model with treatment, country and previous anti-diabetic treatment as fixed effects and baseline HbA1c as a covariate. If liraglutide was superior to placebo then a secondary test of non-inferiority in comparison with glargine was performed, using the per-protocol population, with a 0.4% difference in HbA1c being the criterion for non-inferiority. If non-inferiority was demonstrated then a superiority test was to be performed using the ITT population.

Table 18: Details of Study NN2211-1697

Nr. of subjects with age and sex **Duration of Treatment**	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results** **(efficacy)**	**Adverse** **Reactions**
1036 subjects were screened, 581 were randomised and 576 received study treatment 232 were randomised to liraglutide, 234 to glargine and 115 to placebo 328 (56.5%) were males and 253 (43.5%) were females 207 (89.2%) in the liraglutide group, 219 (93.6%) in the glargine and 96 (83.5%) in the placebo completed the study 6 months	Inclusion criteria: Subjects diagnosed with type 2 diabetes and treated with OAD(s) for at least 3 months. HbA1c: 7.5-10.0% (both inclusive) in subjects on OAD monotherapy, and 7.0-10.0% (both inclusive) in subjects on OAD combination therapy Age 18-80 years, both inclusive BMI ≤45.0 kg/m2. Exclusion criteria: Treatment with insulin within the last 3 months prior to the trial (except for short-term treatment with insulin in connection with intercurrent illness at the discretion of the investigator). Impaired liver function, defined as ALAT ≥2.5 times upper limit normal Subjects known to be Hepatitis B antigen or Hepatitis C antibody positive.	Liraglutide active (1.8 mg/day) + glimepiride (2-4 mg/day) + metformin (2000 mg/day) Liraglutide, active or placebo, was injected SC in the upper arm, abdomen or thigh using the pen injector liraglutide, glimepiride and metformin doses were titrated up to the study doses over 3 weeks Randomisation was performed using Interactive Voice or Web Response System, and was stratified by previous treatment	Liraglutide placebo + glimepiride (2-4 mg/day) + metformin (2000 mg/day) Insulin glargine + glimepiride (2-4 mg/day) + metformin (2000 mg/day) Dosing of glargine was open-label, hence this arm of the trial was open-label. Glargine was titrated to a target HbA1c of <5.5 mmol/L Patients were blinded to liraglutide or placebo in the other two arms	HbA1c, body weight, fasting plasma glucose (FPG), self-measured 8-point plasma glucose profiles, β-cell function (fasting insulin, fasting pro-insulin, fasting C-peptide), fasting glucagon, systolic and diastolic blood pressure, fasting lipid profile (TC, LDL-C, VLDL-C, HDL-C, TG, FFA and ApoB, cardiovascular risk biomarkers (hsCRP, PAI-1 and NT-proBNP) and waist and hip circumference. AEs, physical examination, hypoglycaemic episodes, laboratory safety parameters	For the primary efficacy outcome measure liraglutide was superior to both comparator groups Liraglutide had a greater decrease in HbA1c in black There was a decrease in body weight with liraglutide, and a corresponding increase with glargine. There was a decrease in waist circumference with liraglutide relative to glargine. There was a greater fall in FPG with liraglutide than placebo, but not in comparison with glargine. There was a greater fall in postprandial glucose with liraglutide than placebo, but not in comparison with glargine. There was an increase in fasting insulin levels with liraglutide, and a decrease with placebo. Beta-cell function improved during the study in comparison with placebo	424 AEs reported in 151 (65.7%) subjects in the liraglutide group, 168 in 64 (56.1%) in the placebo group and 295 in 127 (54.7%) in the glargine group. Nausea, vomiting, dyspepsia, diarrhoea and headache were more common in the liraglutide group. There were 9 SAEs reported in 8 (3.5%) subjects in the liraglutide group, 9 in 7 (6.1%) in the placebo and 19 in 18 (7.8%) in the glargine. There were two deaths reported during the study both due to acute myocardial infarction: one in the glimepiride-metformin group and one in the glargine-glimepiride-metformin group. 11 (4.7%) in the liraglutide, 5 (2.1%) in the glargine and 1 (0.9%) in the placebo withdrew due to AEs

For the primary efficacy outcome measure liraglutide was superior to both comparator groups (Table 19). Liraglutide had a greater decrease in HbA1c in Black subjects ($p<0.05$), but gender, age and BMI did not affect efficacy. There was a decrease in body weight with liraglutide, and a corresponding increase with glargine. There was a decrease in waist circumference with liraglutide relative to glargine: least squares mean difference (95% CI) -2.40 (-3.14 to -1.65) cm $p<0.0001$. There was no difference between the groups in waist-hip ratio. There was a greater fall in FPG with liraglutide than placebo, but not in comparison with glargine. There was a greater fall in postprandial glucose with liraglutide than placebo, but not in comparison with glargine. There was no difference between treatments in prandial plasma glucose. There was an increase in fasting insulin levels with liraglutide, and a decrease with placebo: least squares mean difference (95% CI) 13.98 (2.39 to 25.57) pmol/L $p=0.0183$. Fasting C-peptide decreased in both comparator groups but was mostly unchanged in the liraglutide group. Pro-insulin to insulin ratio decreased in the liraglutide

group compared with placebo: least squares mean difference (95% CI) -0.10 (-0.15 to -0.05) p=0.0001. Beta-cell function improved during the study in comparison with placebo, but there was no change in insulin resistance or fasting glucagon concentration. There was a decrease in systolic blood pressure in the liraglutide group in comparison with glargine but no difference for diastolic blood pressure.

Table 19: ANCOVA of Primary Endpoint - Change in HbA1c (%) (LOCF), ITT

Comparison of change from baseline in HbA1c after 26 weeks of treatment

Treatment / Comparison	Estimates			Testing		
Least Square Means	N	LSMean	SE			
Lira 1.80	224	-1.33	(0.09)			
Main	225	-1.09	(0.09)			
Secondary	110	-0.24	(0.11)			
Estimated Treatment Differences	LSMean	95% CI		Hypothesis	P-value	Conclusion
Lira 1.80 - Secondary	-1.09	[-1.28 ; -0.90]		Sup	<.0001*	Yes
Lira 1.80 - Main	-0.24	[-0.39 ; -0.08]		Non-inf	<.0001*	Yes
Lira 1.80 - Main	-0.24	[-0.39 ; -0.08]		Sup	0.0015*	Yes
Main - Secondary	-0.85	[-1.04 ; -0.66]		Sup	<.0001*	Yes

The estimates are from an ANCOVA model with treatment, country and previous treatment as fixed effects and baseline value as a covariate.
The P-values correspond to one-sided hypotheses of either Superiority or Non-inferiority.
An asterisk indicates statistical significance on a 2.5% level.
Main Comparator: Glargine + OAD - Secondary Comparator: OAD

There was a decrease in total cholesterol in the liraglutide group relative to glargine: least squares mean difference (95% CI) -0.13 (-0.26 to -0.01) mmol/L p=0.0377. There was a decrease in LDL cholesterol in the liraglutide group relative to glargine: least squares mean difference (95% CI) -0.13 (-0.23 to -0.02) mmol/L 0.0182. There was an increase in FFA in the placebo group relative to liraglutide: least squares mean difference (95% CI) -0.06 (-0.12 to -0.01) mmol/L p=0.0317. There was no difference between the treatment groups in VLDL-C, HDL-C, triglycerides or ApoB. There was no difference between the treatment groups in highly selective CRP or NT-proBNP. PAI-1 decreased in all three treatment groups, but the decrease in the liraglutide was significantly greater for liraglutide than placebo. There was no difference between the groups in albumin-creatinine ratio.

Study NN2211-1334 was a multi-centre, double-blind, four treatment cohort, parallel group trial with placebo and four doses of liraglutide, in the treatment of Japanese subjects with type 2 diabetes (Table 20). The study was conducted at 63 centres in Japan.

The efficacy outcome measures were: HbA1c, glycaemic control parameters (FPG, 7-point plasma glucose profiles and PPPG), glucose metabolism-related parameters (fasting insulin, fasting pro-insulin, fasting C-peptide and fasting glucagon, post-prandial insulin and post-prandial glucagon), body weight, lipid profile, and biomarkers for cardiovascular effects.

After the 14-week treatment HbA1c decreased with increasing dose of liraglutide (placebo: 8.44%, 0.1 mg: 7.65%, 0.3 mg: 7.22%, 0.6 mg: 6.80% and 0.9 mg: 6.59%). The estimated reduction in HbA1c compared to the placebo group was -0.79% in the 0.1 mg group, -1.22% in the 0.3 mg group, -1.64% in the 0.6 mg group and -1.85% in the 0.9 mg group (baseline value: 8.30%). This was statistically significant compared with placebo at each dose level. There were statistically significant decreases in FPG and postprandial glucose. Plasma insulin, C-peptide levels increased. There was improved β-cell function but no change in

insulin resistance. There were no significant differences between the groups in body weight, serum lipids or cardiovascular safety parameters.

Table 20: Details of Study NN2211-1334

Nr. Of subjects with age and sex Duration of Treatment	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
226 subjects, 151 (66.8%) male and 72 (33.2%) female mean (SD) age 57.3 (8.2) years 45 randomised to 0.1 mg, 46 to 0.3 mg, 45 to 0.6 mg, 44 to 0.9 mg and 46 to placebo 14 weeks	Subjects with type 2 diabetes on diet therapy with or without OAD monotherapy, aged ≥ 20 and < 75 years, body mass index (BMI) < 30.0 kg/m2, HbA1C ≥ 7.0 % and < 10.0 %	Liraglutide: 0.1 mg group: 0.1 mg for 14 weeks, once daily 0.3 mg group: 0.3 mg for 14 weeks, once daily 0.6 mg group: 0.3 mg for a week + 0.6 mg for 13 weeks, once daily 0.9 mg group: 0.3 mg for a week + 0.6 mg for a week + 0.9 mg for 12 weeks, once daily Liraglutide was administered subcutaneously	HbA1C, Glycaemic control parameters (FPG, 7-point plasma glucose profiles and PPPG), Glucose metabolism related parameters (fasting insulin, fasting pro-insulin, fasting C-peptide and fasting glucagon, post prandial insulin and post prandial glucagon), Body weight, Lipid profile, Bio-markers for cardiovascular effects	The HbA1C after 14-week treatment decreased with increasing dose of liraglutide (placebo: 8.44%, 0.1 mg: 7.65%, 0.3 mg: 7.22%, 0.6 mg: 6.80% and 0.9 mg: 6.59%). The estimated reduction in HbA1C compared to the placebo group was -0.79% in the 0.1 mg group, -1.22% in the 0.3 mg group, -1.64% in the 0.6 mg group and -1.85% in the 0.9 mg group (baseline value: 8.30%). This was statistically significant compared with placebo at each dose level There were statistically significant decreases in FPG and postprandial glucose. Plasma insulin, C-peptide levels increased. There was improved β-cell function but no change in insulin resistance There were no significant differences between the groups in body weight, serum lipids or cardiovascular safety parameters	There were 62 AEs in 25 (55.6%) subjects in the 0.1 mg group, 67 in 32 (69.6%) in the 0.3 mg, 78 in 33 (73.3%) in the 0.6 mg, 63 in 33 (75.0%) in the 0.9 mg, and 65 in 31 (67.4%) in the placebo There were two SAEs: one in the 0.6 mg group and one in the 0.9 mg group There were no deaths One patient in the placebo group and one in the 0.9 mg group withdrew because of AEs

Study NN2211-2072 was a multicenter, randomized, double-blind, double-dummy, parallel-group dose-response, efficacy and safety study of metformin and five doses of liraglutide in previously treated OHA monotherapy obese subjects with type 2 diabetes (Table 21). The study was conducted at 31 centres in the US.

The efficacy outcome measures were: body weight, FPG, HbA1c, and fructosamine, body composition, VAS appetite scales, insulin, C-peptide, 7-point blood glucose profile, body measurements, and leptin. The safety outcome measures were AEs, hypoglycaemia and laboratory safety parameters. The dose levels used in the study appeared to have inferior glycaemic control compared to metformin. Metformin was significantly superior to the liraglutide 0.045 mg and 0.225 mg dose levels. There was no significant difference between the treatment groups for body weight.

Table 21: Details of Study NN2211-2072

Nr. of subjects with age and sex Duration of Treatment	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
319 subjects entered the study, 109 failed the run-in period 210 were randomised to treatment, mean (range) age 53.5 (27 to 73) years, 84 (40%) male, 126 (60%) female 179 (85.2%) completed the study 37 were randomised to liraglutide 0.045 mg, 35 to 0.225 mg, 33 to 0.45 mg, 34 to 0.6 mg and 37 to 0.75 mg 12 weeks	The trial was conducted in male and female subjects (age 18-75 yrs inclusive) who had type 2 diabetes, with at least 3 months pre-treatment with OHA monotherapy, with BMI≥27 kg/m2 and ≤42 kg/m2, and HbA1C ≤10%.	Liraglutide 0.75 mg, 0.60 mg, 0.45 mg, 0.225 mg, or 0.045 mg once daily subcutaneous dosing metformin placebo	Liraglutide placebo Metformin 1000 mg twice daily orally	Body weight, FPG, HbA1c, and fructosamine, body composition, VAS appetite scales, insulin, C-peptide, 7-point blood glucose profile, body measurements, and leptin. AEs, hypoglycaemia, laboratory safety parameters	The dose levels used in the study appeared to have inferior glycaemic control. Metformin was superior to the 0.045 mg and 0.225 mg dose levels. There was no significant difference between the treatment groups for body weight	There were 65 AEs reported in 24 (64.9%) subjects in the liraglutide 0.045 mg group, 50 in 21 (60.0%) in the 0.225 mg group, 32 in 17 (51.5%) in the 0.45 mg group, 54 in 23 (67.6%) in the 0.6 mg group, 64 in 25 (67.6%) in the 0.75 mg group and 46 in 19 (55.9%) in the metformin group The pattern of AEs was similar between the six treatment groups Five subjects reported SAEs \: one in the 0.045 mg group, one in the 0.6 mg group, one in the 0.75 mg group and two in the metformin group Five subjects in the liraglutide groups and two in the metformin withdrew because of AEs

Evaluator's comments

Liraglutide was superior to placebo (Study NN2211-1571) and also superior as add-on therapy with metformin (Study NN2211-1499) but the liraglutide/metformin combination was superior to liraglutide alone (Study NN2211-1499). The ED_{50} of liraglutide was 0.51 mg in combination with metformin compared to 1.74 mg for liraglutide monotherapy. Similarly the ED_{90} for liraglutide in combination with metformin was 0.8 mg compared with 2.63 mg in monotherapy. In combination liraglutide appeared to improve β-cell function, while metformin decreased insulin resistance. Liraglutide 1.2 mg and 1.8 mg in combination with metformin were superior to metformin alone (Study NN2211-1572).

Liraglutide was superior to glimepiride and also resulted in weight loss in comparison with glimepiride (Study NN2211-1573). In combination with metformin, liraglutide had similar efficacy to the glimepiride/metformin combination (Study NN2211-1572) but with a decrease in body weight, body fat and waist circumference. Liraglutide 1.2 mg and 1.8 mg improved glycaemic control as add-on therapy to glimepiride to a greater extent than rosiglitazone, and without the weight gain that occurred with rosiglitazone.

Liraglutide also improved glycaemic control as add-on therapy with rosiglitazone/ metformin in combination (Study NN2211-1574), and also in combination with glimepiride and metformin (Study NN2211-1697). Liraglutide in combination with glimepiride and metformin was superior to glargine in combination with glimepiride and metformin (Study NN2211-1697).

Liraglutide had some effects on fasting serum lipids: decrease in LDL-C (Study NN2211-1574, Study NN2211-1697), and a decrease in total cholesterol, LDL-C, VLDL-C and HDL-

C in comparison with rosiglitazone. However, in comparison with metformin, liraglutide had higher HDL-C (NN2211-1572).

With regard to liraglutide as monotherapy:

- In comparison with placebo, liraglutide resulted in clinically relevant improvement in measures of both short term and long-term diabetes control (Study NN2211-1310, Study NN2211-1571). The effect was clinically significant at the 0.60 mg dose level.
- In comparison with active comparator, liraglutide was superior to metformin but inferior to metformin + glimepiride (Study NN2211-1499) and liraglutide was superior to glimepiride (Study NN2211-1573).

With regard to liraglutide in dual therapy

- Liraglutide + metformin was superior to metformin + glimepiride (Study NN2211-1499)
- Liraglutide at the 1.2 mg and 1.8 mg dose levels in combination with metformin was superior to metformin alone (Study NN2211-1499, Study NN2211-1572).
- The ED_{50} of liraglutide decreased in dual therapy with metformin (Study NN2211-1499).
- Liraglutide 1.8mg and 1.2 mg doses + metformin was non-inferior to glimepiride/metformin (Study NN2211-1572) using clinically significant criteria for non-inferiority
- Liraglutide 1.2 mg and 1.8 mg in combination with glimepiride were superior to glimepiride and glimepiride + rosiglitazone (Study NN2211-1436)
- Liraglutide 0.6 mg in combination with glimepiride was superior to glimepiride alone (Study NN2211-1436)
- Liraglutide 0.6 mg in combination with glimepiride was non inferior to rosiglitazone/ glimepiride (Study NN2211-1436) using clinically significant criteria for non-inferiority

With regard to liraglutide in triple therapy:

- Liraglutide + metformin + rosiglitazone was superior to metformin + rosiglitazone (Study NN2211-1574)
- Liraglutide in combination with glimepiride and metformin was superior to glimepiride + metformin (Study NN2211-1697)
- Liraglutide in combination with glimepiride and metformin was superior to glargine + glimepiride + metformin (Study NN2211-1697)

With regard to minimum effective dose:

Liraglutide was effective in doses from 0.6 mg per day, but significant differences were demonstrated at the 1.2 mg and 1.8 mg per day dose levels. Optimal effect appears to be at the 1.8 mg dose level.

With regard to duration of effect:

In randomised controlled trials, the effect of liraglutide was demonstrated to be maintained for up to 12 months. In the open label extensions of Study NN2211-1572 and Study NN2211-1573 (discussed later), Study NN2211-1573 extension (a 12 month open label

extension) demonstrated the effect to be maintained for up to 2 years (this included the reduction in body weight) and Study NN2211-1572-extension indicated that the differences in efficacy between the treatment groups was less apparent by 18 months open-label treatment.

With regard to weight loss:

Change in body weight, waist circumference and hip/waist ratio were included as secondary efficacy variables in the clinical trials. There was a clinically and statistically significant decrease in body weight with liraglutide treatment both in monotherapy and in combination therapy.

With regard to timing of dose:

In the clinical trials dosing was encouraged to be at breakfast time, but subjects were allowed to administer the dose at any time of day provided they consistently dosed at the same time of day. Hence, the results of the clinical trials can be generalised to dosing at any time of day, without reference to meals/food intake.

Safety

Safety Data from Pharmacodynamic Studies

In ***Study NN2211-1149***, 41 of the 54 subjects receiving subcutaneous liraglutide (1.25-20 µg/kg) had 95 adverse events (AEs) and four of the six subjects receiving 5 µg/kg intravenous liraglutide had seven AEs. There were no deaths or serious adverse events (SAEs) reported. In total, there were 84 treatment emergent AEs in 36 subjects with probable or possible relation to liraglutide. There was a relationship between increasing dose and greater frequency of AEs: most AEs occurred at dose levels of 10-20 µg/kg and were mainly central and peripheral nervous system disorders, except for twelve AEs in five subjects at 20 µg/kg dose level which were gastrointestinal system disorders (five of nausea and seven of vomiting).

For ***Study NN2211-1189*** there were 114 AEs in 20 (91%) subjects in the liraglutide group, compared with 36 in nine (75%) subjects in the placebo. Dizziness and nausea were more common in the liraglutide group. Four subjects withdrew due to AEs: one healthy subject with mild-to-moderate dizziness and one Type 2 diabetic patient with severe hyperglycaemia and polydipsia at the 1.25 µg/kg dose level, one healthy subject with mild nausea, dizziness, headache, appetite decrease and dry mouth at the 7.5 µg/kg dose level and another with moderate nausea and diarrhoea at the 10 µg/kg dose level. Thirteen of the 22 subjects on active treatment experienced 36 AEs within the body system gastrointestinal (GI) system disorders, but this did not appear to be dose related. There were nine gastrointestinal system AEs in five of the twelve subjects receiving placebo.

In ***Study NN2211-1644*** there were a total of 37 (62.7%) subjects who reported AEs during liraglutide compared with 22 (38.6%) during placebo. The commonest AEs during liraglutide were: nausea (14), headache (12) and dizziness (5). There were no deaths or SAEs reported during the study.

For ***Study NN2211-1698*** conducted in 18 patients, there were 23 AEs reported in 10 patients, 18 of which were treatment emergent. The commonest AEs were nasopharyngitis (5), headache (3) and dyspepsia (2). There were no deaths or SAEs.

For ***Study NN2211-1589*** conducted in 46 patients, 36 (78.3%) patients experienced treatment emergent AEs: 17 (54.8%) during liraglutide, 21 (67.6%) during glimepiride and 12 (40.0%) during placebo. The most frequently reported AEs for liraglutide and glimepiride were gastrointestinal disorders such as nausea in five (16.1%) and four (12.9%) patients

respectively, diarrhoea in two (6.5%) and constipation in two (6.5%), and nervous system disorders as headache in six (19.4%) and seven (22.6%) patients respectively. Four subjects withdrew from the trial due to non-serious AEs. Three subjects withdrew during liraglutide treatment due to diarrhoea, depressed mood and erythema, respectively, and one subject withdrew during glimepiride treatment because of nausea, anorexia and anxiety. No serious AEs were reported during liraglutide treatment but five serious AEs were reported by two subjects during glimepiride treatment.

During ***Study NN2211-1332*** eight (62%) subjects experienced 19 AEs during liraglutide and three (23%) experienced AEs during placebo. There were no SAEs or deaths during the study. The commonest AEs during liraglutide were nausea (4) and headache (4).

During ***Study NN2211-1219*** conducted in eleven patients, four (36%) patients experienced five AEs during liraglutide (nausea 2, headache 2, vomiting 1), and one (9%) patient experienced one AE during placebo. There were no SAEs or deaths during the study.

For ***Study NN2211-2063*** there were three (33%) patients treated with liraglutide who experienced treatment emergent AEs: headache, anemia, and diarrhoea; compared with two (20%) placebo-treated patients: mild diarrhoea and a procedural site reaction. There were no SAEs or deaths reported during the study.

For ***Study NN2211-1224*** conducted in 19 patients, there were three AEs reported in three (16%) subjects in the liraglutide group: nausea (2), inflicted injury (1). There were two AEs were reported in two (11%) subjects in the placebo group. There were no deaths or SAEs reported during the study.

Safety Data from Pharmacokinetic Studies

In ***Study NN2211-1699*** seven treatment emergent AEs were reported in five subjects: dizziness (5), flatulence (1) and nausea (1). There were no SAEs or deaths.

For ***Study NN2211-1327,*** a study in 32 healthy volunteers, there were fewer treatment emergent AEs in the elderly group: two in one subject compared with 14 in seven subjects. The most frequently occurring AEs were headache (4), vomiting (4) and nausea (3). No deaths or SAEs were reported.

For ***Study NN2211-1328,*** conducted in six healthy and 18 hepatic impaired subjects, three treatment emergent AEs occurred during the study: headache (1), nausea (1) and bronchitis (1). There were no withdrawals due to AEs. There were no SAEs or deaths reported during the study.

For ***Study NN2211-1329,*** conducted in 30 subjects, six with normal renal function and 24 with impaired renal function, a total of 55 AEs were reported in 22 subjects. The most frequently occurring treatment emergent adverse events were headache (eight events in six subjects), vomiting (five events in four subjects) and nausea (four events in four subjects). There were no deaths or SAEs.

For ***Study NN2211-1330*** all 21 subjects participating in the trial reported treatment-emergent AEs during exposure to liraglutide: there were 126 during liraglutide treatment and 32 during placebo treatment. The most common AEs during liraglutide were nausea (15 subjects), headache (15) and decreased appetite (13). No subjects withdrew due to AEs. There were no SAEs or deaths reported during the study.

For ***Study NN2211-1608*** during Part A there were 293 treatment emergent AEs reported in 40 (95%) subjects: 202 during liraglutide and 91 during placebo. There were four SAEs in three subjects during liraglutide: headache (2), abdominal pain upper (1) and hypotonia (1).

There was one SAE during placebo: pelvic fracture. During Part B 198 treatment emergent AEs were reported in 27 (96%) of the 28 subjects: 125 during liraglutide and 73 during placebo. No SAEs were reported. The commonest AEs were nausea (25 in Part A and 14 in Part B) and headache (17 in Part A and 10 in Part B).

In ***Study NN2211-1331*** there were no serious adverse reactions. There were no deaths. Following administration of Test (Phase 3 formulation), nine subjects experienced 16 adverse events and following administration of Reference (Phase 2 formulation), nine subjects experienced 32 adverse events. Ten events occurring in four subjects were judged to be probably drug-related: moderate nausea, retching and vomiting (1); moderate abdominal pain (1); mild nausea (1); and mild nausea, malaise, headache, abdominal pain and diarrhoea (1).

In ***Study NN2211-1636*** a total of 63 treatment emergent adverse events occurred in 20 of the 24 subjects. The incidence of treatment emergent adverse events was similar following administration of all three liraglutide formulations (50%, 61%, and 42% at pH 7.7, 7.9, and 8.15, respectively). The most commonly reported events where relation to trial drug was possible or probable were: gastrointestinal disorders (vomiting and nausea) and nervous system disorders (headache and dizziness). There was one SAE: vomiting of moderate severity.

In ***Study NN2211-1692*** a total of 34 treatment emergent AEs were reported in 17 subjects. Of the 34 AEs, 20 were assessed as possibly related to trial treatment (11 to Formulation 4 and nine to Final Formulation 4). The most commonly reported AEs related to the trial products were nausea (7), headache (3), abdominal pain (2) and diarrhoea (2). All AEs were mild or moderate and equally distributed between the two formulations (17 for each treatment occasion). There were no SAEs or deaths during the trial.

In ***Study NN2211-1693*** there were 25 AEs reported by 13 subjects during the trial. Twenty two AEs were treatment emergent, and 15 were possibly related to study treatment (8 to formulation 4 and 7 to formulation 3). The most commonly reported AEs were nausea and headache. All AEs were mild or moderate. No SAEs or deaths occurred during the trial.

In ***Study NN2211-1745*** there were no SAEs or deaths reported during the trial. Ten AEs were reported in five subjects. Seven AEs were considered to be possibly related to trial products: nausea (6) and sensation of pressure in the head (1).

In ***Study NN2211-1694*** no AEs were reported during the study.

In ***Study NN2211-1551*** there were two AEs in the placebo group and one in the liraglutide (nasopharyngitis).

In ***Study NN2211-1326*** three of the six subjects at the 15 µg dose level experienced nausea and vomiting.

In ***Study NN2211-1591*** there were three treatment emergent AEs in the liraglutide groups: constipation (2) and facial skin depigmentation (1).

