EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 April 2018
EMA/CHMP/380783/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Xultophy

International non-proprietary name: insulin degludec / liraglutide

Procedure No. EMEA/H/C/002647/II/0023

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
BMI	body mass index
SAE	serious adverse event
SD	standard deviation
bpm	beats per minute
CI	confidence interval
CVOT	cardiovascular outcome trial
DEVOTE	Degludec Cardiovascular Outcomes Trial
DPP-4	Dipeptidyl peptidase-4
EAC	event adjudication committee
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FDA	U.S. Food & Drug Administration
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated haemoglobin
HR	hazard ratio
IDeg	Insulin degludec
IGlar	Insulin glargine; 100 units/mL
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	major adverse cardiovascular event
MESI	medical event of special interest
MI	myocardial infarction
MTC	medullary thyroid carcinoma
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PYO	patient year of observation
SAE	serious adverse event
s.c.	subcutaneous
SMQ	standard MedDRA query
T2DM	type 2 diabetes mellitus
U	units
UAP	unstable angina pectoris
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 1 November 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the safety information based on cardiovascular outcomes studies conducted a for each of the monocomponents of Xultophy: LEADER (Liraglutide Cardiovascular Outcomes Trial) and DEVOTE (Insulin Degludec Cardiovascular Outcomes Trial).

The MAH is also proposing to reorganise parts of section 5.1 to improve the reader friendliness and to remove Xultophy from the list of medicines under additional monitoring.

The Package Leaflet is updated accordingly.

The RMP version 7.0 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

Timetable	Dates
Submission date	1 November 2017
Start of procedure:	25 November 2017
CHMP Co-Rapporteur Assessment Report	N/A
CHMP Rapporteur Assessment Report	22 January 2018
PRAC Rapporteur Assessment Report	24 January 2018
PRAC members comments	None
Updated PRAC Rapporteur Assessment Report	1 February 2018
PRAC endorsed relevant sections of the assessment report	8 February 2018
CHMP members comments	12 February 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 February 2018
Request for Supplementary Information	22 February 2018
Submission from MAH	23 March 2018
Re-start of procedure:	28 March 2018
PRAC Rapporteur Assessment Report	3 April 2018
PRAC members comments	4 April 2018
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	9 April 2018
PRAC endorsed relevant sections of the assessment report	12 April 2018
CHMP members comments	16 April 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 April 2018
Opinion	26 April 2018

2. Scientific discussion

2.1. Introduction

Medical background

T2DM is a progressive metabolic disorder characterised by chronic hyperglycaemia associated with increased risk of long-term micro-and macrovascular complications. Diabetes has been identified as an independent risk factor for cardiovascular disease, which represents the leading cause of morbidity and mortality in subjects with diabetes. Thus, the risk of cardiovascular disease is 2−4 times greater for

patients with T2DM compared to the general population, and death from cardiovascular causes is the most common cause of death in patients with T2DM.

Even with use of standard of care therapies to control cardiovascular risk factors, the risk of cardiovascular disease in subjects with diabetes remains to be more than double that in subjects without diabetes. Hence, the cardiovascular safety of antidiabetic drugs is of paramount importance.

Drug profile and target indication

Insulin degludec/liraglutide (IDegLira) is a combination of insulin degludec and liraglutide. Insulin degludec (IDeg) is a basal insulin analogue with a duration of action beyond 42 hours at clinically relevant doses. Liraglutide is an analogue of the endogenous human hormone glucagon-like peptide-1 (GLP-1). Liraglutide stimulates insulin secretion in a glucose-dependent manner and inhibits glucagon secretion when plasma glucose levels are above normal. Liraglutide also reduces body weight and body fat mass through mechanisms involving reduced hunger and decreased energy intake.

IDegLira (Xultophy) is approved for the treatment of adults with type 2 diabetes mellitus (T2DM), to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone, or combined with a GLP-1 receptor agonist (GLP-1 RA) or basal insulin, do not provide adequate glycaemic control.

