European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/379172/2009

ASSESSMENT REPORT

FOR

Victoza

International Nonproprietary Name: liraglutide

Procedure No. EMEA/H/C/001026

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novo Nordisk A/S submitted on 23 May 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Victoza, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 13 December 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 18 November 2004, 14 December 2006, 15 November 2007 and 24 April 2008. The Scientific Advice given in November 2004 pertained to pharmacokinetics, carcinogenicity and the potential for QT-prolongation. The Scientific Advice given in December 2006 related to quality aspects of the dossier such as design of comparability studies, bioequivalence, and drug product specifications. The Scientific Advice given in November 2007 pertained to the paediatric investigation plan. And the Scientific Advice given in April 2008 was related to clinical aspects related to the potential indication of the product.

The Rapporteur and Co-Rapporteur appointed by the CHMP:
Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Steffen Thirstrup**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 23 May 2008.
- The procedure started on 25 June 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 September 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2008. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 23 October 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 October 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 December 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 February 2009.
- During the CHMP meeting on 19 February 2009, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 23 March 2009.
- During the meeting on 20-23 April 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Victoza on 23 April 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 April 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

An important and possibly primary defect in type 2 diabetes may be an impaired incretin function. Treatment with 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. Liraglutide is a GLP-1 analogue. 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.

This application concerns the centralised procedure (Regulation (EC) No 726/2004, article 3(1) indent 3). It is submitted in accordance with Article 8(3) in Directive 2001/83/EC for a new active substance. Conditional approval, an approval under exceptional circumstances or an accelerated review were not requested.

The claimed indication was:

Victoza is indicated as an adjunct to diet and exercise to achieve glycaemic control in patients with type 2 diabetes mellitus. Victoza is indicated for once-daily administration as:

- Monotherapy
- Combination therapy with one or more oral antidiabetic drugs (metformin, sulphonylureas or a thiazolidinedione) when previous therapy does not achieve adequate glycaemic control.

The approved indication is:

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

2.2 Quality aspects

Introduction

The drug substance, liraglutide, is a long acting analogue of the naturally occurring human glucagon-like peptide-1 (GLP-1(7-37)) with 97% homology and a lipophilic substituent for prologation of half life.
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. Unlike GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile in human suitable for once daily administration. Following subcutaneous administration, the protracted action profile is based on three mechanisms: self-association, which results in slow absorption, and binding to albumin and enzymatic stability towards the DPP-IV enzyme both resulting in a prolonged plasma half-life.
The analogue is produced as the polypeptide precursor by r-DNA technology with *Saccharomyces cerevisiae* strain YES2085 as the production strain. The peptide is acylated with a fatty acid chain

during down-stream processing. No animal derived raw materials or excipients are used in the production of liraglutide.

The drug product is a solution for subcutaneous injection containing 6.0 mg/ml of the drug substance presented in a pre-filled, multi-dose pen-injector.

Drug Substance

Liraglutide is a fragment of the naturally occurring human glucagon-like peptide-1 sequence position 7-37 (GLP-1[7-37]) with one amino acid substitution and with addition of a fatty acid chain. The analogue is produced using the recombinant DNA technology in Yeast (*Saccharomyces cerevisiae*).

The theoretical molecular mass of liraglutide is 3751.20 atomic mass units.

- Manufacture

Description of manufacturing process
The liraglutide drug substance manufacturing process has adequately been described and a flow chart has been provided. Briefly, it consists of the following main steps: fermentation of yeast cells, recovery and purification of liraglutide precursor, acylation of the precursor and further purification of liraglutide to drug substance.

Control of starting material
Overall, the control of source and starting materials is considered adequate.

Control of source and starting materials of biological origin:
No animal derived raw materials are used in the production process.

Source, history, and generation of the cell substrate:
The DNA encoding Arg^{34}-GLP-1[7-37] was obtained using synthetic DNA oligonucleotides and standard PCR techniques. The construction of the expression plasmid pKV308, the source and history of *Saccharomyces cerevisiae* strain ME1719 and the generation of S. cerevisiae strain YES2085 producing liraglutide precursor are described in sufficient detail. DNA sequence of important selected regions of the pKV308 has been verified.

Cell bank system, characterisation and testing:
Generation, characterisation and testing of the cell bank system (MCB and WCB) is sufficiently described. Compositions of all media and reagents used in the propagation and storage of cell banks are given together with information on their sterilisation.
-The company provided sufficient justification for the submitted amount of data on genetic stability of the expression system. A stability program for MCB and WCB is established and the protocol for generation of new WCB is provided.

Control of source and starting materials of non-biological origin:
The requested information on the acylation reagent including Certificate of Analysis has been provided and is considered acceptable.

Control of critical steps and intermediates
A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the liraglutide drug substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the drug substance manufacturing process with regard to operational parameters and in-process tests.

Process validation
The liraglutide drug substance manufacturing process has been validated carefully. Consistency in production has been shown on three full scale commercial batches. All acceptance criteria for the operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the purification process consistently produces liraglutide drug substance of reproducible quality that complies with the predetermined specification and in-process tests.

Impurities
Overall the reduction of product related impurities is sufficiently discussed.
The adequate removal of process related impurities during the purification process has been validated in the production facility. These impurities are not part of the liraglutide drug substance specifications.

Manufacturing process development
Detailed and sufficient information is provided on the sites for production and the changes introduced in the manufacturing process.
Although a number of changes have been introduced in the manufacturing of drug substance a good comparability study has been presented in the dossier showing that batches of drug substances derived from the different manufacturing processes and locations are indeed comparable as far as the purity profile is concerned.

Characterization
Extensive structural characterisation studies have been performed on the active substance and physico-chemical properties have been shown. State of the art methods have been used to investigate the primary, secondary and tertiary structure, as well as the physico-chemical properties (peptide mapping, N-terminal amino acid sequence analysis, amino acid composition analysis and mass spectrometry, CD and biological activity, peptide mapping, MALDI mass spec, SE-HPLC, SDS-PAGE, IEF, CE, RP-HPLC). The product related impurities are studied in sufficient depth.

Biological activity:
The biological activity is measured with a cell based bioassay reflecting the expected physiological mechanism in the clinic. In short, liraglutide stimulates a continuous mammalian cell line transfected with human GLP-1 receptors to produce intracellular cAMP in a dose dependent manner. The bioactivity of the sample is calculated relative to the SRM (secondary reference material).

- Specification

Specifications for the liraglutide drug substance were revised based on available batch data and sufficiently justified. the In conclusion, drug substance is routinely controlled by a range of chemical-physical and biological tests covering identity, purity, potency and microbial content to assure consistent production of the drug substance.

Analytical methods
The analytical assays and their validation are deemed acceptable.

Reference material
Reports for the establishment and the analytical testing of the current primary reference material (PRM) and secondary reference material (SRM), as well as protocols for the establishment of future Novo Nordisk liraglutide primary and secondary reference materials are provided. The assignment of the content and bioactivity of these reference materials was further clarified upon request with the response to the LoQ D120. The strategy of Novo Nordisk concerning the reference material is clear from the provided documentation and deemed acceptable after introduction of a unit for bioactivity.

Container closure system
The liraglutide drug substance is filled into High Density Polyethylene (HDPE) containers, the suitability of the HDPE plastic container for the storage and transport of liraglutide drug substance has been demonstrated by studies of integrity, regular compliance of plastic materials and compatibility.
In conclusion, the container closure system for liraglutide drug substance is sufficiently described.

- Stability

Sufficient stability data has been provided to support the proposed shelf lifes of intermediates and drug substance.

Drug Product

Description and composition
Victoza 6 mg/mL is a clear colourless solution containing liraglutide in a 3 mL cartridge presented in a pre-filled, multi-dose pen-injector. The solution is intended for subcutaneous injection.
The formulation is a phosphate–buffered solution with polypropylene glycol as isotonic agent. The list of excipients includes disodium phosphate dihydrate, phenol, propylene glycol, sodium hydroxide, hydrochloric acid, water for injections. These are all known excipients. The pH of the isotonic solution is 8.15.

- Pharmaceutical Development

Formulation development
The formulation development has been adequately described, the choice of excipients is justified and their functions are explained.

The formulation optimization has been based on evaluation of the following aspects: physical stability, chemical stability, preservative efficacy and biological properties. No new impurities are detected in drug product compared to drug substance.

- Manufacture of the Product

Manufacturing process
The manufacturing process of the drug product has been adequately described. The batch formula and the flow charts are provided. Critical steps have been identified and acceptable in-process controls with action limits have been set.

Control of excipients
Excipients are adequately controlled. Specifications, analytical procedures, validation of analytical procedures, and justification of specifications comply with the relevant Ph. Eur requirements. No excipients of human or animal origin and no novel excipients are used in the manufacture of the drug product.

Validation
Process validation data on the product has been presented for sufficient representative batches.

- Product Specification

In general, appropriate drug product specifications have been set and justified. These include tests for appearance, identity, assay, degradation, particulate matter, sterility, endotoxins, dose accuracy and pH.

Analytical methods
In general, analytical methods have been adequately described and validated.

Batch data
Batch analytical data from the proposed production site have been provided. The results demonstrate compliance with the specification.

- Stability of the Product

The submitted stability data sufficiently justify the proposed shelf life of the drug product.

- Adventitious Agents

Liraglutide has been evaluated to be safe with regard to both TSE and viral agents, since no animal derived raw materials are used in the production process. Yeast is not a natural host for mammalian viruses, thus no virus testing has been performed neither on the cell banks nor the drug substance. This is regarded as being acceptable.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrates consistent batch-to-batch production of Victoza achieving a well-defined quality for the drug substance and the drug product. The fermentation, recovery and purification of the drug substance, liraglutide, are adequately controlled and validated. Appropriate drug substance specifications have been set. The drug substance has been well characterised using state-of-the-art methods with regard to its physicochemical characteristics. The manufacturing process of the drug product has been described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications. No excipients of human or animal origin are used in the product manufacture and therefore there is no risk of contamination with viral or TSE agents by these ingredients.

2.3 Non-clinical aspects

Introduction

The non-clinical development of liraglutide has been designed in accordance EU/ICH guidelines. Pivotal safety pharmacology and toxicology studies were performed in compliance with GLP regulations. None of the bioanalytical methods used in pivotal toxicology studies were validated in accordance with GLP; the validations however were performed-in close adherence to GLP principles. Thus, the overall assessment was not considered to be influenced by this.

The rat and monkey were chosen as the most appropriate species for toxicity testing owing to their pharmacological responsiveness and comparable metabolic patterns. Toxicokinetics from embryo-foetal development studies also included rabbits.

Scientific advice was given by the CHMP regarding pharmacokinetics, carcinogenicity and the potential for QT-prolongation.

Pharmacology

- Primary pharmacodynamics

Liraglutide is a long-acting GLP-1 analogue, designed to bind to albumin as the main molecular mechanism of protraction. *In vitro*, this was shown in the receptor cAMP as well as binding assay where addition of albumin right-shifted the dose-response and/or binding curve. The apparent reduced potency of liraglutide underlines that only the free fraction of liraglutide is responsible for its pharmacological effect *in vitro* as well as *in vivo*. Furthermore, liraglutide in a pharmaceutical solution forms a micell-like heptamer which may contribute to the slow absorption from the subcutis.

Liraglutide is a potent, selective and efficacious agonist on the human as well as mouse, rat, rabbit, pig and Cynomolgus monkey GLP-1 receptor. Liraglutide has been shown to exert a number of actions *in vitro* that are known to be specific GLP-1 effects. Liraglutide has also been shown to glucose-dependently stimulate insulin secretion from isolated β-cell islets *in vitro*. Liraglutide attenuated β-cell apoptosis *in vitro* under adverse conditions with high concentrations of free fatty acids and pro-inflammatory cytokines. Moreover, a proliferative effect on primary rat β-cells could be demonstrated for liraglutide *in vitro* whereas no consistent effect was observed under hyperglycaemic conditions *in vivo*.

In vivo, liraglutide lowers blood glucose and body weight in a number of diabetic and obese models using rodents, pigs and monkeys. The mechanism of action *in vivo* involved glucose-dependent increase in insulin secretion, lowered glucagon secretion, decreased gastric emptying, loss of body fat, lowered food intake, altered food preference, and maintained energy expenditure. The mechanism of action is consistent with a specific GLP-1 effect.

- Secondary pharmacodynamics

Liraglutide had no cross-reactivity to a panel of 75 different receptors and ion channels. Moreover, it displayed no affinity to other closely related receptors in the glucagon-receptor super family including receptors for glucagon, GLP-2, secretin, GHRH, VIP and PACAP.

- Safety pharmacology programme

The safety pharmacology programme, focusing on central nervous, respiratory, and cardiovascular systems and renal function, raised no serious issues. Liraglutide was well tolerated, especially in mice and monkeys. The only effects observed were confined to the rat. These adverse effects consisted of decreased specific urinary gravity and osmolality, accompanied by a dose-dependent increase in urine volume and electrolyte excretion. With respect to the cardiovascular system, liraglutide (at 0.2 and 2.0 mg/kg) induced dose-related increases in blood pressures and heart rate in rats, which were generally maintained for up to 24 hours after dosing. Moreover, body temperature was slightly reduced at 0.2 mg/kg and significantly reduced for 13.5 hours at 2.0 mg/kg. According to previous studies performed in rodents, the rat is especially sensitive to GLP-1 agonists, since no adverse effects on the cardiovascular and renal system have been observed in other animals or humans.

- Pharmacodynamic drug interactions

Liraglutide has been shown to lower blood glucose synergistically in combination with the PPARγ agonist pioglitazone, and to increase insulin secretion synergistically in combination with the sulphonylurea glipizide. Although no considerable effect on blood glucose was obtained with the liraglutide-atorvastatin combination treatment in severely diabetic and insulin-resistant ZDF rats, a number of critical diabetic parameters were improved. Concomitant liraglutide and metformin treatment did not give rise to any additive effect on blood glucose during a 15-day study in ob/ob rats.

Pharmacokinetics

The pharmacokinetics of liraglutide has been studied adequately. RIA and ELISA methods were used in the analyses performed
Liraglutide was well absorbed from the injection site after a single subcutaneous (SC) administration. Overall bioavailability following SC administration was estimated to be 53% in monkey, 76% in pig and 55% in human. The distribution volume is low and close to plasma volume, which indicates that a high fraction of liraglutide is circulating in plasma. All species except Sprague Dawley rats demonstrated a plasma protein binding of approximately 99% or higher. The plasma proteins responsible for the high degree of observed plasma protein binding were HSA (99.4%) and AAGP (99.3%).
The observations are consistent among species and demonstrate linear pharmacokinetics of liraglutide with dose-proportional exposures as measured by C_{max} and AUC values or an exposure slightly higher than dose-proportional. No apparent gender-related differences were observed in the animal species. Following repeated administration of liraglutide to mice, rats and monkeys, only a minor tendency towards accumulation was observed. The accumulation ratio was comparable to that observed in humans (<2).
The terminal half-life of liraglutide seems to be similar in pigs (~14 h) and humans (~15 h) while shorter in mice, rats, rabbits and monkeys (4-8 h). Several studies in monkeys, pigs and humans indicated that extravascular administration (SC and pulmonary) of liraglutide prolongs the terminal half-life as compared to intravenous (IV) administration. Furthermore, the terminal half-life seemed also to be prolonged by repeated dosing in rats, monkeys, pigs and humans. This tendency was not apparent for mice and rabbits. The observed time to the maximum concentration seemed also to be

affected by repeated dosing in some studies. The differences in the pharmacokinetic parameters can be explained by the study design or absorption rate limited kinetics (in the latter case following SC administration in pigs and humans).
A low distribution of radioactivity was detected when comparing the results from administration of ^{125}I-liraglutide, ^{14}C-liraglutide and ^{3}H-[Pal]-liraglutide with radioactivity predominantly detected in plasma. This is in accordance with what would be expected for this type of molecule and correlates well with the low volume of distribution found for liraglutide in monkey, pig and human.
The metabolic and excretion patterns were highly similar across species with liraglutide being fully metabolised in the body by sequential cleavage of small peptide fragments and amino acids. The *in vitro* metabolism studies indicate that the initial metabolism involves cleavage of the peptide backbone with no degradation of the glutamate-palmitic acid side-chain. Mice, rats and monkeys displayed similar plasma profiles and showed no significant gender differences. A higher number of metabolites were observed in plasma from the animal species (especially the rat and monkey) as compared to human plasma. This disparity can partly be explained by differences in the sample preparation as human plasma samples were freeze dried prior to analysis causing a removal of volatile metabolites (including tritiated water). All detected metabolites were minor and obtained in low amount (<15%) and therefore no structural identification of these was performed. This is acceptable since the metabolites are only formed in low amounts and since the metabolites are expected to resemble endogenous substances with well-known metabolic pathways.
Clearance of liraglutide is suggested to take place by multiple organs/tissues and a low potential for pharmacokinetic drug interactions related to CYP and protein binding has been demonstrated.
Liraglutide crosses the placental barrier in rats and rabbits. However, the uptake of liraglutide into the amniotic fluid and foetuses is low (<9%). Liraglutide is secreted into milk, but the amount of liraglutide that a pup would receive per day via breast milk is low (at most 3% of the maternal dose). This information is reflected in section 4.6 of the SPC.

Toxicology

- Single dose toxicity

Single dose studies were performed in mice and rats in standard design studies and in monkeys in a maximum tolerated dose (MTD) study. A single dose of 10 mg/kg was generally well tolerated by mice and rats without mortality. In monkeys, a single SC administration of 5 mg/kg was well tolerated without mortality. The observed reductions in body weight and food consumption can be regarded as pharmacologically mediated.