Safety Data from Efficacy Studies

For ***Study NN2211-1571*** conducted in 190 subjects, 123 exposed to liraglutide, 82 AEs were reported in 21 (51.2%) patients in the 1.90 mg/kg group, 77 in 19 (45.2%) of the 1.25 mg/kg group, 48 in 17 (42.5%) of the 0.65 mg/kg group and 52 in 20 (50.0%) of the placebo group. Gastrointestinal AEs were more frequent with liraglutide, but this did not appear to be dose related. There was one SAE in the 1.90 mg/kg group: influenza; and one in the placebo group: fall/hip pain/arthralgia. There were no deaths. There were four AEs leading to

withdrawal in the liraglutide groups, and three in the placebo group. There was one hypoglycaemic episode occurring in the 1.90 mg/kg group. There were no significant abnormalities in laboratory safety parameters.

For ***Study NN2211-1310*** conducted in 190 patients, 135 exposed to liraglutide, AEs were more common in the higher dose groups, particularly headache, dizziness and nausea. There were two SAEs: cerebral haemorrhage in the 0.60 mg group and skin ulceration in the placebo group. There were no deaths reported. There was one hypoglycaemic event in the 0.60 mg group and three in the glimepiride group.

For ***Study NN2211-1499*** there were 84 AEs reported in 27 (25%) subjects in the liraglutide group, 94 reported in 25 (69.4%) in the liraglutide/metformin group, 57 reported in 26 (72.2%) of the metformin group and 36 reported in 18 (50.0%) of the metformin/glimepiride group. Nausea, diarrhoea and headaches were more common in the liraglutide groups. There was one SAE in the liraglutide group: chest pain. There were no deaths reported during the study. Three hypoglycaemic events occurred in the metformin/glimepiride group and one in the metformin/liraglutide group. There were nine withdrawals due to AEs: six from the liraglutide alone group, two from metformin alone, one from liraglutide/metformin and none from metformin/glimepiride. Five subjects in the liraglutide group and four in the liraglutide/metformin group had elevated ALT during the study, compared with six in the metformin group and two in the metformin/glimepiride group. Amylase and lipase levels were not reported.

For ***Study NN2211-1573*** there were 957 AEs occurring in 195 (79.3%) patients in the liraglutide 1.8 mg group, 947 in 207 (82.5%) in the liraglutide 1.2 mg group and 705 in 177 (71.4%) of the glimepiride group. There was one death in the glimepiride group: motor vehicle accident. There were nine SAEs reported in eight (3.3%) patients in the liraglutide 1.8 mg group, 18 in 16 (6.4%) in the liraglutide 1.2 mg and 17 in 13 (5.2%) in the glimepiride. Gastrointestinal AEs: nausea, diarrhoea, constipation and flatulence occurred more frequently in the liraglutide groups in a dose-dependent manner (Table 22). The percentage of patients with nausea in the liraglutide groups was greatest in the first month of the study, then decreased into the second month of the study. There were no clinically significant between group differences in laboratory safety values, but amylase and lipase were not tested. There were no major hypoglycaemic episodes. Minor hypoglycaemic episodes occurred less frequently in the liraglutide groups: 48 episodes in 19 (7.7%) patients in the liraglutide 1.8 mg group, 58 in 28 (11.2%) in the liraglutide 1.2 mg and 365 in 60 (24.2%) in the glimepiride. Five patients developed liraglutide antibodies.

Table 22: Treatment-Emergent Adverse Events (>5%) by System Organ Class and Preferred Term - Safety Population

System Organ Class Preferred Term	Lira1.8 N (%)	 E	Lira1.2 N (%)	 E	Glimepiride N (%)	 E
Safety Analysis Set	246		251		248	
Adverse Events	195 (79.3)	956	207 (82.5)	947	177 (71.4)	705
Gastrointestinal Disorders	126 (51.2)	332	122 (48.6)	282	64 (25.8)	139
Constipation	28 (11.4)	32	21 (8.4)	24	12 (4.8)	12
Diarrhoea	46 (18.7)	61	39 (15.5)	60	22 (8.9)	34
Flatulence	13 (5.3)	14	4 (1.6)	4	4 (1.6)	4
Nausea	72 (29.3)	107	69 (27.5)	91	21 (8.5)	28
Vomiting	23 (9.3)	32	31 (12.4)	35	9 (3.6)	10
General Disorders And Administration Site Conditions	41 (16.7)	59	33 (13.1)	41	37 (14.9)	44
Infections And Infestations	102 (41.5)	184	119 (47.4)	207	90 (36.3)	153
Influenza	20 (8.1)	25	17 (6.8)	20	9 (3.6)	15
Nasopharyngitis	9 (3.7)	10	17 (6.8)	18	13 (5.2)	14
Sinusitis	13 (5.3)	18	15 (6.0)	16	15 (6.0)	17
Upper Respiratory Tract Infection	24 (9.8)	30	23 (9.2)	28	14 (5.6)	21
Urinary Tract Infection	10 (4.1)	13	20 (8.0)	24	10 (4.0)	11
Injury, Poisoning And Procedural Complications	24 (9.8)	27	22 (8.8)	26	29 (11.7)	33
Investigations	23 (9.3)	28	16 (6.4)	21	18 (7.3)	24
Metabolism And Nutrition Disorders	35 (14.2)	42	38 (15.1)	46	28 (11.3)	30
Musculoskeletal And Connective Tissue Disorders	46 (18.7)	59	48 (19.1)	63	38 (15.3)	55
Back Pain	11 (4.5)	11	14 (5.6)	16	11 (4.4)	11
Nervous System Disorders	49 (19.9)	71	56 (22.3)	101	55 (22.2)	78
Dizziness	16 (6.5)	18	13 (5.2)	18	13 (5.2)	14
Headache	18 (7.3)	25	27 (10.8)	47	23 (9.3)	30
Psychiatric Disorders	21 (8.5)	21	21 (8.4)	25	14 (5.6)	17
Respiratory, Thoracic And Mediastinal Disorders	28 (11.4)	39	21 (8.4)	31	28 (11.3)	35
Skin And Subcutaneous Tissue Disorders	24 (9.8)	26	23 (9.2)	26	17 (6.9)	19
Vascular Disorders	15 (6.1)	15	11 (4.4)	12	17 (6.9)	21
Hypertension	8 (3.3)	8	7 (2.8)	7	15 (6.0)	17

N: Number of subjects with adverse events.
%: Proportion of subjects in analysis set having adverse event.
E: Number of adverse events.
A Treatment Emergent Adverse Event is defined as an event occurring between first drug date and last drug date+7 days or starting before first drug date with increasing severity during this period.

In ***Study NN2211-1572*** conducted in 1087 subjects, 724 of whom were exposed to liraglutide, there were a total of 472 AEs were reported in 168 (69.4%) patients in the liraglutide 0.6 mg/metformin group, 516 in 169 (70.4%) in the liraglutide 1.2 mg/ metformin, 556 in 178 (73.6%) in the liraglutide 1.8 mg/metformin, 180 in 74 (61.2%) in the metformin and 437 in 160 (66.1%) in the glimepiride/ metformin. There was an excess of patients reporting nausea, diarrhoea and vomiting in the liraglutide groups, all of which appeared to be dose-related (Table 23). A total of eight SAEs were reported in eight (3.35) patients in the liraglutide 0.6 mg group, 18 in 14 (5.8%) in the liraglutide 1.2 mg, nine in nine (3.7%) in the liraglutide 1.8 mg, four in four (3.3%) in the metformin and twelve in ten (4.1%) in the glimepiride/ metformin. There were greater numbers of patients in the liraglutide groups withdrawn because of AEs: eleven (4.5%) patients in the liraglutide 0.6 mg group, 23 (9.5%) in the liraglutide 1.2 mg group, 29 (12.0%) in the liraglutide 1.8 mg group, two (1.6%) in the metformin and eight (3.3%) in the glimepiride/ metformin. There was one death reported during the run-in period in the metformin group. Median duration of exposure to liraglutide was 182 days. There was one case of pancreatitis in the liraglutide 1.2 mg group (classified

as severe), and one case of acute pancreatitis in the glimepiride/metformin group. There were no clinically relevant between group differences in laboratory values, but neither amylase nor lipase analyses were routinely performed.

Table 23: TEAEs Reported by More than 5% of Subjects Presented by System Organ Class and Preferred Term

	Lira 0.6 + Met N (%)	E	Lira 1.2 + Met N (%)	E	Lira 1.8 + Met N (%)	E	Met N (%)	E	Glim + Met N (%)	E
Safety Analysis Set	242		240		242		121		242	
Adverse Event	168 (69.4)	472	169 (70.4)	516	178 (73.6)	556	74 (61.2)	180	160 (66.1)	437
Gastrointestinal disorders	84 (34.7)	137	95 (39.6)	164	106 (43.8)	219	21 (17.4)	31	41 (16.9)	51
Nausea	26 (10.7)	26	39 (16.3)	46	45 (18.6)	62	5 (4.1)	6	8 (3.3)	11
Diarrhoea	23 (9.5)	26	20 (8.3)	29	36 (14.9)	46	5 (4.1)	5	9 (3.7)	10
Vomiting	13 (5.4)	14	16 (6.7)	18	18 (7.4)	20	1 (0.8)	1	1 (0.4)	2
Dyspepsia	9 (3.7)	10	5 (2.1)	5	17 (7.0)	21	1 (0.8)	4	3 (1.2)	6
Infections and infestations	70 (28.9)	95	69 (28.8)	84	66 (27.3)	87	28 (23.1)	40	65 (26.9)	103
Nasopharyngitis	27 (11.2)	34	21 (8.8)	24	21 (8.7)	22	11 (9.1)	15	30 (12.4)	38
Nervous system disorders	23 (9.5)	29	37 (15.4)	47	46 (19.0)	58	12 (9.9)	13	36 (14.9)	51
Headache	13 (5.4)	16	22 (9.2)	26	30 (12.4)	40	8 (6.6)	8	23 (9.5)	35
Musculoskeletal and connective tissue disorders	27 (11.2)	33	25 (10.4)	26	31 (12.8)	40	20 (16.5)	20	36 (14.9)	40
Metabolism and nutrition disorders	18 (7.4)	20	31 (12.9)	32	27 (11.2)	31	10 (8.3)	10	11 (4.5)	12
Anorexia	6 (2.5)	6	10 (4.2)	10	14 (5.8)	15	1 (0.8)	1	1 (0.4)	1
Decreased appetite	4 (1.7)	4	14 (5.8)	15	10 (4.1)	10	0 (0.0)	0	0 (0.0)	0
Investigations	18 (7.4)	23	13 (5.4)	15	11 (4.5)	13	11 (9.1)	11	14 (5.8)	22
General disorders and administration site conditions	15 (6.2)	15	21 (8.8)	24	14 (5.8)	14	6 (5.0)	9	16 (6.6)	19
Eye disorders	14 (5.8)	16	15 (6.3)	15	15 (6.2)	15	7 (5.8)	9	15 (6.2)	16
Injury, poisoning and procedural complications	12 (5.0)	14	10 (4.2)	15	8 (3.3)	9	5 (4.1)	6	17 (7.0)	24
Vascular disorders	16 (6.6)	17	11 (4.6)	11	11 (4.5)	11	3 (2.5)	3	14 (5.8)	16
Skin and subcutaneous tissue disorders	9 (3.7)	9	13 (5.4)	15	7 (2.9)	7	6 (5.0)	7	14 (5.8)	17
Respiratory, thoracic and mediastinal disorders	11 (4.5)	11	12 (5.0)	16	7 (2.9)	8	2 (1.7)	2	13 (5.4)	16
Cardiac disorders	9 (3.7)	10	14 (5.8)	15	8 (3.3)	8	2 (1.7)	3	6 (2.5)	6
Psychiatric disorders	4 (1.7)	4	7 (2.9)	11	15 (6.2)	15	3 (2.5)	4	6 (2.5)	6

If adverse events in a system organ class were reported by more than 5% of subjects with none of the preferred terms being reported by more than 5% of subjects, then this table includes only the system organ class.
N: Number of subjects with adverse event
%: Proportion of subjects having adverse event
E: Number of adverse events

For ***Study NN2211-1436*** conducted in 1040 subjects, 694 of whom were exposed to liraglutide, there were 425 AEs in 162 (69.5%) subjects in the liraglutide 0.6 mg-glimepiride group, 505 in 158 (69.3%) for liraglutide 1.2 mg-glimepiride, 480 in 164 (70.1%) for liraglutide 1.8 mg-glimepiride; 195 in 73 (64.0%) for glimepiride and 368 in 143 (61.9%) for the rosiglitazone-glimepiride group. Diarrhoea, nausea, dyspepsia and constipation were more frequent in the liraglutide groups (Table 24). There were nine AEs in seven (3.0%) subjects in the liraglutide 0.6 mg-glimepiride group, eight in eight (3.5%) for liraglutide 1.2 mg-glimepiride, twelve in eleven (4.7%) for liraglutide 1.8 mg-glimepiride; four in three (2.6%) for glimepiride and six in six (2.6%) for the rosiglitazone-glimepiride group. There were no deaths reported during the study. Five (2.1%) in the liraglutide 0.6 mg group withdrew due to AEs, eleven (4.8%) in the liraglutide 1.2 mg group, nine (3.8%) in the liraglutide 1.8 mg group, six (5.3%) in the glimepiride group and eight (3.7%) in the rosiglitazone group. The mean (SD) duration of treatment (days) was: 171.1 (36.4) for liraglutide 0.6 mg-glimepiride; 164.8 (47.5) for liraglutide 1.2 mg-glimepiride; 171.9 (37.6) for liraglutide 1.8 mg-glimepiride; 151.0 (58.0) for glimepiride and 165.4 (43.8) for the rosiglitazone-glimepiride group.

Table 24: TEAEs Reported By > 5 % of Subjects Presented by System Organ Class and Preferred Term

	Lira 0.6 + Glim N (%)	E	Lira 1.2 + Glim N (%)	E	Lira 1.8 + Glim N (%)	E	Glim N (%)	E	Rosi + Glim N (%)	E
Safety Analysis Set	233		228		234		114		231	
Adverse Event	162 (69.5)	425	158 (69.3)	505	164 (70.1)	489	73 (64.0)	195	143 (61.9)	368
Infections and infestations	76 (32.6)	111	63 (27.6)	92	62 (26.5)	89	41 (36.0)	73	71 (30.7)	107
Upper respiratory tract infection	25 (10.7)	29	17 (7.5)	21	14 (6.0)	23	12 (10.5)	20	23 (10.0)	30
Nasopharyngitis	13 (5.6)	17	11 (4.8)	17	16 (6.8)	17	5 (4.4)	9	12 (5.2)	14
Gastrointestinal disorders	73 (31.3)	103	83 (36.4)	149	73 (31.2)	132	22 (19.3)	26	35 (15.2)	45
Diarrhoea	16 (6.9)	18	18 (7.9)	31	16 (6.8)	23	2 (1.0)	2	5 (2.2)	6
Nausea	12 (5.2)	14	24 (10.5)	32	16 (6.8)	17	2 (1.8)	3	6 (2.6)	7
Dyspepsia	7 (3.0)	8	10 (4.4)	11	19 (8.1)	19	1 (0.9)	1	6 (2.6)	6
Constipation	9 (3.9)	9	12 (5.3)	13	16 (6.8)	16	1 (0.9)	1	4 (1.7)	4
Abdominal pain	5 (2.1)	6	4 (1.0)	4	5 (2.1)	5	6 (5.3)	6	3 (1.3)	3
Nervous system disorders	25 (10.7)	32	40 (17.5)	68	35 (15.0)	67	20 (17.5)	26	30 (13.0)	42
Headache	14 (6.0)	19	23 (10.1)	37	23 (9.8)	48	14 (12.3)	16	20 (8.7)	26
Musculoskeletal and connective tissue disorders	27 (11.6)	36	27 (11.0)	32	27 (11.5)	40	10 (8.0)	11	26 (11.3)	33
General disorders and administration site conditions	22 (9.4)	23	25 (11.0)	28	26 (11.1)	27	7 (6.1)	7	17 (7.4)	21
Metabolism and nutrition disorders	15 (6.4)	15	24 (10.5)	29	21 (9.0)	23	7 (6.1)	7	15 (6.5)	15
Investigations	12 (5.2)	16	13 (5.7)	14	10 (4.3)	16	6 (5.3)	7	17 (7.4)	23
Eye disorders	11 (4.7)	14	15 (6.6)	15	15 (6.4)	18	7 (6.1)	7	12 (5.2)	13
Injury, poisoning and procedural complications	10 (4.3)	10	9 (3.9)	9	10 (4.3)	13	4 (3.5)	5	12 (5.2)	13
Respiratory, thoracic and mediastinal disorders	17 (7.3)	17	9 (3.9)	12	6 (2.6)	7	4 (3.5)	4	7 (3.0)	8

E: Number of adverse events, N: Number of subjects with adverse events
%: Proportion of subjects having adverse Events

Hypoglycaemic episodes, including nocturnal hypoglycaemic episodes, were more frequent in the liraglutide-glimepiride groups indicating that this problem may be exacerbated by the liraglutide-glimepiride combination.

Pulse rate increased in the liraglutide groups. There were no between-group differences in laboratory safety parameters. Chronic pancreatitis was reported in one patient in the liraglutide 0.6 mg group. Amylase and lipase were not measured as laboratory safety parameters.

In ***Study NN2211-1574*** conducted in 530 subjects, 355 of whom were exposed to liraglutide, there were 632 AEs reported in 148 (83.1%) subjects in the liraglutide 1.8 mg group, 498 in 149 (84.2%) in the liraglutide 1.2 mg and 362 in 123 (70.3%) in the placebo. Nausea, vomiting, diarrhoea, dyspepsia and headache were more common in the liraglutide groups, in a dose dependent manner (Table 25). There were ten SAEs reported in seven (3.9%) subjects in the liraglutide 1.8 mg group, eight in eight (4.5%) in the liraglutide 1.2 mg and 13 in twelve (6.9%) in the placebo. No deaths were reported during the study. Hypoglycaemic episodes were more common, and to a similar extent, in both liraglutide groups. Nine (6.7%) subjects in the liraglutide 1.8 mg group and six (4.1%) in the liraglutide group developed antibodies to liraglutide. These antibodies were neutralizing in three (2.2%) subjects in the liraglutide 1.8 mg group and one (0.7%) in the liraglutide 1.2 mg group. No cases of pancreatitis were reported. One patient in the liraglutide 1.2 mg group had a treatment emergent myocardial infarction. One patient in the liraglutide 1.2 mg group developed congestive cardiac failure. The mean (SD) duration of exposure to liraglutide 1.8 mg-

rosiglitazone-glimepiride was 150.3 (59.9) days, and to liraglutide 1.2 mg-rosiglitazone-glimepiride was 167.3 (42.6) days. There were no clinically significant differences between the treatment groups in laboratory safety parameters.

Table 25: Treatment Emergent Adverse Events (>5%) by System Organ Class and Preferred Term

System Organ Class Preferred Term	Lira1.8+OADs N (%)	 E	Lira1.2+OADs N (%)	 E	OADs N (%)	 E
Safety Analysis Set	178		177		175	
Adverse Events	148 (83.1)	632	149 (84.2)	498	123 (70.3)	362
Eye Disorders	7 (3.9)	7	13 (7.3)	14	5 (2.9)	5
Gastrointestinal Disorders	99 (55.6)	256	80 (45.2)	156	33 (18.9)	57
Constipation	9 (5.1)	11	9 (5.1)	9	2 (1.1)	2
Diarrhoea	32 (18.0)	39	18 (10.2)	22	11 (6.3)	12
Dyspepsia	9 (5.1)	11	8 (4.5)	8	4 (2.3)	4
Nausea	71 (39.9)	94	52 (29.4)	62	15 (8.6)	17
Vomiting	31 (17.4)	49	13 (7.3)	23	5 (2.9)	5
General Disorders And Administration Site Conditions	32 (18.0)	48	29 (16.4)	40	28 (16.0)	40
Fatigue	9 (5.1)	10	9 (5.1)	10	3 (1.7)	3
Oedema Peripheral	3 (1.7)	3	9 (5.1)	12	14 (8.0)	17
Infections And Infestations	60 (33.7)	92	62 (35.0)	83	64 (36.6)	81
Nasopharyngitis	16 (9.0)	17	14 (7.9)	17	9 (5.1)	10
Upper Respiratory Tract Infection	15 (8.4)	20	15 (8.5)	20	19 (10.9)	19
Injury, Poisoning And Procedural Complications	15 (8.4)	16	3 (1.7)	4	8 (4.6)	8
Investigations	13 (7.3)	13	15 (8.5)	19	17 (9.7)	20
Metabolism And Nutrition Disorders	38 (21.3)	42	33 (18.6)	35	12 (6.9)	12
Anorexia	19 (10.7)	20	13 (7.3)	14	0	0
Decreased Appetite	17 (9.6)	17	16 (9.0)	17	2 (1.1)	2
Musculoskeletal And Connective Tissue Disorders	29 (16.3)	39	21 (11.9)	27	23 (13.1)	29
Back Pain	9 (5.1)	9	5 (2.8)	6	4 (2.3)	4
Nervous System Disorders	32 (18.0)	44	26 (14.7)	35	21 (12.0)	27
Headache	16 (9.0)	20	13 (7.3)	14	8 (4.6)	8
Respiratory, Thoracic And Mediastinal Disorders	15 (8.4)	21	18 (10.2)	25	21 (12.0)	25
Skin And Subcutaneous Tissue Disorders	13 (7.3)	14	14 (7.9)	16	13 (7.4)	14

N: Number of subjects with adverse events.
%: Proportion of subjects in analysis set having adverse event.
E: Number of adverse events.
A Treatment Emergent Adverse Event is defined as an event occurring between first drug drug date and last drug date+7 days or starting before first drug date with increasing severity during this period.

In ***Study NN2211-1697*** conducted in 576 subjects, 230 of whom were exposed to liraglutide, there were 424 AEs reported in 151 (65.7%) subjects in the liraglutide/ glimepiride/ metformin group, 168 in 64 (56.1%) in the placebo/ glimepiride/ metformin group and 295 in 127 (54.7%) in the glargine / glimepiride/ metformin group. Nausea, vomiting, dyspepsia, diarrhoea and headache were more common in the liraglutide group (Table 26). There were nine SAEs reported in eight (3.5%) subjects in the liraglutide group, nine in seven (6.1%) in the placebo and 19 in 18 (7.8%) in the glargine. There were two deaths reported during the study, both due to acute myocardial infarction: one in the glimepiride-metformin group and one in the glargine-glimepiride-metformin group. Eleven (4.7%) subjects in the liraglutide, five (2.1%) in the glargine and one (0.9%) in the placebo group withdrew due to AEs. The

mean (SD) duration of exposure was 170.3 (39.9) days for liraglutide, 169.4 (34.5) days for placebo and 176.2 (27.5) days for glargine. There were no clinically significant changes in laboratory parameters. Calcitonin concentrations increased to a greater degree in the liraglutide group compared with the placebo group by Week 26. Pulse rate increased in the liraglutide group relative to the glargine group: least squares mean difference (95% CI) 2.54 (1.10 to 3.98) bpm p=0.0006. Four previously normal opthalmoscopic examinations became abnormal in the liraglutide group. Hypoglycaemia occurred at a similar rate in the liraglutide and glargine groups, and at a lesser rate in the placebo group. Nocturnal hypoglycaemia occurred in the liraglutide at a greater rate than placebo, but a lesser rate than glargine. Twenty (9.8%) subjects in the liraglutide group developed antibodies to liraglutide, these were neutralizing in one subject and cross-reacting to native GLP-1 in twelve subjects. There were no reports of treatment emergent pancreatitis during the study.

Table 26: Treatment Emergent Adverse Event Reported in More than 5 % of the Subjects in Any Treatment Group Presented by System Organ Class and Preferred Term, Safety Analysis Set

	Liral.8 + OAD			OAD			Glargine + OAD		
	N	(%)	E	N	(%)	E	N	(%)	E
Safety Analysis Set	230			114			232		
Adverse Events	151	(65.7)	424	64	(56.1)	168	127	(54.7)	295
Gastrointestinal disorders	87	(37.8)	157	18	(15.8)	27	18	(7.8)	31
Nausea	32	(13.9)	41	4	(3.5)	4	3	(1.3)	3
Diarrhoea	23	(10.0)	29	6	(5.3)	7	3	(1.3)	6
Dyspepsia	15	(6.5)	16	1	(0.9)	1	4	(1.7)	4
Vomiting	15	(6.5)	18	4	(3.5)	4	1	(0.4)	1
Infections and infestations	51	(22.2)	72	36	(31.6)	45	63	(27.2)	89
Nasopharyngitis	21	(9.1)	23	10	(8.8)	10	26	(11.2)	32
Nervous system disorders	29	(12.6)	43	11	(9.6)	18	24	(10.3)	32
Headache	22	(9.6)	33	9	(7.9)	14	13	(5.6)	18
Musculoskeletal and connective tissue disorders	22	(9.6)	35	15	(13.2)	20	34	(14.7)	43
Metabolism and nutrition disorders	20	(8.7)	23	7	(6.1)	7	5	(2.2)	5
General disorders and administration site condit	13	(5.7)	15	4	(3.5)	5	10	(4.3)	13
Investigations	12	(5.2)	14	2	(1.8)	3	6	(2.6)	8
Respiratory, thoracic and mediastinal disorders	7	(3.0)	9	6	(5.3)	8	10	(4.3)	17
Psychiatric disorders	4	(1.7)	4	7	(6.1)	8			
Injury, poisoning and procedural complications	1	(0.4)	1	6	(5.3)	7	8	(3.4)	8

If adverse events in a system organ class were reported by more than 5% of subjects with none of the preferred terms being reported by more than 5% of subjects, then this table includes only the system organ class.
N: Number of subjects with adverse event
%: Proportion of subjects in analysis set having adverse event
E: Number of adverse events

In ***Study NN2211-1334*** there were 62 AEs in 25 (55.6%) subjects in the 0.1 mg group, 67 in 32 (69.6%) in the 0.3 mg, 78 in 33 (73.3%) in the 0.6 mg, 63 in 33 (75.0%) in the 0.9 mg, and 65 in 31 (67.4%) in the placebo. Diarrhoea and nausea were more common in the liraglutide groups. There were two SAEs: one in the 0.6 mg group and one in the 0.9 mg group. There were no deaths. One patient in the placebo group and one in the 0.9 mg group withdrew because of AEs.

In ***Study NN2211-2072*** there were 65 AEs reported in 24 (64.9%) subjects in the liraglutide 0.045 mg group, 50 in 21 (60.0%) in the 0.225 mg group, 32 in 17 (51.5%) in the 0.45 mg group, 54 in 23 (67.6%) in the 0.6 mg group, 64 in 25 (67.6%) in the 0.75 mg group and 46 in 19 (55.9%) in the metformin group. The pattern of AEs was similar between the six treatment groups. Five subjects reported SAEs: one in the 0.045 mg group, one in the 0.6 mg group, one in the 0.75 mg group and two in the metformin group. Five subjects in the

liraglutide groups and two in the metformin group withdrew because of AEs. Symptomatic hypoglycaemic episodes were more common in the liraglutide groups. There were no reports of pancreatitis during the study.

Additional Safety Data

Study NN2211-1573-extension (Table 27) was an open-label, extension of a double blind study that included subjects completing the double-blind parallel group section of Trial NN2211-1573. The study was conducted at 101 sites in two countries: US (89) and Mexico (12).