Xultophy received regulatory approval in the EU in September 2014.

Rationale for the variation application and assessment

The cardiovascular risk profiles as well as long-term safety profiles of the components of IDegLira have recently been established through CVOTs for liraglutide (Trial 3748) and IDeg (Trial 4080). Based on the long-term exposure and safety data obtained in these trials, updates to the Victoza (liraglutide) and Tresiba (IDeg) product information have been made.

The MAH considers that several of these modifications are also relevant for IDegLira, and is therefore submitting this variation application proposing updates to the Xultophy product information, sections 4.1, 4.2, 4.8 and 5.1.

Since both trials already have been thoroughly assessed by the CHMP, the following assessment will focus on the data supporting the specific changes to the product information for Xultophy. Emphasis is put on the proposed inclusion of reference to the effect of Xultophy on cardiovascular events in section 4.1.

2.2. Non-clinical aspects

2.2.1. Pharmacology

Primary pharmacodynamic studies

Two non-GLP in vivo studies have been conducted to assess the effect of liraglutide in animal models of atherosclerosis.

Effect on atherosclerotic plaques in ApoE knock-out mice treated with liraglutide (Gura140701; divided in 3 sub-studies GuRa140701, GuRa 141101 and BidR13101)

The effect of liraglutide on prevention and regression of atherosclerotic plaques was studied in female Apolipoprotein E (ApoE) KO mice 9-12 weeks old at study start. The animals were fed western diet (WD)

and treated with either liraglutide (1.0 mg/kg) or vehicle s.c. for 6-15 weeks. Since liraglutide reduce food intake and body weight it was also investigated if the body weight reduction alone could prevent athesclerotic plaque formation in WD fed ApoE KO mice. Finally the gene expression in the plaque and plasma lipids was measured.

Liraglutide prevented aortic plaque progression and prevented further aorta intima thickening in animals fed WD. Weight loss was not able to show similar effect on plaque prevention as liraglutide treatment. Triglyceride and total cholesterol levels were not affected in neither of the treated groups.

In animals with established plaques aortic plaque area was not affected by liraglutide treatment. However, the triglyceride, VLDL cholesterol and LDL cholesterol were decreased by liraglutide whereas HDL cholesterol was increased. Body weight was slightly lower in the liraglutide treated group compared to vehicle.

Liraglutide led to changes in 21 genes compared to the vehicle treated group. Liraglutide prevented WD induced changes involved in inflammatory genes encoding for proteins comprising inflammatory processes related to leukocyte recruitment (e.g. Ccr2, Cxcl12, Cx3cr1) and adhesion (Cx3cr1, Itga3, Thy1) as well as lipid signalling (e.g Ptgir) and fibrinolysis (Plat).

Effect on atherosclerosis in LDL receptor knock out mice treated with liraglutide (GuRa 141102)

The effect of liraglutide in plaque formation was studied in male pro-atherosclerotic low density lipoprotein (LDL) receptor (r) KO mice 10-11 weeks of age at study start. The animals were fed (WD) and were treated with liraglutide at 1.0 mg/kg/day for 17 weeks. At termination plasma triglycerides (TG), total cholesterol (T-Chol), vLDL, LDL and HDL were measured and thoracic aorta was excised and plaque lesion levels were quantified. Thoracic aorta was further used to evaluate the expression levels of several inflammatory markers by NanoString analyses.

In pro-atherosclerotic male LDLr KO mice liraglutide prevented development of plaque in the aorta. Treatment with liraglutide also showed beneficial effects on plasma lipids resulting in a significant reduction in plasma TG, VLDL, LDL and an increase in HDL. Liraglutide treatment reduced body weight and body weight gain. In addition, treatment with liraglutide prevented the WD induced up regulation of, Interleukin-6, Matrix metalloproteinase 12 and 13, CD68, Cathepsin S, Neutrophil gelatinase-associated lipocalin, interleukin 1 Receptor Antagonist, macrophage scavanger 1, serum amyloid A3 and secreted Phosphoprotein 1, predominantly genes related to inflammation.