- Repeat dose toxicity (with toxicokinetics)

Pivotal repeat dose studies were performed in mice, rats and Cynomolgus monkeys. An overview of the toxicological programme can be found in the tables below:

Study ID	**NN203261**	**NN204082**
Species/strain	CD-1 mice	CD-1 mice
Drug	Liraglutide	Liraglutide
Dose Route	SC	SC
Animals/sex/group	Main study: 5 groups:10 males, 10 females/group Satellite study: 5 groups:16 males, 16 females/group	Main study: 4 groups:10 males, 10 females/group Satellite study: 4 groups:28 males, 28 females/group Antibody study: 4 groups 5-15 males, 5-15 females/group
Dose groups (mg/kg/day)	0, 0.1, 0.5, 1.0, 5.0	0, 0.2, 1.0, 5.0
Duration	4 weeks	13 weeks

NOEL/ NOAEL (mg/kg/day)	NOEL <0.1mg/kg NOAEL 5mg/kg	NOEL < 0.2mg/kg NOAEL 5mg/kg

Study ID	**NN980183**	**NN980189**	**NN200239**
Species Strain	Rats/Sprague Dawley	Rats/Sprague Dawley	Rats/Sprague Dawley
Drug	Liraglutide	Liraglutide	Liraglutide
Dose Route	SC	SC	SC
Animals/Sex/Group	Main study: 4 groups: 10 males, 10 females/group Satellite study: 3 groups:10 males, 10 females/group.	Main study: 4 groups:10 males, 10 females/group Satellite study: 4 groups:10 males, 10 females/group. Recovery study: 2 groups: 5 males, 5 females/group	4 groups: 15 males, 15 females/group
Dose Groups (mg/kg/day)	0, 0.1 , 0.25, 1.0	0, 0.1 , 0.25, 1.0	0, 0.1 , 0.25, 1.0
Duration	4 weeks	13 weeks treatment + 4 weeks recovery	26 weeks
NOEL/ NOAEL (mg/kg/day)	NOEL <0.1 mg/kg. NOAEL 1.0 mg/kg	NOEL <0.1 mg/kg NOAEL 1.0 mg/kg	NOEL <0.1 mg/kg NOAEL 1.0 mg/kg

Study ID	**NN980184**	**NN990191**	**NN200241**
Species/strain	Cynomolgus Monkeys	Cynomolgus Monkeys	Cynomolgus Monkeys
Drug	Liraglutide	Liraglutide	Liraglutide
Dose Route	SC	SC	SC
Animals/sex/group	4 groups: 3 males, 3 females/group	Main study: 4 groups: 4 males, 4 females/group. Recovery study: 2 groups: 2 males, 2 females/group	Main study: 4 groups: 4 males, 4 females/group. Recovery study: 2 groups: 2 males, 2 females/group
Dose groups (mg/kg/day)	0, 0.05, 0.5, 5.0	0, 0.05, 0.5, 5.0	0, 0.05, 0.5, 5.0
Duration	4 weeks	13 weeks treatment + 2 weeks recovery	52 weeks treatment + 4 weeks recovery
NOEL/ NOAEL (mg/kg/day)	NOEL < 0.05mg/kg NOAEL 5mg/kg	NOEL < 0.05mg/kg NOAEL 5mg/kg	NOEL 0.05mg/kg NOAEL 5mg/kg

Liraglutide was well-tolerated in rats and monkeys with NOAEL values corresponding to plasma exposure levels approximately 8- and 70-fold higher than observed in the clinic, respectively. In all species, decreased body weight gain and food consumption were seen in the first weeks of dosing. These effects are result of the pharmacological action of liraglutide. Following this initial period, in general, the animals resumed a more "normal" growth pattern (i.e. comparable to that of the control group) and food consumption. In rats, males seemed more affected than females. A slight trend towards increased effects in males was also noted in the monkey.
Some effects on haematology, clinical chemistry and sometimes also urine were seen. However, the effects were generally small, and for most parameters there was no consistent pattern across the studies. Histological examination did not reveal any clear treatment-related effects apart from C-cell hyperplasia in the thyroid of treated mice seen after 9-13 weeks of dosing. Effects on C-cells (focal accumulations of C-cells) were already seen in the 4-week mice study but these findings were not considered to be treatment-related. No effects on C-cells were seen in the rat and monkey studies up to 26 and 52 weeks.

An increased pancreatic weight was observed in cynomolgus monkeys following 52 weeks treatment at plasma exposure levels below and 8-9-fold higher than is observed in the clinic, respectively.

Further investigations of the pancreatic tissues collected in the 52-week monkey study showed that the increased pancreatic weight was due to a 67% increase in absolute duct cell mass and 64% increase in exocrine cells when compared to the vehicle group. Considering that concerns have been raised regarding the potential induction of acute pancreatitis following treatment with GLP-1 receptor agonists, there was a request to evaluate the clinical relevance of this finding. The applicant substantiated that the statistical significant differences in pancreatic weight observed in mid and high dose animals were driven by the pancreas weight of the controls, which was low compared to that of the CRO historical control data. Moreover, normal histological morphology of the pancreas was seen in all studies and no clinical or biochemical changes were seen in any of the four non-human primate studies and also there was no histopathology indicative of inflammation. In addition, no effect on pancreatic weight was observed in the 87-week study. Based on the above, it was concluded that the findings made in the 52-week cynomolgus monkeys study do not suggest a safety concern for humans with respect to treatment related pancreatitis.
At the end of the 52-week monkey study, antibodies were found in a few monkeys which cross-reacted with GLP-1. This implies that an immunological reaction against the body's own GLP-1 could be possible. Data on antibody formation will be reported in the PSURs.

Toxicokinetics
Toxicokinetic analysis was performed as part of every study with blood samples colleted and analysed for the presence of liraglutide. Liraglutide was not detected in blood samples of control animals. In the 26-week rat study, only two animals per sex were subjected to blood sampling and the samples were collected pre-dosing. This is not in line with CPMP/SWP/1094/04 "Guideline on the evaluation of control samples in non-clinical safety studies" but the study was conducted before the release of the guideline. The results from the toxicokinetic evaluations are presented in the table below.

Study duration	**Dose (mg/kg/day)**	**C_{max} (nmol/L)**		**AUC (h•nmol/L)**		**Multiple of MRHD C_{max}**		**Multiple of MRHD AUC**	
				CD-1 mice					
		♂	♀	♂	♀	♂	♀	♂	♀
13 weeks	0.2	145	247	1876	2042	3.2	5.5	2.3	2.5
	1	1012	1320	11854	18592	22.6	29.5	14.7	23.0
	5	5927	6289	74212	62857	132.6	140.7	91.7	77.7
				SD Rat					
		♂	♀	♂	♀	♂	♀	♂	♀
7 days	0.125	115	68	1270	769	2.6	1.5	1.6	1.0
	0.25	151	264	2063	3142	3.4	5.9	2.6	3.9
	1	425	470	6222	5696	9.5	10.5	7.7	7.0
4 weeks	0.1	44	32	549	460	1	0.7	0.7	0.6
	0.25	155	173	1915	2485	3.5	3.9	2.4	3.1
	1	763	371	11993	6155	17	8.3	14.8	7.6
13 weeks	0.1	39	53	643	865	0.9	1.2	0.8	1.1
	0.25	144	368	2445	3731	3.2	8.2	3.0	4.6
	1	358	768	9188	12208	8.0	17.2	11.4	15.1
26 weeks	0.1	24.8	44.5	379	583	0.6	1.0	0.5	0.7
	0.25	85.2	128	1270	1900	1.9	2.9	1.6	2.4
	1	468	668	5640	6840	10.5	14.9	7.0	8.5
				Cynomolgus monkey					
		♂	♀	♂	♀	♂	♀	♂	♀
4 weeks	0.05	15	11	233	170	0.3	0.2	0.3	0.2
	0.5	157	127	2285	1430	3.5	2.8	2.8	1.8
	5	2679	945	35381	14938	59.9	21.1	43.7	18.5
13 weeks	0.05	NC	NC	NC	NC	NC	NC	NC	NC
	0.5	NC	NC	NC	NC	NC	NC	NC	NC
	5	NC	NC	NC	NC	NC	NC	NC	NC
52 weeks	0.05	29.9	62.4	523	1110	0.7	1.4	0.6	1.4
	0.5	439	406	7610	6430	9.8	9.1	9.4	8.0
	5	3680	3370	62100	56300	82.4	75.4	76.8	69.6

NC; not calculated
The maximal recommended human dose is 1.8 mg/day SC which gives rise to C_{max} and AUC values of 44.7 nmol/L and 809 h·nmol/L, respectively, at steady-state.

- Genotoxicity

Results of the Ames test, the *in vitro* chromosome aberrations assay and the *in vivo* micronucleus tests indicate no genotoxic potential.

- Carcinogenicity

In carcinogenicity studies, C-cell tumours were observed in mice and rats. A NOAEL value for these findings was established in mice at 0.2 mg liraglutide/kg/day, which results in plasma exposure levels similar to what is obtained in the clinic. A NOAEL value was not established in rats. A number of exploratory studies have been conducted in order to evaluate the mechanism behind liraglutide's non-genotoxic carcinogenic effect on rodent C-cells (see below).

Uterus leioma and leiosarcoma were observed in mice but not in rats. Although there seemed to be an increased number of tumours in treated mice, there was no dose-response relationship and furthermore, mice are very sensitive to this tumour. Skin sarcomas were increased in mice at high dose. In many of these animals, sarcomas were situated around the microchip which may have influenced their appearance. At the NOEL of 1.0 mg/kg/day, the safety margin was 13.
In rats, pituitary gland carcinomas in the anterior lobe as well as uterus stromal polyps were increased in high dose females. However, when benign and malignant tumours of pituitary gland and uterus were combined, there was no relevant dose related effect. Furthermore, on an individual animal basis there was no relation between stromal polyps and pituitary carcinoma or adenoma. It is not considered likely that the pituitary carcinoma and stromal polyps are a risk for humans.

An extensive package of mechanistic studies was performed to investigate the human relevance of the C-cell tumours which was considered of crucial importance and identified as a major objection during the procedure. In these studies, GLP-1 receptors were shown to be present in C-cells of all investigated species. GLP-1 receptors were present in higher amounts per cell in rat cell lines than in a human cell line. In addition, literature indicates C-cells are less abundant compared to other endocrine cells in human thyroid than in rodent thyroid. In rat C-cell lines, liraglutide induced cAMP and calcitonin secretion (though at much higher EC50 than exenatide). In a human cell line, the response was marginal.
Using human thyroid tissue, co-localization of the GLP-1 receptor and calcitonin within C-cells was confirmed by double-staining, while GLP-1 receptor mRNA was non-detectable via in situ hybridisation in human C-cells. In all other mechanistic studies, the human TT cell line was used; however concerns were raised whether this cell line was representative for normal (non-transformed) human tissue. To address this concern a new study was performed in order to compare GLP-1 receptor mRNA content in thyroid extracts from human donors with levels in the TT C-cell line. It was however not possible to correct the calculated mRNA content for the ratio of C-cells to total thyroid. The species difference in GLP-1 expression was however confirmed by in situ ligand binding. Overall, data show that GLP-1 expression in human C-cells is likely to be low, but not completely absent.
In mice, liraglutide produced a sustained increase in plasma calcitonin. An increase in calcitonin mRNA, indicating increased calcitonin synthesis, was visible after 2 weeks. Focal accumulation of C-cells which was not considered to be treatment- related started to be visible after 4 weeks. Treatment-related C-cell hyperplasia was observed after 9 weeks. C-cell hyperplasia was also observed after exenatide continuous infusion up to 16 weeks, but not after bolus injections during the same period of time.
In rats, increased plasma calcitonin levels were observed after 4 weeks administration. No information was provided regarding weeks 1-3 in this study. After a single dose, a decrease was observed in plasma calcitonin after an initial increase. This lowering in calcitonin can be explained by a massive loss of calcium in the urine due to a marked diuretic effect of a single dose of liraglutide in rats. In a long-term study (up to 16 months), plasma calcitonin showed no overall consistent change. This may be because the half-life of calcitonin is very short in rats, approximately 4 minutes; this may have played a role in this respect that it may be difficult to observe increases in plasma calcitonin in rats; however, half-lives in other species are not mentioned. In rats, following long-term dosing, the increase in calcitonin did not persist. This may be due to a high spontaneous frequency of C-cell

hyperplasia in combination with a decrease in diffuse C-cell hyperplasia in aging rats. This is supported by the higher incidence in control rats compared to control mice. In literature, spontaneous C-cell tumours have been reported to occur with high frequency in rats. Martin-Lacave (2002) reports a frequency between 16% and 40% in most strains and Kaspareit-Rittinghausen (1990) reported 51.5 – 60% in Han:SPRD rats. Statistical analyses of individual animal data in rats revealed a correlation between early plasma calcitonin change (day 0 to day 28) and terminal focal C-cell hyperplasia score. In addition, the early calcitonin change was clearly larger in rats that later developed adenomas than in rats that did not. This finding supports the hypothesis that the C-cell hyperplasia and adenomas observed in the rodent carcinogenicity studies are caused by the continuous release of calcitonin due to persistent activation of C-cell GLP-1 receptors and the accompanying increased demand for calcitonin synthesis. The possibility that an additional mechanism for C-cell stimulation on calcitonin, not related to GLP-1R, may exist was addressed during the procedure. Data regarding a large number of receptors and ion channels indicate that liraglutide only shows affinity to the GLP-1 receptor.

C-cell hyperplasia started to occur from 28 days dosing in aged rats and from 210 days dosing in young rats. Adenoma started to occur in both aged and young rats from 210 days of dosing. No changes in C-cell mass were observed after 26 weeks in young rats.
In cynomolgus monkeys, no effect of liraglutide on plasma calcitonin was observed up to 87 weeks. No C-cell hyperplasia was observed after 87 weeks (animals were 15-19 months old at start). No changes in C-cell mass were observed after 52 weeks (animals were 12-17 months old at start). Literature data indicate that if there would have been evidence for a carcinogenic mechanism in monkeys based on C-cell proliferation in response to receptor stimulation, it would have been visible within these periods of time.

It is concluded that the findings in rodents are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance for humans is likely to be low but cannot be completely excluded. Section 5.3 of the SPC reflects this information.

- Reproduction Toxicity

Studies were performed in rats in which male and female fertility and embryonic development were combined. Decreased body weight gain, decreased food consumption, and reduced faecal output are considered due to the pharmacological action of liraglutide. As decreased body weight gain and decreased food consumption can be considered desired effects of liraglutide, they were not considered adverse effects in the determination of the NOAEL.
Fertility parameters were not affected except for a slight decrease in the number of live implants/ slight increase in early embryonic deaths at 1.0 mg/kg. In the foetuses, a slight increase in skeletal variations was observed. The safety margin for the effects on live implants and foetal effects was 3.
In a pre and postnatal study in rats, in F0 animals, pharmacologically mediated effects were observed on body weight gain and food consumption. In F1 animals, a decreased weight gain was observed in all treated groups in the pre-weaning period. Post-weaning, at high dose, a slightly decreased body weight gain was also observed in F1 males up to week 16 and in F1 females during gestation and lactation but not in the pre-mating phase. In the F2 generation, a slight decrease in mean pup weight which was consistent among males and females was observed at high dose. This finding was not statistically significant, but considered remarkable because it suggests that there could be an effect on body weight up to the second generation.

In embryofoetal toxicity studies in rabbits, a large decrease in food consumption was observed in rabbits. Again, decreased body weight gain, decreased food consumption, and reduced faecal output in the F0 generation are considered due to the pharmacological action of liraglutide. Foetal effects were a reduced foetal weight, an increase in the number of skeletal variations and a slight increase in the number of gall bladder abnormalities. There was no safety margin for these effects, but they may well have been due to the markedly decreased food consumption.

No studies were performed in juvenile animals.

- Local tolerance

Single SC injection of liraglutide or vehicle in pigs caused a mild subacute inflammation in the injection site tissue. These studies evaluated the local tissue reaction after one SC injection and not after repeated dosing or after IV, intramuscular or intra arterial injection. Repeated dose administration was sufficiently investigated in the repeated dose studies.
Generally mild effects at the injection site have been noted in rats and monkeys in the repeated dose toxicity studies.
Local tolerance following intramuscular, IV or intraarterial injection was studied in rabbits, with no relevant differences between liraglutide-treated sites and vehicle-treated sites observed after intramuscular or IV administration. Injection site reactions consisting mainly of perivascular haemorrhage and periarterial fibrosis/oedema were slightly more pronounced following intraarterial administration. A slight, treatment-related reaction can not be excluded should accidental intraarterial injection occur in humans.

- Other toxicity studies

Immunotoxicity
Immunotoxicity studies were not performed. This is acceptable as no relevant findings on the immune system organs were observed in the repeat dose studies, and immunotoxicity is not expected based on the mechanism of action.

Metabolites
The major metabolite of liraglutide is at least 235-fold less potent than liraglutide. All human metabolites were also observed in the animal species studied in the toxicology studies and therefore, it is considered that these metabolites have been sufficiently investigated.

Studies on impurities
A study was performed to compare a formulation which was forcedly degraded by storage at 37 °C for 2 months (to get sufficiently high levels of impurities) to a normal, non-degraded formulation. In this study, there were no relevant toxicological differences between the two formulations. Antibody formation was investigated and no higher potential for immunogenicity was observed after 4 weeks. As the liraglutide-related impurities were present either at percentages which were at least as high as the specified percentages or at a sufficient safety margin when absolute amounts in mg/kg/day were taken into account, they were considered sufficiently qualified in this study. Possible genotoxicity of the impurities was not discussed. Normally this should also have been tested. In this case however, no genotoxicity is expected of the liraglutide-related impurities as they consist of peptides.
According to the documentation in the quality part of the dossier, the product may contain residues from leachables from the packaging of the product, consisting of xylenes and Br-phenols. The amount of xylenes that can maximally be taken in by users of Victoza is far below the Permitted Daily Exposure of 21.7 mg/day and the amount of Br-phenols that can maximally be taken in is below the threshold for toxicological concern (TTC) of 1.5 µg/day. Therefore, no relevant risk is expected of these leachables.

Ecotoxicity/environmental risk assessment

The CHMP agrees with the view of the applicant that since liraglutide is a peptide, consisting of natural amino acids and a natural fatty acid, a further environmental risk assessment is not deemed necessary as per the EMEA/CHMP/SWP/4447/00 guidance.

2.4 Clinical aspects

Introduction

Overall, the liraglutide clinical development program comprised 38 completed trials. The trials were conducted world-wide, with the majority conducted in Europe. Two trials investigated liraglutide delivered by alternative routes of administration and one investigated treatment of obese, non-diabetic

subjects for a separate indication. These three trials are included as they provide liraglutide safety information.
In addition, two complete reports describing data from subjects enrolled in the extension periods from Trials 1573 and 1572 are included.

An overview of the therapeutic confirmatory trials can be found in the Clinical Efficacy section.

The claimed indication for Victoza was:

"as an adjunct to diet and exercise to achieve glycaemic control in patients with type 2 diabetes mellitus. Victoza is indicated for once-daily administration as:
• Monotherapy
•Combination therapy with one or more oral antidiabetic drugs (metformin, sulphonylureas or a thiazolidinedione) when previous therapy does not achieve adequate glycaemic control.

The approved indication and posology are the following:

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

Posology
To improve gastro-intestinal tolerability, the starting dose is 0.6 mg liraglutide daily. After at least one week, the dose should be increased to 1.2 mg. Some patients are expected to benefit from an increase in dose from 1.2 mg to 1.8 mg and based on clinical response, after at least one week the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended.
Victoza can be added to existing metformin or to a combination of metformin and thiazolidinedione therapy. The current dose of metformin and thiazolidinedione can be continued unchanged.
Victoza can be added to existing sulphonylurea or to a combination of metformin and sulphonylurea therapy. When Victoza is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.