Table 27: Details of Study NN2211-1573 Extension

Nr. of subjects with age and sex	**Duration of Treatment**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
440 subjects were enrolled in the open-label extension 79 (51.3%) of 154 subjects enrolled in the liraglutide 1.8 mg group, 92 (61.7%) of the liraglutide 1.2 mg group and 66 (48.2%) of the glimepiride group completed the study Altogether 223 (50.68%) were male and 217 (49.32%) were female The age range was 22 to 79 years	26 weeks (In addition to the 52 weeks double-blind treatment)	Liraglutide 1.8 mg Liraglutide 1.2 mg Administered by subcutaneous injection once daily	Glimepiride 8 mg once daily orally	HbA1c, fasting plasma glucose, body weight, blood pressure, fasting serum lipids AEs	The improvement from baseline in HbA1c was maintained through from baseline The decrease in body weight in the liraglutide groups was maintained through to Week 76, but did not improve beyond week 52 The decrease in systolic blood pressure was maintained through to Week 76 The change in waist to hip ratio from baseline persisted in the liraglutide groups through to Week 76	There were 763 AES reported in 134 (87.0%) subjects in the liraglutide 1.8 mg group, 750 in 133 (89.3%) in the liraglutide 1.2 mg group and 537 in 111 (81.0%) in the glimepiride group There were 10 SAEs in 8 (5.2%) subjects in the liraglutide 1.8 mg group, 14 in 11 (7.4%) in the liraglutide 1.2 mg group and 13 in 8 (5.8%) in the glimepiride group Two subjects in the liraglutide 1.8 mg group and one in the liraglutide 1.2 mg group withdrew because of AEs There were no deaths reported during the study One patient each in the liraglutide group and the glimepiride group had pancreatitis There were no clinically significant changes in laboratory parameters

There were 763 AEs reported in 134 (87.0%) subjects in the liraglutide 1.8 mg group, 750 in 133 (89.3%) in the liraglutide 1.2 mg group and 537 in 111 (81.0%) in the glimepiride group. Nausea, diarrhoea and constipation occurred more frequently with liraglutide. There were ten SAEs in eight (5.2%) subjects in the liraglutide 1.8 mg group, 14 in eleven (7.4%) in the liraglutide 1.2 mg group and 13 in eight (5.8%) in the glimepiride group. Two subjects in the liraglutide 1.8 mg group and one in the liraglutide 1.2 mg group withdrew because of AEs. There were no deaths reported during the study. One patient each in the liraglutide group and

the glimepiride group had pancreatitis reported as a SAE. There were no clinically significant changes in laboratory parameters.

The change from baseline in HbA1c was maintained through to week 76: mean (SD): -1.04 (1.146) for liraglutide 1.8 mg, -0.77 (1.254) for liraglutide 1.2 mg and -0.27 (1.377) for glimepiride. Fasting plasma glucose was similarly affected. The decrease in body weight in the liraglutide groups was maintained through to Week 76, but did not improve beyond Week 52. The change in waist to hip ratio from baseline persisted in the liraglutide groups through to Week 76: mean (SD) change -2.65 (6.930) for liraglutide 1.8 mg, -3.61 (7.159) for liraglutide 1.2 mg and -0.55 (5.929) for glimepiride. The decrease in systolic blood pressure was maintained through to Week 76. The fall in mean FFA values in the liraglutide treatment groups persisted as did the increase in the glimepiride group but other than this there were no differences between the groups in fasting serum lipids.

Study NN2211-1572-extension (Table 28) was an open label extension of a randomised double-blind clinical trial of liraglutide as add-on therapy to metformin, in comparison with metformin alone and glimepiride/metformin combination.

Table 28: Details of Study NN2211-1572-extension

Nr. Of subjects with age and sex	**Duration of Treatment**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
780 subjects continued into the extension: There were 184 in the liraglutide 0.6 mg group, 178 in the liraglutide 1.2 mg, 174 in the liraglutide 1.8 mg group, 61 in the metformin and 183 in the glimepiride/ metformin 453 (58.1%) were male and 327 (41.9%) were female Age range was 25 to 78 years 171 (92.9% in the liraglutide 0.6 mg group completed, 168 (94.4%) in the liraglutide 1.2 mg, 164 (94.3%) in the liraglutide 1.8 mg, 48 (78.7%) in the metformin and 166 (90.7%) in the glimepiride/ metformin	18 months Mean (SD) duration of exposure was 515.4 (92.1) days for liraglutide 0.6 mg, 522.1 (84.1) days for liraglutide 1.2 mg and 520.4 (81.8) days for liraglutide 1.8 mg	Liraglutide (0.6 mg/day) + metformin (1.5-2.0 g/day) Liraglutide (1.2 mg/day) + metformin (1.5-2.0 g/day) Liraglutide (1.8 mg/day) + metformin (1.5-2.0 g/day) Liraglutide was injected subcutaneously in the upper arm, abdomen or thigh using a pen injector. Administration was at any time of the day but subjects were encouraged to inject liraglutide at the same time each day	Metformin (1.5-2.0 g/day) Glimepiride (4 mg/day) + metformin (1.5-2.0 g/day)	HbA1c, weight, fasting plasma glucose, 7-point plasma glucose profiles (self-measured), fasting insulin, fasting pro-insulin, fasting C-peptide, fasting glucagons, fasting lipid profile, blood pressure, AEs, laboratory safety parameters, hypoglycaemic episodes, liraglutide antibody formation	The differences between the treatment groups in the efficacy outcome measures was less apparent by 18 months of treatment, but the decrease in body weight in the liraglutide groups was maintained throughout the study There was no difference between the groups in systolic or diastolic blood pressure by the end of the study There was no significant difference between the groups in fasting serum lipids	A total of 664 AEs were reported in 147 (79.9%) subjects in the liraglutide 0.6 mg group, 676 in 143 (80.3%) in the liraglutide 1.2 mg, 620 in 140 (80.5%) in the liraglutide 1.8 mg, 125 in 42 (68.9%) in the metformin and 607 in 133 (72.7%) in the glimepiride/ metformin. 32 SAEs were reported in 27 (14.7%) subjects in the liraglutide 0.6 mg group, 22 in 15 (8.4%) in the liraglutide 1.2 mg, 15 in 12 (6.9%) in the liraglutide 1.8 mg, 8 in 5 (8.2%) in the metformin and 10 in 9 (4.9%) in the glimepiride/ metformin group Nausea, diarrhoea and vomiting were more common in the liraglutide groups. Cardiac disorders were more common in the liraglutide 0.6 mg and 1.2 mg groups No deaths were reported for subjects continuing into the extension phase

There were a total of 664 AEs reported in 147 (79.9%) subjects in the liraglutide 0.6 mg group, 676 in 143 (80.3%) in the liraglutide 1.2 mg, 620 in 140 (80.5%) in the liraglutide 1.8

mg, 125 in 42 (68.9%) in the metformin and 607 in 133 (72.7%) in the glimepiride/ metformin. There were 32 SAEs were reported in 27 (14.7%) subjects in the liraglutide 0.6 mg group, 22 in 15 (8.4%) in the liraglutide 1.2 mg, 15 in 12 (6.9%) in the liraglutide 1.8 mg, eight in five (8.2%) in the metformin and ten in nine (4.9%) in the glimepiride/ metformin group. Nausea, diarrhoea and vomiting were more common in the liraglutide groups (Table 29). Cardiac disorders were more common in the liraglutide 0.6 mg and 1.2 mg groups. Hypoglycaemia was less common in the liraglutide groups than in the glimepiride/ metformin group. Pulse rate was higher at end of study in the liraglutide groups. No deaths were reported for subjects continuing into the extension phase. No additional cases of pancreatitis were reported in the extension study.

Table 29: TEAEs in >5% of Subjects by System Organ Class and Preferred Term - 18-month Data – Safety Analysis Set

	Lira 0.6 + Met		Lira 1.2 + Met		Lira 1.8 + Met		Met		Glim + Met	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Respiratory, thoracic and mediastinal disorders	15 (8.2)	21	18 (10.1)	23	12 (6.9)	14	4 (6.6)	4	16 (8.7)	22
Cough	6 (3.3)	7	6 (3.4)	6	2 (1.1)	3	1 (1.6)	1	10 (5.5)	12
General disorders and administration site conditions	19 (10.3)	23	21 (11.8)	24	11 (6.3)	13	2 (3.3)	2	13 (7.1)	18
Skin and subcutaneous tissue disorders	13 (7.1)	14	19 (10.7)	23	10 (5.7)	12	3 (4.9)	5	15 (8.2)	19
Psychiatric disorders	4 (2.2)	4	7 (3.9)	13	9 (5.2)	10	1 (1.6)	1	7 (3.8)	7
Cardiac disorders	22 (12.0)	24	21 (11.8)	27	8 (4.6)	14	5 (8.2)	6	2 (1.1)	2
Renal and urinary disorders	9 (4.9)	10	7 (3.9)	8	6 (3.4)	6	3 (4.9)	3	10 (5.5)	10
Hepatobiliary disorders	11 (6.0)	12	3 (1.7)	4	4 (2.3)	4	0 (0.0)	0	10 (5.5)	10

If adverse events in a system organ class were reported by more than 5% of subjects with none of the preferred terms being reported by more than 5% of subjects, then this table includes only the system organ class.
N: Number of subjects with adverse event
%: Proportion of subjects having adverse event
E: Number of adverse events

	Lira 0.6 + Met		Lira 1.2 + Met		Lira 1.8 + Met		Met		Glim + Met	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Safety Analysis Set	184		178		174		61		183	
Adverse Event	147 (79.9)	664	143 (80.3)	676	140 (80.5)	620	42 (68.9)	125	133 (72.7)	607
Infections and infestations	84 (45.7)	154	77 (43.3)	158	83 (47.7)	142	20 (32.8)	35	84 (45.9)	167
Nasopharyngitis	35 (19.0)	56	29 (16.3)	50	26 (14.9)	32	7 (11.5)	13	38 (20.8)	54
Influenza	10 (5.4)	11	11 (6.2)	13	17 (9.8)	25	2 (3.3)	2	13 (7.1)	19
Bronchitis	7 (3.8)	7	9 (5.1)	12	9 (5.2)	10	2 (3.3)	2	13 (7.1)	16
Gastroenteritis	8 (4.3)	9	7 (3.9)	9	9 (5.2)	9	1 (1.6)	1	5 (2.7)	6
Upper respiratory tract infection	9 (4.9)	13	10 (5.6)	12	9 (5.2)	10	3 (4.9)	5	7 (3.8)	11
Gastrointestinal disorders	74 (40.2)	135	77 (43.3)	145	73 (42.0)	159	9 (14.8)	13	47 (25.7)	76
Diarrhoea	24 (13.0)	27	17 (9.6)	29	29 (16.7)	36	2 (3.3)	2	12 (6.6)	13
Nausea	22 (12.0)	25	26 (14.6)	29	26 (14.9)	35	3 (4.9)	4	5 (2.7)	9
Dyspepsia	7 (3.8)	8	4 (2.2)	4	13 (7.5)	16	0 (0.0)	0	7 (3.8)	11
Vomiting	10 (5.4)	11	10 (5.6)	13	12 (6.9)	12	0 (0.0)	0	0 (0.0)	0
Toothache	4 (2.2)	4	12 (6.7)	13	5 (2.9)	6	0 (0.0)	0	3 (1.6)	3
Musculoskeletal and connective tissue disorders	36 (19.6)	51	42 (23.6)	55	45 (25.9)	70	11 (18.0)	15	51 (27.9)	79
Back pain	10 (5.4)	12	11 (6.2)	11	13 (7.5)	14	2 (3.3)	3	18 (9.8)	20
Arthralgia	8 (4.3)	9	2 (1.1)	2	8 (4.6)	11	2 (3.3)	2	14 (7.7)	16
Nervous system disorders	35 (19.0)	49	41 (23.0)	50	40 (23.0)	58	4 (6.6)	4	33 (18.0)	56
Headache	19 (10.3)	25	25 (14.0)	27	23 (13.2)	36	1 (1.6)	1	20 (10.9)	39
Metabolism and nutrition disorders	24 (13.0)	27	28 (15.7)	28	21 (12.1)	27	7 (11.5)	7	18 (9.8)	19
Decreased appetite	4 (2.2)	4	9 (5.1)	9	6 (3.4)	6	0 (0.0)	0	0 (0.0)	0
Vascular disorders	17 (9.2)	26	13 (7.3)	14	18 (10.3)	21	3 (4.9)	3	16 (8.7)	19
Hypertension	7 (3.8)	7	7 (3.9)	8	9 (5.2)	9	1 (1.6)	1	9 (4.9)	9
Investigations	21 (11.4)	30	16 (9.0)	23	17 (9.8)	21	7 (11.5)	9	16 (8.7)	27
Eye disorders	17 (9.2)	21	14 (7.9)	17	12 (6.9)	12	7 (11.5)	9	15 (8.2)	17
Injury, poisoning and procedural complications	21 (11.4)	28	18 (10.1)	31	12 (6.9)	15	5 (8.2)	6	20 (10.9)	27

If adverse events in a system organ class were reported by more than 5% of subjects with none of the preferred terms being reported by more than 5% of subjects, then this table includes only the system organ class.
N: Number of subjects with adverse event
%: Proportion of subjects having adverse event
E: Number of adverse events

Study NN2211-1333 was a single-centre, randomised, double-blind, parallel-group, placebo-controlled mechanism of action trial in subjects with type 2 diabetes. The study was primarily designed to investigate effects on obesity. The study included obese subjects of both sexes, with type 2 diabetes, diet treated and/or sulphonylurea (SU)/repaglinide treated (as monotherapy), age ≥18 years, HbA1c between 6.5-12% (diet treated) or HbA1c ≤10% (sulphonylurea/repaglinide), and body mass index (BMI) >27 kg/m^2. In addition, at randomization fasting blood glucose had to be within 6-13 mmol/L. Treatment duration was for 8 weeks. There were 39 AEs reported in 16 (76%) patients in the liraglutide group and 15 AEs reported in seven (58%) in the placebo group. The most commonly reported AEs in the liraglutide group were: headache in 7 (33%) patients, nausea in 5 (24%), and diarrhoea in 3 (14%). There were no SAEs. There were no deaths.

Study NN2211-1464 was a single-centre, open-label, five-period crossover trial in healthy male volunteers investigating the relative bioavailability of liraglutide by pulmonary administration compared to a subcutaneous injection. The study included 32 healthy male volunteers aged 18 to 45 years with a BMI 20 to 30 kg/m^2. There were no SAEs.

Study NN8022-1807 (Table 30) was a multinational, multicentre, randomised, double-blind, placebo-controlled, six-armed parallel-group trial of the effect of liraglutide on body weight in obese subjects without diabetes with an open label orlistat comparator arm. The study was conducted at 19 sites in eight countries: Denmark (3), Sweden (2), Finland (3), UK (3), Netherlands (1), Belgium (1), Spain (4) and Czech Republic (2).

Table 30: Details of Study NN8022-1807

Nr. Of subjects with age and sex Duration	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
564 subjects, 135 (23.9%) male, 429 (76.1%) female, age range 18 to 65 years. 20 weeks	Main inclusion criteria: body mass index ≥30.0 and ≤40.0 kg/m2; stable body weight; age between 18 and 65 yrs; fasting plasma glucose < 7.0 mmol/L.	Liraglutide 1.2 mg, 1.8 mg, 2.4 mg or 3.0 mg daily	Liraglutide placebo Orlistat 120 mg three times daily (open label)	Weight loss, fasting lipid profile, glycaemic control, β-cell function AEs, clinical laboratory tests	liraglutide resulted in to a significantly higher weight loss compared to placebo ($p<0.005$). in a dose-dependent manner, ranging from 4.8 (1.2 mg liraglutide) to 7.2 kg (3.0 mg liraglutide). liraglutide doses 2.4 and 3.0 mg led to a significantly greater mean weight loss compared to orlistat	There were 225 AEs reported in 81 (85.3%) patients in the liraglutide 1.2 mg group, 282 in 79 (87.8%) in the 1.8 mg, 308 in 84 (90.3%) in the 2.4 mg, 316 in 88 (94.6%) in the 3.0 mg, 226 in 81 (82.7%) in the placebo and 215 in 81 (85.3%) in the orlistat Nine patients in the liraglutide group had SAEs but this did not appear to be dose dependent. There was a dose related excess of GI AEs in the liraglutide groups

There were 225 AEs reported in 81 (85.3%) patients in the liraglutide 1.2 mg group, 282 in 79 (87.8%) in the 1.8 mg, 308 in 84 (90.3%) in the 2.4 mg, 316 in 88 (94.6%) in the 3.0 mg, 226 in 81 (82.7%) in the placebo and 215 in 81 (85.3%) in the orlistat group. Nine patients in the liraglutide group had SAEs but this did not appear to be dose-dependent. There was an excess of gastrointestinal AEs in the liraglutide groups that was dose related. Metabolic and laboratory adverse events were also increased in the liraglutide groups in a dose dependent manner. No deaths occurred during the study.

Study NN9233-1898 was a sequential, single dose, escalating trial to assess safety and estimate relative bioavailability of intranasal liraglutide in healthy male volunteers. The study included healthy males aged between 18 and 45 years with a BMI of 19 to 29 kg/m^2,

inclusive. There were twelve volunteers, nine were randomised to active, and three to placebo. The study treatments were liraglutide 2.5 mg, 5.0 mg and 10.0 mg by intranasal administration, liraglutide 0.6 mg subcutaneous and placebo (intranasal and subcutaneous). The outcome measures were relative bioavailability and local and systemic tolerability. There were twelve treatment emergent AEs in four subjects in the liraglutide group. There were no SAEs or deaths reported during the study.

Evaluator's comments:

Treatment with liraglutide resulted in an excess of gastrointestinal side effects, mainly nausea, vomiting, diarrhoea and constipation. These side effects were dose related and limited the maximum dose of liraglutide that could be used. Titration of treatment from a commencing dose of 0.6 mg, to 1.2 mg over a week then 1.8 mg after another week appeared to decrease the rate of gastrointestinal side effects. These side effects occurred early in treatment and appeared to improve over the first few months of treatment. Whilst these side effects may affect tolerability, they did not result in permanent morbidity.

In general, the rate of withdrawal as a result of AEs was higher in the liraglutide groups. This is in keeping with the overall higher rate of AEs with liraglutide.

There were few serious adverse effects, and an excess of pancreatitis was not apparent in the data. There were few deaths during the development program and none appeared to be related to treatment.

There was an excess of hypoglycaemic events when liraglutide was administered in combination with glimepiride. Whilst these events were not serious in the trials, there was an increase in nocturnal events and the evaluator was concerned that serious hypoglycaemic events could occur in relation to this combination.

Cardiovascular safety did not appear to be a concern from the safety data. Liraglutide appeared to result in a more favourable profile of plasma lipids than rosiglitazone. However, the duration of exposure in the studies (up to 18 months), and the number of patients in long-term studies (1220) limits the ability of the development program to examine long-term cardiovascular safety.

Clinical Summary and Conclusions

Liraglutide is an interesting new chemical entity with the potential to improve the care of patients with type 2 diabetes. Although the clinical development program has been thorough, the sponsor does not clearly indicate how liraglutide should best be used in clinical practice, and what long-term safety monitoring should be undertaken. The latter was subsequently addressed in the sponsor's reply to the supplementary evaluation reports (refer page 98).

The pharmacodynamic data indicate that liraglutide increases the secretion of insulin in response to a glucose load, and decreases the secretion of glucagon. Liraglutide delayed gastric emptying and increased sensations of satiety. However it is not clear to what extent basal insulin secretion is also increased.

The pharmacokinetics of liraglutide are linear with respect to absorption and elimination. There was no effect of age or gender upon liraglutide pharmacokinetics. AUC decreased, unbound concentrations decreased and volume of distribution increased in hepatic impairment. AUC decreased in renal impairment.

Liraglutide increased T_{max}, and decreased C_{max} for atorvastatin, lisinopril and digoxin. Liraglutide decreased AUC for lisinopril and digoxin. Liraglutide had no effect on ethinyloestradiol exposure, and a clinically insignificant increase in exposure to levonorgestrel. The data from these studies indicate that liraglutide has the potential to delay

the absorption of many drugs, and to also decrease overall exposure. For some medicines these interactions may be clinically significant. The sponsor does not make this apparent in the Product Information.

There were slight differences in absorption between injection sites, with greater absorption from the abdomen than the upper arm or thigh. The clinical effects of these differences in absorption have not been explored.

The studies conducted in Japanese subjects raise the question as to why there should have been such a high frequency of AEs at the 15 μg/kg dose level when in the previous studies that dose level was well tolerated. This confirms the need to titrate the dose up at weekly increments.

With regard to efficacy, liraglutide was superior to placebo (Study NN2211-1571) and also superior as add-on therapy with metformin (Study NN2211-1499) but the liraglutide/metformin combination was superior to liraglutide alone (Study NN2211-1499). The ED_{50} of liraglutide was 0.51 mg in combination with metformin compared to 1.74 mg for liraglutide monotherapy. Similarly the ED_{90} for liraglutide in combination with metformin was 0.8 mg compared with 2.63 mg in monotherapy. In combination liraglutide appeared to improve β-cell function, while metformin decreased insulin resistance. Liraglutide 1.2 mg and 1.8 mg in combination with metformin were superior to metformin alone (Study NN2211-1572).

Liraglutide was superior to glimepiride and also resulted in weight loss in comparison with glimepiride (Study NN2211-1573). In combination with metformin, liraglutide had similar efficacy to the glimepiride/metformin combination (Study NN2211-1572) but with a decrease in body weight, body fat and waist circumference. Liraglutide 1.2 mg and 1.8 mg improved glycaemic control as add-on therapy to glimepiride to a greater extent than rosiglitazone, and without the weight gain that occurred with rosiglitazone.

Liraglutide also improved glycaemic control as add-on therapy with rosiglitazone/ metformin in combination (Study NN2211-1574), and also in combination with glimepiride and metformin (Study NN2211-1697). Liraglutide in combination with glimepiride and metformin was superior to glargine in combination with glimepiride and metformin (Study NN2211-1697).

Liraglutide was efficacious in monotherapy, dual therapy and triple therapy. With regard to monotherapy, liraglutide was superior to placebo (Study NN2211-1310 and Study NN2211-1571) metformin alone (Study NN2211-1499) and glimepiride alone (Study NN2211-1573). In dual therapy, liraglutide + metformin was superior to metformin + glimepiride (Study NN2211-1499); liraglutide at the 1.2 mg and 1.8 mg dose levels in combination with metformin was superior to metformin alone (Study NN2211-1499 and Study NN2211-1572); liraglutide 1.8mg and 1.2 mg doses in combination with metformin were non-inferior to glimepiride/metformin (Study NN2211-1572) using clinically significant criteria for non-inferiority; liraglutide 1.2 mg and 1.8 mg in combination with glimepiride were superior to glimepiride and glimepiride + rosiglitazone (Study NN2211-1436); liraglutide 0.6 mg in combination with glimepiride was superior to glimepiride alone (Study NN2211-1436); and liraglutide 0.6 mg in combination with glimepiride was non inferior to rosiglitazone/ glimepiride (Study NN2211-1436) using clinically significant criteria for non-inferiority. In triple therapy liraglutide + metformin + rosiglitazone was superior to metformin + rosiglitazone (Study NN2211-1574); liraglutide in combination with glimepiride and metformin was superior to glimepiride + metformin (Study NN2211-1697); liraglutide in

combination with glimepiride and metformin was superior to glargine + glimepiride + metformin (Study NN2211-1697).

Liraglutide was effective in doses from 0.6 mg per day, but significant differences were demonstrated at the 1.2 mg and 1.8 mg per day dose levels. Optimal effect appears to be at the 1.8 mg dose level.

Liraglutide was demonstrated to maintain its effect for up to 12 months in randomised controlled trials. In the open label extension of Study NN2211 effect was maintained for up to 2 years (this included the reduction in body weight) but Study NN2211-1572-extension indicated that the differences in efficacy between the treatment groups was less apparent by 18 months open-label treatment.

In the clinical trials dosing was encouraged to be at breakfast time, but subjects were allowed to administer the dose at any time of day provided they consistently dosed at the same time of day. Hence, the results of the clinical trials can be generalised to dosing at any time of day, without reference to meals/food intake.

Liraglutide resulted in an excess of gastrointestinal side effects, mainly nausea, vomiting, diarrhoea and constipation. These side effects were dose related and limited the maximum dose of liraglutide that could be used. Titration of treatment from a commencing dose of 0.6 mg, to 1.2 mg over a week then 1.8 mg after another week appeared to decrease the rate of gastrointestinal side effects. These side effects occurred early in treatment and appeared to improve over the first few months of treatment. Whilst these side effects may affect tolerability, they did not result in permanent morbidity. The rate of withdrawal as a result of AEs was higher in the liraglutide groups.

There were few serious adverse effects, and an excess of pancreatitis was not apparent in the data. There were few deaths during the development program and none appeared to be related to treatment.

There was an excess of hypoglycaemic events when liraglutide was administered in combination with glimepiride. Whilst these events were not serious in the trials, there was an increase in nocturnal events and the evaluator was concerned that serious hypoglycaemic events could occur in relation to this combination.

In the opinion of the evaluator, these efficacy and safety data indicate that the optimal use of liraglutide is in combination with metformin, and that the combination of liraglutide with a sulphonylurea should be discouraged. The combination with rosiglitazone is unlikely given the current concerns regarding the cardiovascular safety of rosiglitazone, but the effects of liraglutide in combination with rosiglitazone upon long-term cardiovascular safety remain unknown. Interactions with other thiazolidinediones have not been studied and until this has been performed such combinations should also be discouraged.

Cardiovascular safety did not appear to be a concern from the safety data. Liraglutide appeared to result in a more favourable profile of plasma lipids than rosiglitazone. However, the duration of exposure in the studies (up to 24 months), and the number of patients in long-term studies (1220) limits the ability of the development program to examine long-term cardiovascular safety. Liraglutide did have some effects on fasting serum lipids: decrease in LDL-C (Study NN2211-1574, Study NN2211-1697), and a decrease in total cholesterol, LDL-C, VLDL-C and HDL-C in comparison with rosiglitazone (Study NN2211-1436). However, in comparison with metformin, liraglutide had higher HDL-C (NN2211-1572).

Deficiencies in the Submission

The submission contained few data relating to long term safety. There were two studies of 18 months duration (Study NN2211-1573-extension and Study NN2211-1572-extension). The numbers of patients in these studies and their duration limit the ability of this development program to determine long-term cardiovascular safety.

Serum amylase and/or lipase do not appear to have been determined in the patients with nausea, vomiting and abdominal pain. Hence, it is not clear what proportion of these patients might have been suffering from pancreatitis. The sponsor should be encouraged to include serum amylase and lipase as routine biochemical tests in future clinical trials of liraglutide. In addition, patients reporting nausea, vomiting and abdominal pain as adverse events should have serum amylase and lipase determined.

Recommendations

Liraglutide should be approved for marketing for the indication:

Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.

The sponsor should be required to provide a plan for comprehensive long-term safety monitoring including the outcomes of pancreatitis and cardiovascular disease.

Supplementary Clinical Evaluation

Introduction

The supplementary clinical submission was a response to the Nonclinical Evaluation Report and also the provision of additional data in support of the clinical safety of liraglutide (rys) (Victoza). The primary issue identified by the Nonclinical Evaluation Report was the risk of C-cell carcinoma, with elevated calcitonin, of the thyroid identified in pre-clinical animal studies.