During the development of liraglutide, consultations with various authorities were sought. Scientific advice was obtained from the CHMP in 2004 prior to the initiation of the phase 3a programme.
The main clinical issues of the CHMP advice were the clinical programme for monotherapy, dose selection and delayed disease progression.

The clinical development programme included special populations such as those with impaired renal function and impaired hepatic function. The effect of gender, age, race and ethnicity on the pharmacokinetics of liraglutide was also studied. No pharmacokinetic studies were performed in children.

GCP

The CHMP requested a GCP inspection of the clinical study NN2211-1572. Two investigator sites and the sponsor site in Denmark were inspected in this routine GCP inspection. The inspection revealed major findings and one critical finding. The Inspectors did not find evidence that the deficiencies found had impact on the overall validity and credibility of the data reported in this clinical trial and therefore deemed the inspected clinical trial as valid for use in the assessment of the marketing authorisation application for Victoza.

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The clinical pharmacology programme performed to evaluate the pharmacokinetic and pharmacodynamic properties of liraglutide included 26 clinical pharmacology trials (see table below). These comprised 19 trials in healthy subjects (including bioequivalence trials, trials in elderly subjects, subjects with renal or hepatic impairment and Japanese subjects) and 7 trials in subjects with type 2 diabetes (including one trial in Japanese subjects). The programme was supported by evidence from 5 phase 2 trials, a population pharmacokinetic analysis from the therapeutic confirmatory Trial 1573 and from 10 *in vitro* studies performed with human biomaterials, i.e. cells, recombinant enzymes, plasma or plasma proteins.

An ELISA assay was developed to measure plasma concentrations of liraglutide. The assay validation and analysis of samples were performed in accordance with current practice. The ELISA was found valid for analysing liraglutide in plasma samples regarding recovery, linearity, intermediary precision, sensitivity, goodness of fit and stability.

During the assessment there was concern because the doses used in the pharmacokinetic and pharmacodynamic studies do not correspond to the doses used in the clinical phase III studies (except studies investigating drug-drug interactions, gastric emptying and appetite assessments), and therefore it was unclear why results from these studies could be transferred to the therapeutic doses. The CHMP accepted that that based on the results from the clinical development programme the observations made in the early trials performed with lower doses of liraglutide are found to be relevant and transferable to the effects and results obtained in the later long-term confirmatory therapeutic trials using higher doses.

- Absorption

The absolute bioavailability of liraglutide after SC injection was estimated to be 55% (Sd 37%). No clinical significant differences between the three most commonly used injection sites (thigh, abdomen and upper arm) were found and all three injection sites can be used interchangeably.
During the liraglutide clinical development programme four formulations were used. Bioequivalence was assessed between the different adjacent formulations used (study 1331, 1636, 1693 and 1692). No bioequivalence studies were performed with the first formulations and the final formulation (e.g. formulation 1 or 2 versus formulation 4). Thus, results from studies with the earlier formulations can not be extrapolated *per se* for the final liraglutide product. However, differences in the pharmacokinetic results of the different formulations were very small and did not give rise to different pharmacokinetic profiles, and the most important studies have been performed with formulation 3 or 4. Moreover additional statistical calculations were used to prove that formulations 2 (considered essentially the same as 1) and 4 can be regarded as bioequivalent.

- Distribution

The apparent volume of distribution (V_z/F) following SC administration was approximately 11-17 L. The mean volume of distribution (V_z) following IV administration of liraglutide was 0.07 L/kg at 5µg/kg (approximately 5 L for subjects weighing 75 kg). This volume is small and close to the plasma volume, indicating that a high fraction of liraglutide is circulating in the blood. The *in vitro* protein binding was above 98% in human plasma at total liraglutide plasma concentrations of 0.1 to 1000 nmol/L. The *in vitro* binding of liraglutide to HSA and AAGP, was 99.4% and 99.3%, respectively. Liraglutide can cross the placental barrier and is secreted in dog breast milk in preclinical studies. Liraglutide crosses the blood-brain barrier to a limited amount.

- Elimination

Metabolism: Liraglutide has two minor metabolites (presence each less than 10%) with no clinical relevant activity. Only low amounts of liraglutide metabolites and no intact liraglutide are found in urine and faeces. Liraglutide is analogous, metabolised as endogenous GLP-1 involving dipeptidyl peptidase-IV (DPP-IV) and neutral endopeptidase (NEP). Liraglutide is considered almost completely metabolised and degraded into peptides, amino acids and fatty acid fragments, and subsequently completely degraded yielding carbon dioxide and water. The slow metabolism and elimination of liraglutide compared to endogenous GLP-1 can be explained by the stability against DPP-IV and NEP but also to the high protein binding which prevents it from being rapidly eliminated from the circulation by renal filtration.
DPP-IV and NEP are known to have genetic polymorphisms. However, variations of the DPP-IV gene have mainly been associated with immunodeficiency and hypertension and single nucleotide polymorphisms (SNPs) in the NEP gene have mainly been associated with diseases like Alzheimer's, cerebral amyloid angiopathy, immune-mediated diseases and anxiety. No groups of subjects could be identified with different elimination parameters, therefore it is considered that if genetic polymorphism had been present, the effect on the pharmacokinetics of liraglutide is minor, or that genetic polymorphism is rare.

Excretion: The $t_{½}$ following SC administration of liraglutide was approximately 13 hours and apparent clearance (CL/F) ranged from 0.6-1.2 L/h. Following IV administration $t_{½}$ was shorter ($t_{½}$ = 8 hours), probably caused by prolonged release of liraglutide from the injection site, and clearance was 1.2 L/h for a median body weight on 90 kg (population pharmacokinetic).

- Dose proportionality and time dependencies

The liraglutide plasma concentration increased with increasing doses and the increase in AUC and C_{max} were proportional with dose in the range from 2.5 to 20 µg/kg administered as single dose. This dose range corresponds to 0.18–1.44 mg (based on actual body weight). At steady state, dose proportionality was demonstrated for AUC_{τ} and C_{max} in the dose range 0.38–0.93 mg (5-12.5 µg/kg). Also dose proportionality in the dose range 1.2–1.8 mg was sufficiently demonstrated. The accumulation ratio was 1.4 to 1.8 which is in agreement with the elimination pharmacokinetics and dosing frequency of liraglutide.
Study 1189 shows time independence from Day 1 until Day 11. The population PK analysis shows that liraglutide clearance is not time dependent, with essentially the same clearance from week 2 until week 52.

Variability: After single dose (Phase I studies) the estimated coefficient of variation (CV) was 20% for $AUC_{0-\infty}$. The estimated intra-subject CV was 11% for $AUC_{0-\infty}$. At steady state, a CV for AUC_{τ} was 26% and the intra-subject CV was 19%. In most other studies the variability was moderate as described above, however, in some studies, for example study 1224, inter-individual variability was much higher being up to 65 % and 75 % for AUC and C_{max}, respectively.

- Special populations

Pharmacokinetics in target population: The pharmacokinetic properties of liraglutide were overall comparable between healthy volunteers and subjects with type 2 diabetes.

Special populations: As liraglutide is not cleared by one specific organ, renal and hepatic impairment have only a limited effect on the pharmacokinetics of liraglutide. Subjects with renal impairment, indifferent to the grade of impairment have a decreased exposure to liraglutide (approximately 14-26%). Subjects with hepatic impairment, have a decreased exposure to liraglutide (approximately 13-44%), lowest in subjects with severe hepatic impairment (see Clinical studies in special populations).
No clinically significant differences in liraglutide pharmacokinetics were found between male and female subjects, subjects with different race, or elderly and younger subjects.

- Pharmacokinetic interaction studies

Liraglutide has no clinically relevant potential to inhibit or induce cytochrome P450 drug metabolising enzymes. No clinically relevant drug-drug interaction related to protein binding is anticipated either.
The effect of liraglutide on the absorption pharmacokinetics of co-administered oral drugs was investigated for paracetamol (acetaminophen), digoxin, lisinopril, griseofulvin and atorvastatin. In addition, the effect of liraglutide on the absorption pharmacokinetics of ethinylestradiol and levonorgestrel administered in an oral combination contraceptive drug was investigated. An interaction study with warfarin was not performed.
Concomitant administration of liraglutide and the selected orally administered drugs resulted in small changes in C_{max} as well as minor delays in t_{max} of the investigated drugs. The changes observed in exposure and absorption of the investigated drugs was not considered clinically significant. However, it should be kept in mind that the small delay in gastric emptying with liraglutide may potentially influence absorption of concomitantly administered oral drugs and result in drug-drug interaction. The results of the performed studies should be extrapolated with caution to other drugs. Clinically significant interactions can not be excluded, especially, with drugs with poor solubility and a small therapeutic window, such as warfarin. A warning has been included in section 4.5 of the SPC to this respect with inclusion of a recommendation to monitor INR upon initiation of liraglutide treatment.
Combination of liraglutide with insulin has not been evaluated and is therefore not recommended. This is also reflected in the SPC.
Diarrhoea may affect the absorption of concomitant oral drugs. This is reflected in section 4.5 of the SPC as 12.6% of patients treated with liraglutide reported at least one episode of diarrhoea.

- Pharmacokinetics using human biomaterials

Ten *in vitro* studies were performed with human biomaterials, i.e. cells, recombinant enzymes, plasma or plasma proteins. Metabolism was studied in studies NN205145, NN206480, NN206665, NN207147, and NN207312, protein binding in studies NN200152 and NN201223, and drug-drug interaction in studies NN980278, NN201224, NN203029.

Pharmacodynamics

The pharmacodynamic properties of liraglutide were investigated in 9 randomised, double-blind and placebo-controlled clinical pharmacology trials: 3 trials in healthy subjects (Trials 1149, 1189 and 1608) and 6 trials in subjects with type 2 diabetes (Trials 1219, 1224, 1332, 1589, 1698 and 2063).
Furthermore, results from pharmacodynamic assessments in 4 exploratory therapeutic trials were included (Trials 1310, 1333, 1571 and 2072). Pharmacodynamics were also investigated in healthy Japanese subjects (Trials 1326, 1551 and 1694) and in Japanese subjects with type 2 diabetes (Trial 1591).

- Mechanism of action

Liraglutide is a GLP-1 analogue in which lysine at position 34 has been replaced with arginine, and palmitic acid has been attached via glutamoyl spacer to lysine at position 26. Like native GLP-1, the mechanism of action of liraglutide is mediated via a specific action on GLP-1 receptors. *In vitro* receptor studies have shown that liraglutide is equipotent to endogenous GLP-1. Thus, liraglutide is expected to induce the same pharmacological effects as native GLP-1 resulting in lowering of blood glucose.
Following SC injection, liraglutide has a protracted pharmacokinetic and pharmacodynamic profile due to self-association which results in delayed absorption from the injection site, a high degree of plasma protein binding and decreased susceptibility to metabolism by DPP-IV and neutral endopeptidase (NEP). The protracted action profile makes liraglutide suitable for once-daily administration.

- Primary and Secondary pharmacology

The effects of liraglutide on glucose, insulin and glucagon response, beta-cell function and gastric emptying were investigated. In addition, the glucose-dependency of these effects (except gastric emptying) was assessed. The effect of liraglutide on appetite, energy intake and energy expenditure were also assessed to explain observed lowering of body weight.

The pharmacodynamic properties of liraglutide with respect to glucose, insulin and glucagon response, gastric emptying and appetite were mainly evaluated by concentration-time profiles of glucose, insulin, glucagon and paracetamol as well as profiles of visual analogue scales (VAS) ratings.
For assessments of beta-cell function, the insulin secretion rate was estimated by mathematical analysis (deconvolution) of peripheral C-peptide concentrations using a two-compartment model and standard C-peptide kinetic parameters. Furthermore, HOMA-B and HOMA-IR were applied to estimate beta-cell function and insulin resistance.

A range of liraglutide doses were tested, but in most studies doses were lower than the final doses (0.6, 1.2 and 1.8mg) chosen for the Phase III trials. The dose range in healthy subjects was not higher than 1.4 mg for single dose administration; in multiple dose administration healthy subjects were dosed up to 1.8 mg in three trials.
Studies in healthy volunteers revealed that glucose levels were lower at highest liraglutide dose used (1.4mg) vs. placebo; insulin levels were increased with liraglutide only at elevated glucose levels during IV glucose tolerance test vs. placebo.
Studies in subjects with type 2 DM showed that liraglutide lowers overall glucose levels during 24 hours and suppresses endogenous glucose release. Furthermore, postprandial glucose levels were decreased in a dose-dependent manner. Effects on insulin levels were inconsistent when liraglutide dose of 0,55 mg (0,6 micrg/kg) was used, but increased with higher liraglutide doses. Effects on insulin appeared to be glucose-dependent.
A statistically significantly lower $iAUC_{glucose,0\text{-}5h}$ (27% to 38%) was observed for liraglutide compared to placebo. Fasting insulin concentration ($C_{insulin,0h}$) and maximum insulin concentration ($C_{insulin,max}$) were higher for liraglutide at all three dose levels. Overall, there was a dose-dependent increase in both fasting and postprandial insulin estimates.
After a single dose of 10µg (0.87mg) an increase in insulin secretion rate was seen in the basal period before glucose pulse induction (9-10h post dosing) and there was a trend towards higher insulin levels during glucose pulse induction (10.5-11.5h post dosing). However, in general insulin levels were very similar for placebo and liraglutide.
In all studies, glucose levels following liraglutide were lower compared to placebo.
First and second phase insulin secretion was higher with liraglutide compared to placebo and appeared dose related.
With respect to beta cell function, an increase in HOMA-B was measured, which signifies insulin secretion. HOMA-IR (insulin resistance) did not change. Pro-insulin/insulin ration was decreased with liraglutide. Counter regulation in case of hypoglycaemia seems to be intact. However, the study in

which these parameters were measured only investigated the effects of a low dose (0.68mg) of liraglutide.
Liraglutide has minor effects on gastric emptying, appetite and energy intake. The choice of the doses for the clinical phase III studies is studied further in the therapeutic exploratory studies.

Clinical efficacy

- Dose response studies

The clinical programme included six therapeutic exploratory studies (see table below). These trials were conducted in subjects with type 2 DM previously treated with diet/exercise or oral antidiabetic drug(s) (OADs), and investigated the efficacy and mechanism of actions of liraglutide in patients treated up to 14 weeks. The primary endpoints of these trials were to evaluate the effect and dose-response relationship of liraglutide on glycaemic control and/or body weight in comparison with glimepiride (Trial 1310), metformin (Trials 2072 and 1499), combination of glimepiride and metformin (Trial 1499) and placebo (Trials 1310, 1333 and 1571). As the liraglutide dose in these trials was relatively low, and the duration relatively short, data are considered supportive only to the results of the therapeutic confirmatory studies, providing additional efficacy and safety data (see Supportive studies).
Trials 1571 and 1310 demonstrated a dose response of liraglutide with respect to glycaemic parameters. The lowest dose with efficacy comparable to glimepiride was 0.60 mg; the highest dose of 1.90 mg had only modest additional effect to the dose of 1.25 mg.

Therapeutic Exploratory Trials

Trial ID	No. Subjects Exposed	Treatment	Treatment duration	Primary endpoint
1571	163	Liraglutide 0.65 mg Liraglutide 1.25 mg Liraglutide 1.90 mg Placebo	14 weeks	HbA1c
1310	190	Liraglutide 0.045 mg Liraglutide 0.225 mg Liraglutide 0.45 mg Liraglutide 0.6 mg Liraglutide 0.75 mg Placebo Glimepiride 1-4 mg	12 weeks	HbA1c
1333	33	Liraglutide 0.6 mg Placebo	8 weeks	Body weight
2072	210	Liraglutide 0.045 mg Liraglutide 0.225 mg Liraglutide 0.45 mg Liraglutide 0.6 mg Liraglutide 0.75 mg Metformin 500 mg bid	12 weeks	Body weight
1499	144	Liraglutide (0.5-2.0) + metformin 1g bid Placebo + metformin 1g bid Glimepiride (2-4 mg) + metformin 1g bid Liraglutide (0.5-2.0) + placebo	5 weeks	FSG
1334 (Japan)	226	Liraglutide 0.1 mg Liraglutide 0.3 mg Liraglutide 0.6 mg Liraglutide 0.9 mg Placebo	14 weeks	HbA1c

A clear justification for the chosen dosages of liraglutide 1.2 and 1.8 mg is lacking as most of the pharmacodynamic studies and clinical exploratory trials used lower dose regimens. The CHMP accepted that based on the results from the clinical development programme the observations made in

the early trials performed with lower doses of liraglutide are found to be relevant and transferable to the effects and results obtained in the later long-term confirmatory therapeutic trials using higher doses.
From a pharmacological point of view it is true that a dose-response effect is generally found in the monotherapy trial. However, clinically, results in combination therapy are also relevant. A dose-response effect was seen in the monotherapy trial, but the dose-response was not apparent in combination. As far as the magnitude of the effect can be compared between trials, data suggest that the efficacy of the 1.2 mg is less in the monotherapy trial as compared to the combination trials. The dose-response in the monotherapy trial might be due to this lower efficacy of the 1.2 mg dose.
Overall, percentages of AEs were comparable between doses in the long-term trials. However, there were differences in gastrointestinal (GI) events, especially in trial 1572 (combination with metformin) and trial 1574 (triple therapy with metformin and rosiglitazone). The withdrawals in these trials were higher on liraglutide 1.8 mg.
It is concluded that the results of the pharmacodynamic studies and exploratory trials can be considered supportive and that the chosen dosages of 1.2 and 1.8 mg SC are considered acceptable, however, in the dual and combination treatment, only limited effect can be expected from an increase in dose to 1.8 mg, this is reflected in section 4.2 of the SPC.

- Main studies

Long-term efficacy and safety was initially studied in five therapeutic confirmatory trials (see table below), considered the main trials for this application. In addition to these, another trial (study 1797) was submitted as part of the responses to the Day 120 LoQ. This trial does not add further indications, but provides supportive safety and efficacy data for liraglutide in the treatment of type II diabetes in a non-switching setting (where liraglutide was added to MET, SU or MET+SU). No thorough efficacy discussion was provided during the procedure. As the study design and study results of trial 1797 have not been object of in-depth assessment it is not considered acceptable to draw any efficacy conclusions from this study.
All trials were double-blind (except 1797 which was open-label), randomised, parallel group, multi-centre trials in which the therapeutic response to liraglutide was compared with that of placebo and/or a specific active comparator drug.

Key Features of the Liraglutide Therapeutic Confirmatory Trials

Trial ID	No. Subjects Exposed	Treatment	Treatment Duration	Primary Endpoint
Monotherapy				
1573	Total: 745 Liraglutide 1.2 mg: 251 Liraglutide 1.8 mg: 246 Glimepiride: 248	Liraglutide 6 mg/mL (1.2 or 1.8 mg/day, s.c., q.d.) Glimepiride tablets (8 mg/day, p.o., q.d.) No protocol defined concomitant treatment	52 weeks (+ 48 months open-label extension)	Change in HbA1c after 52 weeks
Dual therapy				
1572	Total: 1087 Liraglutide 0.6 mg + metformin: 242 Liraglutide 1.2 mg + metformin: 240 Liraglutide 1.8 mg + metformin: 242 Metformin: 121 Glimepiride + metformin: 242	Liraglutide 6 mg/mL (0.6, 1.2 or 1.8 mg/day, s.c., q.d.) Metformin tablets (2 g/day, p.o., b.i.d.) Glimepiride tablets (4 mg/day, p.o., q.d.)	26 weeks (+ 18 months open-label extension)	Change in HbA1c after 26 weeks
1436	Total: 1040 Liraglutide 0.6 mg + glimepiride: 233 Liraglutide 1.2 mg + glimepiride: 228 Liraglutide 1.8 mg + glimepiride: 234 Glimepiride: 114 Rosiglitazone + glimepiride: 231	Liraglutide 6 mg/mL (0.6, 1.2 or 1.8 mg/day, s.c., q.d.) Glimepiride tablets (4 mg/day, p.o., q.d.) Rosiglitazone tables (4 mg/day, p.o., q.d.)	26 weeks	Change in HbA1c after 26 weeks

Triple therapy				
1574	Total: 530 Liraglutide 1.2 mg + metformin + rosiglitazone: 177 Liraglutide 1.8 mg + metformin + rosiglitazone: 178 Metformin + rosiglitazone: 175	Liraglutide 6 mg/mL (1.2 or 1.8 mg/day, s.c., q.d.) Metformin tablets (2 g/day, p.o., b.i.d.) Rosiglitazone tablets (8 mg/day, p.o., b.i.d.) No active control	26 weeks	Change in HbA1c after 26 weeks
1697	Total: 576 Liraglutide 1.8 mg + metformin + glimepiride: 230 Metformin + glimepiride: 114 Insulin glargine + metformin + glimepiride: 232	Liraglutide 6 mg/mL (1.8 mg/day, s.c., q.d.) Metformin tablets (2 g/day, p.o., b.i.d.) Glimepiride tablets (4 mg/day, p.o., q.d.) Insulin glargine (100 IU/mL) (individual titration, s.c., q.d.)	26 weeks	Change in HbA1c after 26 weeks
In response to Day 120 List of Questions:				
1797	Total: 467 Liraglutide 1.8 mg + OAD: 235 Exenatide 20 µg + OAD: 232	Liraglutide 6 mg/mL (1.8 mg/day, s.c., q.d.) Exenatide 10 µg/dose (20 µg/day, s.c., b.i.d) Metformin tablets (prestudy dose level to be kept throughout trial) Sulfonylurea tablets (pre-study dose level could be reduced to no less than 50%)	26 weeks	Change in HbA1c after 26 weeks

1573
Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on glycaemic control of liraglutide versus glimepiride in type 2 diabetes.
Conducted at 138 sites in the US and Mexico.
Study period: 7 February 2006 - 2 November 2007

1572
Liraglutide Effect and Action in Diabetes (LEAD-2): Effect on glycaemic control after once daily administration of liraglutide in combination with metformin versus metformin monotherapy versus metformin and glimepiride combination therapy in subjects with type 2 diabetes.
Conducted at 170 centres in 21 countries, mainly in Europe as well as in Croatia, Australia, Russia, South Africa, India, New Zealand, Argentina.
Study period: 30 May 2006 to 04 May 2007

1436
Liraglutide Effect and Action in Diabetes (LEAD-1): Effect on glycaemic control after once daily administration of liraglutide in combination with glimepiride versus glimepiride monotherapy versus glimepiride and rosiglitazone combination therapy in subjects with type 2 diabetes.
Conducted at 116 centers in Europe, Turkey, Croatia, Switzerland, Argentina, Hong Kong, India, Korea, Malaysia, Philippines, Taiwan, Thailand, and South Africa.
Study period: 29 May 2006 to 07 May 2007

1574
Liraglutide Effect and Action in Diabetes (LEAD 4): Effect on glycaemic control of liraglutide in combination with rosiglitazone plus metformin versus rosiglitazone plus metformin in type 2 diabetes.
Conducted at 96 centers in USA and Canada.
Study period: 30 May 2006 to 14 August 2007

1697
Liraglutide Effect and Action in Diabetes (LEAD-5): Effects on glycaemic control after once daily administration of liraglutide in combination with glimepiride and metformin versus glimepiride and

metformin combination therapy, and versus insulin glargine added to glimepiride and metformin combination therapy in subjects with type 2 diabetes.
Conducted at 107 centers in 17 countries in Europe as well as Russia, Serbia and Montenegro, Argentina, India, Philippines, and South Africa.
Study period: 30 May 2006 to 20 April 2007

1797
Liraglutide Effect and Action in Diabetes (LEAD-6): Effect on glycaemic control of liraglutide or exenatide added to metformin, sulphonylurea or a combination of both in subjects with type 2 diabetes.
Conducted at 133 centers in 15 countries in Europe as well as Switzerland, The Former Yugoslav Republic of Macedonia, and the USA.
Study period: 24 August 2007 to 9 April 2008

METHODS

Study Participants
All the trials were similar in design. Subjects with type 2 DM, aged between 18 and 80 years were included and stratified with respect to previous diabetes treatment.
Most of the subject selection criteria were the same in all trials.
With respect to previous antidiabetic therapy and baseline HbA_{1c}, the inclusion criteria differed among trials, reflecting the different treatment combinations being studied:

- Trial 1573 included subjects treated with diet/exercise or one OAD for at least two months. If treated with an OAD (sulphonylureas, meglitinides, amino acid derivatives, biguanides, alphaglucosidase inhibitors or thiazolidinediones), the dose was to be no more than half maximal dose, except subjects previously treated with metformin (≤1500 mg) or pioglitazone (≤30 mg). HbA_{1c} at screening was to be in the range 7.0–11.0% for subjects on diet/exercise treatment and 7.0–10.0% for subjects on OAD therapy.
- Trials 1572 and 1436 included subjects treated with OAD(s) for at least 3 months. HbA_{1c} at screening was to be in the range 7.0–11.0% for subjects on OAD monotherapy and 7.0–10.0% for subjects on OAD combination therapy.
- Trial 1574 included subjects treated with OAD(s) and/or exenatide for at least 3 months. HbA_{1c} at screening was to be in the range 7.0–11.0% for subjects on OAD monotherapy or exenatide therapy alone and 7.0–10.0% for subjects on combination therapy including OADs and/or exenatide.
- Trial 1697 included subjects treated with OAD(s) for at least 3 months. HbA_{1c} at screening was to be in the range 7.5–10.0% for subjects on OAD monotherapy and 7.0–10.0% for subjects on OAD combination therapy.
- Trial 1797 included subjects treated with metformin, SU or a combination for at least 3 months on maximally tolerated doses. HbA_{1c} at screening was to be in the range of 7.0-11.0% (both inclusive).

Patients on insulin therapy and with renal or liver dysfunction or with active cardiovascular disease including history of myocardial infarction within the past 6 months and/or heart failure (New York Heart Association class III and IV) were among the exclusion criteria.

Treatments
Three liraglutide doses (0.6, 1.2 and 1.8 mg) were evaluated in Trials 1572 and 1436, whereas Trials 1573 and 1574 investigated the two proposed therapeutic doses, 1.2 and 1.8 mg and Trial 1697 investigated only the 1.8 mg dose. Study 1797 only investigated the 1.8 mg dose. In order to mitigate GI symptoms related to initiation of treatment at higher doses, a step-wise titration scheme was employed. All subjects initiated treatment at liraglutide 0.6 mg, increasing to 1.2 mg after one week and to 1.8 mg after one additional week, according to the dose level they were randomised to. Administration could be at any time of the day. Still, subjects were encouraged to inject liraglutide at the same time of the day during the whole treatment period.
Trial 1573 was extended to a total of 5 years and Trial 1572 was extended to a total of 2 years. Trial 1573 is still ongoing.

The chosen dosing of the comparators in study 1573, in 1697 and in 1436 was questioned during the assessment. Glimepiride 8 mg was used as comparator in 1573 (see Clinical safety, section Hypoglycaemic episodes).

For insulin glargine in study 1697 the treatment was titrated twice weekly for the first 8 weeks. There after the fasting plasma glucose (FPG) was to be measured and the dose of insulin glargine to be potentially revised at least at visits 8 (week 12) and 9 (week 18) but otherwise at the discretion of the investigator. Evidence was provided to support that effective dose titration (AT.LANTUS treatment algorithm) of insulin glargine was undertaken in trial 1697. This titration algorithm is reflected in section 5.1 of the SPC.

The dose of rosiglitazone in trial 1436 was 4 mg daily, a rather low dose. In Trial 1574 the maximal dose of 8mg/day rosiglitazone was used. Therefore, the comparison with rosiglitazone should be made keeping in mind the fact that the dose in Trial 1436 was low, while the dose in trial 1574 was the right one for Europe (see Results section).

The trial designs are not in line with the design recommended in the CHMP "Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus" (CHMP/EWP1080/00). According to the guideline add-on studies should be carried out by adding the new drug to non-responders of the first drug which is not the case in the present trials. The study design for trials 1572, 1436, and 1574 represented a switch-over scenario for a large portion of included subjects rather than an add-on scenario. Furthermore the guideline states, that it would be desirable to select patients who did not need any change or adjustment in previous medication during the 8-12 weeks preceding the study to ensure that the maximal effect of the previous medication has been observed and that HbA_{1c} is stabilised at baseline. In the present studies patients with elevated HbA_{1c} at inclusion and elevated FPG at randomisation could have been treated with any OAD(s) previously. In response to this concern a post-hoc analyses as well as supportive efficacy data from study 1797 were provided that supported that the switch-over trial design had no major impact on the results of HbA_{1c} change, in view of which the issue was regarded as resolved.

Objectives and endpoints
The primary objective of the therapeutic confirmatory trials was to assess the effect of liraglutide on glycaemic control as measured by change in HbA_{1c} in subjects with type 2 DM. Change in body weight was a key secondary endpoint in all trials. Other secondary endpoints were FPG, postprandial glucose and blood pressure.

Safety endpoints were:
- incidence of hypoglycaemic episodes
- formation of liraglutide and exenatide (study 1797) antibodies
- safety and tolerability of liraglutide in combination with glimepiride and metformin (1697)/ glimepiride (1436)/ metformin (1572)

Sample size
The sample size calculations were based on standard normal theory. For change from baseline HbA_{1c}, the non-inferiority margin was set 0.4% and the difference to detect superiority against placebo was set to 0.5% and a standard deviation 1.2 or 1.3%. For body weight, a CV of 3% was assumed (based on liraglutide phase 2 trials) and the difference to detect was set to 3%. A combined power (calculated as the product of the marginal powers for HbA_{1c} and weight) of at least 85% was required. Drop-out rates of 25% or 30% were accounted for.

Randomisation and blinding
In Trials 1573 and 1574 randomisation was 1:1:1. In Trial 1797 patients were randomized in a 1:1 manner. In Trials 1572 and 1436 it was 2:2:2:1:2 and in Trial 1697 it was 2:1:2. The latter three trials had half the number of subjects in the placebo treatment arms in order to maximise exposure to liraglutide and the active comparator drug while maintaining statistical integrity.

All trials except study 1797 were double-blind with regard to liraglutide treatment (active or placebo). For the active comparators in Trials 1573, 1572 and 1436, blinding was ensured by applying a double-dummy technique (i.e. administering active treatment/placebo for both liraglutide and the active comparator). The active comparator in Trial 1697, insulin glargine, was administered open-label. The OAD treatments administered in all treatment arms within a trial were given open-label.

Statistical methods
The primary objective of the therapeutic confirmatory trials was to demonstrate that glycaemic control, measured by change from baseline in HbA_{1c}, achieved with liraglutide treatment was superior to placebo treatment (not applicable for Trials 1573 and 1797) and non-inferior to the comparator (not applicable for Trial 1574), with a non-inferiority margin of 0.4%. If non-inferiority compared to the active comparator was demonstrated, superiority to the comparator treatment was tested.
Superiority/non-inferiority were tested at 2.5% significance level using the 95% confidence interval (CI) for the appropriate difference: if 95% CI upper limit for the decrease of HbA_{1c} is below 0% or 0.4%, superiority or non-inferiority is claimed, respectively.

The differences between treatments in primary and other endpoints were estimated using an ANCOVA model with treatment, country and previous antidiabetic treatment as fixed effects and baseline (if applicable) as covariate.

The type I error for testing 1) superiority against placebo and 2) non-inferiority against comparator is protected at 2.5% because 2) is only declared if 1) and 2) are significant.
Switching from non-inferiority to superiority for the comparison with comparator is a closed testing procedure and therefore protects the type I error.
As more than one dose level of liraglutide was investigated, hypothesis testing was performed hierarchically (pre-defined sequence) for descending doses of liraglutide in order to protect the family wise type I error. To this end, hierarchical testing or an extension of this (Edwards et al. Statistics in Medicine, 2007, 26, p.5116-5124) was used. The handling of multiplicity was considered well-planned and performed

Efficacy analyses were based on the ITT analysis set (all subjects randomised and exposed to treatment). No interim analyses were planned or performed. A safety committee monitored the trial.

Missing data were imputed using the last observation carried forward (LOCF). A completers analysis was used as sensitivity analysis. No other method for imputating missing data was planned as a sensitivity analysis. During the assessment it was ~~is~~ unclear whether subjects withdrawn due to ineffective therapy received rescue medication, and if withdrawn subjects were still monitored after their withdrawal. To assess the sensitivity of the results different sensitivity analyses were requested showing that the primary analysis (ANCOVA with LOCF) was acceptable.

The changes made to the analysis plan are considered non-essential.

RESULTS

Participant flow
In the five long-term therapeutic confirmatory trials (1573, 1572, 1436, 1574 and 1697), a total of 3992 subjects were randomized, 3987 were exposed to treatment and 3190 completed. Of the 3987 subjects exposed, 2501 were exposed to liraglutide and of these 2041 completed. Most of the withdrawals in the liraglutide treatment groups occurred in the first 1–3 months.
Numbers of patients in the placebo group are smaller than in active treatment groups. This has been done in order to maximise exposure to liraglutide and the active comparator. The liraglutide 0.6 mg group is also relatively small, but this dose is not submitted for registration. Percentages of subjects who completed the trials differed somewhat between trials, but are acceptable. There were less completers in the placebo group compared to the liraglutide groups and active comparators due to ineffective therapy.
The following table shows the subject disposition of the trials.

Subject disposition in the five confirmatory trials (trial 1573, 1572, 1436, 1574 and 1697)

	Liraglutide 0.6 mg N (%)	Liraglutide 1.2 mg N (%)	Liraglutide 1.8 mg N (%)	Placebo N (%)	Active Comparator N (%)	Total N (%)
Trial 1573						
Randomized		251(100.0)	247(100.0)		248(100.0)	746(100.0)
Exposed		251(100.0)	246(99.6)		248(100.0)	745(99.9)
Withdrawals		89(35.5)	74(30.0)		96(38.7)	259(34.7)
Adverse Events		25(10.0)	18(7.3)		15(6.0)	58(7.8)
Non-compliance with the protocol		11(4.4)	11(4.5)		5(2.0)	27(3.6)
Ineffective therapy		15(6.0)	9(3.6)		25(10.1)	49(6.6)
Other		38(15.1)	36(14.6)		51(20.6)	125(16.8)
Completers		162(64.5)	173(70.0)		152(61.3)	487(65.3)
Trial 1572						
Randomized	242(100.0)	241(100.0)	242(100.0)	122(100.0)	244(100.0)	1091(100.0)
Exposed	242(100.0)	240(99.6)	242(100.0)	121(99.2)	242(99.2)	1087(99.6)
Withdrawals	34(14.0)	44(18.3)	51(21.1)	48(39.3)	34(13.9)	211(19.3)
Adverse Events	11(4.5)	23(9.5)	29(12.0)	2(1.6)	8(3.3)	73(6.7)
Non-compliance with the protocol	2(0.8)	4(1.7)	4(1.7)	4(3.3)	5(2.0)	19(1.7)
Ineffective therapy	19(7.9)	8(3.3)	13(5.4)	29(23.8)	9(3.7)	78(7.1)
Other	2(0.8)	9(3.7)	5(2.1)	13(10.7)	12(4.9)	41(3.8)
Completers	208(86.0)	197(81.7)	191(78.9)	74(60.7)	210(86.1)	880(80.7)
Trial 1436						
Randomized	233(100.0)	228(100.0)	234(100.0)	114(100.0)	232(100.0)	1041(100.0)
Exposed	233(100.0)	228(100.0)	234(100.0)	114(100.0)	231(99.6)	1040(99.9)
Withdrawals	25(10.7)	32(14.0)	21(9.0)	31(27.2)	38(16.4)	147(14.1)
Adverse Events	5(2.1)	11(4.8)	9(3.8)	6(5.3)	7(3.0)	38(3.7)
Non-compliance with the protocol	3(1.3)	5(2.2)	3(1.3)	2(1.8)	6(2.6)	19(1.8)
Ineffective therapy	12(5.2)	8(3.5)	7(3.0)	20(17.5)	16(6.9)	63(6.1)
Other	5(2.1)	8(3.5)	2(0.9)	3(2.6)	9(3.9)	27(2.6)
Completers	208(89.3)	196(86.0)	213(91.0)	83(72.8)	194(83.6)	894(85.9)

	Liraglutide 0.6 mg N (%)	Liraglutide 1.2 mg N (%)	Liraglutide 1.8 mg N (%)	Placebo N (%)	Active Comparator N (%)	Total N (%)
Trial 1574						
Randomized		178(100.0)	178(100.0)	177(100.0)		533(100.0)
Exposed		177(99.4)	178(100.0)	175(98.9)		530(99.4)
Withdrawals		25(14.0)	45(25.3)	56(31.6)		126(23.6)
Adverse Events		11(6.2)	27(15.2)	6(3.4)		44(8.3)
Non-compliance with the protocol		4(2.2)	4(2.2)	5(2.8)		13(2.4)
Ineffective therapy		3(1.7)	3(1.7)	29(16.4)		35(6.6)
Other		7(3.9)	11(6.2)	16(9.0)		34(6.4)
Completers		153(86.0)	133(74.7)	121(68.4)		407(76.4)
Trial 1697						
Randomized			232(100.0)	115(100.0)	234(100.0)	581(100.0)
Exposed			230(99.1)	114(99.1)	232(99.1)	576(99.1)
Withdrawals			25(10.8)	19(16.5)	15(6.4)	59(10.2)
Adverse Events			11(4.7)	1(0.9)	5(2.1)	17(2.9)
Non-compliance with the protocol			1(0.4)	1(0.9)	5(2.1)	7(1.2)
Ineffective therapy			2(0.9)	13(11.3)	1(0.4)	16(2.8)
Other			11(4.7)	4(3.5)	4(1.7)	19(3.3)
Completers			207(89.2)	96(83.5)	219(93.6)	522(89.8)

In study 1797 a total of 663 subjects were screened, and 464 randomised: 233 to liraglutide+OAD and 231 to exenatide+OAD. There were 33 (14%) and 45 (19.4%) withdrawals in the liraglutide group and exenatide group respectively. Most common reasons for withdrawal were adverse events: 23 (9.8%) and 31 (13.4%) respectively in the liraglutide and exenatide groups.