Although no additional efficacy claims are being made by the sponsor on the basis of the supplementary data, efficacy data from the following studies were provided in the supplementary data:

- Study NN2211-1572 2-year Clinical Trial Report
- Study NN2211-1573 2-year Clinical Trial Report
- Study NN2211-1797 (Table 31)
- Trial ID: NN8022-1807 (Table 32)

Additional safety data and amended analyses of previously submitted data from the following studies were provided in the Supplementary data:

- Clinical Trial Report Amendment 1: Study NN2211-1436
- Study NN2211-1572 2-year Clinical Trial Report
- Study NN2211-1573 2-year Clinical Trial Report
- Clinical Trial Report Amendment 1: Study NN2211-1574
- Clinical Trial Report Amendment 1: Study NN2211-1697
- Clinical Trial report for Study NN2211-1797 (Table 31)
- Safety data from 14-week extension of Study NN2211-1797

- Clinical Trial report for Study NN8022-1807 (Table 32)

Efficacy

Study 2211-1572 2-year Clinical Trial Report

The 2-year Clinical Trial Report for ***Study NN2211-1572*** contained additional efficacy data extended out to 2 years. The efficacy data extending out to 18 months of treatment was discussed in the Clinical Evaluation Report. ***Study NN2211-1572*** was a multicentre, multinational, double-blind, double-dummy, randomised, active control, parallel-group, trial with an 18 months extension period investigating the safety and efficacy of liraglutide as add-on to metformin.

The 2 year treatment duration was completed by 130 (53.7%) subjects in the liraglutide 0.6 mg/metformin group, 137 (56.8%) in the liraglutide 1.2 mg/metformin group, 118 (48.8%) in the liraglutide 1.8 mg/metformin group, 31 (25.4%) in the metformin only group and 113 (46.3%) in the glimepiride/metformin group. For the primary efficacy outcome measure (change in HbA1c) efficacy was maintained for up to 2 years of treatment. Liraglutide for all dose levels was superior to metformin alone and non-inferior to glimepiride/metformin. There were supportive findings for other measures of glycaemic control including FPG and postprandial BG. Body weight decreased in the liraglutide/metformin groups compared with glimepiride/metformin ($p<0.0001$) but not compared with metformin alone. There was no difference between the groups in fasting insulin, HOMA beta cell and HOMA insulin resistance. Fasting glucagon levels were lower in the liraglutide/metformin group than the glimepiride metformin group. Proinsulin to insulin ratio was lower in the liraglutide 1.2 mg and 1.8 mg/metformin groups than with metformin alone.

Evaluator's comments:

Diabetes control was better when liraglutide was added to metformin, and weight control was better with liraglutide/metformin than glimepiride metformin.

Study NN2211-1573 was a multicentre, double-blind, double-dummy, randomised, parallel, active-controlled clinical trial of liraglutide 1.2 mg daily, liraglutide 1.8 mg daily or glimepiride for 52 weeks treatment duration followed by a 52-week, open-label extension. The study has been previously evaluated, including the results up to the 18 month visit (6 months of open label extension). The present submission includes data up to the end of the 12 month open label extension.

Of the subjects enrolled in the study, a total of 114 (46.2%) in the liraglutide 1.8 mg group, 110 (43.8%) in the liraglutide 1.2 mg and 97 (39.1%) in the glimepiride group completed the study. For those subjects completing the 52 week open label extension, the improvement in HbA1c from baseline was significantly better in both liraglutide groups compared with glimepiride. Body weight decreased in the liraglutide groups compared with the glimepiride. In the completers, FPG was lower in the liraglutide groups: least squared mean difference, liraglutide 1.8 mg – glimepiride was -1.161 (-1.755 to -0.568) mmol/L, $p=0.0001$; and liraglutide 1.2 mg – glimepiride was -0.966 (-1.561 to -0.372) mmol/L, $p=0.0015$. There was no difference between the groups in plasma insulin concentrations, C-peptide concentrations or HOMA-B. Proinsulin to C-peptide ratio was lower in the liraglutide groups than the glimepiride ($p<0.0001$). HOMA-IR was also lower in the liraglutide groups, for the ITT population on analysis of LOCF. At the end of the study, using LOCF for the ITT population, fewer subjects were classified as having metabolic syndrome in the liraglutide 1.8 mg group compared with the glimepiride. Waist circumference decreased in the liraglutide groups compared with glimepiride. For those subjects undergoing DEXA scan, the

percentage of body weight that was fat decreased in the liraglutide groups was comparable with glimepiride.

Fasting glucagon levels decreased to a greater extent in the liraglutide 1.2 mg group compared with glimepiride. There was no difference between the groups in change in systolic or diastolic blood pressure. FFA decreased to a greater extent in the liraglutide 1.8 mg group than the glimepiride. There were no other significant differences in serum lipid profile. There were no significant differences in cardiovascular biomarkers: HsCRP, PAI-1 or NT-proBNP.

Evaluators comments

The results of the 2-year analysis of Study NN2211-1573 indicate better glycaemic control for liraglutide compared with glimepiride, in addition to less insulin resistance and better weight control.

Study NN2211-1797 was a multinational, multicentre, randomised, open-label, active comparator, two arm, parallel group study of liraglutide in comparison with exenatide (Table 31). The study was sponsored by Novo Nordisk and conducted at 133 centres in 15 countries.

Table 31: Details of Study NN2211-1797

Nr. of subjects with age and sex Duration	**Diagnosis + criteria for incl/exclusion**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
663 screened 464 subjects were randomised: 233 to liraglutide and 231 to exenatide All randomised subjects were included in the ITT analysis set 241 (51.9%) were male and 223 (48.1%) were female Age range 25 to 78 years 202 (86.0%) in the liraglutide group and 187 (80.6%) in the exenatide completed 6 months	Subjects diagnosed with type 2 diabetes and treated with either metformin, sulfonylurea or a combination of both, in a stable treatment regimen for at least 3 months prior to screening on maximally tolerated doses of these therapies HbA1c 7.0 to 11.0% inclusive Age 18 to 80 years BMI ≤45.0 kg/m^2 Exclusions: Previous treatment with insulin, exenatide or liraglutide Impaired liver function, defined Impaired renal function, Unstable angina, acute coronary event, other significant cardiac event or cerebral stroke within the past 6 months History of heart failure (NYHA class IV)	Liraglutide 0.6 mg daily for one week, followed by 1.2 mg daily for one week, followed by 1.8 mg daily Subcutaneous injection Subjects continued on metformin and/or sulfonylurea at their stable pre-study dose level Randomised, open label Randomised using IVRS or IWRS	Exenatide 5 µg twice daily for 4 weeks followed by 10 µg twice daily Subcutaneous injection	Primary efficacy outcome measure was the change from baseline in HbA1c at Week 26. Secondary efficacy outcome measures: FPG, seven-point plasma glucose profiles (self-measured), body weight, Beta cell function: fasting insulin, fasting C-peptide, proinsulin to insulin ratio, beta-cell function (HOMA-B), insulin resistance (HOMA-IR), fasting glucagon, blood pressure, lipid profiles, biomarkers of cardiovascular risk, waist circumference and waist to hip ratio, DTSQ	For change in HbA1c from baseline, liraglutide was superior to exenatide with no covariate effect for co-medication, gender or ethnicity. FPG improved to a greater extent in the liraglutide group. There was a greater decrease in prandial and postprandial plasma glucose in the exenatide group than the liraglutide. There was no difference between the groups in change in body weight. Both treatment groups had a decrease in mean body weight: -3.24 (SE, 0.33) kg for liraglutide and -2.87 (0.33) for exenatide. Fasting insulin concentrations increased in the liraglutide group relative to exenatide. There was an increase in HOMA-B in the liraglutide group compared with the exenatide. There was no significant difference between the treatment groups in waist circumference or waist-hip ratio.	TEAEs occurred in, 176 (74.9%) subjects in the liraglutide group, compared with the exenatide group, 183 (78.9%) subjects. Gastrointestinal AEs occurred at a similar frequency in both treatment groups. No deaths were reported during the study. SAEs were reported more frequently in the liraglutide group: 12 (5.1%) subjects compared with six (2.6%) subjects in the exenatide group. One subject with adenocarcinoma of the pancreas, and another with thyroid neoplasia in the liraglutide group. One patient with pancreatitis in the liraglutide group. DEAs were less common in the liraglutide group, 23 (9.8%) subjects compared with 31 (13.4%) subjects in the exenatide, and were predominantly GI. One subject in the liraglutide group had an elevated serum calcitonin concentration

The primary efficacy outcome measure was the change from baseline in HbA1c at Week 26. The secondary efficacy outcome measures were:

- Glycaemic control parameters: FPG, seven-point plasma glucose profiles (self-measured)
- Body weight
- Beta cell function: fasting insulin, fasting C-peptide, proinsulin to insulin ratio, beta-cell function (HOMA-B), insulin resistance (HOMA-IR)
- Fasting glucagon
- Blood pressure
- Lipid profiles: TC, LDL-C, VLDL-C, HDL-C, TG, FFA, ApoB

- Biomarkers of cardiovascular risk: HsCRP, PAI-1, NT-pro-BNP, IL-6, adiponectin and TNF-α
- Waist circumference and waist to hip ratio
- Patient reported outcomes using DTSQ in a subset of subjects

The safety outcome measures were AEs, vital signs, hypoglycaemic episodes and clinical laboratory tests (including haematology, biochemistry and antibodies to liraglutide and exenatide. There was also a pharmacokinetic sub-study of 16 subjects from centres in Poland: eight treated with liraglutide and eight with exenatide.

The study was designed to test for non-inferiority. The margin for non-inferiority was a 0.4% difference in HbA1c. Non-inferiority was concluded if the upper limit of the 95% CI for the treatment difference, liraglutide – exenatide, was less than 0.4%. Superiority was concluded if the upper limit of the 95% CI for the treatment difference, liraglutide – exenatide, was less than 0%.

For the primary efficacy outcome measure, liraglutide was superior to exenatide. There was no covariate effect for co-medication, gender or ethnicity. FPG improved to a greater extent in the liraglutide group. There was a greater decrease in prandial and postprandial plasma glucose in the exenatide group than the liraglutide. There was no difference between the groups in change in body weight. Both treatment groups had a decrease in mean body weight: -3.24 (SE, 0.33) kg for liraglutide and -2.87 (0.33) for exenatide. Fasting insulin concentrations increased in the liraglutide group relative to exenatide. There was an increase in HOMA-B in the liraglutide group compared with the exenatide. There was no significant difference between the groups in fasting C-peptide, proinsulin to insulin ratio, HOMA-IR, or glucagon (using LOCF). There was no difference between the groups in SBP or DBP.

There was an increase in VLDL-C in both treatment groups that was greater in the exenatide group. TG decreased to a greater extent in the liraglutide group. FFA also decreased to a greater extent in the liraglutide group. There was no significant difference between the treatment groups in TC, LDL-C, HDL-C or ApoB. There was no significant difference between the treatment groups in biomarkers of cardiovascular risk: HsCRP, PAI-1, NT-pro-BNP, IL-6, adiponectin and TNF-α.

There was no significant difference between the treatment groups in waist circumference or waist-hip ratio. There was an increase in patient satisfaction in both treatment groups, but the increase was greater in the liraglutide group. However, this was a subjective measure and the results may have been influenced by patient expectations given the open label design.

Evaluator's comments:

At the doses examined in Study NN2211-1797, liraglutide provided better control of diabetes as measured by HbA1c and FPG. There was no difference between the treatments in weight control.

Study NN8022-1807 was a multinational, multicentre, randomised, double blind, placebo and comparator controlled, six parallel groups, efficacy and safety trial comparing the effects on obesity of four doses of liraglutide with placebo and orlistat (Table 32). The study was not described in detail because the report provided in the submission appears to be an interim report. This study was also reported in the clinical evaluation report but only for safety, not efficacy (Table 30). The data were primarily for the extension population rather than the double blind period. The study included obese subjects without type 2 diabetes. The study was sponsored by Novo Nordisk, Denmark and conducted at 19 sites in eight countries.

Table 32: Additional Details of Study NN8022-1807

Nr. of subjects with age and sex	**Duration of Treatment**	**Test Product Dosage Regimen Route of administration, Formulation**	**Reference therapy Dose regimen Route of administration**	**Criteria for evaluation**	**Results (efficacy)**	**Adverse Reactions**
733 subjects were screened and 564 were randomised. 472 (83.7%) completed the 20 week double blind phase and 356 (63.1%) completed 62 weeks 398 were enrolled in the extension phase: 298 (74.9%) female and 100 (25.1%) male age range 18 to 65 years	Total of 104 weeks: 20 week double blind treatment period 32 weeks single blinded medication 4 weeks dose unblinded dose escalation 48 weeks open label maintenance Interim report covers the 20 week double blind and 32 week single blind phases	1. Liraglutide 1.2 mg/day 2. Liraglutide 1.8 mg/day 3. Liraglutide 2.4 mg/day 4. Liraglutide 3.0 mg/day All treatments were administered subcutaneously	5. Placebo 6. Orlistat 120 mg capsules	Change from baseline in body weight at 52 weeks, waist circumference, SBP, DBP, pre-diabetes status, fasting lipid profile, metabolic syndrome status Safety: AEs, PR, ECG, haematology and biochemistry, calcitonin	For the primary efficacy outcome measure, liraglutide 1.8 mg, 2.4 mg and 3.0 mg were superior to placebo; and liraglutide 2.4 mg and 3.0 mg were superior to orlistat. For waist circumference, there was a greater reduction compared to placebo for the liraglutide 2.4 mg and 3.0 mg groups. There was a decrease in SBP in the liraglutide 2.4 mg group compared with placebo and Orlistat. There was an improvement in pre-diabetes status compared to both placebo and Orlistat in the liraglutide 1.8 mg. 2.4 mg and 3.0 mg groups.	AEs were reported at a slightly greater frequency in the active treatment groups than the placebo: 88 (92.6%) subjects for liraglutide 1.2 mg, 84 (93.3%) for liraglutide 1.8 mg, 88 (94.6%) for liraglutide 2.4 mg, 89 (95.7%) for liraglutide 3.0 mg, 89 (93.7%) for Orlistat, and 87 (88.8%) for placebo . The most commonly reported TEAEs for liraglutide were gastrointestinal AEs, which occurred at increasing frequency with increasing dose of liraglutide. Nausea was reported more frequently with liraglutide in a dose dependent manner: 23 (24.2%) subjects for liraglutide 1.2 mg, 29 (32.2%) for liraglutide 1.8 mg, 35 (37.6%) for liraglutide 2.4 mg, 45 (48.4%) for liraglutide 3.0 mg, 7 (7.4%) for Orlistat, and 7 (7.1%) for placebo. Vomiting was reported more frequently with liraglutide in a dose dependent manner: 5 (5.3%) subjects for liraglutide 1.2 mg, 9 (10.0%) for liraglutide 1.8 mg, 14 (15.1%) for liraglutide 2.4 mg, 12 (12.9%) for liraglutide 3.0 mg, 2 (2.1%) for Orlistat, and 2 (2.0%) for placebo. There were no deaths reported during the trial. SAEs were more common with the higher doses of liraglutide. There was one report of acute pancreatitis as a SAE in the liraglutide 3.0 mg group.

The primary efficacy outcome variable was the change from baseline in body weight at 52 weeks. Secondary efficacy outcome variables were:

- Waist circumference
- SBP, DBP
- Pre-diabetes status (using ADA criteria)
- Fasting lipid profile
- Metabolic syndrome status

The statistical analysis plan and sample size calculations were not reported in detail. The safety outcome variables were: AEs, PR, ECG, haematology and biochemistry, calcitonin

For the primary efficacy outcome measure, liraglutide 1.8 mg, 2.4 mg and 3.0 mg were superior to placebo; and liraglutide 2.4 mg and 3.0 mg were superior to orlistat. For waist circumference, there was a greater reduction compared to placebo for the liraglutide 2.4 mg and 3.0 mg groups. There was a decrease in SBP in the liraglutide 2.4 mg group compared

with placebo and orlistat. There was no significant difference between the groups in DBP. There was an improvement in pre-diabetes status compared to both placebo and orlistat in the liraglutide 1.8 mg. 2.4 mg and 3.0 mg groups. There was no difference between the treatment groups in fasting serum lipid parameters or in metabolic syndrome status.

Evaluator's comments:

The efficacy data for Study NN8022-1807 were not presented in sufficient detail to enable evaluation. The study methods were not described adequately and the efficacy data appeared to relate only to the population of subjects entering the extension phase. The efficacy data relate to a different indication, and will need to be submitted in much greater detail should that indication be requested in the future.

Safety

Clinical Trial Report Amendment 1: Study NN2211-1436

Study NN2211-1436 has been summarised in the clinical evaluation report. The amendment concerned the classification of PAI-1 values that were outside the range of the assay (reference range). In the original analysis values outside of the reference range were included in the analysis. In the amended report, values below 9 U/ml and above 40 U/mL were reclassified as "<9 U/mL" and ">40 U/mL" respectively, and were excluded from the analysis. The amended analysis used nonlinear mixed modelling rather than ANCOVA for hypothesis testing (as was used for the original analysis). The amended analysis indicated that subjects treated with liraglutide 1.2 mg/day and 1.8 mg/day had lower levels of PAI-1 at 26 weeks compared to those subjects treated with glimepiride.

Evaluator's comments:

The amended analysis should be viewed as a post-hoc analysis and as such carries less weight than the primary analysis.

Study NN2211-1572 2-year Clinical Trial Report

AEs

TEAEs were reported in 197 (81.4%) subjects in the liraglutide 0.6 mg/metformin group, 196 (81.7%) in the liraglutide 1.2 mg/metformin, 201 (83.1%) in the liraglutide 1.8 mg/metformin, 88 (72.7%) in the metformin and 188 (77.7%) in the glimepiride/ metformin. There was an excess of gastrointestinal AEs in the liraglutide groups, of which nausea and diarrhoea appear to be dose related.

Deaths and SAEs

There were four deaths during the trial. Three deaths occurred during treatment: two in the liraglutide 0.6 mg/metformin group (one from tuberculosis and one from acute renal failure/ pyelonephritis) and one in the liraglutide 1.2 mg/metformin group (hepatic cirrhosis/ hepatic malignant neoplasm). There was one death during the run-in period in the metformin group. SAEs were more slightly common in the liraglutide 0.6 mg/metformin group. This appears to be due to a higher rate of cardiac disorders.

Laboratory adverse events

One subject in the liraglutide 0.6 mg/metformin group had an elevated calcitonin at baseline (2.98 pmol/L) that became further elevated after 1 month of participation in the trial extension (3.83 pmol/L). The subject discontinued study treatment and recovered. Thyroid ultrasound was normal. One subject in the metformin group had elevated calcitonin during the titration phase. There were no significant differences between the groups in calcitonin concentrations, although mean concentrations at many of the visits were slightly higher in the

liraglutide groups. A reanalysis of calcitonin concentrations up to Week 78 did not result in any significant changes to the results. There were no clinically significant differences between the groups in haematology or clinical chemistry parameters.

There was an increase in mean pulse rate of 1.89 bpm (95% CI: 0.03 to 3.74) p=0.0459. Hypoglycaemia was more common in the glimepiride/ metformin group. Nocturnal hypoglycaemia was also more common in the glimepiride/ metformin group. Liraglutide antibodies occurred in approximately 4% of subjects treated with liraglutide, and neutralising antibodies in approximately 1%.

Study NN2211-1573 2-year Clinical Trial Report

AEs

For ***Study NN2211-1573*** extension, TEAEs were reported in 207 (84.1%) subjects in the liraglutide 1.8 mg group, 213 (84.9%) in the liraglutide 1.2 mg and 194 (78.2%) in the glimepiride. Gastrointestinal disorders (nausea, diarrhoea, vomiting and constipation) were more common in the liraglutide groups.

Deaths, SAEs and DAEs

Two deaths were reported during the study: one in the liraglutide 1.8 mg group from acute pancreatitis; and one in the glimepiride group from a motor vehicle accident. SAEs were reported in similar proportions of the treatment groups: 22 (8.9%) subjects in the liraglutide 1.8 mg group, 23 (9.2%) in the liraglutide 1.2 mg group and 20 (8.1%) in the glimepiride. These included one subject in the liraglutide 1.2 mg group with diffuse C-cell hyperplasia/ papillary micro-carcinoma and multiple benign adenomatous nodules. There were two additional reports of pancreatitis in the liraglutide groups, both of which recovered after withdrawal of treatment. TEAEs leading to discontinuation (DAEs) were more common in the liraglutide groups, and were predominantly gastrointestinal. Thyroid related TEAEs were more common in the liraglutide groups, including elevations in serum calcitonin.

Laboratory results

The shift table analysis indicated a similar proportion of subjects in each treatment group shifted from normal to above normal ranges for serum calcitonin concentration. There were no significant differences between the treatment groups in haematology or biochemistry results. There was no difference between the groups in clinically significant abnormal ECG findings. Hypoglycaemia was more common in the glimepiride group. Nocturnal hypoglycaemia was more common in the glimepiride group. Liraglutide antibodies were detected in around 4% of subjects treated with liraglutide, and neutralising antibodies in around 1%.

Clinical Trial Report Amendment 1: Study NN2211-1574

Study NN2211-1574 has been summarised in the clinical evaluation report. The amendment concerned the classification of PAI-1 values that were outside the range of the assay (reference range). The amended analysis did not indicate any difference between treatments in the effects upon PAI-1 at 26 weeks.

Clinical Trial Report Amendment 1: Study NN2211-1697

Study NN2211-1697 has been summarised in the clinical evaluation report. The amendment concerned the classification of PAI-1 values that were outside the range of the assay (reference range). The amended analysis did not indicate any difference between treatments in the effects upon PAI-1 at 26 weeks.

Clinical Trial report for Study NN2211-1797

AEs

For ***Study NN2211-1797*** (Table 31), there was a slightly lower rate of TEAEs in the liraglutide group, 176 (74.9%) subjects, compared with the exenatide group, 183 (78.9%) subjects. Gastrointestinal AEs occurred at a similar frequency in both treatment groups.

Deaths, SAEs and DAEs

No deaths were reported during the study. SAEs were reported more frequently in the liraglutide group: 12 (5.1%) subjects compared with six (2.6%) subjects in the exenatide group. There was a higher rate of neoplasia in the liraglutide group, including one subject with adenocarcinoma of the pancreas, and another with thyroid neoplasia. There was one patient reported with pancreatitis during the trial, in the liraglutide group. DAEs were less common in the liraglutide group, 23 (9.8%) subjects compared with 31 (13.4%) subjects in the exenatide, and were predominantly gastrointestinal disorders.

Laboratory AEs and vital signs

Mean serum calcitonin levels were similar for the treatment groups. One subject in the liraglutide group had an elevated serum calcitonin concentration during the study. There were no clinically significant abnormalities in haematology or biochemistry. Pulse rate increased in the liraglutide group relative to exenatide: least square mean difference (95% CI) 2.58 (1.03 to 4.13) bpm, p=0.0012. Hypoglycaemic episodes occurred at a similar rate. No subjects in the liraglutide group developed antibodies to the treatment, compared with six in the exenatide, three of which were neutralising.

Safety data from 14-week extension

A total of 389 subjects entered the 14-week extension, all of whom were treated with liraglutide. Of these subjects, 187 had been transferred from exenatide to liraglutide. A total of 376 (96.7%) subjects completed the 14-week extension.

A total of 146 (37.5%) subjects reported AEs. No individual AEs were reported by more than 5% of the study population. Gastrointestinal disorders were reported in 55 (14.1%) of the study population. A total of nine (2.3%) subjects reported SAEs. There were two deaths: one for cerebral infarction; one from myocardial infarction. Six (1.5%) subjects discontinued because of AEs, which were predominantly gastrointestinal. There were no clinically relevant changes in haematology or biochemistry. There were no reports of elevated calcitonin as an AE. One subject developed antibodies to liraglutide that were not neutralising.

Clinical Trial report for Study NN8022-1807

AEs

AEs were reported at a slightly greater frequency in the active treatment groups than the placebo: 88 (92.6%) subjects for liraglutide 1.2 mg, 84 (93.3%) for liraglutide 1.8 mg, 88 (94.6%) for liraglutide 2.4 mg, 89 (95.7%) for liraglutide 3.0 mg, 89 (93.7%) for orlistat and 87 (88.8%) for placebo. The most commonly reported TEAEs for liraglutide were gastrointestinal AEs, which occurred at increasing frequency with increasing dose of liraglutide. Nausea was reported more frequently with liraglutide in a dose dependent manner: 23 (24.2%) subjects for liraglutide 1.2 mg, 29 (32.2%) for liraglutide 1.8 mg, 35 (37.6%) for liraglutide 2.4 mg, 45 (48.4%) for liraglutide 3.0 mg, 7 (7.4%) for orlistat and 7 (7.1%) for placebo. Vomiting was reported more frequently with liraglutide in a dose dependent manner: 5 (5.3%) subjects for liraglutide 1.2 mg, 9 (10.0%) for liraglutide 1.8 mg,

14 (15.1%) for liraglutide 2.4 mg, 12 (12.9%) for liraglutide 3.0 mg, 2 (2.1%) for orlistat and 2 (2.0%) for placebo. Most reports of nausea were in the first 12 weeks of the trial, but nausea was reported in approximately 5% to 10% of the liraglutide 3.0 mg group throughout the trial.

Deaths, SAEs and DAEs

There were no deaths reported during the trial. SAEs were more common with the higher doses of liraglutide. There was one report of acute pancreatitis as a SAE in the liraglutide 3.0 mg group. There were no reports of thyroid or parathyroid cancer as SAEs. DAEs were more common in the liraglutide groups, but the frequency did not appear to increase with dose.

Laboratory test AEs

Two subjects in the liraglutide treatment groups had elevated plasma calcitonin. Increased ALT did not appear to be more frequent in the liraglutide groups. Mean pulse rate increased in the liraglutide groups by 3 bpm during the study.

Evaluator's comments:

The data presented in the current application demonstrated a higher rate of gastrointestinal AEs with liraglutide compared with placebo, glimepiride and metformin.

In Study NN2211-1573, one subject in the liraglutide 1.2 mg group was reported with diffuse C-cell hyperplasia/ papillary micro-carcinoma and multiple benign adenomatous nodules. There were two additional reports of pancreatitis in the liraglutide groups, both of which recovered after withdrawal of treatment. Thyroid related TEAEs were more common in the liraglutide groups, including elevations in serum calcitonin.

In Study NN2211-1797 there was a higher rate of neoplasia in the liraglutide group, including one subject with adenocarcinoma of the pancreas, and another with thyroid neoplasia. There was one patient reported with pancreatitis during the trial, in the liraglutide group.

In Study NN8022-1807 there was one report of acute pancreatitis as a SAE in the liraglutide 3.0 mg group.

Conclusion

Conclusions regarding efficacy

The two-year analysis of Study NN2211-1572 indicates that diabetes control was better when liraglutide was added to metformin, and weight control was better with liraglutide/metformin than glimepiride/metformin.

The results of the 2-year analysis of Study NN2211-1573 indicate better glycaemic control for liraglutide compared with glimepiride, in addition to less insulin resistance and better weight control.

At the doses examined in Study NN2211-1797, liraglutide provided better control of diabetes as measured by HbA1c and FPG. There was no difference between the treatments in weight control. There were also decreases in TG and FFA, the significance of which is uncertain.

The efficacy data for Study NN8022-1807 were not presented in sufficient detail to enable evaluation, and the study was conducted for a different indication to that sought in the present application. The study methods were not described adequately and the efficacy data appeared to relate only to the population of subjects entering the extension phase. The efficacy data relate to a different indication, and will need to be submitted in much greater detail should that indication be requested in the future.

Conclusions regarding safety

The data presented in the current application demonstrated a higher rate of gastrointestinal AEs with liraglutide compared with placebo, glimepiride and metformin.