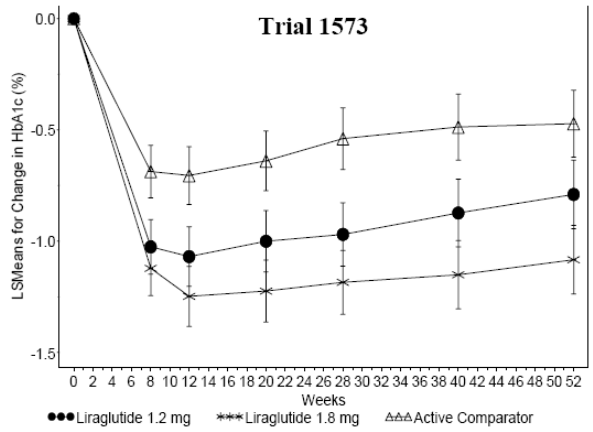
Conduct of the study
Protocol amendments were made to all studies during their conduct, none of them however influenced the quality of the study or the results in a negative way.

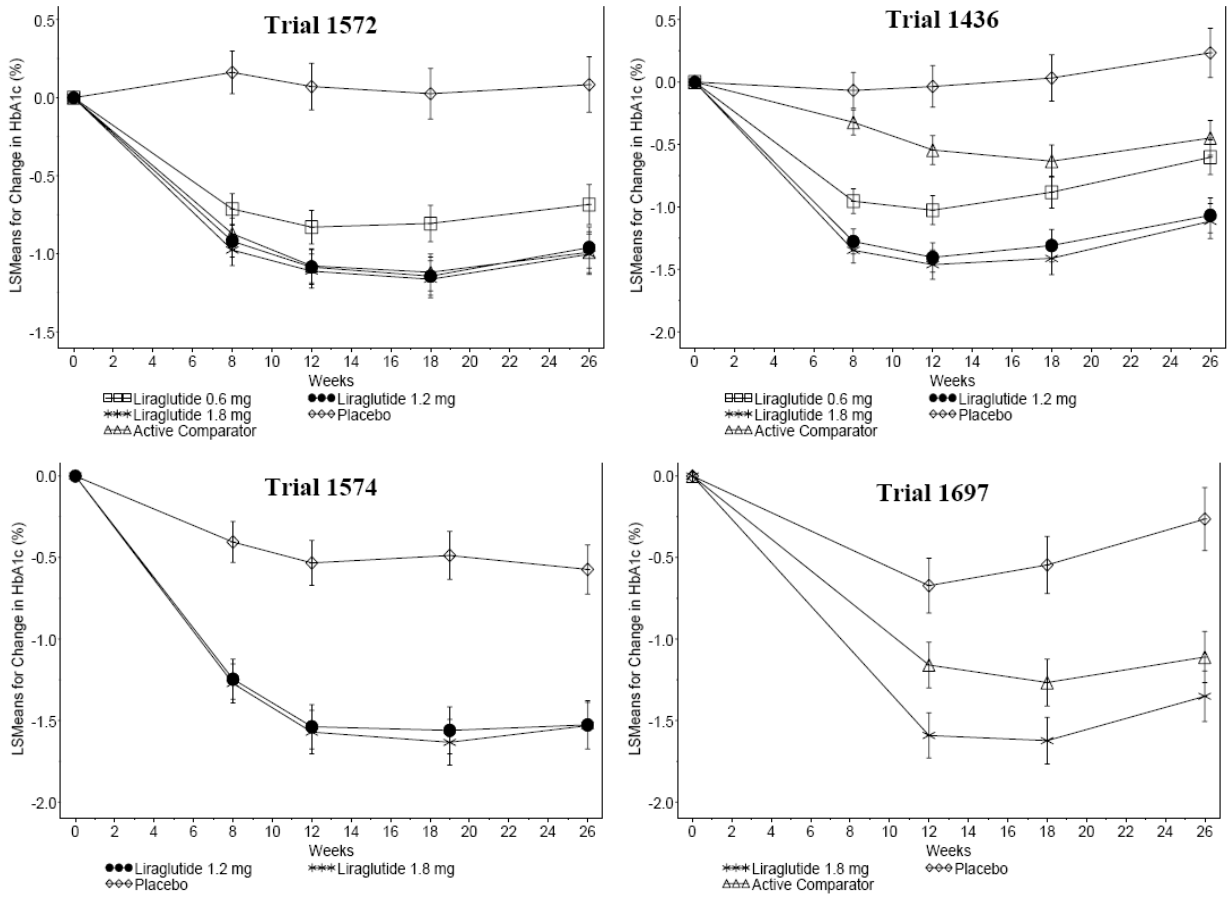
Baseline data
The treatment arms within each trial were generally well matched with regard to baseline demographics. Mean age was approximately 55 years, ranging from 19–80 years. Mean body weight ranged from approximately 80–100 kg. Trial 1436 had a relatively high percentage of subjects of Asian origin which explains why mean body weight at baseline was slightly lower in this trial (approximately 82 kg) compared with the remaining trials (approximately 85–95 kg). Mean BMI ranged from approximately 30 to 35 kg/m^2. Treatment groups were not stratified by gender in any of the trials, but men and women were generally equally distributed in all trials.
The distribution of race was generally comparable among treatment groups within each trial. Within trials, all baseline diabetes characteristics were generally comparable among treatment groups in all the therapeutic confirmatory and exploratory trials.
Overall, the majority of subjects in the therapeutic confirmatory trials had been treated with OAD mono- or combination therapy for at least 3 months before entering the trial. An exception was Trial 1573, in which subjects had previously been treated with either diet and exercise (36%) or OAD monotherapy (64%) for at least 2 months.
Between trials, duration of diabetes was different, as expected duration was shorter in the monotherapy trial and longer in the triple therapy trial.

Outcomes and estimation

HbA_{1c}
Change in HbA_{1c} was the primary endpoint in all studies. The following figure provides an overview of estimated mean change in HbA_{1c} over time for the five main long-term studies.

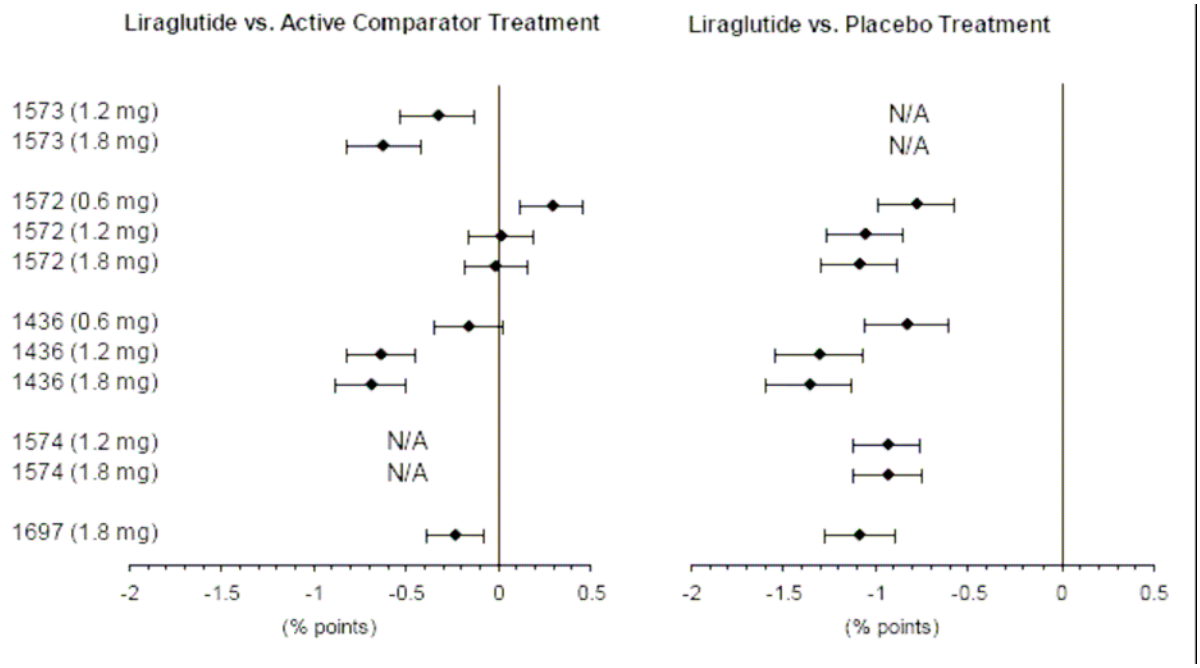
Estimated Mean Change in HbA1c Over Time (± 2 SEM) – Therapeutic Confirmatory Trials. Note the difference in X-axis for trial 1573





The following figure provides an overview of the treatment comparisons with the active comparator and placebo.

Forest Plot of HbA1c (%) Analysis, Estimated Mean Difference ± 95%CI –Therapeutic Confirmatory Trials (LOCF, ITT Analysis Set)



The following table presents the analysis of change in HbA_{1c} from baseline. Used as **monotherapy** (trial 1573), liraglutide 1.2 and 1.8 mg was more effective than glimepiride 8 mg daily, although this dose of 8 mg glimepiride is high for Europe. In addition, liraglutide 1.8 mg resulted in significantly

lower HbA_{1c} values compared to liraglutide 1.2 mg. A comparison with metformin would have been preferred as metformin is currently the first choice of treatment in type 2 DM.

Given in **dual therapy**, liraglutide+metformin (trial 1572) was equally effective as metformin+glimepiride; liraglutide+glimepiride (trial 1436) was more effective than glimepiride+rosiglitazone. The dose of rosiglitazone in this trial (4mg) was rather low. It is acknowledged that the highest approved dose could not be exceeded in the participating countries, which is 4mg in some countries. However, for rosiglitazone a dose-response was clearly demonstrated as greater decreases in HbA_{1c} and FPG were observed at the 8 mg rosiglitazone dose compared to the 4 mg dose. The dose of rosiglitazone however was considered low; in which case the safety of rosiglitazone arm may have been enhanced, but the efficacy may also have been decreased. This issue is resolved by SPC changes. The duration of the trial was also rather short (26 weeks) taking into account that the efficacy of rosiglitazone is expected to be more pronounced after one year, therefore limiting conclusions. It should be noted that dual therapy when added to rosiglitazone has not been studied. In trials 1572 and 1436 no difference was observed between liraglutide 1.8 and 1.2 mg. Liraglutide 1.2 mg lowered HbA_{1c} significantly more than treatment with liraglutide 0.6 mg.

The initially claimed indication of liraglutide as add-on therapy to a thiazolidinedione was based on an extrapolation of efficacy and safety data from trial 1572 and trial 1574, and that the efficacy of liraglutide was independent of metformin being part of the background antidiabetic therapy. This extrapolation was not considered correct. Furthermore, study populations differed with respect to duration of diabetes and background anti-diabetic treatment. In view of these points this indication was not granted.

In **triple therapy** liraglutide+metformin+rosiglitazone (trial 1574) was more effective than dual therapy with metformin+rosiglitazone. Here again, there was no difference in effect between the two liraglutide doses. The combination of liraglutide+metformin+glimepiride (trial 1679) resulted in lower HbA_{1c} values than insulin+ metformin+glimepiride.

Analysis of HbA_{1c} (%) Change from Baseline – Therapeutic Confirmatory Trials (LOCF, ITT Analysis Set)

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

The P-values corresponds to a two-sided test for superiority on a 5% significant level (statistical significance for p <0.05).
Test for non-inferiority with switch to superiority if non-inferiority is shown.
Non-inferiority is concluded if the upper limit of the 95% confidence interval for the treatment difference is below 0.4%, i.e. non-inferiority to comparator is shown for all liraglutide groups, except for the 0.6mg liraglutide group in trial 1572.
A hierarchical testing procedure is used.

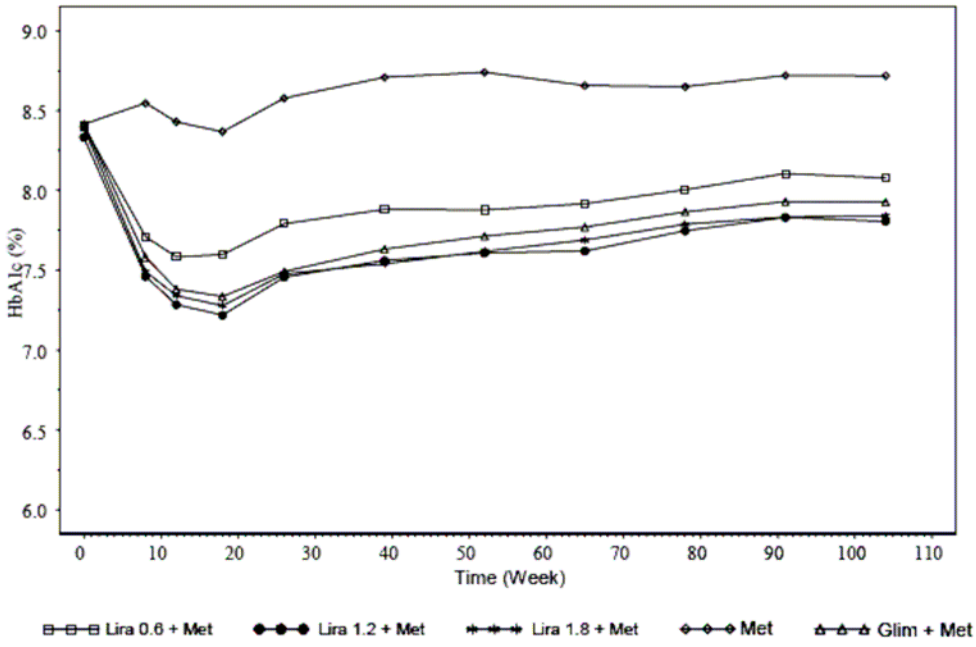
The percentages of subjects who reached the pre-defined ADA target for HbA_{1c} (<7%) are shown in following table. This effect was most pronounced in subjects previously treated with diet/exercise (Trial 1573) or one OAD (Trials 1572 and 1436) at entry into the trial.

Percentage of Subjects Achieving ADA Target (HbA1c <7%) – Therapeutic Confirmatory Trials (LOCF, ITT Analysis Set)

Trial ID	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo	Active Comparator
1573					
All subjects (%)	NA	42.8	50.9	NA	27.8
Previously diet-treated subjects (%)		58.3	62.0		30.8
1572					
All subjects (%)	28.0	35.3	42.4	10.8	36.3
Previously OAD monotherapy subjects (%)	43.2	52.8	66.3	22.5	56.0
1436					
All subjects (%)	24.1	34.5	41.6	7.5	21.9
Previously OAD monotherapy subjects (%)	32.4	57.4	55.9	11.8	36.1
1574					
All subjects (%)	NA	57.5	53.7	28.1	NA
1697					
All subjects (%)	NA	NA	53.1	15.5	45.8

Long-term data (2-year) were submitted in response to Day 180 List of Outstanding Issues for Trial 1573 (monotherapy) and 1572 (add-on to metformin). Results of trial 1572 are shown in the figure below. HbA_{1c} increases after 20 weeks. However, the difference between the liraglutide groups compared to the control is persistent.

HbA1c Mean HbA1c by Treatment and Week (LOCF), Trial 1572, ITT Population



Cross-reference: Clinical Trial Report for Trial 1572 (Module 5, Section 5.3.5.1)

Data was provided showing no statistically significant difference in the HbA_{1c} lowering effect of liraglutide 1.2mg and 1.8mg when administered in the morning vs. in the evening as the preferred dosing time. However, it is preferable that Victoza is injected around the same time of the day, when the most convenient time of the day has been chosen; this is reflected in section 4.2 of the SPC.

Separate efficacy results for patients on previous combination OADs (dual and triple or more OADs) for study 1697 were requested by the CHMP. In this study 84% (N=486) of the subjects were previously treated with a dual OAD combination therapy and 10% (N=57) were previously treated with OAD combination therapy of 3 or more OADs. The percentage of subjects on previous OAD monotherapy, dual OAD therapy or triple OAD therapy was comparable across the three treatment groups with the majority of patients on previous dual therapy. As expected, the HbA_{1c} improvements for patients on previous triple therapy were less than for dual therapy patients for the active treatment groups and a slight rise was noted for patients in the placebo group. No significant differences in HbA_{1c} improvement were noted between liraglutide and placebo and liraglutide and active comparator, respectively, in the few previous monotherapy patients.

Fasting plasma glucose
In all five long-term therapeutic confirmatory trials, treatment with liraglutide (alone or in combination with one or two OADs) led to a lowering of FPG ranging from 0.72 to 2.42 mmol/L (13–44 mg/dL) within the first 2–4 weeks of treatment. Baseline values were around 9–10 mmol/L (162–180 mg/dL). The decrease in FPG was maintained throughout the treatment period. The comparisons to placebo (not applicable to trial 1573) were significantly in favour of liraglutide, whereas the analysis against comparators (not applicable for trial 1574) only showed significance for trial 1573 and trial 1436 (liraglutide 1.2 and 1.8 mg).

Body Weight
Treatment with liraglutide as monotherapy or in combination with one or two OADs induced weight loss within the first 8 weeks of treatment which overall was maintained for the rest of the treatment period. Weight loss was highest in the monotherapy trial (1573) and add-on to metformin trial (1572), with a mean loss of 2-2.5 kg. A potential relationship between the observed weight loss and prolonged duration of nausea was investigated by analysis of the change in body weight by different durations and onsets of nausea. It was concluded that no relationship was found between the occurrence of GI events, their duration and the change in body weight.

Beta cell function
The effect of liraglutide on beta-cell function and insulin sensitivity was examined by means of the homeostasis model assessment index of beta-cell function (HOMA-B), homeostasis model assessment index of insulin resistance (HOMA-IR) and measurement of pro-insulin. However, these are inadequate measures (the HOMA-IR is a measure of insulin resistance and not insulin secretion). For a reliable evaluation of the impact on the pancreatic beta-cell function dynamic estimates from an intravenous glucose tolerance test (IVGTT) or clamps would be necessary. In some studies significant effects were observed, but in general changes were small and results influenced by the choice of the comparator or baseline therapy. In response to this concern data from phase 1 and 2 studies as well as from study 1573 (monotherapy) was provided, suggesting that liraglutide improves beta-cell function, however, this data was considered limited and not to have been substantiated by robust and reliable results from the 5 long-term phase III trials. The results are difficult to interpret and measures inadequate for final conclusions on the effect of liraglutide on the progression of the disease.

Gastric emptying
A minor delay in the postprandial rate of gastric emptying was observed at liraglutide dose of 0.9 mg and above.
Due to the risk of delayed gastric emptying section 4.5 of the SPC includes a warning regarding a potential interaction with active substances with poor solubility or with narrow therapeutic index such as warfarin. This warning includes a recommendation to monitor INR more frequently upon initiation of liraglutide treatment.

Ancillary analyses

- Analysis performed across trials

To assess whether demographic factors played a role in the therapeutic confirmatory trials, statistical tests for interaction on glycaemic response as measured by HbA_{1c} were performed among treatment and different baseline demographic characteristics. The analyses were carried out on both data from

the individual trial as well as on pooled data from the four 26-weeks combination therapy trials (Trials 1572, 1436, 1574 and 1697).
The difference among treatments in glycaemic response did not depend on gender or age, ethnicity, race, BMI, body weight (except trial 1436). For subjects above 90 kg change in HbA_{1c} was larger with increasing liraglutide dose, demonstrating an advantage with the highest dose of 1.8 mg for these subjects when used in combination with glimepiride. It should be noted that only approximately 1/3 of the subjects had a body weight above 90 kg.

- Clinical studies in special populations

No studies in special populations have been submitted.

It was demonstrated that in patients with impaired renal and hepatic function, exposure of liraglutide in these groups of patients is reduced by 14-33% and 13-44% respectively.

Hepatic impairment (defined as ALAT levels ≥ 2.5 times ULN) was an exclusion criterion in the 5 confirmatory studies. In spite of this, 312 subjects with ALAT levels >UNR were included in the long-term trials. Efficacy data were provided for these patients. However, ALAT has limitations as regards to categorising patients as having mild, moderate or severe hepatic impairment. In addition, no differentiation was made as to whether the elevated ALAT-levels were due to acute or chronic alterations.
Child-Pugh scoring system was applied (post-hoc) to the 312 subjects, as two out of the five Child-Pugh parameters were systematically collected as part of the long-term clinical trials namely albumin and bilirubin. Ten subjects were identified to have mild hepatic impairment; however, the score could also have been moderate. It is concluded that the use of liraglutide in patients with any degree of hepatic impairment can currently not be recommended.

Renal impairment was also an exclusion criterion, defined by serum creatinine, in the five confirmatory trials. Nevertheless, when evaluating estimated creatinine clearance using the Cockroft-Gault formula, 659 patients with mild or moderate decreased renal function appeared to be included.
As regards efficacy (change in HbA_{1c}) of liraglutide in patients with mild renal impairment sufficient data has been presented to support the use of liraglutide in this patient group. The change in HbA_{1c} in liraglutide treated patients with mild renal impairment was similar to the change observed in the overall liraglutide treated population. No dose adjustment is required for patients with mild renal impairment (creatinine clearance ≤ 60-90 mL/min). There is very limited therapeutic experience in patients with moderate renal impairment (creatinine clearance of 30-59 mL/min) and no therapeutic experience in patients with severe renal impairment (creatinine clearance below 30 mL/min).

Data was provided for **age** groups (<60, >60, >70, >75). Results on HbA_{1c} were comparable between age groups, but an increase in total adverse event rate was seen in the liraglutide group while no such an increase was observed in the active comparator group and total comparator group (see safety section). In addition, the number of patients > 75 years of age was very low.

- Supportive studies

In addition to the therapeutic confirmatory trials, six therapeutic exploratory trials (Trials 1571, 1310, 1333, 2072, 1499 and 1334 (Japan) provide additional efficacy and safety data (see Dose response studies). These trials investigated the efficacy and mechanism of actions of liraglutide in subjects with type 2 diabetes mellitus treated up to 14 weeks. The primary endpoints were to evaluate the effect and dose-response relationship of liraglutide on glycaemic control and/or body weight. Secondary endpoints included in these trials were change in FPG or fasting serum glucose (FSG), and pancreatic beta-cell function and insulin sensitivity.

Baseline demographics
In the therapeutic exploratory trials 1571, 1310, and 1333, all or close to 100% of the subjects were White/Caucasian. In Trial 2072, approximately 80% of subjects were White/Caucasian and the remaining were of Black or Hispanic origin. In Trial 1499, the majority (86%) of subjects were White. In Trial 1334 all subjects were Japanese.

Baseline diabetes characteristics
The majority of subjects had previously been treated with OAD mono- or combination therapy. In Trials 1571 and 1310 a fraction of the subjects (19% and 18%, respectively) had previously been treated with diet and exercise, whereas in Trial 1334 (Japanese) this population constituted 54% of the subjects.

Subjects disposition and analysis of withdrawals
All trials had a high completion rate. The overall number of withdrawals within each trial was generally comparable among treatment groups. The majority of withdrawals in the liraglutide groups occurred in the beginning of the treatment period and were due primarily to 'Other' reasons or 'Adverse events', primarily GI adverse events. In the trials that investigated lower dose levels of liraglutide (0.045–0.6 mg, Trials 1310 and 2072) withdrawals due to 'Ineffective therapy' increased with lower dose level. In OAD treated groups the primary reason for withdrawal was 'Ineffective therapy'.

HbA_{1c}
Glycaemic control was investigated. In these phase 2 trials the duration of treatment ranged from 5 to 14 weeks and liraglutide dose levels ranged from 0.045 to 2.0 mg. Five trials evaluated liraglutide monotherapy. Trial 1499, in addition to liraglutide monotherapy, also evaluated the combination with metformin.

Trial 1571 showed that 14 weeks of liraglutide monotherapy at doses 0.65, 1.25 or 1.9 mg resulted in a decrease in HbA_{1c} statistically significantly different from the increase in HbA_{1c} observed in the placebo group.

Trials 1310 and 2072 evaluated monotherapy in the dose range 0.045–0.75 mg. In Trial 1310 the two highest liraglutide dose levels (0.6 and 0.75 mg) resulted in a glycaemic control comparable to that of glimepiride (1-4 mg/day). In trial 2072 the three highest liraglutide dose levels (0.45, 0.6 and 0.75 mg) resulted in a glycaemic control comparable to that of metformin (1000 mg/day).

In Trial 1333, 8 weeks of liraglutide 0.6 mg monotherapy resulted in a decrease in HbA_{1c} significantly different from the increase in HbA_{1c} with placebo ($p=0.0281$).

In Trial 1334 (Japanese), 14 weeks of treatment with liraglutide at the dose levels 0.1, 0.3, 0.6 and 0.9 mg was found to lower HbA_{1c} in a linear fashion where HbA_{1c} decreased with increasing doses of liraglutide ($p<0.0001$).

Five weeks of treatment with liraglutide, individually dosed in the range 0.5–2.0 mg, in combination with metformin (Trial 1499) was shown to improve HbA_{1c} more than metformin alone ($p<0.0001$).

Change in Body Weight
Liraglutide at doses of 0.6 mg or above induced a weight loss ranging from -0.6 to -3.0 kg, depending on the dose. The weight loss observed with lower doses of liraglutide was limited and not consistent among trials. In the Japanese trial, change in body weight was evaluated after 14 weeks of treatment with liraglutide at doses of 0.1, 0.3, 0.6 and 0.9 mg. In this trial no change in body weight was seen in any of the liraglutide treatment groups compared with placebo. It should be noted, however, that baseline body weight was low (63 kg) for these Japanese subjects.

It is concluded that the liraglutide dose and treatment duration is relative low in these therapeutic exploratory trials. Results of monotherapy with higher liraglutide dose support the findings on **HbA_{1c}** reduction, body weight and beta cell function from the therapeutic exploratory studies.

Clinical safety

All safety data initially available for trials with completed statistical analysis up to 31 Jan 2008 was included in the safety evaluation. Data from trial 1797 were not quantitatively incorporated in the overall safety evaluation.

At Day 121 the data initially submitted was updated with the 120-day Safety Update from the US Regulatory approval process. Data from 26-week OAD add-on study vs. exenatide (1797) was also submitted at D121. At Day 181 2-year efficacy and safety data from Trials 1572 and 1573 was provided. For thyroid and neoplasm adverse events, the original pooled clinical safety dataset on thyroid disorders and neoplasm disorders was updated with a cut-off date 1 December 2008.
The conclusions from the updated safety data do not change the conclusions derived from the original safety assessment.

- Patient exposure

During the liraglutide clinical development programme in the original Marketing Authorisation Application 4211 subjects were exposed to liraglutide, 1122 subjects to placebo, and 1165 subjects to an active comparator. The majority of the subjects exposed to liraglutide had T2DM (79%) and most of these were from the long-term (therapeutic confirmatory) trials. 70–80% of the randomised subjects completed these trials. 2085, 840, and 497 subjects were treated with liraglutide for at least 24, 50, and 76 weeks, respectively.
Based on the cut-off date for the updates submitted at Day 121 and Day 181, 1 December 2008, 5076 subjects were exposed to liraglutide, 1210 subjects to placebo, and 1529 subjects to an active comparator. Of these, 4631 were subjects with type 2 diabetes exposed in the long-term therapeutic confirmatory trials (liraglutide: 2922 subjects, placebo: 524 subjects and active comparator: 1185 subjects).
Exposure by dose in the long-term trials is presented in the below table.

Subject exposure – Long term trials

	Liraglutide 0.6 mg N (Exp¤)	Liraglutide 1.2 mg N (Exp¤)	Liraglutide 1.8 mg N (Exp¤)	Placebo N (Exp¤)	Active Comparator N (Exp¤)
Trial 1573		251 (269.0)	246 (269.4)		248 (250.7)
Trial 1572	242 (278.1)	240 (271.2)	242 (264.4)	121 (93.2)	242 (271.1)
Trial 1436	233 (109.2)	228 (102.9)	234 (110.1)	114 (47.1)	231 (104.6)
Trial 1574		177 (81.1)	178 (73.3)	175 (71.8)	
Trial 1697			230 (107.3)	114 (52.9)	232 (111.9)
Total	475 (387.3)	896 (724.1)	1130 (824.5)	524 (265.0)	953 (738.4)

¤ Exp: Subject years of exposure is defined as duration of exposure divided by 365.25.

Updated with Trial 1797 and with 2-year Data for Trials 1573 and 1572 and Trial 1797

Trial 1573		251 (325.2)	246 (329.2)		248 (304.1)
Trial 1572	242 (343.1)	240 (337.4)	242 (324.1)	121 (109.6)	242 (328.6)
Trial 1797			235 (107.7)		232 (101.5)
Total	242 (343.1)	491 (662.6)	723 (761)	121 (109.6)	722 (734.2)

¤ Exp: Subject years of exposure is defined as duration of exposure divided by 365.25.

Overall, 788 subjects withdrew for the following reasons: AEs (228 subjects), non-compliance (81 subjects), and ineffective therapy (240 subjects) or for 'other' reasons (239 subjects).
In trial 1573 the withdrawal rate due to "other reasons" was very high. However, the numbers were roughly comparable across the treatment groups and no preponderance for any of the reasons seems evident for liraglutide.

- Adverse events

The most frequent reasons for withdrawal were AEs (7%) in the liraglutide group and ineffective therapy (17%) in the placebo group.
Generally, the majority of AEs were mild and <10% of subjects in the long-term trials experienced severe adverse events. Within the different severity categories (mild, moderate, severe) the overall picture was similar.
The overall AE rates and withdrawals due to AEs were higher in the higher liraglutide vs lower dose groups. There were more subjects reporting AEs in the liraglutide groups (especially 1.2 and 1.8mg)

compared to placebo and active comparator. This is also seen in the severity rates: proportion and rates are higher in the 1.2 and 1.8mg liraglutide groups compared to placebo and active comparator.

- Serious adverse event/deaths/other significant events

During the clinical development programme 8 deaths (liraglutide: 3; comparators: 3; pre-randomisation: 2) were reported as of the clinical cut-off date (31 Jan 2008). All deaths were reported in long-term trials. Two deaths in Trials 1697 and 1572 were reported after completion of the trials and one death was reported in the ongoing Trial 1700. All deaths were assessed as unlikely related to the treatment regimen, except in one case (renal cell carcinoma, subject treated with liraglutide 1.8 mg + glimepiride + metformin). The investigator reported 'underlying disease' as an alternative aetiology to the renal cell carcinoma. No deaths were reported up until 21 Feb 2008 in the ongoing extension trials (Trials 1573 and 1572), however 2 deaths were reported in study 1572 after the cut-off date for the 120-Day Safety Update and were therefore not included previously (causes of death were reported as: acute renal failure and pyelonephritis (Subject 318018) and tuberculosis (Subject 393004)).
In general the observed causes of deaths are not unexpected in a population with type 2 DM.

Deaths during the initial liraglutide development programme

Trial ID	Subject ID	Age / Gender	Treatment Regimen	Preferred Term (MedDRA)	Onset after Treatment Initiation	Investigator's Causal Relationship
1697	698004	47 years / male	Liraglutide 1.8 mg + glimepiride + metformin	Renal cell carcinoma stage IV	117 days	Possibly
1572	225011	63 years / male	Liraglutide 1.2 mg + metformin	Liver cirrhosis and hepatocellular carcinoma	160 days	Unlikely
1700	9025	63 years / female	Liraglutide 0.9 mg	Gastroenteritis	34 days	Unlikely
1697	689012	67 years / female	Glimepiride + metformin	Acute myocardial infarction	78 days	Unlikely
1697	827005	54 years / male	Insulin glargine + glimepiride + metformin	Acute myocardial infarction	117 days	Unlikely
1573	504036	56 years / female	Glimepiride	Road traffic accident	194 days	Unlikely
1572	391030	76 years / male	Metformin (run-in period)	Cardio-respiratory arrest	NA	Unlikely
1436	489011	71 years / male	No drug given	Pancreatic carcinoma	NA	Unlikely

NA: not applicable

The total rates of serious adverse events (SAEs) appeared lower in the liraglutide group than in the non-liraglutide group (86.6 vs. 97.5 events per 1000 subject years of exposure, respectively). The rates of serious and the non-serious AEs, and the total AEs for thyroid, pancreatitis and immunogenicity are however higher in the liraglutide group than the non-liraglutide group.
Based on long-term trials, a dose-dependency of SAEs with liraglutide was not apparent as the rate decreased from liraglutide 0.6 mg to liraglutide 1.8 mg. It was lower as compared to the placebo group.
The most frequently reported SAEs comparing liraglutide vs. non-liraglutide were: cardiac disorders (17.4 vs. 16.7 events per 1000 subject years of exposure), GI adverse events (10.7 vs. 10.5 events per 1000 subject years of exposure), and neoplasms (8.9 vs. 5.3 events per 1000 subject years of exposure).

Frequently reported AEs with liraglutide treatment were GI adverse events, headache and upper respiratory infection. Important potential risks have been selected based on pre-clinical experience with liraglutide (C-cell carcinogenicity), from experience with another drug in the same class (exenatide: pancreatitis, cardiac events, neoplasms and antibody formation), for theoretical reasons

(antibody formation, immunogenicity, injection site reactions) and from clinical trial experience (pancreatitis, neoplasms, antibody formation).

Gastrointestinal adverse events
These were the most frequently reported adverse events with liraglutide treatment, and they seemed to be dose related. In the liraglutide group the AEs reported by most subjects were nausea (20 % in the 2 high-dose groups), diarrhoea (11-14%) and vomiting (8%) and the corresponding numbers for the active comparator group were 4.1%, 4.6% and 1.3%, respectively. These events were in general transient.
In combination with metformin more GI adverse events are seen.

Headache and Upper Respiratory Tract Infection (influenza and nasopharyngitis)
These events were equally distributed across all treatment groups. As headache and upper respiratory tract infection were commonly reported in the background population these events are not considered related to the treatment.

C-Cell Carcinogenicity (Medullary thyroid cancer)
A total of 12 thyroid SAEs were reported in 9 subjects treated with liraglutide. Four of these were events of papillary thyroid cancer in 4 subjects. One papillary thyroid cancer was reported in a subject treated with comparators. No medullary thyroid cancers (C-cell origin) were reported. In the completed trials, the rate of papillary thyroid cancer appeared slightly higher in subjects treated with liraglutide (1.8 vs. 0.9 events per 1000 subject years).
In one case, reported as thyroid neoplasm, diffuse C-cell hyperplasia was found after thyroidectomy, however no medullary carcinoma was found. This subject was diagnosed with a papillary microcarcinoma (within the context of a multinodal goitre) with the additional diagnosis of C-cell hyperplasia (CCH). This case represents the first report of CCH in the clinical development programme. This subject had a baseline calcium stimulation test that peaked at 90-95th percentile for females in the substudy. CCH in a non-nodular form as defined by an increase in overall C-cell numbers, is not an uncommon finding in human thyroid material, and identification requires a specific staining for C-cells. C-cell hyperplasia has been found in up to 33 % of autopsies of expected normal thyroid glands. Furthermore CCH has been observed at an increased frequency in connection with papillary carcinomas.
As described in non-clinical section, it has been concluded that the thyroid C-cell tumours induced in mice and rats by dosing of liraglutide are caused by a non-genotoxic, specific receptor-mediated mechanism to which mice and rats are particularly sensitive and monkeys and humans are not.

There is no accurate screening tool for CCH and medullary thyroid carcinoma (MTC). Calcitonin looks like the best alternative. Calcitonin is almost exclusively expressed by thyroid C-cells and as such is a biomarker for increased C-cell activity. In humans with C-cell hyper- or neoplasia, both basal and calcium stimulated calcitonin levels increase. However, routine use of calcitonin screening, has not been formally validated, and there are no well-established absolute serum cut-offs for distinguishing between benign and malignant disease, or between CCH and MTC.

In general, the calcitonin data provided were characterised by a large proportion of the values being below the lower limit of quantification (LLOQ, 0.7 ng/L) and calcitonin levels remained below the upper normal range at weeks 26/28 and 52, whereas a substantial number of calcitonin values had shifted to below LLOQ at week 76/78. There was a tendency for a shift in calcitonin levels towards a higher category (mainly within normal range) with liraglutide 1.8 mg compared to the other treatment groups at week 26/28, but there was no difference between the treatment groups at weeks 52 or 76/78. Baseline calcitonin values were comparable between treatment groups. In all treatment groups, a comparable increase in calcitonin from baseline to week 26/28 was observed (both females and males).
A repeated measurement analysis demonstrated that there was an increase in calcitonin in all treatment groups, but the estimated geometric means at end-of-trial were within the normal range for all groups.
Significant differences between treatments were seen for liraglutide 1.2 mg vs. placebo (Trial 1574) and liraglutide 1.8 mg vs. placebo (Trial 1697).