In addition, the data confirm the signals of pancreatitis and thyroid carcinoma through the following findings:

- In Study NN2211-1573, one subject in the liraglutide 1.2 mg group was reported with diffuse C-cell hyperplasia/ papillary micro-carcinoma and multiple benign adenomatous nodules. There were two additional reports of pancreatitis in the liraglutide groups, both of which recovered after withdrawal of treatment. Thyroid related TEAEs were more common in the liraglutide groups, including elevations in serum calcitonin.
- In Study NN2211-1797 there was a higher rate of neoplasia in the liraglutide group, including one subject with adenocarcinoma of the pancreas, and another with thyroid neoplasia. There was one patient reported with pancreatitis during the trial, in the liraglutide group.
- In Study NN8022-1807 there was one report of acute pancreatitis as a SAE in the liraglutide 3.0 mg group.

Conclusions with regard to risk benefit

The risk benefit profile of liraglutide is in favour of approval for registration for marketing in Australia. Liraglutide is superior to metformin and exenatide for diabetes control, and to glimepiride for both diabetes and weight control. In addition, liraglutide results in fewer hypoglycaemic episodes than glimepiride.

However, liraglutide has a greater frequency of gastrointestinal adverse events, including nausea and vomiting. In addition there are signals for potentially an increased risk of thyroid neoplasia and pancreatitis with liraglutide.

Deficiencies in the Submission

The sponsor has not attempted to quantify the risk of pancreatitis or thyroid neoplasia by performing pooled analyses of the available data.

The sponsor has not provided details of the methodology and protocols for the cardiovascular outcome trial and the database study.

Recommendations

1. The sponsor should provide pooled analyses of the risk for pancreatitis and thyroid neoplasia from the available data.
2. The sponsor should provide details of the methodology and protocols for the cardiovascular outcome trial and the database study.

Provided the requested additional information was provided to the satisfaction of the TGA, liraglutide (rys) (Victoza) should be registered for the indication:

Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.

In addition, pancreatitis should be added to the Adverse Reactions section of the Product Information document.

The reader is referred to the sponsor's reply to the supplementary evaluation reports provided on page 97-98, for details of the response given by the sponsor to these recommendations.

V. Pharmacovigilance Findings

Risk Management Plan

There was no Risk Management Plan submitted with the initial application as it was not a requirement at the time of submission. However, in response to the nonclinical evaluation

report the sponsor prepared a Risk Management Plan (RMP). In the RMP the sponsor outlined the following concerns:

Identified Risks:

- Hypoglycaemia
- Gastrointestinal AEs: nausea; diarrhoea; vomiting; constipation; and dyspepsia

Important potential risks:

- Medullary thyroid cancer (C-cell carcinogenicity)
- Neoplasms
- Pancreatitis
- Immunogenicity – antibody development and allergic reactions
- Cardiac co-morbidity
- Late stage microvascular eye complication

Important missing information:

- Pregnant and lactating women
- Children and adolescents < 18 years
- Overdose
- Abuse due to weight lowering potential
- Congestive heart failure NYHA I-IV
- Drug-drug interaction with warfarin
- Benefit-risk in patients with hepatic or renal impairment/ end stage renal disease
- Off-label use

The RMP outlines the following strategy that the sponsor proposed to follow to address these concerns:

Identified risks:

- Routine pharmacovigilance: including monitoring of clinical trials for AEs, analysis of spontaneous reports[21]
- Labelling text: The sponsor intends to update the Product Information document with known risks for liraglutide. The need to titrate the dose of liraglutide in order to minimise gastrointestinal AEs will be stated in the Product Information document.

[21] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Important potential risks

- Routine pharmacovigilance and Targeted Safety Surveillance (Data Capture Aid): the Data Capture Aid appears to be a questionnaire that will be sent requesting further follow up for all thyroid AEs that are notified to the sponsor. A Data Capture Aid (questionnaire) will be used to follow up pancreatitis events reported to the sponsor. A Data Capture Aid (questionnaire) will be used to follow up immunogenicity events (antibody formation, allergic reactions and injection site disorders) reported to the sponsor.
- Labelling text: symptoms and course of action for pancreatitis will be included in the Special Warnings section.
- Clinical trials: these include the extensions to Study NN2211-1572 and NN2211-1573. There is also an ongoing three year extension to Study NN2211-1573. Planned clinical trials include NN2211-1800 (Phase I adolescents) and NN2211-3659 (safety and efficacy in paediatric population aged 10 to 17 years).
- Cardiovascular outcome trial: This was stated to be a "large international randomised controlled trial" and was still being designed.
- Database study (cardiovascular events, neoplasms and pancreatitis): the methodology for the database study and the databases that will be used are not stated in the Risk Minimisation Plan. The database study is stated to be "under discussion".

Important missing information:

- Routine pharmacovigilance
- Labelling text
- Clinical trials
- Cardiovascular outcome trial

Evaluator's comments

The sponsor has identified similar safety concerns to those identified in the nonclinical evaluation report and the clinical evaluation report. The RMP proposes actions for each of the identified concerns. For the most part, these actions are routine pharmacovigilance activities, such as collating reports of AEs from clinical trials and from spontaneous reports to the sponsor. The cardiovascular outcome trial and the database study are additional to the routine pharmacovigilance activities, but the methodology and protocols for these studies were not provided.

The pharmacovigilance activities that will be conducted in Australia were not specifically stated. It was not clear whether the sponsor intends to sponsor studies using cancer databases, clinical toxicology databases or the National Death Index in Australia. The sponsor should be required to submit the protocols for the proposed studies prior to registration.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator noted that liraglutide is a substituted fragment of GLP-1. Liraglutide is expressed in transformed Brewer's yeast by recombinant DNA technology and further chemically modified by an addition of a Glu-spaced hexadecanoic (palmitic) acid residue.

Specifications have been revised and agreed, test methods are validated and impurities have been toxicologically qualified. Liraglutide is light sensitive and needs to be protected from light and high temperatures during use. A shelf life has been agreed. However, batch testing of the first 5 batches has been recommended as a condition of registration.

With regard to bioavailability, the chemistry evaluator noted that the "for marketing formulation" was used in the Phase 3 clinical trials.

The Delegate noted that the evaluator stated: "The products 'should be administered once daily, at any time independent of meals'. As an injection this was accepted without data." This was a comment about the lack of need for a study on the effect of food upon bioavailability and not upon the clinical implications of dosing without regard to food intake or concomitant antidiabetic medication.

Nonclinical

Initial Nonclinical Evaluation

The evaluator concluded that the primary pharmacology of liraglutide is consistent with being an analogue of GLP-1. It had *in vitro* proliferative effects on pancreatic β-cells in an obese mouse model. In animal models of diabetes and/or obesity, liraglutide stimulated insulin secretion. Subcutaneous administration of liraglutide reduced blood glucose levels (several animal models of diabetes), improved glucose tolerance (obese mice, diabetic and pre-diabetic rats, diabetic and non-diabetic pigs), increased plasma insulin, increased pancreatic β-cell proliferation and mass, inhibited gastric emptying (in mini-pigs), reduced food consumption and decreased body weight (numerous studies).

In pharmacodynamic studies, additive effects upon blood glucose levels were not observed with liraglutide in combination with metformin (in diabetic mice) but were seen with pioglitazone or atorvastatin in diabetic rats. Additive effects with glipizide were seen *in vitro*. Secondary pharmacology studies did not suggest other activity.

Nonclinical studies investigating pharmacokinetic or toxicological interactions between liraglutide and metformin, a thiazolidinedione or a sulfonylurea were not performed.

Liraglutide is slowly absorbed from the site of injection in several species, possibly due to the molecule's tendency for self-association, is distributed predominantly to well-vascularised tissues and is said to have "poor" penetration of the blood-brain barrier. Metabolism is by enzymatic degradation by DPP-4 and neutral endopeptidase and degradation of the palmitic acid component. There is one weakly active metabolite, liraglutide (9–37), in humans. Liraglutide does not inhibit human CYP liver enzymes.

Acute (single dose) toxicity was low in three species. In regard to repeat dose toxicity, thyroid carcinogenicity and hepatic adverse effects are of interest. Increased incidences of hepatic centrilobular hypertrophy (in males) and Kupffer cell pigmentation (in females) occurred at ≥0.03 and ≥1 mg/kg/day, respectively (relative exposure levels, 0.3 and 7.7) in the 2-year carcinogenicity study in mice. There was no NOEL for hypertrophy, while abnormal cell pigmentation was not seen at 0.03 mg/kg/day. The evaluator opined: "The relatively high safety margin in monkeys and inconsistency of effects in rodent species suggests that liraglutide is unlikely to be hepatotoxic at the normal clinical exposure levels".

Liraglutide did not exhibit genotoxicity or mutagenicity *in vitro*. Liraglutide was carcinogenic in mice and rats, causing thyroid C-cell adenomas and carcinomas. Exposure

ratios based upon no observed effect levels for C-cell neoplasia are low: 2.0 in mice and <0.5 in rats. Focal (nodular) C-cell hyperplasia, a pre-neoplastic lesion, was first observed following 9 weeks of treatment in mice (a species with a very low spontaneous incidence of C cell proliferative lesions) and 40 weeks in rats (a species with a high background level of C cell proliferative lesions). This may be taken to mean that rats are sensitive to liraglutide at all doses and that mice have almost no margin of safety with respect to dosing. Thyroid C-cell hyperplasia was observed in mice at all doses tested in the 3-month study (≥0.2 mg/kg/day; relative exposure,≥2.3). No thyroid C -cell lesions were observed in monkeys treated with liraglutide for up to 20 months. The evaluator did not accept the applicant's synthesis in regard to rodent carcinogenicity:

1. The findings were not relevant to humans because GLP-1 receptor-mediated calcitonin release could be shown in rat C-cell carcinoma cell lines but not human ones.

2. Chronic GLP-1 receptor activation on C-cells causes ongoing calcitonin release and increased calcitonin synthesis, driving hyperplasia and leading to neoplasia in rodents.

3. No thyroid C-cell lesions were observed in monkeys treated with liraglutide for up to 20 months.

Objections raised by the evaluator included:

1. Cancer-derived cells may not be good models for normal C cells.

2.1. Calcitonin was not a credible biomarker for proliferative C-cell lesions in rats (that is, focal C-cell hyperplasia developed and progressed to adenoma in the absence of any sustained increased in calcitonin synthesis/release, or even a decrease in calcitonin levels).

2.2. C-cell neoplasia in rodents developed in a manner unlike that expected in cases where C-cell proliferation occurs in response to increased physiological demand (that is, there was no initial increase in diffuse C cell hyperplasia).

3. Increased plasma calcitonin has been observed *in vivo* in humans treated with liraglutide. This would damage the applicant's suggested explanation, if it were true. Given the variability in the time to lesion development evident in mice and rats and considering that, as a proportion of the animals' life span, the treatment duration in monkeys is much shorter than that required for lesion development in rats, the absence of C-cell lesions in monkeys is not fully reassuring as to a lack of human relevance for the C-cell neoplasia produced by liraglutide in rodents.

Liraglutide was not considered to be teratogenic.

Registration was initially opposed on non-clinical grounds due to concerns regarding the potential for carcinogenicity in humans. Another nonclinical concern is the lack of combination toxicity studies with commonly used medication in the treatment of diabetes mellitus type 2. Subsequent to additional nonclinical (and clinical) information being provided, registration was approved.

The Delegate noted that, in addition, hepatotoxicity is of concern for patients with diabetes mellitus type 2 because this patient group is already at risk of hepatic disease. No consistent pancreatic toxicity was seen but there is a signal of pancreatic inflammation. Pancreatitis has been reported in patients receiving exenatide.

The Delegate further noted that although the nonclinical evaluator has accepted the following statement, the Delegate did not:

"Liraglutide has been shown to delay the progression of diabetes in animal models of pre-diabetes. Liraglutide has been shown in vitro to be a potent agent for specific stimulation of beta-cell proliferation and prevention of both cytokine and free fatty acid induced beta-cell death (apoptosis). In vivo, liraglutide increases insulin biosynthesis, and beta-cell mass in diabetic animal models. When glucose is fully normalised, liraglutide does not increase beta-cell mass."

A less promotional interpretation of the data would be: "Liraglutide has shown anti-hyperglycaemic efficacy in animal models of pre-diabetes. Liraglutide has been shown *in vitro* to be a potent agent for specific stimulation of beta-cell proliferation and prevention of both cytokine and free fatty acid induced beta-cell death (apoptosis). *In vivo*, liraglutide increases insulin biosynthesis, and beta-cell mass in diabetic animal models. The relevance of this to humans is not known. When hyperglycaemia is fully normalised, in animal studies, liraglutide does not increase beta-cell mass."

Supplementary Nonclinical Evaluation:

In response to the above, the sponsor submitted supplementary nonclinical data in support of the application. The data were about the mechanism and relevance of thyroid C-cell proliferative changes (focal hyperplasia, adenoma and carcinoma) produced by liraglutide in mice and rats. A correlation between the increase in plasma calcitonin levels after 1 month of treatment with liraglutide and the terminal focal C-cell hyperplasia score in a 16-month mechanistic study in rats was demonstrated by the sponsor. There were still some reservations by the TGA evaluator about the precision of histopathological diagnosis and some reservations about the mechanistic model. The relevance for humans of the rodent findings is now considered "likely to be low" but cannot currently be completely excluded. There was an absence of C-cell proliferative changes in cynomolgus monkeys treated with liraglutide in a 20-month study (≤5 mg/kg/day SC; relative exposure, ≤64). The duration of this study was considered adequate to reveal potential proliferative lesions mediated by receptor stimulation (but not neoplastic transformation).

The evaluator now concluded: "Considering the original and supplementary data, a revised recommendation is in order: there are no nonclinical objections to the registration of Victoza for the proposed indication provided there is no evidence of stimulation of calcitonin release in humans treated with the drug. A pharmacovigilance program to further assess potential C-cell proliferative changes in patients is warranted."

Clinical

Initial Clinical Evaluation

Pharmacokinetic Studies

There were 15 studies conducted in 397 subjects, with 373 exposed to liraglutide in support of pharmacokinetics.

Studies in healthy volunteers:

Study NN2211-1699 was a single-centre, open label trial investigating the metabolites in plasma, urine and faeces after a single subcutaneous dose of tritiated liraglutide (Each subject received 0.75 mg liraglutide and a nominal radiochemical dose of 12.0 MBq administered subcutaneously in the abdomen) in seven healthy adult volunteers - no unchanged liraglutide was detected in urine or faeces. Three metabolites were detected in urine. There were three metabolites detected in faeces. No quantification of the individual components was possible. Other information obtained included: "Up to Day 14, 26.3% of the total radioactivity was

excreted in urine and faeces, with 11.5% of the total radioactivity excreted as liraglutide-related and 14.8% as tritiated water. T_{max} was 11.7 hours and $t_{½}$ was 15.4 hours."

Study NN2211-1327 was a single centre, open label, single dose trial with two groups comparing the pharmacokinetics of liraglutide in young (21 to 45 years) versus elderly (65 to 83 years) subjects of both sexes. As might be expected, no important pharmacokinetic effects of age or sex were noted. Tolerability was better in the elderly.

Study NN2211-1328 was conducted in healthy volunteers and those with hepatic impairment. Liraglutide 0.75 mg was injected subcutaneously from a pen injector into the thigh of 24 trial subjects of whom 23 completed - AUC decreased and volume of distribution increased with increasing hepatic impairment. The Delegate noted that the latter reflects lower protein binding.

Study NN2211-1329 was similar to the above, investigating the pharmacokinetics of liraglutide in subjects with normal renal function and in subjects with impaired renal function. Thirty subjects were enrolled. There were no clear differences in pharmacokinetic parameters on the basis of renal function.

Drug Interaction Studies

These randomised, double-blind studies examined the effect of liraglutide, at steady state, upon the pharmacokinetics, in healthy volunteers, of orally administered ethinyloestradiol and levonorgestrel (Study NN2211-1330) and 40 mg atorvastatin, 20 mg lisinopril (Part A), 500 mg griseofulvin and 1 mg digoxin (Part B) and on intragastric pH (Part B) (Study NN2211-1608). Significant findings regarding extent of absorption were limited to digoxin and lisinopril:

- lisinopril $AUC_{¥}$ mean ratio (90% CI) 0.849 (0.747 to 0.966),

- digoxin 0.843 (0.722 to 0.984) $AUC_{¥}$ mean ratio (90% CI)

The rate of absorption was affected.

Regarding atorvastatin, lisinopril and digoxin, T_{max} was delayed by 1.25 hours, 2.00 hours and 1.125 hours respectively after liraglutide compared to placebo. Griseofulvin's T_{max} was not affected by treatment. The C_{max} of griseofulvin was 37% higher ratio (90% CI) 1.369 (1.243 to 1.507). The C_{max} for other test drugs was reduced.

The evaluator's conclusions are broadly reflected in the proposed product information document (PI).

However, the Delegate noted the following comment: "There were slight differences in absorption between injection sites, with greater absorption from the abdomen than the upper arm or thigh. The clinical effects of these differences in absorption have not been explored."

Pharmacodynamic Studies

There were nine studies conducted in 284 subjects, 250 exposed to liraglutide, in support of pharmacodynamics.

Studies in healthy volunteers:

Study NN2211-1149 was an important study that also produced absolute bioavailability data. It was of double-blind, placebo-controlled, dose escalation design, using single doses of liraglutide or placebo, administered as single subcutaneous doses of from 1.25 μg/kg to 20 μg/kg.

The absolute bioavailability for the 5 µg/kg subcutaneous dose was 55%. Dose-proportionality for $AUC_{¥}$ and C_{max} were not shown if the 12.5 µg/kg dose group's data were included. Blood glucose levels were not affected in these healthy volunteers except in those in the intravenous GTT substudy: overall (p=0.0002) and within the 2.5, 5, 12.5 and 20 µg/kg dose levels average insulin was statistically significantly higher following liraglutide.

Study NN2211-1644 was a safety pharmacology study in 51 adult volunteers. It compared liraglutide with moxifloxacin with respect to effects on cardiac conduction in a multidose, two period, double blind, crossover design. There was no significant prolongation of QTc with liraglutide in comparison with placebo.

Studies in Patients:

Study NN2211-1189 was similar to study NN2211-1149. The study failed to recruit enough subjects and only 2 diabetics completed the study. Dose-proportional pharmacokinetics were reported as well as accumulation on repeat dosing.

Study NN2211-1698 was a single centre, randomised, placebo controlled, double-blind, two-period cross-over trial in eighteen diabetic patients. Paracetamol was used as marker of the effect of liraglutide on gastric emptying: the Tmax of orally administered paracetamol increased from about 46 minutes (after placebo) to about 97 minutes after liraglutide. Three doses of liraglutide were used: 0.6, 1.2 and 1.8mg daily. A dose-dependent reduction in the estimates of fasting plasma glucose (FPG), glucose $AUC_{0\text{-}60min}$, $AUC_{0\text{-}180min}$ and C_{max} was observed across all three dose levels of liraglutide in comparison to placebo. Insulin (fasting, C_{max} and $AUC_{0\text{-}300min}$) was affected by the 1.8mg dose. Similarly, hunger and food intake were affected only by the largest dose.

Study NN2211-1589 was a double-dummy, randomised, double-blind, two-centre, weekly dose-escalation study with balanced incomplete Latin square design comparing the effect of liraglutide (1.8 mg), glimepiride and placebo on numerous exploratory endpoints including:

- energy intake at an ad libitum buffet meal,
- duration of the meal,
- macronutrient distribution,
- appetite sensations and nausea,
- gastric distension (assessed by ultrasound measurements of antral area),
- gastric emptying (assessed by paracetamol absorption); and
- metabolic and hormonal responses.

Of note, there was no statistically significant difference for the energy intake between liraglutide treatment versus placebo and glimepiride at the ad libitum meal, despite lower reported hunger for liraglutide versus placebo. However, liraglutide managed to reduce weight and fasting plasma glucose levels; liraglutide significantly lowered the mean fasting plasma glucose after a 4-week treatment period compared to placebo and glimepiride treatment. There were no differences regardless of treatment for insulin and glucagon levels. Paracetamol's T_{max} was observed about 20 minutes later after liraglutide treatment, compared with placebo and glimepiride.

Study NN2211-1332 was a single-centre, randomised, double-blind, crossover trial in subjects with type 2 diabetes. Liraglutide and placebo were each injected subcutaneously for 9 to 10 days. Oral hypoglycaemic agents were discontinued 2-3 weeks prior to treatment. A dose of 6 µg/kg (1.2 µL/kg) of either liraglutide or placebo was administered subcutaneously in the abdomen each morning before breakfast using a pen injector. A hyperglycaemic clamp was used to measure insulin release. The results were variable:

- The 24 hour glucose profile was lower for liraglutide: mean AUC (SE) 187.46 (14.02) mmol/L.h for liraglutide and 232.30 (21.94) mmol/L.h for placebo;
- There was no significant difference in 24 hour insulin profile;
- There was no significant difference in C-peptide levels;
- There was a decrease in 24 hour glucagon profile with liraglutide; and
- There was no difference between treatments in free fatty acids, pro-insulin, leptin or of insulin secretion rate.

During the hyperglycaemic clamp:

- insulin secretion was higher for liraglutide during the first phase;
- insulin secretion was higher for liraglutide during steady state;
- Endogenous glucose release and glycogenolysis were decreased with liraglutide, but gluconeogenesis was not affected.

Study NN2211-1219 was a single-centre, randomised, placebo-controlled, double-blind, crossover trial to assess the effect of liraglutide on pulsatile secretion of insulin in subjects with Type 2 diabetes in the post-prandial state. The exploratory study showed a secretagogue effect for liraglutide. Basal secretion of insulin was higher with liraglutide; there was no difference in insulin resistance and gastric emptying was delayed with liraglutide.

Study NN2211-2063 was a double-blind, randomized, single-centre, placebo controlled, crossover study to examine acute beta-cell responsiveness to graded glucose infusion in patients with type 2 diabetes, and in comparison with a control group of healthy volunteers. Liraglutide, given as a single-dose of 7.5 μg/kg, or placebo, was administered by subcutaneous injection. In response to a glucose infusion, the insulin secretion rate (measured using C-peptide levels) following liraglutide was higher than for placebo, and was similar to that observed in healthy volunteers. There was no significant difference between groups in glucagon secretion. Glucagon release was not materially affected.

Study NN2211-1224 was a double-blind, placebo-controlled, randomised, two-period crossover study of the effect of liraglutide (7.5 μg/kg s/c)on hypoglycaemic counter-regulation during a stepwise hypoglycaemic clamp procedure in nineteen adult type 2 diabetic subjects. The clamp was conducted at four different plasma glucose levels. There was no statistically or clinically significant difference between liraglutide and placebo in glucagon levels, glucose infusion rate, mean cortisol levels, adrenaline levels, noradrenaline levels; mean glucose levels were slightly higher in the liraglutide group for the lower ranges of the hypoglycaemic clamp.

Growth hormone secretion was decreased in the liraglutide group ($p=0.0320$). Of note, C-peptide levels were higher in the liraglutide group ($p<0.0001$) and insulin secretion rate was higher in the liraglutide group

Efficacy

There were 10 studies conducted in 4947 subjects, with 3187 exposed to liraglutide in support of efficacy. The studies were of acceptable design (double-blind, randomised, parallel group) with ITT analyses. Glycosylated haemoglobin was the primary endpoint. There were numerous secondary glycaemic endpoints and numerous exploratory endpoints.

As stated by the applicant, "The primary objective of the therapeutic confirmatory Trials 1573, 1572, 1436, 1574 and 1697 was to demonstrate that glycaemic control, measured by change from baseline in HbA1c, achieved with liraglutide treatment was better (superior) than with placebo treatment (not applicable for Trial 1573) and at least as good (non-inferior) as that achieved with the comparator (not applicable for Trial 1574). If non-

inferiority was demonstrated, it was further investigated if the glycaemic control achieved with liraglutide was also superior to that of the comparator treatment. The noninferiority margin for HbA1c in these trials was 0.4% points, which was defined as the clinically acceptable non-inferiority difference."

Monotherapy Studies:

These studies all included dose-finding in their designs.

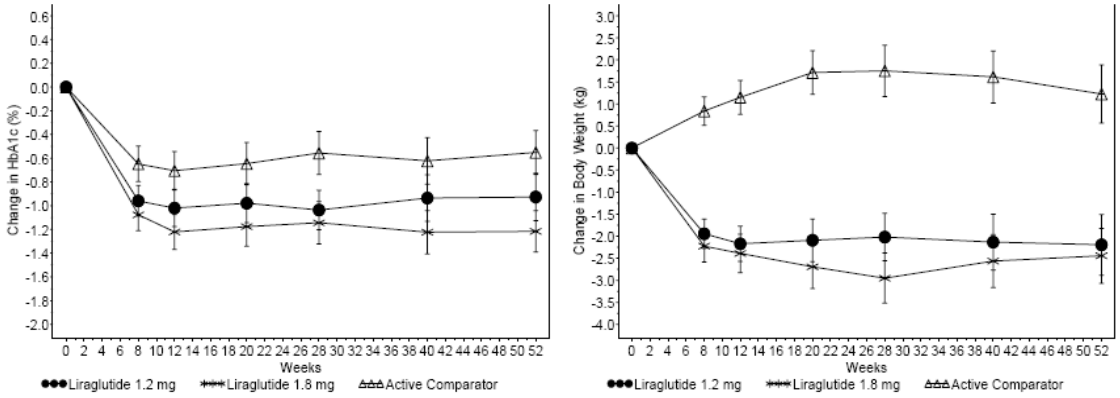
Study NN2211-1571 was a 14 week, multicentre, multi-national, double-blind, randomised, parallel-group, clinical trial of the effect on glycaemic control of three doses of liraglutide (0.65 mg, 1.25 mg and 1.90 mg) as monotherapy versus placebo in 163 enrolled subjects with type 2 diabetes. The patients who were naive to drug treatment were able to be enrolled. The outcome measures were glycaemic control as assessed by HbA1c (primary efficacy outcome measure). There was a dose dependent effect on the primary endpoint for all doses used (Table 6). Similar results were seen for secondary endpoints (fasting plasma glucose and beta cell function, as measured by HOMA).

Study NN2211-1310 was a 12 week study that was of similar design but which used five doses of liraglutide (0.045 mg, 0.225 mg, 0.45 mg, 0.60 mg, and 0.75 mg s/c once daily before breakfast), placebo or glimepiride 1-4 mg/day. The one hundred and ninety patients had received treatment for at least three months with oral agents or diet alone. The doses used were lower than in Study NN2211-1571 (see above) but efficacy and adverse effects were noted at the two highest doses used. For the two higher dose levels (0.60 mg and 0.75 mg) compared with placebo there were statistically significant decreases in HbA1c, fasting serum glucose, fructosamine, and mean blood glucose

Study NN2211-1573 was a multicentre, double-blind, double-dummy, randomised, parallel, active-controlled clinical trial of 52 weeks treatment duration followed by a 52-week, open-label extension. The patients studied had type 2 diabetes mellitus, were treated with diet/exercise or not more than half-maximal oral antidiabetic drug dose (monotherapy with sulphonylureas, meglitinides, amino acid derivatives, biguanides, alpha-glucosidase inhibitors and thiazolidinediones) for at least 2 months. Subjects treated with metformin 1500 mg or pioglitazone 30 mg were eligible for the trial. At Randomisation (Visit 2) the mean FPG meter reading had to be $\geq$7.0 mmol/L $\leq$13.9 mmol/L for subjects previously treated with diet/exercise therapy or $\leq$12.2 mmol/L for subjects previously treated with half-maximal or less dose of a single oral agent.