The calcium stimulation test performed on a subset of subjects from long-term Trials 1573 and 1574 did not show any significant effect of treatment with liraglutide on stimulated levels of calcitonin. Based on the consolidated preclinical and clinical data and a thorough review of available literature regarding use of monitoring for CCH and MTC by use of calcitonin and other methods, it is concluded that forced systematic use of a marker for screening CCH in patients would result in unnecessary and unwarranted medical evaluation potentially leading to adverse effects in otherwise healthy subjects.

Neoplasms

Based on the pooled long-term trials, neoplasms appeared at higher rates in particular at high liraglutide doses (12.9-26.2-20.6-11.3 and 6.8 events/1,000 subject years of exposure (SYE) for liraglutide 0.6mg-1.2mg-1.8mg-placebo and active comparator). No dose-dependent relationship was observed. Serious neoplasms were more frequently reported in subjects treated with liraglutide as compared to non-liraglutide (8.9 vs. 5.3 events/1,000 SYE).

A total of 32 malignant neoplasms (liraglutide: 24, non-liraglutide: 8) were identified in the completed and ongoing clinical trials. The rates of malignant neoplasms in all completed trials were comparable for liraglutide vs. non-liraglutide-treated subjects. The 32 malignant neoplasms included 5 events of thyroid related neoplasms (liraglutide: 4 subjects, comparator: 1 subject) and 6 cases of prostate cancer (liraglutide: 5 subjects and non-liraglutide: 1 subject). In 3 of the prostate cancers, medical history of prostatic hyperplasia or hypertrophy was reported. Apart from these cases, there did not appear to be a clustering in types of malignant neoplasms.

During the assessment the need for further discussion regarding the occurrence of neoplasms was considered of great importance and as such raised as a major objection in the Day 120 LoQ. After the review of the responses it was concluded that combining the preclinical and the clinical experience, available literature and background data, it is still not clear whether there is a direct carcinogenic or a growth promoting effect of liraglutide. Additionally there remained the problem that there are no long term data for malignancies. To address this, the original pooled clinical safety dataset on thyroid disorders and neoplasm disorders was updated with a cut-off date 1 December 2008 was submitted.

From this update it was considered that the updated rates of all neoplasms, malignant and benign neoplasms are similar to the data previously submitted, and there was no signal of an increased risk for malignancies over time. This is considered reassuring.

Further long-term data are awaited to evaluate effects of liraglutide on neoplasia, in particular thyroid neoplasms, in particular a large, cardiovascular outcome trial. This will be addressed as a post-marketing commitment.

Thyroid Adverse Events

The rate of thyroid AEs appeared higher with liraglutide compared to non-liraglutide treatment based on all completed trials (35.7 vs. 22.0 events per 1000 SYE.) This difference was mainly driven by events of increased blood calcitonin, goitre and thyroid neoplasms. In the liraglutide group, more subjects with thyroid AEs during the trial had a medical history of thyroid disease compared to subjects treated with non-liraglutide. No liraglutide dose-dependency was observed for these events in the pooled long-term trials, and the number of subjects with events was relatively low. Calcitonin levels were slightly more increased with liraglutide at week 26/28, but CI were wide and this effect was temporary, and most calcitonin values were within the normal range.

The most frequently reported thyroid AE in the completed trials was thyroid neoplasm, reported at a higher rate in subjects treated with liraglutide as compared to non-liraglutide (7.1 vs. 3.5 events per 1000 SYE). In the completed trials, none of these events of thyroid neoplasm were serious, the majority were mild. Concerns regarding thyroid AEs were raised as a Major Objection in the Day 120 LoQ and in response the last safety update which had been submitted to the FDA was submitted. The rate of all thyroid neoplasms was comparable for subjects treated with liraglutide and placebo, and higher than for subjects treated with active comparator. The rates of malignant neoplasm AEs were higher for the liraglutide group; 10.9, 6.3, 7.2 and 6.9 events per 1,000 SYE for total liraglutide, placebo, active comparator and total comparator, respectively. Compared with the US background population, incidence rates of malignant neoplasms are not higher in the liraglutide trials. The papillary (follicular) thyroid cancers occur at a higher frequency in the liraglutide clinical development programme than in the referenced background population. However, subjects included in the

liraglutide clinical trial programme underwent careful thyroid related assessments, leading to the high number of thyroidectomies and can explain the imbalance.
Subjects with pre-existing thyroid disease had a higher rate of thyroid AEs in comparison to subjects without pre-existing thyroid disease: 68.1, 87.7, and 51.4 respectively for liraglutide, placebo and active control in patients with pre-existing thyroid disorders, versus 29.5, 25.4 and 15.5 for liraglutide, placebo and active control in patients without pre-existing thyroid disorders. In subjects with pre-existing thyroid disease the rate of overall thyroid AEs was lower for subjects treated with liraglutide (68.1) compared to placebo (87.7) and somewhat higher than active control (51.4). For these patients neoplasms occurred at a higher rate compared to placebo and active comparator (34.0, 29.3 and 0.0) however, the rates of thyroid neoplasms were comparable for liraglutide and placebo (28.8 and 29.3; none in active comparator).
As stated previously neoplasm adverse events including thyroid neoplasms will be studied as part of a large cardiovascular outcome trial.
Information is included in the "Special warnings and precautions for use" section of the SPC particularly for patients with pre-existing thyroid disease.

Pancreatitis
Seven AEs of pancreatitis (liraglutide: 6, non-liraglutide: 1) of which 6 were serious (liraglutide: 5 and non-liraglutide: 1) have been reported. Concerning the 5 serious cases reported, four cases were associated with liraglutide, and one to OAD (placebo group). In some of the cases there were independent risk factors for pancreatitis such as relevant medical history. An alternative aetiology to drug could be present in three of the cases on liraglutide. Of the 4 subjects that continued in the trials, two subjects did not experience reoccurrence of pancreatitis and two subjects, diagnosed with chronic pancreatitis, did not experience any worsening. Thus no definite conclusion of causal relationship to liraglutide exposure can be made. Reporting rates of acute pancreatitis and pancreatitis in Phase 3a Trials was 1.6/1,000 SYE for liraglutide and 1.4/1,000 SYE for OAD. For comparison, population based studies have provided the following incidences for pancreatitis: 1/1,000/year in the type 2 diabetes population. Epidemiology for pancreatitis is 0.05-0.8/1,000/year (background population) and 1-5.4/1,000 SYE (type 2 diabetes population).

Immunological events
Adverse events of immunogenicity appeared to be reported at higher rates in subjects treated with liraglutide than in subjects treated with comparators across the completed trials (11.6 vs. 4.4 events per 1000 SYE), and there appeared to be a dose-dependent relationship to liraglutide. Only 1 event (with liraglutide) was serious, the majority were non-serious (liraglutide: 96% and comparators: 100%).
The majority of events were from the group of angioedema (mainly urticaria) and included one SAE (angioedema). The remaining events were mainly various types of oedema, not necessarily based on an immunological mechanism.
Injection site disorders in the long-term trials were all non-serious. The rate of injection site disorders in the highest liraglutide dose group (1.8 mg) was comparable to the placebo group but the rate appeared to increase in a dose-dependent manner with liraglutide. The increasing reporting rate may be related to the injected volume which increases with increasing dose. The most frequently reported were injection site bruising and pain.
Due to the high degree of homology between liraglutide and native GLP-1, a low risk of antibody formation would be expected. At week 27 (26 weeks + ≥5 days off drug), the percentage of subjects with samples positive for liraglutide antibodies, antibodies with cross-reactivity towards native GLP-1 and antibodies with a neutralising effect of liraglutide *in vitro* were generally low and comparable for the three liraglutide treatment groups. Antibodies did not appear to have any effect on neither the glycaemic response (HbA_{1c}) nor the AE profile. However, the formulation-to-be-marketed was only used in one trial. This point was considered of concern and in response data from 3 new trials were submitted. Trial 1797 provided data on a limited number of patients over 26 weeks. The Japanese trials (1700 and 1701) provide more long-term data. With these new trials, the number of subjects exposed to the to-be-marketed-formulation is substantial, although about half of them were Japanese subjects. A comparison was made between immunogenicity side effects in subjects treated with the trial-formulation and subjects treated with the to-be-marketed-formulation. There was no correlation between experiencing an immunogenicity or injection site disorder related side effect and antibody status using any of the two formulations. The majority of adverse events in these categories were

reported in subjects not being positive for liraglutide antibodies. Antibody formation will be monitored and submit information in the future PSURs.

Cardiovascular events
Cardiac disorders were reported with higher rates for liraglutide 0.6mg and 1.2 mg whereas, the rate for liraglutide 1.8mg was comparable with the rates for placebo and active comparator. When pooling the 3 liraglutide treatment groups in one liraglutide group, the rates of cardiac events in the liraglutide group were comparable to the placebo group and slightly higher as compared to the active comparator and the total comparator groups.
The most frequently reported SAEs were cardiac disorders. The rate of serious cardiac AEs were also reported with a higher frequency for liraglutide 0.6mg whereas liraglutide 1.2mg and 1.8mg were comparable with placebo and comparator. The most frequently reported SAEs were angina pectoris, acute myocardial infarction and myocardial infarction. Generally, the rates and types of serious cardiac adverse events were comparable between the treatment groups. With the present data, liraglutide treatment does not seem clearly associated with an increased risk of cardiovascular events, however due to the higher incidence in the liraglutide group the relationship can not be excluded either. At present cardiac events are covered by routine pharmacovigilance activities. Due to the high risk of CV disease in diabetes type 2 patients the data provided on cardiac safety necessitates long-term follow-up safety measures to assess CV morbidity and mortality post-marketing.
Adverse events of vascular disorders in general occurred at comparable rates across treatment groups and were comparable in subject treated with liraglutide as compared to placebo.
The most frequently reported AEs were hypertension, vascular calcification and hypotension. In all completed trials, SAEs of vascular disorders in general were few and occurred at comparable rates in liraglutide vs. non-liraglutide groups. Major adverse cardiovascular events (MACE) were not more frequent in liraglutide compared to any of the comparators; however, overall events were low. Therefore, it was neither possible to confirm nor dismiss a potential dose-relationship. A cardiovascular outcome trial will be conducted as a post-authorisation follow up measure will provide further data.

Blood pressure
In the five confirmatory trials liraglutide 1.8mg resulted in a decrease in systolic blood pressure by -3 to -6 mm Hg from baseline. Compared to active comparator the decrease was -1.8 to -4.5 mm Hg. Weight reduction could be responsible for the decrease in blood pressure. However, blood pressure started to decrease before the weight reduction. Other mechanisms, like diuresis and sodium excretion or effect on endothelium-mediated vasodilation could also be responsible.

Hypoglycaemic Episodes
Overall, few hypoglycaemic episodes were reported during treatment with liraglutide and the majority of the episodes were classified as ‘minor’ (<3.1 mmol/L (56 mg/dL), no third party assistance required).
In Trial 1573 (monotherapy) a dose of 8mg/day glimepiride was used. However, in Europe usually 4 mg daily (6 mg is the maximum approved dose) is recommended. Therefore, the safety of liraglutide (especially hypoglycaemic events) may be overestimated by this high dose. The percentage of subjects experiencing minor hypoglycaemic episodes during the main trial and open-label extension period was lower in the 2 liraglutide groups (liraglutide 1.2 mg: 11.6% and liraglutide 1.8 mg, 7.7%) than in the glimepiride group (glimepiride, 25.0%). The corresponding rates were liraglutide 1.2 mg: 241.6, liraglutide 1.8 mg: 230.1 and glimepiride: 1659.2 episodes per 1000 subject years of exposure. Although only speculation, it seems unlikely that the difference in hypoglycaemia rates between the 4mg dose and the 8mg dose would have been so large as to reverse the favourable safety profile of liraglutide with regard to hypoglycaemic event compared to glimepiride.
Sections 4.2, 4.4 and 4.8 of the SPC include a information regarding the combination of liraglutide with a sulphonylurea as this may increase the risk of hypoglycaemia. The risk of hypoglycaemia can be reduced by a reduction in the dose of sulphonylurea

- Laboratory findings

Liraglutide treatment did not seem to be associated with any pathological alterations in laboratory parameters; haematology, liver or kidney parameters. During the long-term trials (inclusive extensions of study 1572 and 1573) almost no alterations outside the normal range in calcitonin levels were observed, that could support a human relevance of the reported C-cell findings in rodents in the pre-clinical program. Calcitonin is not suitable as biomarker in routine screening for the development of medullary thyroid cancer.

- Safety in special populations

The therapeutic experience in patients with all degrees of **hepatic impairment** is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment (see Clinical efficacy section).

As regards the safety profile in patients with **mild renal impairment** the rates (events per 1000 subject years of exposure) of total AEs and withdrawals due to AEs were clearly much higher in the 1.2 mg (4725 and 414) and 1.8 mg (4708 and 442) groups compared to the 0.6mg group (2832 and 74), active comparator (2960 and 108) and placebo (2794 and 58). The rate of SAEs for liraglutide 0.6mg and 1.2mg was lower than placebo and active comparator, whereas it was higher for liraglutide 1.8mg.
The higher rate of AEs was primarily driven by higher rates in GI AEs. In the total liraglutide group of patients with CrCL ≤60-90 ml/min at baseline the rate of gastro intestinal disorders amounted to 4233 events per 1000 subject years of exposure vs. 3810 in patients with CrCL > 90 ml/min at baseline. This safety concern is reflected in section 4.8 of the SPC.
As regards patients with CrCL below 60 ml/min insufficient efficacy data has been presented to support the use of liraglutide in this patient group. Only 51 patients were included across all 5 pivotal studies (with different treatment combinations; only 8 patients from the monotherapy study 1573) in the combined liraglutide 1.2mg and 1.8mg treatment groups. Use in patients with moderate to severe renal impairment is currently not recommended.

An overview of AEs in the sub-populations of the **elderly population** (>65 years, > 70 years and > 75 years) was provided. Both the rates of AEs, SAEs and withdrawals due to AEs increased by age for liraglutide 1.2 mg and 1.8 mg. The number of elderly > 75 years was very low (liraglutide 0.6 mg: 8; liraglutide 1.2 mg: 17; liraglutide 1.8 mg: 23, placebo: 7; active comparator: 28) why conclusions in this sub-group should be drawn cautiously. The rate of AEs was clearly higher for elderly above the age of 70 years for the highest doses of liraglutide (1.2 mg: 5102.3 and 1.8mg: 6103.4 compared to placebo (3441.6) and active comparator (2018.0). Also for the elderly >75 years of age the rate was higher for the highest dose of liraglutide (1.8mg: 8756.5) vs. placebo (5358.2), the latter however being higher than for liraglutide 1.2mg. For all age groups the majority of AEs were non-serious and mild to moderate in intensity. The higher rate of AEs was primarily driven by higher rates in GI AEs particularly for patients above the age of 70 years. The rates (events pr 1000 SYE) for GI AEs were as follows for the sub-groups <65, >65, >70 and 75years: liraglutide 0.6 mg: 712, 985, 1018 and 446; liraglutide 1.2 mg: 1117, 1132, 1669 and 989; liraglutide 1.8 mg: 1385, 1955, 2222 and 3313. Section 4.8 of the SPC includes a statement to this respect.

- Safety related to drug-drug interactions and other interactions

Liraglutide has been shown in animals to lower blood glucose synergistically in combination with the PPARγ agonist pioglitazone, and to increase insulin secretion synergistically in combination with the sulphonylurea glipizide.
Liraglutide has no clinically relevant potential to inhibit or induce cytochrome P450 drug metabolising enzymes, and no clinically relevant drug-drug interaction related to protein binding is anticipated.
Concomitant administration of liraglutide and selected drugs (see Pharmacokinetic interaction studies) resulted in changes in exposure and absorption of the investigated drugs that was not considered to clinically significant. However, it should be kept in mind that the small delay in gastric emptying with

liraglutide may potentially influence absorption of concomitantly administered oral drugs and result in drug-drug interaction. This is of special relevance with drugs with poor solubility and small therapeutic window, such as warfarin.
Combination of liraglutide with insulin has not been evaluated and is therefore not recommended. Diarrhoea may affect the absorption of concomitant oral drugs.

- Discontinuation due to adverse events

Across all completed trials 5.9% of liraglutide-treated subjects and 3.0% of non-liraglutide-treated subjects withdrew due to AEs. Adverse events leading to withdrawal were mainly non-serious in both groups. There are more withdrawals due to common adverse events in the higher liraglutide group.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Safety Issues		
Hypoglycaemia	• Routine and targeted pharmacovigilance • Analyses of ongoing and planned clinical trials	Labelling – SPC: • Sec. 4.2 Posology and method of administration: A reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia. • Sec. 4.4 Special warnings and precautions for use: The risk of hypoglycaemia can be lowered by a reduction in the dose of sulphonylurea. • Sec. 4.8 Listed as Undesirable effects
Gastrointestinal adverse events including nausea, diarrhoea, vomiting, constipation, dyspepsia	• Routine pharmacovigilance • Analyses of ongoing and planned clinical trials	Labelling – SPC: • Sec. 4.2 Posology and method of administration: To improve gastro-intestinal tolerability, the starting dose is 0.6 mg liraglutide daily. • Sec 4.8 Listed as Undesirable effects
Potential Safety Issues		
Medullary Thyroid cancer	• Routine and targeted pharmacovigilance • Database study • Analyses of ongoing and planned clinical trials	
Neoplasm	• Routine and targeted pharmacovigilance • Database study • Analyses of ongoing and planned clinical trials	
Cardiac co-morbidity	• Routine pharmacovigilance • Analyses of ongoing and planned clinical trials including a cardiovascular outcome study	Labelling – SPC Sec. 4.4 Special warnings and precautions for use: 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.
Late stage microvascular complication of the eye	• Routine pharmacovigilance • Analyses of ongoing and planned clinical trials	
Immunogenicity (antibody formation, allergic reactions and injection site disorders)	• Routine and targeted pharmacovigilance • Analyses of ongoing and planned clinical trials	Labelling – SPC Sec. 4.8 Listed as Undesirable effects
Pancreatitis	• Routine and targeted pharmacovigilance • Database study • Analyses of ongoing and planned clinical trials	Labelling – SPC Sec. 4.4 Special warnings and precautions for use: Patients should be informed of the characteristic symptom of acute pancreatitis. Suspect medicinal products should be discontinued.
Missing information		

Abuse due to weight lowering potential	• Routine pharmacovigilance	Available as prescription only
Children and adolescents	• Clinical trial including children between 10 and 17 years of age • Routine pharmacovigilance	Labelling – SPC Sec. 4.2 Posology and method of administration: Not recommended for use in children below 18 years of age.
Overdose	• Routine pharmacovigilance	
Pregnant and lactating women	• Routine pharmacovigilance	Labelling – SPC Sec. 4.6 Pregnancy and lactation: Not to be used during pregnancy. Should not be used during breast-feeding.
Potential interaction with warfarin	• Routine pharmacovigilance	Labelling – SPC Sec. 4.5 Interaction with other medicinal products and other forms of interaction: Upon initiation of liraglutide treatment in patients on warfarin more frequent monitoring of INR is recommended.
Cardiac co-morbidity	• Routine pharmacovigilance	
Renal and hepatic impairment/endstage renal failure	• Routine pharmacovigilance	Labelling – SPC Sec. 4.2. Posology and method of administration*:* *Renal impairment*: Not recommended for use in patients with moderate and severe renal impairment including patients with end-stage renal disease. *Hepatic impairment:* The therapeutic experience in patients with all degree of hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment.
Off-label use	• Routine pharmacovigilance	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Overall, the documentation on the quality demonstrates consistent batch-to-batch production of Victoza achieving a well-defined quality for the drug substance and the drug product. No excipients of human or animal origin are used in the product manufacture and therefore there is no risk of contamination with viral or TSE agents by these ingredients.