There was a dose dependent, greater reduction in HbA1c in the liraglutide groups than for glimepiride (Table 11, Figure 4)). Of interest, weight fell on both doses of liraglutide and more so at the higher doses (Figure 4).

Figure 4: Change in mean HbA1c (%) and body weight (kg) over 52 weeks, mean ±2 trial 1573



Study NN2211-1573 – Open Label Extension from 53 - 104 weeks

The extension lasted for 52 weeks, in addition to the original 52 weeks double-blind treatment. The outcome measures were: HbA1c, fasting plasma glucose, body weight, blood pressure, fasting serum lipids and AEs. 440 subjects were enrolled (not re-randomised) in the open-label extension. Of these subjects, 79 (51.3%) of 154 subjects enrolled in the liraglutide 1.8 mg group, 92 (61.7%) of 149 in the liraglutide 1.2 mg group and 66 (48.2%) of 137 in the glimepiride group completed the study.

The improvement from baseline in HbA1c was maintained through from baseline to Week 26 of the extension. The full 12 month data were submitted in the supplementary submission (see below).

Add-On Studies – Dual Therapy

In these studies, patients could be inadequately controlled but were not necessarily in secondary failure, that is, patients could be recruited who were inadequately controlled on diet and exercise alone.

Add-on to Metformin

Study NN2211-1499 was a double blind, double-dummy, randomised, parallel-group, multicentre, dose titration study (with an open labelled oral agent arm i.e. glimepiride + metformin) of the effect on glycaemic control of individual maximum effective dose of liraglutide as add on therapy to metformin compared to monotherapy (metformin or liraglutide alone). Liraglutide was given in doses of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, once-daily subcutaneous injection in the abdomen or thigh (in the evening) The study was of five weeks duration.

As noted by the evaluator, liraglutide alone was superior to metformin alone but inferior to metformin + glimepiride whereas liraglutide + metformin was superior to metformin + glimepiride. There were similar results concerning HbA1c – the study was somewhat insensitive for this outcome due to its short duration. Body weight decreased in the liraglutide and metformin groups but not for the metformin/glimepiride group.

The Delegate noted that the study was of insufficient duration to establish the therapeutic role of liraglutide by reference to glycosylated haemoglobin. Otherwise, the numbers allocated to each treatment group were adequate to explore dose-response for fasting plasma glucose but insensitive for safety. The study is a dose finding study that would inform a longer term study in patients who are inadequately controlled on metformin monotherapy. The weight changes shown with metformin or liraglutide alone or in combination are small but potentially useful if sustained.

Study NN2211-1572 was a multicentre, multinational, double-blind, double-dummy, randomised, active control, parallel-group trial with an 18 months extension period investigating the safety and efficacy of liraglutide as add-on to metformin.

The primary efficacy outcome measure was the change from baseline in HbA1c after 26 weeks of treatment (Table 13). Liraglutide 1.8mg and 1.2 mg doses were superior to metformin alone, and non-inferior to glimepiride/metformin. Liraglutide 1.2 mg and 1.8 mg in combination with metformin were superior to metformin alone. In combination with metformin, liraglutide had similar efficacy to the glimepiride/metformin combination.

The evaluator was of the view that liraglutide 1.8 mg and 1.2 mg plus metformin was non-inferior to glimepiride plus metformin. Liraglutide 0.60mg per day was inferior to metformin + glimepiride. The evaluator observed, “There was an apparent plateau in the effect with the liraglutide 1.2 mg dose. The effect was independent of prior treatment, gender, age or BMI. Significant weight loss also occurred with liraglutide and this effect also had a plateau with the 1.2 mg dose...”

The Delegate noted that liraglutide’s effects on weight showed dose-dependency and this is consistent with other studies but, as there was inferiority shown in the primary endpoint, there is some doubt about the value of testing secondary endpoints.

Extension Study:

Study NN2211-1572-extension was an open label extension of the above. The study was conducted at 143 centres. The study was of 18 months duration. Patient numbers: there were 184 in the liraglutide 0.6 mg, 178 in the liraglutide 1.2 mg, 174 in the liraglutide 1.8 mg, 61 in the metformin and 183 in the glimepiride/ metformin groups.

Completion to 18 months was above 90% except in the metformin group (78.7%). Mean duration of exposure was 81.8 - 92.1 days. The results (Figures 5 and 6) suggest some loss of efficacy over time (the last observation is carried forward).

Figure 5: Mean Change in HbA1c (%) by Treatment and Week - 18-month Data (LOCF). Only Subjects Completing 12-month Period are Included.

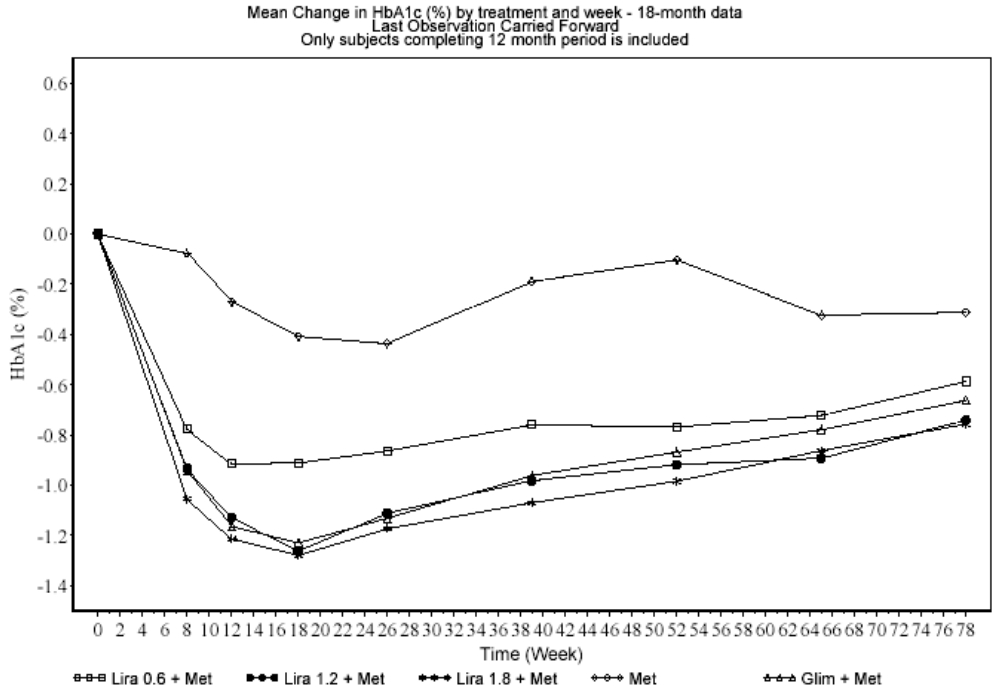
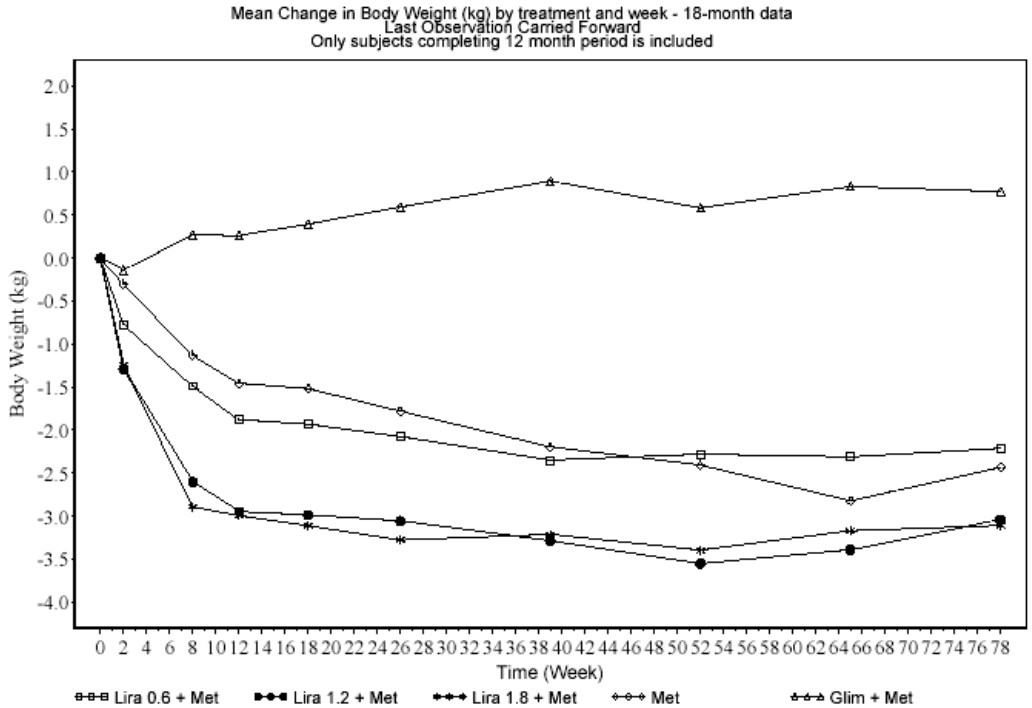


Figure 6: Mean Change in Body Weight (kg) by Treatment and Week - 18-month Data (LOCF). Only Subjects Completing 12-month Period are Included.



Add-On Studies – Glimepiride

Study NN2211-1436 was a multicentre, multinational, randomised, double blind, double dummy, active control, parallel group clinical trial of 6 months duration. Its design was somewhat similar to the above metformin study, Study NN2211-1572, and it also ran for 6 months. It enrolled patients diagnosed with type 2 diabetes and "treated with OAD(s)" for at least 3 months, with an HbA1c: 7.0-11.0 % (inclusive) in subjects on oral monotherapy or 7.0-10.0 % (inclusive) in subjects on oral combination therapy.

The primary efficacy outcome measure was the change from baseline in HbA1c after 26 weeks of treatment. Secondary efficacy outcome measures were numerous and included fasting plasma glucose, weight as well as waist and hip circumference.

The evaluator found that: "For the primary efficacy outcome measure, liraglutide 1.2 mg and 1.8 mg in combination with glimepiride were superior to both comparator groups, and liraglutide 0.6 mg in combination with glimepiride was superior to glimepiride alone and non-inferior to rosiglitazone/ glimepiride".

Liraglutide plus glimepiride did not increase weight compared to glimepiride alone whereas glimepiride and rosiglitazone were associated with weight gain. The Delegate noted that:

1. The study would have been expected to show acute and subchronic weight gain with rosiglitazone and continuous weight gain with glimepiride.
2. It would be perhaps unusual in Australia to discontinue metformin monotherapy in insufficiently responsive patients on, say metformin and then to switch them to glimepiride alone or to glimepiride with a thiazolidinedione unless metformin was poorly tolerated. It is therefore not clear what relevance this treatment model has except to reinforce the secondary endpoints concerning weight loss.
3. The study enrolled patients on monotherapy who might need a second agent and those already on two agents that might need a third agent. The results as presented do not separate these two groups. However, this would only be exploratory.

Add-On Studies – Triple Therapy

Study NN2211-1574 was a multicentre, double-blind, randomised, parallel group trial of twenty-six weeks duration to assess liraglutide as add-on treatment to rosiglitazone (6 mg/day) - metformin (2 g per day) combination in patients with type 2 diabetes. The study lasted for 26 weeks. The inclusion criteria did not limit enrolment to those insufficiently controlled on metformin plus rosiglitazone nor a requirement for insufficient control on dual therapy.
Both liraglutide add-on treatments were similarly superior to placebo plus metformin and rosiglitazone for the primary efficacy endpoint (Table 17).

Changes in fasting plasma glucose were consistent with the results for HbA1c.

Of interest, considering that a thiazolidinedione was involved, there was a decrease in body weight for both liraglutide groups relative to placebo. Changes in waist circumference were consistent with the results for body weight. It is relevant that the higher dose of liraglutide was less well tolerated.

Study NN2211-1697 was a 6 month, multicentre, multinational, double-blind (except insulin glargine), randomised, parallel group clinical trial comparing liraglutide, glargine and placebo as add-on therapy to glimepiride and metformin in patients with type 2 diabetes.

The population was a little less heterogeneous than in that above study because patients enrolled had not received exenatide but at least one oral agent. The larger dose that was used

in the preceding study was selected in this study. As with the above study, the primary efficacy outcome measure was the change from baseline in HbA1c. However, there were numerous secondary endpoints that were not explored until after testing of two hypotheses on the primary endpoint:

"If liraglutide [were] superior to placebo then a secondary test of non-inferiority in comparison with glargine was performed, using the per-protocol population, with a 0.4% difference in HbA1c being the criterion for non-inferiority. If non-inferiority [were] demonstrated then a superiority test was to be performed using the ITT population."

The sponsor's tabulated results refer to insulin as the main comparator. The primary endpoint results are shown in Table 19. Further, body weight changes were as expected in regard to insulin and placebo.

The evaluator concluded that liraglutide improved glycaemic control in combination with glimepiride and metformin and it was superior to glargine in combination with glimepiride and metformin. The Delegate noted that the study recruited a heterogeneous mix of patients.

Other Studies:

Study NN2211-1334 was a 14 week, multi-centre, double-blind, four treatment cohort, parallel group trial with placebo and four doses of liraglutide in the treatment of Japanese subjects with type 2 diabetes who were either managed by diet and exercise or by oral monotherapy. It was a fixed dose study with some titration in the two higher doses selected. Dose dependent-reductions in HbA1c were seen. The Delegate noted that the study contributes dose-ranging and safety information but is rather short in duration and it enrolled only about 45 patients per group.

Study NN2211-2072 was a 12 week, multicentre, randomised, double-blind, double-dummy, parallel-group dose-response, efficacy and safety study of metformin and five doses of liraglutide in previously treated OHA monotherapy obese subjects with type 2 diabetes. The study treatments were: liraglutide 0.75 mg, 0.60 mg, 0.45 mg, 0.225 mg, or 0.045 mg (plus metformin placebo) or metformin 1000 mg twice daily orally plus liraglutide placebo. The Delegate noted that the study was small but is of interest because liraglutide monotherapy at the two lowest doses was inferior to metformin. Dose ranging was therefore satisfactory.

Overall Efficacy Conclusions

The evaluator has summarised and interpreted the principal findings of the studies. Liraglutide was effective in doses from 0.6 mg per day, but significant differences against this lower dose were demonstrated at the 1.2 mg and 1.8 mg per day dose levels. The optimal efficacy appears to be at the 1.8 mg dose level.

The evaluator concluded: "Liraglutide resulted in an excess of gastrointestinal side effects, mainly nausea, vomiting, diarrhoea and constipation. These side effects were dose related and limited the maximum dose of liraglutide that could be used. Titration of treatment from a commencing dose of 0.6 mg, to 1.2 mg over a week then 1.8 mg after another week appeared to decrease the rate of gastrointestinal side effects. These side effects occurred early in treatment and appeared to improve over the first few months of treatment...

... In general, the rate of withdrawal as a result of AEs was higher in the liraglutide groups. This is in keeping with the overall higher rate of AEs with liraglutide.

... There was an excess of hypoglycaemic events when liraglutide was administered in combination with glimepiride. Whilst these events were not serious in the trials, there was an

increase in nocturnal events and the Evaluator has concerns that serious hypoglycaemic events could occur in relation to this combination."

The Delegate noted that liraglutide appeared to result in a more favourable profile of plasma lipids than rosiglitazone. If pioglitazone had been the comparator, this effect would possibly not have been present.

Evaluator's Recommendations

The evaluator recommends approval of a broad indication, *Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus*, but sought to specify the developmental limitations by use of other sections in the product information document (PI).

Further Comments by Evaluator

The pharmacodynamic data indicate that liraglutide increases the secretion of insulin in response to a glucose load and decreases the secretion of glucagon. Liraglutide delayed gastric emptying and increased sensations of satiety. The evaluator also commented that: "Although the clinical development program has been thorough, the sponsor does not clearly indicate how liraglutide should best be used in clinical practice, and what long-term safety monitoring should be undertaken."

Data Limitations

The primary clinical data set was limited by duration of experience and sensitivity to detect adverse events of concern, for example pancreatitis and cardiovascular safety. The monotherapy trials lacked comparison with metformin.

Sponsor's Response

The Delegate stated that an area of difficulty is that the sponsor has misunderstood the evaluator's concern that it is still not clear how liraglutide might best be used in practice – the response centres upon the drug development program but does not say what treatment algorithm is to be applied subsequent to the initiation of liraglutide, whether as first-line monotherapy, monotherapy after switching to it, as add-on therapy in dual or triple agent use. This is because no evidence exists on what might best be done as patients escape from control on liraglutide.

Supplementary Data

Supplementary data were submitted during the course of this application. The covering letter states that the data support safety of liraglutide; there are no efficacy claims. There are five clinical trials all, double blind randomised studies with an extension phase that have up to 84 weeks of extension phase data. The new clinical data were submitted to address the concerns of the toxicological evaluator who noted thyroid cell cancers in rat studies. Carcinogenicity studies in rats and mice have demonstrated an increased incidence of thyroid C-cell adenomas and carcinomas. There were five papillary cell carcinoma among liraglutide treated patients.

Also mentioned in the letter, the US FDA requested long term morbidity studies to assess the effect of cardiovascular events.

The nonclinical evaluation report was rewritten and is described above; the clinical evaluation report was provided as a supplementary report.

Supplementary Clinical Evaluation Report

The supplementary data comprised efficacy and safety data.

Study NN2211-1572 – Extension to Two Years

Eighteen month extension phase data were presented in the primary evaluation report; a further 6 months' extension data are available for 130 (53.7%) subjects in the liraglutide 0.6 mg/metformin group, 137 (56.8%) in the liraglutide 1.2 mg/metformin group, 118 (48.8%) in

the liraglutide 1.8 mg/metformin group, 31 (25.4%) in the metformin only group and 113 (46.3%) in the glimepiride/metformin group.

Efficacy: Liraglutide for all dose levels was superior to metformin alone and non-inferior to glimepiride/metformin. Consistent with the 18 month results, body weight decreased in the liraglutide/metformin groups compared with glimepiride/metformin but not compared with metformin alone. The evaluator concluded, regarding efficacy, that diabetes control was better when liraglutide was added to metformin, and weight control was better with liraglutide/metformin than glimepiride metformin.

Safety: Serum calcitonin levels are of interest in the light of the nonclinical findings. It can be said that increases are least for completers to 104 weeks in the metformin only group. One subject in the liraglutide 0.6 mg/metformin group had an elevated calcitonin at baseline (2.98 pmol/L) that became further elevated after 1 month of participation in the trial extension (3.83 pmol/L). The subject discontinued study treatment and recovered. Thyroid ultrasound was normal. One subject in the metformin group had elevated calcitonin during the titration phase.

Hypoglycaemic events were most frequent in the glimepiride + metformin group and least in the metformin only group. There was an excess of gastrointestinal AEs in the liraglutide groups, of which nausea and diarrhoea appear to be dose related.

Study NN2211-1573 (see above) was a 52 week study that followed by a 52-week, open-label extension. The evaluator described the results to 52 weeks and mentioned the 6 month interim extension results. Of the patients enrolled in the study, a total of 114 (46.2%) in the liraglutide 1.8 mg group, 110 (43.8%) in the liraglutide 1.2 mg and 97 (39.1%) in the glimepiride group completed the study.

Efficacy: The evaluator concluded that there was better glycaemic control for liraglutide compared with glimepiride, in addition to less insulin resistance and better weight control

Safety: Gastrointestinal disorders (nausea, diarrhoea, vomiting and constipation) were more common in the liraglutide groups. One patient, in the liraglutide 1.2 mg group, was reported with diffuse C-cell hyperplasia/ papillary micro-carcinoma and multiple benign adenomatous nodules. One death in the liraglutide 1.8 mg group was due to acute pancreatitis. There were two additional reports of pancreatitis in the liraglutide groups, both of which recovered after withdrawal of treatment. Thyroid related TEAEs were more common in the liraglutide groups, including elevations in serum calcitonin.

<u>New Studies included in the Supplementary Data:</u>

Study NN2211-1797 was a multinational, multicentre, randomised, open-label, active comparator, two arm, parallel group study of liraglutide in comparison with exenatide as add-on therapy: patients (HbA1c 7.0 to 11.0% inclusive) continued on metformin and/or sulfonylurea (that is, single agent or dual therapy) at their stable pre-study dose level. The study comprised a 26 week randomised period, a 14-week non randomised extension, and a planned 28-week extension in which all subjects were changed to liraglutide. Four hundred and sixty-four diabetes mellitus type 2 patients were randomised: 233 to liraglutide and 231 to exenatide.

Efficacy: The primary efficacy outcome measure was the change from baseline in HbA1c at Week 26. The study was designed to test for non-inferiority. The margin for non-inferiority was a 0.4% difference in HbA1c. Non-inferiority was concluded if the upper limit of the 95% CI for the treatment difference, liraglutide – exenatide, was less than 0.4%. Superiority was concluded if the upper limit of the 95% CI for the treatment difference, liraglutide –

exenatide, was less than 0%. For the primary efficacy outcome measure, liraglutide was superior to exenatide. There was no difference between the treatments in weight control.

Safety: There was a higher rate of neoplasia in the liraglutide group, including one subject with adenocarcinoma of the pancreas and another with thyroid neoplasia. One subject in the liraglutide group had an elevated serum calcitonin concentration during the study. There was one patient reported with pancreatitis during the trial, in the liraglutide group. Gastrointestinal AEs occurred at a similar frequency in both treatment groups. There were two deaths: one for cerebral infarction; one from myocardial infarction.

Study NN8022-1807 was a multinational, multicentre, randomised, double blind, placebo and comparator controlled, six parallel groups, efficacy and safety trial comparing the effects on obesity of four doses of liraglutide in comparison with placebo and orlistat. The study was not described in detail because the report provided in the submission appears to be an interim report. This indication will presumably be pursued in a future submission. The evaluator considered that this was an interim report. With regard to safety, there was one report of acute pancreatitis as a SAE in the liraglutide 3.0 mg group. There were no reports of thyroid or parathyroid cancer as SAEs. Two subjects in the liraglutide treatment groups had elevated plasma calcitonin.

Evaluator's Conclusions on Supplementary Data

The data demonstrated a higher rate of gastrointestinal AEs with liraglutide compared with placebo, glimepiride and metformin. The data confirm the signals of pancreatitis and thyroid carcinoma.

There is a risk management plan proposed – the evaluator commented that the cardiovascular outcome trial and the database study are additional to the routine pharmacovigilance activities, but the methodology and protocols for these studies are not provided,

"The pharmacovigilance activities that will be conducted in Australia are not specifically stated. It is not clear whether the sponsor intends to sponsor studies using cancer databases, clinical toxicology databases or the National Death Index in Australia. The sponsor should be required to submit the protocols for the proposed studies prior to registration."

The proposed Australian Product Information is still deficient in regard to pancreatitis.

"The risk benefit profile of liraglutide is in favour of approval for registration for marketing in Australia. Liraglutide is superior to metformin and [exenatide] for diabetes control, and to [glimepiride] for both diabetes and weight control. In addition, liraglutide results in fewer hypoglycaemic episodes than glimepiride."

The suggested indication is, "Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus" that is, liraglutide is to be used as monotherapy.

Sponsor's Reply to Supplementary Evaluation Reports:

The evaluator had asked that:

- The sponsor should provide pooled analyses of the risk for pancreatitis and thyroid neoplasia from the available data.
- The sponsor should provide details of the methodology and protocols for the cardiovascular outcome trial and the database study.

The sponsor responded, using completed Phase 2 and 3 studies (14 weeks-156 weeks in duration) to generate pooled analyses of risk of pancreatitis and thyroid neoplasia. The sponsor's contentions are summarised below.

Pancreatitis

As far as liraglutide is concerned, the absolute number of cases is still low. Nine cases were found in the data set (7 acute, 2 chronic) 8 of which occurred with liraglutide (n=4,505 subjects). One was found in 2,381 comparator group subjects. Two new cases were recorded after this application was made. No statistical analysis was performed but the rates for total pancreatitis are 2.2, 0.0, 0.8 and 0.6 per 1,000 subject years of subject exposure for liraglutide, placebo, active comparator and total comparator respectively.

Eight of the nine pancreatitis cases were serious (including the one in the comparator group) and the one death occurred in the liraglutide group. The two cases of chronic pancreatitis were in patients who received liraglutide as add-on therapy to oral agents. Three patients continued on treatment and recovered. The latency time from onset of therapy was 50-699 days with liraglutide +/- oral agents and 63 days for metformin + glimepiride. The overall rate of acute pancreatitis (1.6 events per 1,000 subject years of exposure) is similar to the rate for non-diabetic patients (1.5 per 1,000 patient years) whereas one published source states that the type 2 diabetic cohort has an overall acute pancreatitis incidence rate of 421.87 per 100,000 person-years vs. 149.29 in the non-diabetic cohort.[22]

Thyroid Neoplasia

Calcitonin is a valid biomarker for C-cell activation and mass. Calcitonin was regularly monitored in the clinical trials, in over 5,500 Phase 3 clinical trial subjects [presumably, patients with diabetic and non-diabetic indications]. *Elevated calcitonin was not consistently seen in the clinical trials. In diabetes trials over two years' duration, about 90% of patients were below the upper limit of the normal range for calcitonin with no difference between liraglutide and the active comparator. There were no substantial temporal trends. Increases in calcitonin from baseline to two years were seen in 3.1% of both liraglutide and comparator groups. A calcium stimulation substudy in each of trials 1573 and 1574 did not suggest a treatment effect on stimulated levels of calcitonin.*

C-cell hyperplasia was seen in six patients in the clinical trial programme, the cases were proportionate between liraglutide and comparator groups. Three of four liraglutide associated cases could have arisen prior to exposure to liraglutide.

Thyroid adverse event data were discussed by the sponsor.

In addition, a copy of the draft protocol of the proposed placebo-controlled cardiovascular outcomes study was provided. The study will be conducted in type 2 diabetics. It will run for 3.5-5 years. Nine thousand patients in 30 countries will be enrolled. The patients will be at high risk for cardiovascular events. Oral agents, insulin and its analogues will be allowed. Outcomes will include cardiovascular and microvascular outcomes, all-cause mortality, weight, serious and special adverse events.

The sponsor slightly revised the proposed Indication (and has not accepted the evaluator's text):

Victoza is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

[22] Noel, R.A. et al. 2009 Diabetes Care 32:834-838.

Risk-Benefit Analysis

Delegate Considerations

The slight marketing experience internationally (The European Commission granted a marketing authorisation valid throughout the European Union for Victoza to Novo Nordisk A/S on 30 June 2009) and the limited safety profile warrant the provision of a Risk Management Plan and further research on the cardiovascular benefits or harms when liraglutide is used for several years in the treatment of diabetes mellitus, insulin resistance or obesity. The data suggest that liraglutide may be expected to be associated with pancreatitis, including fatal pancreatitis, as has been exenatide. More targeted data capture is need on this aspect.

In regard to the originally submitted data set, a prospective study that compares liraglutide with insulin in terms of cardiovascular safety and events suggestive of gut ischaemia would be instructive. Targeted research into gastrointestinal and cardiac outcomes is now essential given the failure of thiazolidinediones to show worthwhile cardiovascular benefits and the failure of centrally acting anorectic agents – sibutramine and endocannabinoid antagonists included – to exhibit long term safety consistent with short and medium term studies.