Non-clinical pharmacology and toxicology

Overall the primary PD studies provided adequate evidence that liraglutide is a potent, selective and efficacious agonist on the GLP-1 receptor, glucose-dependently stimulating insulin secretion. This effect has been seen *in vitro* from isolated beta-cell islets and *in vivo* in a number of diabetic and obese models using rodents, pigs and monkeys. *In vivo* the effect was accompanied by a decrease in body weight. The mechanism of action *in vivo* involved glucose-dependent increase in insulin secretion, lowered glucagon secretion, decreased gastric emptying, loss of body fat, lowered food intake, altered food preference, and maintained energy expenditure. The mechanism of action is consistent with a specific GLP-1 effect. The safety pharmacology programme did not reveal any findings of concern for humans.

From the PK point of view, the disposition characteristics were generally similar across the species tested, showing liraglutide to be well absorbed from the injection site. The distribution volume is low and close to plasma volume, indicating that a high fraction of liraglutide is circulating in plasma. Liraglutide was seen to have linear pharmacokinetics with dose-proportional exposures or an exposure slightly higher than dose-proportional. The accumulation ratio was comparable to that observed in humans. The terminal half-life seems to be similar in pigs and humans while shorter in mice, rats,

rabbits and monkeys. These differences however were explained by the study design or absorption rate limited kinetics. Clearance of liraglutide is suggested to take place by multiple organs/tissues and low potential for PK drug interactions related to CYP and protein binding have been demonstrated.

Liraglutide crosses the placental barrier in rats and rabbits. However, the uptake of liraglutide into the amniotic fluid and foetuses is low. Liraglutide is secreted into milk, but the amount that a pup would receive per day via breast milk is low.

Overall the general toxicology programme revealed that liraglutide had effects on body weight (gain) and food consumption in the first weeks of dosing. These effects can be seen as the result of the pharmacological action of liraglutide. A clear treatment effect was C-cell hyperplasia found in the thyroid of treated mice. Effects on C-cells (focal accumulations of C-cells) were already seen in the 4-week mice study, while after 9-13 weeks C-cell hyperplasia was seen. No effects on C-cells were seen in the rat and monkey studies up to 26 and 52 weeks. Effects on C-cells in rats were seen however in longer carcinogenicity studies. In a few monkeys antibodies were found which cross-reacted with GLP-1. This implies that an immunological reaction against the body's own GLP-1 could be possible. Data on antibody formation will be reported in the PSURs.

In carcinogenicity studies thyroid C-cell tumours were observed in mice and rats. It is concluded that these tumours induced by dosing of liraglutide are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive and monkeys and humans are not. The relevance for humans is therefore likely to be low but cannot be completely excluded. Section 5.3 of the SPC has been adjusted accordingly.

Liraglutide was not seen to be genotoxic or teratogenic.

Efficacy

The product is a solution for subcutaneous injection containing 6.0 mg/ml of liraglutide to be administered once daily.

Core studies of the application are five phase III trials, the so called therapeutic confirmatory trials. Based on these trials a marketing authorisation for liraglutide initially as monotherapy, as well as dual and as triple therapy was sought. The claim for monotherapy was withdrawn during the procedure (see below). Study duration, chosen endpoints, in- and exclusion criteria of the studies were generally adequate and in accordance with the current guideline.

Used as **monotherapy** (trial 1573), liraglutide 1.2 and 1.8 mg was more effective than glimepiride 8 mg daily, although this dose of 8 mg glimepiride is high for Europe. The consequences of this are primarily safety issues (hypoglycaemia) and have been discussed. A comparison with metformin would have been preferred as metformin is currently the first choice in T2DM. Additionally, there is limited long-term data on the safety and efficacy of liraglutide. Initially a second line monotherapy indication in patients who are intolerant to or have contraindications to metformin treatment was proposed. However, the most essential contraindications for metformin (moderate and severe renal impairment, hepatic impairment, heart failure and recent myocardial infarction) are conditions for which there is limited experience for liraglutide. This indication was withdrawn during the procedure.

Given in **dual therapy**, when added to metformin, liraglutide (1.2 or 1.8 mg) was equally effective as glimepiride, and better than metformin monotherapy. Long-term data of study 1572 showed that, although HbA_{1c} started to increase after 20 weeks, the difference with the control was also persistent. As an add-on to SU, liraglutide was more effective than rosiglitazone in Trial 1436. Statistically and clinically criteria for superiority were met. The dose of rosiglitazone however was considered low; in which case the safety of rosiglitazone arm may have been enhanced, but the efficacy may also have been decreased. In addition to the low dose of rosiglitazone, the duration of the trial was only 26 weeks, while the efficacy of rosiglitazone is expected to be more pronounced after one year, therefore limiting its conclusion. It should be noted that dual therapy when added to rosiglitazone has not been studied. The initial claim for this combination was withdrawn.

In **triple therapy** liraglutide+metformin+rosiglitazone (trial 1574) was more effective than dual therapy with metformin+rosiglitazone. The combination of liraglutide+metformin+glimepiride (trial 1697) resulted in lower HbA_{1c} values than insulin+ metformin+glimepiride. The dose of insulin glargine was individually titrated on basis of the fasting glucose value< 5.5 mmol/L following a titration guideline and on advise of the investigator. The combination of liraglutide with insulin has not been evaluated and is therefore not recommended.

A clear justification from the dose finding studies for the chosen dosages of liraglutide 1.2 and 1.8 mg is lacking as most of the pharmacodynamic studies and clinical exploratory trials used lower dose regimens. However, on the basis of the results from the clinical development programme, it is accepted that the observations made in the early trials are relevant and transferable to the effects and results obtained in the later long-term confirmatory therapeutic trials using higher doses.
A dose-response effect was seen in the monotherapy trial, but was not apparent in the combination trials. However, clinically, results in combination therapy are also relevant. As far as the magnitude of the effect can be compared between trials, data suggest that the efficacy of the 1.2 mg is less in the monotherapy trial as compared to the combination trials.
Overall, percentages of adverse events were comparable between doses in the long-term trials. However, there were differences in GI events and withdrawals, especially in trial 1572 (combination with metformin) and trial 1574 (triple therapy with metformin and rosiglitazone), being higher with the 1.8 mg dose.
It is concluded that in dual and combination treatment, only limited effect can be expected from an increase in dose to 1.8 mg, while GI adverse events might increase.

The therapeutic experience in patients with all degrees of hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment.

Therapeutic experience in patients with moderate to severe renal insufficiency is too limited to recommend use in these patients.

Change in body weight was a key secondary endpoint in all five trials. Liraglutide induced weight loss, varying between 1 – 2.5 kg within the first 8 weeks of treatment which overall was maintained for the rest of the treatment period.
Liraglutide also has some beneficial effect on the beta cell function compared with placebo. However, limited data has been provided and the results are difficult to interpret and measures inadequate for final conclusions on the effect of liraglutide on the progression of the DM.

Safety

Most of the data were obtained from the five long-term trials using the 1.2 and 1.8 mg dosages. Dosages used in trials other than the long-term trials were rather low. This might have consequences for the incidence of AEs in the "all completed trials safety analysis", and "for the long-term trial safety analysis" when dosages are pooled. The duration of exposure was initially relatively short, in particular with regard to the development of neoplasms and extension studies are ongoing, however further long-term data from trial 1797, 1572 and 1573 were submitted during the procedure.
The most common AEs associated with liraglutide treatment were *gastrointestinal disorders*, mostly nausea, diarrhoea and vomiting. Withdrawal rates due to these adverse events were higher in liraglutide treated groups than with placebo or active comparator. The GI adverse events were seen in the first two months after start of liraglutide and were dose related. In combination with metformin more GI adverse events were reported. Headache and upper respiratory tract infection were commonly reported in the background population, but not considered related to the treatment.

Special focus was given to the following potential safety signals based on non-clinical findings (thyroid C-cell tumours in carcinogenicity studies in rats and mice) and the use of exenatide, another GLP-1 receptor agonist:
Most *malignancies* were reported in the liraglutide group, although the types of malignancy were heterogeneous and the numbers small. It remains unclear whether *malignant* neoplasms are dose related to liraglutide, there were not sufficient data provided to this respect.

Thyroid events, consisting of goitre, thyroid neoplasms and increase calcitonin levels occurred more often in liraglutide group, both in patients with and without pre-existing thyroid pathology. However, the rates of thyroid events in patients with concomitant thyroid illness were lower than placebo. It is not clear if thyroid illness becomes worse under liraglutide treatment. Calcitonin levels were slightly more increased with liraglutide at week 26/28, but the CI were wide, the effect was temporary, and most calcitonin values were within the normal range. The problem remains that there is no appropriate screening tool for C-cell hyperplasia (CCH) and medullary thyroid carcinoma (MTC). Even though calcitonin appears to be the best biomarker for increased C-cell activity as it is almost exclusively expressed by thyroid C-cells, its routine use as a screening tool presents limitations. This was considered as a major objection during the procedure in response to which additional data was submitted. At this point in time however the possibility that there is a causal relationship between liraglutide and thyroid neoplasms/goitre can not be totally ruled. In subjects with pre-existing thyroid disease**,** the overall rate of all adverse events in the liraglutide group is very high. Monitoring these events in these patients in clinical practice would result in extra and unwarranted medical evaluation. In view of all the above~~,~~ information is included in the "Special warnings and precautions for use" section of the SPC particularly for patients with pre-existing thyroid disease.
Information regarding malignancies, including thyroid neoplasms will be collected in a large post-authorisation cardiovascular long-term outcome trial.

Pancreatitis was seen more frequently in liraglutide treated patients than in the control groups but overall the rates were similar to those known in the T2DM population. However, this AE should be closely monitored post marketing, in particular because recently some severe cases have been reported during use of exenatide.

More AEs of *immunogenicity* were seen with liraglutide treatment, but most events were non serious. The percentage of subjects with samples positive for liraglutide antibodies, antibodies with cross-reactivity towards native GLP-1 and antibodies with a neutralising effect of liraglutide *in vitro* was generally low. The formulation-to-be-marketed was only used in one trial. In response to this, data from 3 new trials were submitted. In spite of the results being reassuring, antibody formation will be monitored as a post-authorisation commitment.

Reported incidence rate of *cardiac events* does not indicate an increased risk in subjects allocated to liraglutide treatment, but the duration of the studies was limited. It is noted that patients with severe cardiac co-morbidity were not included in the submitted studies. Given the absence of data and the prevalence of these conditions in the target population, cardiac events represent a possible concern and as such are included in the RMP as a potential risk. A potential relationship of liraglutide treatment and increase in cardiovascular events can not be entirely excluded, reason why long-term follow up data on cardiac safety will be collected in a cardiovascular outcome study.

Liraglutide is associated with *minor hypoglycaemic events*, but less than seen with a sulphonylurea. It should be noted that the dose of glimepiride used in the monotherapy trial was higher than that registered in Europe and this will have increased the hypoglycaemia rate in the glimepiride group. A comparison with metformin is lacking. Major hypoglycaemic events were rare. Especially when liraglutide was added to a SU (dual or triple therapy) the number of minor and major events was increased. Therefore, the dose of SU should be reduced in these cases.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

User consultation of the package leaflet of the 1.8 mg solution for injection was performed. The results were satisfactory, i.e. 90% of the participants were able to find the information and of those 90% were able to express the information in their own words. A bridging statement was submitted for the PL of

the 1.2 mg pen. There are no significant differences between the content of the parent (1.8 mg) and the daughter (1.2 mg) leaflet because they contain the same active substance.

During the procedure a single three-dose pen injector was introduced instead of the original 2 pens which administered 0.6 mg/1.2 mg and 1.8 mg doses. No additional user testing has been performed for the new PL of the three-dose pen; neither a formal bridging statement has been submitted. The difference between the new pen and the former 1.2 mg pen is that the new pen offers the possibility for the selection of three instead of two (or one, in the case if 1.8 mg) doses. Referring to the acceptability of the former bridging statement for the 1.2 mg pen, additional testing is not required, because patients will use the leaflet in conjunctions with guidance from their doctor or nurse.

Risk-benefit assessment

Liraglutide treatment 1.2 and 1.8 mg had a clear effect on lowering HbA_{1c}. This effect was statistically significant both for liraglutide as **1**) monotherapy (compared to glimepiride) (effect size -1.14 and -0.84 for 1.8 mg and 1.2 mg respectively) and **2**) as dual therapy as add-on to metformin vs metformin and glimepiride + metformin (effect size: -1.00 and -0.97 for 1.8 mg and 1.2 mg respectively) or as add-on to glimepiride vs. glimepiride and glimepiride + rosiglitazone (effect size: -1.36 and -1.08 for 1.8 mg and 1.2 mg respectively), and **3**) as triple therapy as add-on to metformin + glimepiride vs metformin + glimepiride and metformin + glimepiride + insulin glargine (effect size: -1.33 for 1.8 mg). In addition, the number of subjects reaching the predefined ADA and AACE HbA_{1c} targets of < 7.0% and 6.5% respectively, was significantly higher in the liraglutide groups (as monotherapy vs. glimepiride and as add-on therapy vs. placebo). The effect on HbA_{1c} of liraglutide 1.8 mg as monotherapy was statistically significantly superior to the effect of liraglutide 1.2 mg, whereas, the effect as add-on therapy was without a definite dose-relationship with respect to liraglutide 1.2 mg and 1.8 mg.
Decreases in FPG and postprandial glucose were supportive of the efficacy of liraglutide.
Change in body weight was a key secondary endpoint in all five trials showing weight loss, similar to exenatide, the other drug with GLP-1 mediated mode-of-action.

The effects shown on HbA_{1c}, however have important limitations. For the monotherapy indication no comparison has been made to metformin. The indication "monotherapy in patients who cannot tolerate metformin" is not accepted due to the concerns of the CHMP regarding the unknown efficacy and safety of liraglutide in patients for whom metformin is contraindicated (congestive heart failure, recent acute myocardial infarction and renal and hepatic impairment) as well as lack of overall beneficial long-term efficacy and safety data. The exclusion criteria in the efficacy studies showed an overlap with the contraindications of metformin and patients intolerant to metformin have not been studied. Long-term safety is not known for liraglutide in particular with respect to cardiovascular safety, neoplasm, thyroid events, pancreatitis and immunogenicity.

The trial designs are not in line with the design recommended in the CHMP "Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus" (CHMP/EWP1080/00): according to the guideline add-on studies should be carried out by adding the new drug to non-responders of the first drug which is not the case in the present trials. The study design for trials 1572, 1436, and 1574 represented a switch-over scenario for a large portion of included subjects rather than an add-on scenario. It was considered that this could have biased the efficacy results in favour of liraglutide which made the interpretation of the overall efficacy results difficult. However, further post-hoc analyses support that the switch-over trial design had no major impact on the results of HbA_{1c} change.

None of the studies support a dual combination treatment of liraglutide with TZD. However, efficacy and safety in triple therapy (liraglutide + metformin + rosiglitazone) has sufficiently been demonstrated. The risk of off-label use as dual therapy is expected to be very limited due to the restricted monotherapy indication of TZDs in the EU.

Exposure in patients with renal and hepatic impairment is decreased. Its implications for clinical use have insufficiently been studied. As such, Victoza is not recommended for use in patients with

moderate and severe renal impairment including patients with end-stage renal disease or in patients with mild, moderate or severe hepatic impairment.

A sufficient number of patients were studied during the first year of treatment, but the duration of exposure is relatively short, in particular with regard to the development of thyroid illnesses and neoplasms.
As expected for a GLP-1 analogue, the most common adverse events associated with liraglutide treatment were *gastrointestinal disorders*, mostly nausea, diarrhoea and vomiting,
Special focus was given to a number of potential safety signals based on non-clinical findings and the use of exenatide, another GLP-1 receptor agonist.
The types of malignancies seen in the clinical studies were heterogeneous and the numbers small, most however were reported in the liraglutide group. Another important concern which remains at this point is the occurrence of thyroid events (goitre, neoplasms and increased calcitonin) that occurred more often in liraglutide group, both in patients with and without pre-existing thyroid pathology. Updating the safety data revealed that neoplasms occurred at a higher rate compared to placebo and active comparator. However, the relevance of these data is doubtful due to the low numbers. The rates of thyroid neoplasms were comparable for liraglutide and placebo.

Pancreatitis was also seen more frequently in liraglutide treated patients and warrants further attention.
Events of immunogenicity were seen with liraglutide, but most events were non serious and antibody formations was generally low. This issue is also known for exenatide. The rate of local skin reactions was also low and comparable to the placebo group. Liraglutide is associated with minor hypoglycaemic events, but major events were rare.
Given the absence of data and the prevalence of these conditions in the target population, cardiac events represent a possible concern and inclusion in the RMP as a potential risk is deemed necessary.
In summary, most safety issues are in accordance with those reported for other GLP-analogues. The occurrence of neoplasms, thyroid disease will be studied within in the large cardiovascular outcome trial.

Liraglutide has demonstrated a clinically relevant effect on glycaemic control in type 2 diabetic patients if used in combination with sulphonylurea, with metformin, with metformin and thiazolidinedione or with metformin and sulphonylurea. In these combinations the B/R ratio for liraglutide is considered positive. However, efficacy and safety data for the use of liraglutide as monotherapy, and in combination with thiazolidinedione alone has not been provided. Therefore, these two indications cannot be granted.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Victoza in the treatment of 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 was favourable and therefore recommended the granting of the marketing authorisation.