Patients should have realistic expectations of Victoza, that is, the extent of weight loss and the nature of the gastrointestinal effects, and to understand that nausea or vomiting may be severe. The CMI should address this.

The primary clinical evaluation suggested that liraglutide was effective in dual and triple therapy but one could have wished for studies with more specific enrolment criteria that mirror Australian practice, for example, a study of drug-naive patients who had failed diet and exercise; a study on patients who were insufficiently responsive to first-line metformin monotherapy or who were failing to remain controlled after first line metformin monotherapy, etc.

On the other hand, group mean data in diverse studies with broader inclusion criteria than are preferable suggest adequate efficacy and acceptable safety. The "average" patient was representative, based on the sponsor's description,

"Duration of diabetes was shortest in the monotherapy trial (Trial 1573: mean duration 5.4 years) and increased in trials with combination therapy with OAD(s) and was longest in the triple combination therapy trial (Trial 1697: mean duration 9.4 years). Correspondingly, the proportion of subjects previously treated with OAD monotherapy (Trial 1573: 63.5%) was lowest in the trials with liraglutide in combination with two OADs (e.g. Trial 1697: 5.7%). This illustrates that subjects in the combination trials with two OADs were further along the continuum of disease progression than the subjects in the monotherapy and one OAD combination trials."

Thyroid tumours are not likely to be detectable in this data set.

The EU indication is somewhat reflective of the submitted data but has not included monotherapy:

Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

In combination with:

– Metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea.

In combination with:

– Metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy.

It is certainly less restrictive than the sponsor's indication that is restricted to monotherapy but which is presumed to be unintended. There is no monotherapy option at all in the EU, however the US has a monotherapy (but not a first line) indication. Another issue is that pioglitazone was not studied and that rosiglitazone has very much restricted uses that exclude triple therapy. The Delegate would therefore not allow reference to the thiazolidinedione class because the two marketed members of it (there will be no others) are not clinically equivalent or interchangeable. Moreover, to invite use with Avandamet would require all of Avandamet's safety statements and contraindications to be referred to in the PI for liraglutide. Further, the experience so far with liraglutide and rosiglitazone is rather limited. Study NN2211-1436 was of limited value, for reasons mentioned above. Study NN2211-1574 was also suboptimal due to unusual inclusion criteria and it included switching from exenatide. The difference in rosiglitazone doses between Trial 1436 and Trial 1574 (4 versus 8 mg/day) reflected the different local maximal doses but it limits applicability in Australia where 8mg per day is permissible. Metformin, rather than a sulfonylurea, is likely to be far more commonly used in dual therapy in this country.

The monotherapy data are difficult to interpret because liraglutide may well be better than placebo but it is of limited value to compare it with glimepiride unless used in a patient population that was not suitable for metformin.

Practitioners might want to use metformin + sitagliptin or vildagliptin in patients who are failing metformin monotherapy because of the reduced tendency to weight gain versus add-on sulfonylureas. No study to compare liraglutide with vildagliptin or sitagliptin in this context has been presented.

A preferable indication is:

Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in dual combination, added to:

– metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea.

In triple combination, added to:

– metformin and a sulphonylurea in patients with insufficient glycaemic control despite dual therapy.

Findings of Fact

1. Registration is no longer opposed by the nonclinical evaluator.

2. Registration is conditionally supported by the clinical evaluator.

3. The developmental package makes liraglutide approvable on efficacy and safety grounds, within the limits of the clinical trial models used.

Questions asked of the Advisory Committee by the Delegate

1. Can triple therapy with rosiglitazone be supported by the submitted data?

2. Is it agreed that risk and benefit are adequately supported?

3. Is monotherapy supportable, given the lack of an active comparator study, in particular involving metformin? The TGA-adopted EU guideline on products in the treatment of

diabetes suggests a preference for an active comparator as well as placebo (see section 2.3.3.3).[23]

The Delegate proposed that the application by Novo Nordisk Pharmaceuticals Pty Ltd to register a new chemical entity, Victoza brand of liraglutide, injection solution 6 mg/mL may be supported for the indication:

Victoza is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in dual combination, added to:

– metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin or sulphonylurea.

In triple combination, added to:

– metformin and a sulphonylurea in patients with insufficient glycaemic control despite dual therapy.

A Risk Management Plan, active data gathering for adverse events of interest (including thyroid tumours, pancreatitis, gut ischaemia) and a long term cardiovascular safety study should be conducted and the results submitted.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval with the following indication:

Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control

- *in dual combination, added to metformin or a sulphonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulphonylurea monotherapy.*
- *in triple combination, added to metformin and a sulphonylurea in patients with insufficient glycaemic control despite dual therapy.*

In making this recommendation the ACPM considered that the studies were of short duration and did not involve the appropriate active comparator, metformin. In view of the absence of long term safety data, the ACPM did not support the use of liraglutide as first line therapy. There were no data to support the applicant's suggestion that liraglutide might be used as a second-line monotherapy agent in persons who are intolerant of metformin. The ACPM advised against the combined use of liraglutide with rosiglitazone in view of the limited evidence supporting the safety and efficacy of this combination. The lack of evidence also did not support the use in combination with pioglitazone.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Victoza containing liraglutide (rys) 6 mg/mL solution for injection pre-filled pen indicated for:

as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

[23] EMEA, Committee for Proprietary Medicinal Products (CPMP), 30 May 2002. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus, CPMP/EWP/1080/00.

- *in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.*
- *in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

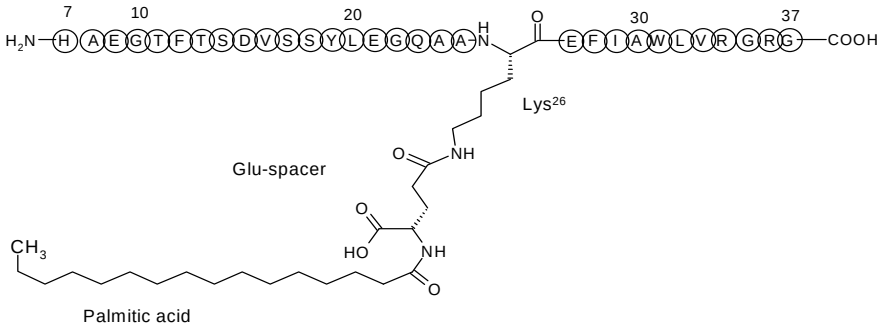
LIRAGLUTIDE

Victoza®

NAME OF THE MEDICINE

Liraglutide (rys)

Liraglutide (rys) has the molecular formula $C_{172}H_{265}N_{43}O_{51}$ and a molecular weight of 3751.20 daltons.



CAS No.: 204656-20-2

DESCRIPTION

Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analogue that binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Liraglutide exhibits 97% homology to human GLP-1. In liraglutide, the lysine at position 34 has been replaced with arginine, and a palmitic acid has been attached via a glutamoyl spacer to lysine at position 26.

Liraglutide is produced by recombinant DNA technology using *Saccharomyces cerevisiae*. One mL contains 6 mg liraglutide salt-free anhydrous liraglutide. Victoza® is a sterile, clear, colourless, isotonic solution of liraglutide 6 mg/mL (pH=8.15). Victoza is a solution for injection.

Each mL of Victoza also contains the following inactive ingredients: 1.42 mg dibasic sodium phosphate dihydrate, 14.0 mg propylene glycol, 5.5 mg phenol, hydrochloric acid q.s., sodium hydroxide q.s. and water for injections to 1 mL.

PHARMACOLOGY

Mechanism of action

Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in humans suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association (which results in slow absorption), binding to albumin and enzymatic stability towards the dipeptidyl peptidase (DPP-IV) and neutral endopeptidase (NEP) enzymes, resulting in a long plasma half life.

Liraglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Liraglutide stimulates insulin secretion in a glucose-dependent manner and improves beta-cell function. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, during hypoglycaemia liraglutide diminishes insulin secretion and does not impair glucagon secretion.

The mechanism of blood glucose lowering also may involve a minor delay in gastric emptying. (see Interactions).

Liraglutide has shown anti-hyperglycaemic efficacy in animal models of pre-diabetes. Liraglutide has been shown *in vitro* to stimulate beta-cell proliferation and prevent both cytokine and free fatty acid induced beta-cell death (apoptosis). *In vivo*, liraglutide increases insulin biosynthesis, and beta-cell mass in diabetic animal models. The relevance of this to humans is not known. When hyperglycaemia is fully normalised, in animal studies, liraglutide does not increase beta-cell mass.

Pharmacodynamics

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

The difference between liraglutide 1.8 mg / 1.2 mg and placebo in reduction of mean fasting glucose was found to be 3.90 mmol/L / 3.33 mmol/L (Figure 1). Following a standard meal, the difference in mean 2-hour postprandial glucose concentration was 6.02 mmol/L / 5.63 mmol/L. In addition, liraglutide decreased postprandial glucose excursion (incremental postprandial glucose) on average by 1.1 mmol/L / 1.08 mmol/L.

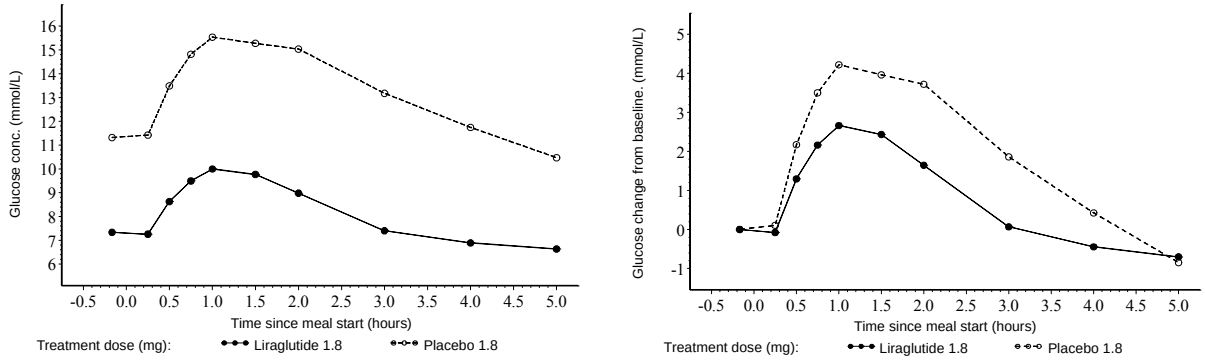


Figure 1 Mean absolute (left) and incremental (right) postprandial glucose concentrations. Subjects with type 2 diabetes treated with liraglutide 1.8 mg or placebo in a cross-over design (N=18) (Trial 1698)

Glucose dependent insulin secretion
Liraglutide increased insulin secretion in relation to increasing glucose concentrations. Using a stepwise graded glucose infusion, the insulin secretion rate was increased following a single injection of liraglutide in subjects with type 2 diabetes to a level indistinguishable to that observed in healthy subjects (Figure 2).

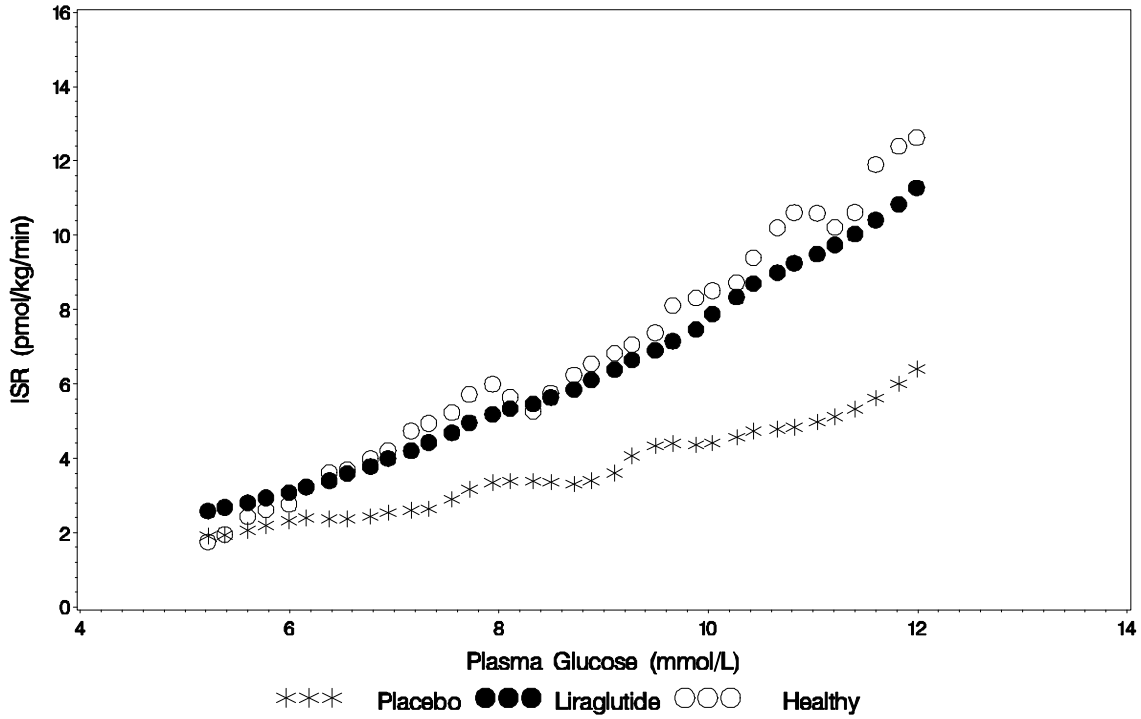


Figure 2 **Mean Insulin Secretion Rate (ISR) versus glucose concentration following a single injection of liraglutide 7.5 µg/kg (~0.66 mg) or placebo in subjects with type 2 diabetes (N=10) and untreated healthy subjects (N=10) during graded glucose infusion (Trial 2063)**

Beta-cell function
Liraglutide improved beta-cell function as measured by first- and second phase insulin response and maximal beta-cell secretory capacity. A pharmacodynamic study in subjects with type 2 diabetes demonstrated restoration of first phase insulin secretion (intravenous bolus of glucose), improved second phase insulin secretion (hyperglycaemic clamp) and maximal insulin secretory capacity (arginine stimulation test) (Figure 3).

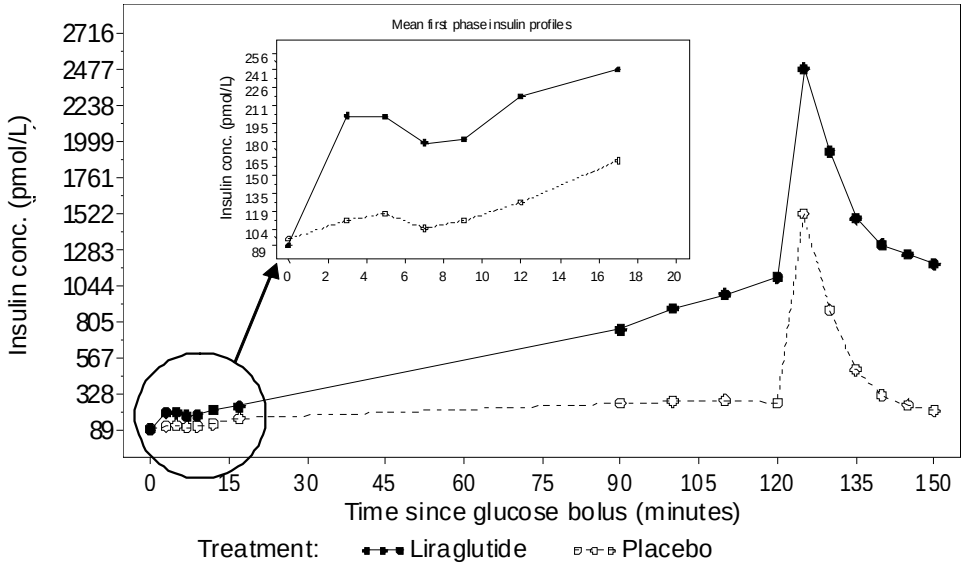


Figure 3 Mean insulin profiles during glucose bolus (inserted), hyperglycaemic clamp and arginine stimulation test (at 120 min) following 6 µg/kg (~0.55 mg) liraglutide or placebo for 10 days in subjects with type 2 diabetes (Trial 1332)

Clinical studies up to 52 weeks have shown a durable secretagogue effect with liraglutide, as well as improvements from baseline in the homeostasis model assessment for beta-cell function (HOMA-B) and the proinsulin to insulin ratio. Liraglutide has not yet been evaluated for use in individuals with impaired glucose tolerance or those who do not yet meet the diagnostic criteria for diabetes mellitus.

Glucagon secretion
Liraglutide lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. Liraglutide did not impair glucagon response to low glucose concentration. Furthermore, a lower endogenous glucose release has been observed with liraglutide.

Gastric emptying
Liraglutide caused a minor delay in gastric emptying, thereby reducing the rate at which postprandial glucose appeared in the circulation.

Body weight
In clinical studies up to 52 weeks involving subjects with elevated body weight liraglutide was observed to significantly lower body weight. [See Clinical Trials, Adverse Effects.] Specific weight loss studies have not been assessed in type 2 diabetes mellitus

Cardiac Electrophysiology (QTc)
In a cardiac repolarisation study liraglutide at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

Pharmacokinetics

Absorption
The absorption of liraglutide following subcutaneous administration is slow, reaching maximum concentration 8-12 hours post dosing. Estimated maximum liraglutide concentration was 9.4 nmol/L for a subcutaneous single dose of liraglutide 0.6 mg. At 1.8 mg liraglutide, the average steady state concentration of liraglutide ($AUC_{\tau/24}$) reached approximately 34 nmol/L. Liraglutide exposure increased

proportionally with dose. The intra-subject coefficient of variation for liraglutide AUC was 11% following single dose administration. Liraglutide can be administered subcutaneously in the abdomen, thigh, or upper arm.

Distribution
The apparent volume of distribution after subcutaneous administration is 11-17 L. The mean volume of distribution after intravenous administration of liraglutide is 0.07 L/kg. Liraglutide is extensively bound to plasma protein *(>98%).*

Metabolism/biotransformation
During the 24 hours following administration of a single [^{3}H]-liraglutide dose to healthy subjects, the major component in plasma was intact liraglutide. Two minor plasma metabolites were detected (≤ 9 % and ≤ 5% of total plasma radioactivity exposure). Liraglutide is endogenously metabolised in a similar manner to large proteins without a specific organ as major route of elimination.

Elimination
Following a [^{3}H]-liraglutide dose, intact liraglutide was not detected in urine or faeces. Only a minor part of the administered radioactivity was excreted as liraglutide-related metabolites in urine or faeces (6% and 5%, respectively). The urine and faeces radioactivity was mainly excreted during the first 6-8 days, and corresponded to three minor metabolites.

The mean clearance following s.c. administration of a single dose of liraglutide is approximately 1.2 L/h with an elimination half-life of approximately 13 hours.

Special populations
Elderly
No dosage adjustment is required based on age. Age had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results from a pharmacokinetic study in healthy subjects and population pharmacokinetic data analysis of subjects (18 to 80 years).

Gender
No dosage adjustment is required based on gender. Gender had no clinically meaningful effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic data analysis of male and female subjects and a pharmacokinetic study in healthy subjects.

Ethnicity
No dosage adjustment is required based on ethnicity. Ethnicity had no clinically relevant effect on the pharmacokinetics of liraglutide based on the results of population pharmacokinetic analysis.

Obesity
No dosage adjustment is required based on obesity. Population pharmacokinetic analysis suggests that body mass index (BMI) has no significant effect on the pharmacokinetics of liraglutide.

Hepatic impairment
The pharmacokinetics of liraglutide was evaluated in subjects with varying degree of hepatic impairment in a single-dose trial. Liraglutide exposure was decreased by 23% and 13% in subjects with mild or moderate hepatic impairment respectively, compared to healthy subjects.

Exposure was significantly lower (44%) in subjects with severe hepatic impairment (Child Pugh score >9).

Renal impairment
Liraglutide exposure was mildly reduced in subjects with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%, 27% and 26%,

respectively, in subjects with mild (creatinine clearance, CrCL 50-80 mL/min), moderate (CrCL 30-50 mL/min), and severe (CrCL <30 mL/min) renal impairment and in end-stage renal disease requiring dialysis.

Paediatrics
Liraglutide has not been studied in paediatric subjects.

CLINICAL TRIALS

Phase 2
Study NN2211-1499 was a phase 2, exploratory study. It was a double-blind, double-dummy, randomised, parallel-group, multicentre, dose titration study (with an open labelled oral agent arm i.e. glimepiride + metformin) to assess the effect on glycaemic control of individual maximum effective dose of Victoza as add on therapy to metformin compared to monotherapy (metformin or Victoza alone). Victoza was given in doses of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, as a once daily subcutaneous injection in the abdomen or thigh (in the evening) The study was of five weeks duration. One hundred and forty-four patients were randomised (36 per group). They were on at least 50% of the maximal dose of their oral agent. Fasting serum glucose after five weeks of treatment was the primary endpoint. Victoza alone was superior to metformin alone but inferior to metformin + glimepiride whereas Victoza + metformin was superior to metformin + glimepiride. Results were similar for HbA1c but the short duration of the study limits the interpretation of these results.

Phase 3
There were 3992 subjects with type 2 diabetes randomised in five double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of Victoza on glycaemic control.

These studies included 3978 exposed subjects (2501 subjects treated with Victoza), 53.7% men and 46.3% women, 797 subjects (508 treated with Victoza) were ≥ 65 years of age and 113 subjects (66 treated with Victoza) were ≥ 75 years of age.

The studies included four studies (LEAD 1, 2, 4 and 5) assessing Victoza in various combinations with metformin, a sulfonylurea and rosiglitazone plus one study where Victoza was used as a single agent (LEAD 3). In the dual therapy studies, patients could be inadequately controlled but were not necessarily failing to respond to monotherapy at baseline.

LEAD 1 (Trial 1436) and LEAD 2 (Trial 1572) evaluated 26 weeks of treatment with Victoza in combination with the oral antidiabetic drug (OAD) glimepiride or metformin respectively. Both trials employed a placebo comparator (LEAD 1 glimepiride alone; LEAD 2 metformin alone) and an active comparator (LEAD 1 glimepiride + rosiglitazone; LEAD 2 metformin + glimepiride).

LEAD 5 (Trial 1697) evaluated 26 weeks treatment with Victoza in combination with metformin + glimepiride. LEAD 5 assessed the 1.8 mg Victoza dose and compared this with a placebo comparator (metformin + glimepiride) and an active comparator (insulin glargine + metformin + glimepiride).

Primary outcomes for the LEAD studies are presented in Table 1 and 2. Treatment with Victoza produced clinically and statistically significant improvements versus the placebo comparators in haemoglobin $A1_C$ (HbA_{1c}), fasting plasma glucose (FPG) and postprandial glucose (PPG).

Victoza in combination with one OAD (LEAD 1 and 2 respectively)
LEAD 1 enrolled patients diagnosed with type 2 diabetes, treated with OAD(s) for at least 3 months, with an HbA1c: 7.0-11.0 % (inclusive) in subjects on oral monotherapy or 7.0-10.0 % (inclusive) in subjects on oral combination therapy. All were switched to glimepiride in the trial. The study enrolled patients on monotherapy who might need a second agent and those already on two agents that might need a third agent. In LEAD 1, the analysis of change in HbA1c from baseline showed that treatment

with Victoza at both 1.2 mg and 1.8 mg (+ glimepiride) was superior to treatment with glimepiride alone, and superior to treatment with rosiglitazone + glimepiride (Table 1). For the primary efficacy outcome measure, Victoza 1.2 mg and 1.8 mg in combination with glimepiride were superior to both comparator groups, and Victoza 0.6 mg in combination with glimepiride was superior to glimepiride alone and non inferior to rosiglitazone/glimepiride. Amongst secondary outcomes, Victoza plus glimepiride did not increase weight compared to glimepiride alone whereas glimepiride and rosiglitazone were associated with weight gain.

LEAD 2 enrolled patients diagnosed with type 2 diabetes, treated with OAD(s) for at least 3 months, with an HbA1c: 7.0-11.0 % (inclusive) in subjects on oral monotherapy or 7.0-10.0 % (inclusive) in subjects on oral combination therapy. All were switched to metformin in the trial. The analysis of change in HbA1c from baseline showed that treatment with Victoza (1.2 mg and 1.8 mg) + metformin was superior to metformin alone and non-inferior to treatment with glimepiride and metformin (Table 1). The primary efficacy outcome measure was the change from baseline in HbA1c after 26 weeks of treatment. Victoza 1.8 mg and 1.2 mg doses in combination with metformin were superior to metformin alone, and non-inferior to glimepiride/metformin. In combination with metformin, Victoza had similar efficacy to the glimepiride/metformin combination. In this study, Victoza 1.2 mg daily was as effective as the higher dose.

Table 1 Results of two 26 week trials of Victoza (LEAD 2 and LEAD 1) in combination with an OAD in subjects previously treated with one or more OADs.

LEAD 2 - Metformin Add-on Therapy				
	Victoza 1.8 mg + metformin	**Victoza 1.2 mg + metformin**	**Metformin** [1]	**Glimepiride +metformin** [2]
N	242	240	121	242
HbA_{1c} (%) (Mean)				
Baseline	8.4	8.3	8.4	8.4
Change from baseline	-1.00*	-0.97*	0.09	-0.98
Subjects (%) achieving HbA_{1C} <7%				
All subjects	42.4*	35.3*	10.8	36.3
Previous OAD monotherapy	66.3	52.8	22.5	56.0
LEAD 1 - Glimepiride Add-on Therapy				
	Victoza 1.8 mg + glimepiride	**Victoza 1.2 mg + glimepiride**	**Glimepiride** [3]	**Rosiglitazone +glimepiride** [4]
N	234	228	114	231
HbA_{1c} (%) (Mean)				
Baseline	8.5	8.5	8.4	8.4
Change from baseline	-1.13*#	-1.08*#	0.23	-0.44
Subjects (%) achieving HbA_{1C} <7%				
All subjects	41.6*#	34.5*#	7.5	21.9
Previous OAD monotherapy	55.9	57.4	11.8	36.1

[1] placebo comparator (metformin)
[2] active comparator (metformin + glimepiride)
[3] placebo comparator (glimepiride)
[4] active comparator (glimepiride + rosiglitazone)
*Significantly different from placebo comparator ($p < 0.02$)
Significantly different from active comparator ($p < 0.05$)

Victoza compared to a basal insulin (LEAD 5)
LEAD 5 enrolled patients diagnosed with type 2 diabetes, previously treated with oral agent(s) for at least 3 months with an HbA1c: 7.5-10.0 % (inclusive) in subjects on oral monotherapy or 7.0-10.0 % (inclusive) in subjects on oral combination therapy. In LEAD 5, the analysis of change in HbA1c from baseline demonstrated that treatment with Victoza 1.8 mg + glimepiride + metformin was superior to treatment with glimepiride + metformin alone and superior to treatment with insulin glargine + glimepiride + metformin (Table 2).

Table 2 Results of a 26 week trial of Victoza (LEAD 5) in combination with OADs in previous OAD-treated subjects. LEAD 5 also included a comparison with basal insulin.

LEAD 5 - Metformin + Glimepiride Add-on Therapy			
	Victoza 1.8 mg + metformin + glimepiride	**Metformin + glimepiride** [1]	**Glargine + metformin + glimepiride** [2]
N	230	114	232
HbA_{1c} (%) (Mean)			
Baseline	8.3	8.3	8.1
Change from baseline	-1.33*#	-0.24	-1.09
Subjects (%) achieving HbA_{1C}			
<7% All subjects	53.1*#	15.3	45.8

[1] placebo comparator (metformin + glimepiride)
[2] active comparator (glargine + metformin + glimepiride)
*Significantly different from placebo comparator ($p < 0.01$)
Significantly different from active comparator ($p < 0.02$)

Glycaemic control
HbA1c

Victoza in combination therapy for 26 weeks with metformin or a sulfonylurea resulted in statistically significant ($p < 0.001$) and sustained reductions in HbA_{1c} compared with subjects in the placebo comparator groups (Figure 4).

The efficacy of Victoza 0.6 mg was also tested in combination with a sulfonylurea or with metformin and was found to be superior to placebo but less effective than the other Victoza doses of 1.2 mg and 1.8 mg.

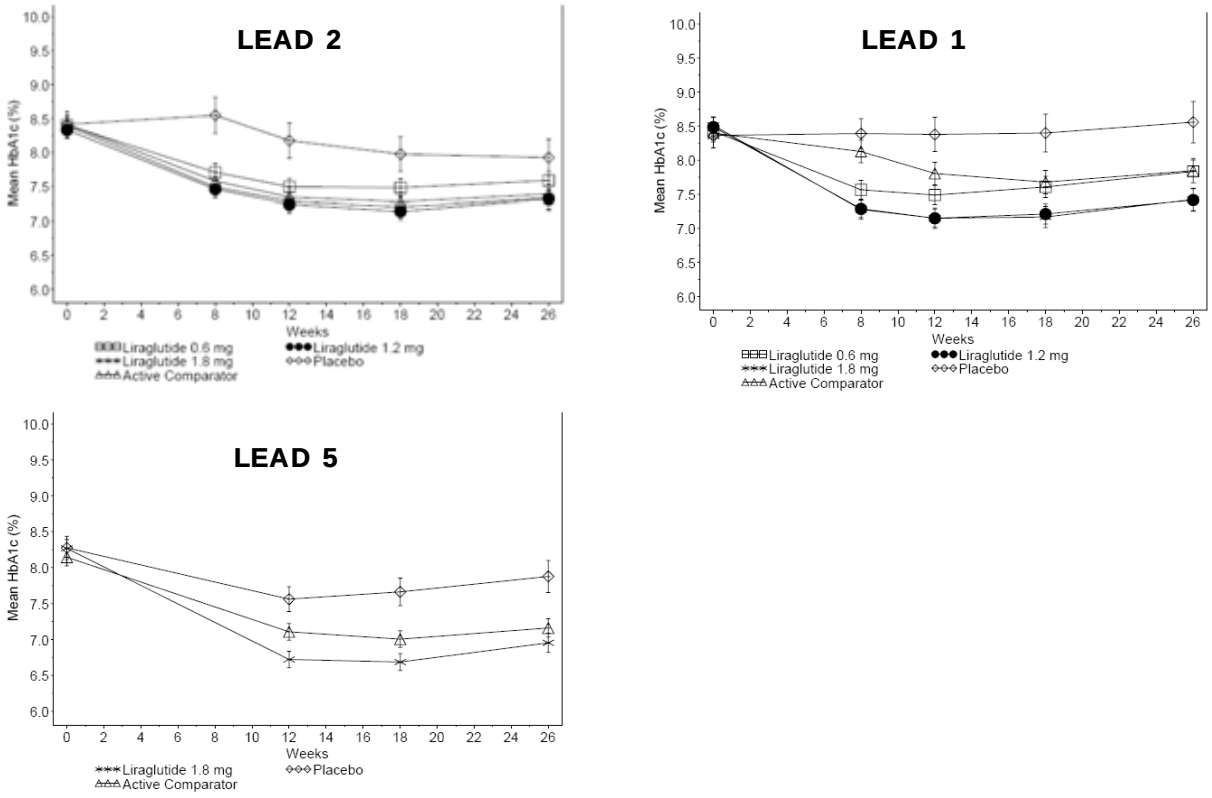


Figure 4: Mean HbA1c (%) over Time ± SEM, ITT Analysis Set Note: The Primary endpoint was change from baseline to the end of the study.

Fasting Plasma Glucose
Treatment with Victoza resulted in a reduction in fasting plasma glucose of 0.72-2.42 mmol/L. This reduction was observed within the first two weeks of treatment.

Postprandial glucose
Victoza reduced postprandial glucose across all three daily meals by 1.68-2.71mmol/L.

Body Weight
Body weight was assessed amongst predefined secondary endpoints. Specific weight loss studies have not been assessed in type 2 diabetes. In the clinical programme, statistically significant reductions in mean body weight from baseline were consistently observed. Treatment with Victoza was associated with an initial reduction in mean body weight within the first 8 weeks, that was sustained over the duration of studies (Figure 5). Larger weight reduction was observed with increasing body mass index at baseline. Reductions in body weight were seen, irrespective of the occurence of nausea.

No morbidity data or mortality data are presently available to support long term benefit from Victoza induced weight loss in patients with type 2 diabetes.

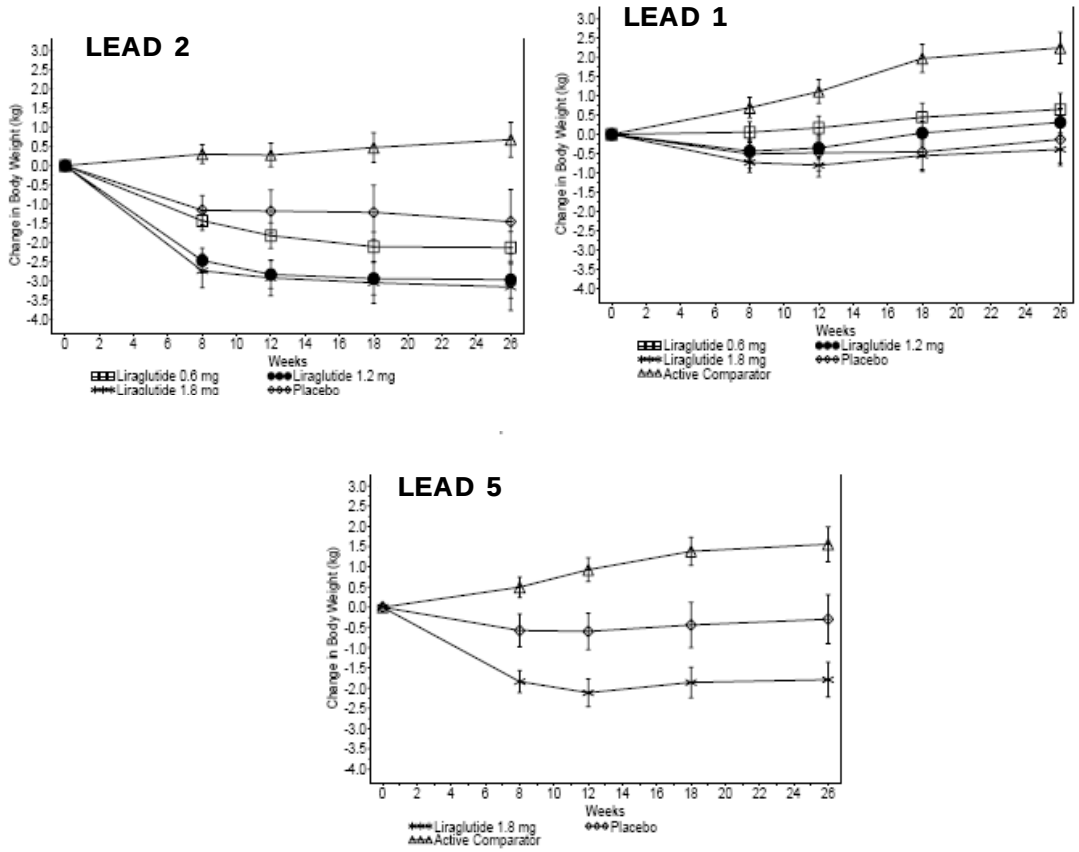


Figure 5 Change in Body Weight over Time, Mean ±2 SEM

Effect on blood pressure
Victoza reduced systolic blood pressure with a mean range of 2-6 mm Hg within the first two weeks of treatment in long-term clinical trials. The reduction in systolic blood pressure occurred before weight loss.

Effect on lipids
Victoza showed no adverse effects on lipid parameters.

Other effects
Victoza improved insulin sensitivity compared to a sulfonylurea for 52 weeks as assessed by HOMA-IR. The clinical significance of this has not been established.

Macrovascular outcomes
There have been no clinical studies establishing conclusive evidence of the long term benefits or adverse effects of Victoza on cardiovascular morbidity or mortality.

INDICATIONS

Victoza is indicated as an adjunct to diet and exercise for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control:

- in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy.

- in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.

CONTRAINDICATIONS

Liraglutide is not to be used in:

- patients with hypersensitivity to liraglutide or any of its excipients.
- patients with a past history of GLP-1 analogue associated pancreatitis

PRECAUTIONS

Victoza should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Insulin is the correct treatment for these conditions. Victoza should not be administered intravenously or intramuscularly.

There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II. There is no experience in patients with congestive heart failure NYHA class III-IV.

There is limited experience in patients with inflammatory bowel disease and diabetic gastroparesis and Victoza is therefore not recommended in these patients. The use of Victoza is associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.

Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials in particular in patients with pre-existing thyroid disease.

Pancreatitis

In clinical trials of Victoza, there were 7 cases of pancreatitis among Victoza-treated patients and 1 case among comparator-treated patients (2.2 vs. 0.6 cases per 1000 patient-years). Five cases with Victoza were reported as acute pancreatitis and two cases with Victoza were reported as chronic pancreatitis. In one case in a Victoza-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. One additional case of pancreatitis has subsequently been reported in a Victoza-treated patient. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse. There are no conclusive data establishing a risk of pancreatitis with Victoza treatment. After initiation of Victoza, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). In most cases, treatment of pancreatitis has led to recovery. If pancreatitis is suspected, Victoza and other potentially suspect medications should be discontinued promptly, confirmatory tests should be performed and appropriate management should be initiated. If pancreatitis is confirmed, Victoza should not be restarted.

Hypoglycaemia

Due to the glucose-dependent insulinotropic mechanism of action of Victoza, when used in combination with metformin alone, no increase in the frequency of hypoglycaemia was observed over that of placebo in combination with metformin.

Patients receiving Victoza in combination with a sulfonylurea may have an increased risk of hypoglycaemia (see Table 4 in Adverse Effects). The risk of hypoglycaemia can be lowered by a reduction in the dose of sulfonylurea.

No studies on the effects on the ability to drive and use machines have been performed. It is unlikely that the ability to drive or use machines should be impaired by Victoza. Patients should be advised to

take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza is used in combination with a sulfonylurea.

Genotoxicity
Liraglutide was not mutagenic in the bacterial Ames assay, and not clastogenic in human lymphocytes *in vitro*, or in rat lymphocytes and bone marrow *in vivo*.

Carcinogenicity
Liraglutide caused thyroid C-cell adenomas and carcinomas in two-year studies in mice and rats. C-cell neoplasia was observed in mice at subcutaneous doses ≥1mg/kg/day (relative exposure based on plasma AUC, ≥7.7) and in rats at all doses tested (≥0.075mg/kg/day subcutaneously; relative exposure, ≥0.5). No tumours or other C-cell proliferative changes were seen in monkeys treated with liraglutide for 20 months (≤5 mg/kg/day subcutaneously; relative exposure, ≤64). The findings in mice and rats are mediated by a specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot presently be completely excluded.

Effects on fertility
No adverse effects on fertility were observed in male and female rats given subcutaneous doses of liraglutide at ≤1mg/kg/day, yielding exposure to liraglutide (plasma AUC) 11-13 times higher than that of patients at the maximum recommended human dose.

Use in Pregnancy
Pregnancy Category: B3

Increased embryofetal death and minor fetal skeletal abnormalities (kinked ribs) were observed in rats given liraglutide at 1mg/kg/day by subcutaneous injection (yielding 11-times the plasma AUC in humans at the maximum recommended clinical dose). In rabbits treated at doses ≥0.01mg/kg/day (relative exposure, ≥0.2), there was retardation of fetal growth and an increased incidence of several minor skeletal and visceral abnormalities. Postnatal body weight gain was reduced in the offspring of rats treated with liraglutide during gestation and lactation. These findings may have occurred secondary to reduced maternal food consumption. Placental transfer of liraglutide and/or its metabolites was demonstrated in the animal species.

There are no adequate data from the use of Victoza in pregnant women. Victoza should not be used during pregnancy and the use of insulin is recommended. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Victoza should be discontinued.

Use in Lactation
It is not known whether Victoza is excreted in human milk. Studies in lactating rats have shown that the transfer of Victoza and metabolites of close structural relationship into milk is low. Due to lack of experience, Victoza must not be used during breast-feeding.

Interactions with other medicines
In vitro assessment of drug-drug interaction
Liraglutide has shown very low potential to be involved in pharmacokinetic drug-drug interactions related to cytochrome P450 (CYP) and plasma protein binding.

In vivo assessment of drug-drug interaction
Drug-drug interaction has been investigated using medicines that were carefully selected to represent compounds of various degrees of solubility and permeability properties, including paracetamol (acetaminophen), digoxin, lisinopril, griseofulvin and atorvastatin. In addition, the effect of liraglutide on the absorption of ethinyloestradiol and levonorgestrel administered in an oral combination contraceptive drug has been investigated.

The delay of gastric emptying caused by liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption of the compounds that were studied, however clinically relevant interactions with other compounds where the effect is dependent on C_{max} and t_{max}, drugs with narrow therapeutic index, or medications associated with local gastrointestinal irritation (e.g. bisphosphonates, potassium chloride) cannot be excluded.

Few patients treated with liraglutide reported at least one episode of severe diarrhoea. Diarrhoea may affect the absorption of concomitant oral medicinal products.

Paracetamol (Acetaminophen)
Liraglutide did not change the overall exposure of paracetamol following a single dose of 1000 mg. Paracetamol C_{max} was decreased by 31% and median t_{max} was delayed up to 15 min. No dose adjustment for concomitant use of paracetamol is required.

Atorvastatin
Liraglutide did not change the overall exposure of atorvastatin to a clinically relevant degree following single dose administration of atorvastatin 40 mg. Therefore, no dose adjustment of atorvastatin is required when given with liraglutide. Atorvastatin C_{max} was decreased by 38% and median t_{max} was delayed from 1 h to 3 h with liraglutide.

Griseofulvin
Liraglutide did not change the overall exposure of griseofulvin following administration of a single dose of griseofulvin 500 mg. Griseofulvin C_{max} increased by 37% while median t_{max} did not change. Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required.

Lisinopril and digoxin
Single dose administration of lisinopril 20 mg or digoxin 1 mg with liraglutide showed a reduction of lisinopril and digoxin AUC by 15% and 16%, respectively; C_{max} decreased by 27% and 31%, respectively. Lisinopril median t_{max} was delayed from 6 h to 8 h with liraglutide; whereas digoxin median t_{max} was delayed from 1 h to 1.5 h. No dose adjustment for concomitant use of lisinopril or digoxin is required based on these results.

Oral contraceptives
Liraglutide lowered ethinyloestradiol and levonorgestrel C_{max} by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. T_{max} was 1.5 h later with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinyloestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide.

Warfarin
No interaction study has been performed. Upon initiation of Victoza treatment in patients on warfarin more frequent monitoring of INR (International Normalised Ratio) is recommended.

Insulin
Combination of liraglutide and insulin has not been evaluated and its use is therefore not recommended.

Incompatibilities
Substances added to Victoza may cause degradation of liraglutide. Victoza must not be mixed with other medicinal products, e.g. infusion fluids.

ADVERSE EFFECTS

Summary of safety profile:
The most frequently reported adverse events during clinical trials were gastrointestinal adverse events: nausea, diarrhoea (reported by > 10% of subjects) and vomiting, constipation, abdominal pain, and dyspepsia (reported by ≥ 1% and ≤ 10% of subjects).

At the beginning of Victoza therapy these gastrointestinal adverse events may occur more frequently. These reactions usually diminish within a few days or weeks on continued treatment. Headache and upper respiratory tract infections are also reported relatively frequently (by 1-10% of subjects). Furthermore, hypoglycaemia may occur, especially when Victoza is used in combination with sulfonylurea (>10% of subjects). Major hypoglycaemia has primarily been observed when combined with a sulfonylurea.

Very few of the reported adverse events were serious in nature.

Tabulated summary of adverse reactions:
Table 3 lists related adverse reactions identified from Phase 3 studies with Victoza. The table presents adverse reactions that occurred with a frequency ≥ 5 % if the frequency was higher among Victoza-treated subjects than subjects treated with comparator. The table also includes adverse reactions that occurred with a frequency ≥1% if the frequency was > 2 times the frequency for comparator-treated subjects. The reactions are listed in Table 3 as MedDRA preferred term by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10) and common (≥ 1/100, < 1/10).

Table 3 Adverse reactions reported in long term phase 3 controlled studies

Body system/ adverse reaction terms	**Frequency of occurrence**	
Reactions	Common (≥ 1/100, < 1/10)	Very Common (≥ 1/10)
Metabolism and nutrition disorders		
Hypoglycaemia	x	
Anorexia	x	
Appetite decreased	x	
Nervous system disorders		
Headache	x	
Gastrointestinal disorders		
Nausea		x
Diarrhoea		x
Vomiting	x	
Dyspepsia	x	
Abdominal pain upper	x	
Constipation	x	
Gastritis	x	
Flatulence	x	
Abdominal distension	x	
Gastroesophageal reflux disease	x	
Eructation	x	
Infections and infestations		
Upper respiratory tract infection	x	

N= 2501 Victoza-treated subjects

Description of selected adverse events:
Hypoglycaemia
Most episodes of confirmed hypoglycaemia in clinical studies were minor.

No episodes of major hypoglycaemia were observed in the study with Victoza used as monotherapy. Major hypoglycaemia may occur uncommonly and has primarily been observed when Victoza is combined with a sulfonylurea (0.02 events/subject year). Very few episodes (0.001 events/subject year) were observed with administration of Victoza in combination with a non-sulfonylurea.

Table 4 presents the incidence of confirmed hypoglycaemic episodes (number of episodes divided by subject years of exposure).

Table 4 Hypoglycaemia in long-term controlled clinical studies of Victoza monotherapy or combinations with oral antidiabetic drugs (OAD)

	Number of episodes divided by subject years of exposure	
Monotherapy (LEAD 3)	**Liraglutide**	**Placebo + Sulfonylurea**
(52 week study)	0.27	1.70
Combination with Metformin (LEAD 2)	**Liraglutide + Metformin**	**Metformin + Sulfonylurea**
(26 week study)	0.05	0.87
Combination with Sulfonylurea (LEAD 1)	**Liraglutide + Sulfonylurea**	**Sulfonylurea + Rosiglitazone**
(26 week study)	0.43	0.14
Combination with Metformin + Rosiglitazone (LEAD 4)	**Liraglutide + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
(26 week study)	0.50	0.18
Combination with Metformin + Sulfonylurea (LEAD 5)	**Liraglutide + Metformin + Sulfonylurea**	**Insulin glargine + Metformin + Sulfonylurea**
(26 week study)	1.21	1.33

Gastrointestinal adverse events
Most episodes of nausea were mild to moderate, transient and rarely led to discontinuation of therapy. In long term clinical trials, some patients (0.6%) reported decreased weight as an adverse event.

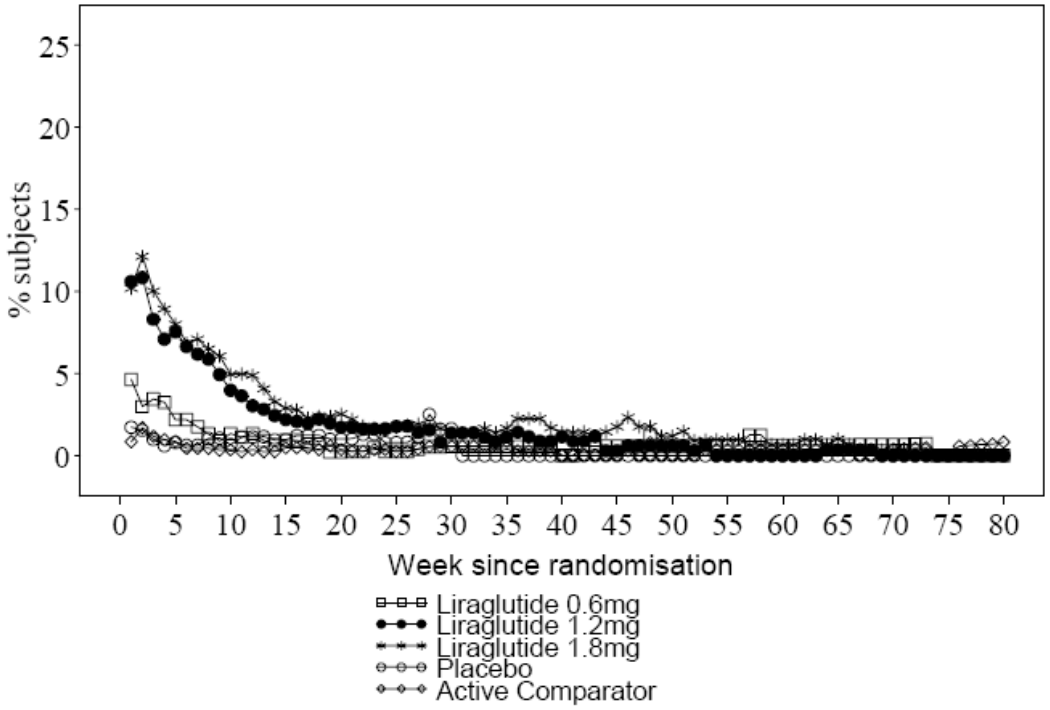


Figure 6 Percentage of subjects with nausea adverse events by week and treatment - all long-term trials - safety analysis set

In subjects treated with Victoza combined with metformin 20.7% reported at least one episode of nausea, and 12.6% reported at least one episode of diarrhoea, respectively. When combining Victoza with a sulfonylurea 9.1% of subjects reported at least one episode of nausea and 7.9% of subjects reported at least one episode of diarrhoea.

The incidence of withdrawal due to adverse events was 7.8 % for Victoza-treated subjects and 3.4% for comparator treated subjects in the long-term controlled trials (26 weeks or longer). The most common adverse events leading to withdrawal for Victoza-treated subjects were nausea (2.8% of subjects) and vomiting (1.5%).

Patients >70 years may experience more gastrointestinal effects when treated with Victoza. Patients with mild renal impairment (creatinine clearance 60-90 mL/min) may experience more gastrointestinal effects when treated with Victoza.

Immunogenicity
Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients may develop anti-liraglutide antibodies following treatment with Victoza. On average, 8.6% of subjects developed antibodies. Antibody formation has not been associated with reduced efficacy of Victoza.

Injection site reactions
Injection site reaction has been reported in approximately 2% of subjects receiving Victoza in long-term (26 weeks or longer) controlled trials. These reactions have usually been mild and did not lead to discontinuation of Victoza.

Pancreatitis
Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza. However, this information is too limited to characterise the incidence of a rare event. A causal

relationship between Victoza and pancreatitis can neither be established nor excluded. See Contraindications and Precautions.

Thyroid events
The overall rates of thyroid adverse events in all intermediate and long-term trials are 33.5, 30.0 and 21.7 events per 1000 subject years of exposure for total Victoza, placebo and total comparators; 5.4, 2.1 and 0.8 events, respectively for serious thyroid adverse events.

In subjects treated with Victoza, thyroid neoplasms, increased blood calcitonin and goiters are the most frequent thyroid adverse events and were reported in 0.5%, 1% and 0.8% of subjects respectively.

Spontaneous reports
N/A

DOSAGE AND ADMINISTRATION

Administration
Victoza is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that Victoza is injected around the same time each day, when the most convenient time of the day has been chosen.

Victoza must **not** be administered intravenously or intramuscularly.

Dosage
For all patients the starting dose is 0.6 mg liraglutide daily. After at least one week, the dose should be increased to 1.2 mg. Based on clinical response and tolerability, and after at least one week, the dose can be increased to 1.8 mg to achieve maximum efficacy. Daily doses higher than 1.8 mg are not recommended.

Victoza may be used when previous therapies provide insufficient glycaemic control in dual combination with metformin or a sulfonylurea, or in triple combination with metformin and sulfonylurea.

When Victoza is added to existing metformin therapy, the current dose of metformin can be continued unchanged.

When Victoza is added to sulfonylurea therapy or to a combination of metformin and sulfonylurea therapy, a reduction in the dose of sulfonylurea should be considered to reduce the risk of hypoglycaemia (see Precautions). During clinical trials physicians were advised, at their discretion, to lower the dose of the sulfonylurea by approximately half to minimize the risk of unacceptable hypoglycaemia.

Self-monitoring of blood glucose is not needed in order to adjust the dose of Victoza. However, when initiating treatment with Victoza in combination with a sulfonylurea, blood glucose self-monitoring may become necessary to adjust the dose of the sulfonylurea.

Specific patient groups
Elderly
(> 65 years old): No dose adjustment is required based on age. Therapeutic experience in patients ≥ 75 years of age is limited (see Pharmacokinetics).

Patients with hepatic impairment
The therapeutic experience in patients with hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment (see Pharmacokinetics).

Patients with renal impairment
No dose adjustment is required for patients with mild renal impairment. There is limited experience in patients with moderate renal impairment. Victoza can currently not be recommended for use in patients with severe renal impairment including patients with end-stage renal disease (see Pharmacokinetics).

Children and adolescents
Victoza is not recommended for use in children below 18 years of age due to lack of data.

Special precautions for disposal and other handling
Victoza should not be used if it does not appear clear and colourless.

Victoza should not be used if it has been frozen.

After the first use of the Victoza pen, the product can be stored for 1 month at room temperature (not above 30°C) or in a refrigerator (2 - 8°C).

Victoza can be administered with needles up to a length of 8 mm and as thin as 32G. The pen is designed to be used with NovoFine or NovoTwist disposable needles.

The patient should be advised to discard the injection needle in accordance with local requirements after each injection and to store the Victoza pen without the injection needle attached. This prevents contamination, infection and leakage. It also ensures that dosing is accurate.

OVERDOSAGE

In a clinical study of Victoza, one subject with type 2 diabetes experienced a single overdose of 17.4 mg subcutaneous (more than 9 times the maximum recommended maintenance dose of 1.8 mg). Effects of the overdose included severe nausea and vomiting. No hypoglycaemia was reported. The subject recovered without complications. In the event of overdosage, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

PRESENTATION AND STORAGE CONDITIONS

Cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polyolefin and polyacetal.

Each pen contains 3 mL solution , delivering 30 doses of 0.6 mg, 15 doses of 1.2 mg or 10 doses of 1.8 mg.

Pack sizes of 1, 2, 3, 5 or 10 pre-filled pens. Not all pack sizes may be marketed.

Store in a refrigerator (2°C to 8°C). Keep away from the cooling element. Do not freeze Victoza and do not use Victoza if it has been frozen.

After first use of the Victoza pen, the product can be stored for 1 month at room temperature (not above 30°C) or in a refrigerator (2 to 8°C).

Keep the pen cap on when the Victoza pen is not in use in order to protect from light.

Victoza should be protected from excessive heat and sunlight.

Always remove the injection needle after each injection and store the Victoza pen without an injection needle attached. This prevents contamination, infection, and leakage. It also ensures that the dosing is accurate.

The shelf-life for Victoza is 30 months. The in-use time is 1 month.

NAME AND ADDRESS OF SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 18 August 2010.

Therapeutic Goods Administration

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