2.2.2. Ecotoxicity / environmental risk assessment

Xultophy consists of two drug substances, insulin degludec and liraglutide, which are characterized as peptides.

According to the Guideline on the environmental risk assessment of medical products for human use, substances like amino acids, peptides, proteins, carbohydrates and lipids are exempted from environmental risk assessment since they are unlikely to result in significant risk to the environment.

It is agreed that no environmental risk assessment is necessary for insulin degludec and liraglutide.

2.2.3. Discussion on non-clinical aspects

The studies have recently been submitted and assessed in a variation for Victoza EMEA/H/C/001026/II/0042. EPAR-AR Var dated 22 June 2017 and published 14 September 2017. The studies demonstrate that liraglutide attenuates the development of plaques in two different animal

models of atherosclerosis. The reduced plaque formation was not attributed to weight loss, or reduced body weight gain, as an active comparator causing greater body weight reduction than liraglutide, did not have an inhibitory effect on plaque formation.

Liraglutide has in addition a beneficial effect on plasma lipids, reducing TG, VLDL; LDL and increasing HDL. This may also contribute to the prevention of plaque formation according to the MAH.

In the aorta, liraglutide significantly affected mRNA expression encoding for proteins associated with atherosclerosis, primarily representing inflammatory pathways such as leukocyte recruitment, adhesion and migration.

The new data supports that liraglutide reduces the formation of atherosclerotic plaques and additionally has an anti-inflammatory effect in the cardiovascular system in ApoE- and LDLreceptor knock out (KO) mice fed a Western Diet (WD). However, in animals with established plaques aortic plaque area was not affected by liraglutide treatment.

The proposed "non-clinical" changes in the SmPC section 5.1 in bold italics below have been agreed and included in the SmPC for Victoza and are considered to be acceptable:

5.1 Pharmacodynamic properties

[……]

Mechanism of action

[……]

GLP-1 receptors are also expressed in specific locations in the heart, vasculature, immune system, and kidneys. In mouse models of atherosclerosis, liraglutide prevented aortic plaque progression and reduced inflammation in the plaque. In addition, liraglutide had a beneficial effect on plasma lipids. Liraglutide did not reduce the plaque size of already established plaques.

[……]

2.2.4. Conclusion on the non-clinical aspects

Considering the above data, insulin degludec and liraglutide are not expected to pose a risk to the environment.

The proposed "non-clinical" changes in the SmPC section 5.1 as indicated above (in bold italics) is acceptable and in line with the SmPC for Victoza.

2.3. Clinical aspects

2.3.1. Introduction

In this dossier, the results of two cardiovascular outcome trials are presented. Both studies have been previously assessed by the CHMP, therefore an abbreviated description of the studies is provided in this assessment report.

- Trial 3748 – LEADER - inclusion of data in the SmPC for Victoza (liraglutide) was approved in July 2017 through procedure EMEA/H/C/001026/II/0042.

- Trial 4080 – DEVOTE - inclusion of data in the SmPC for Tresiba (IDegLira) was approved in Sept 2017 through procedure EMEA/H/C/002498/II/0028.

With this application the MAH propose to include reference to the effect of Xultophy on cardiovascular events in section 4.1. Therefore the relevance of the data obtained with the monocomponents has to be justified. Other changes proposed with this application mainly relates to updated safety information concerning liraglutide based on new safety data obtained with trial 3478.

Both studies were designed to investigate the cardiovascular safety of liraglutide and IDeg, respectively. However, as the data on cardiovascular outcome is relevant for the assessment of the proposed change to the indication, the cardiovascular outcome is presented in the efficacy part of this report.

GCP

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

The MAH 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.

2.4. Clinical efficacy

2.4.1. Main studies

LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results. A long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events

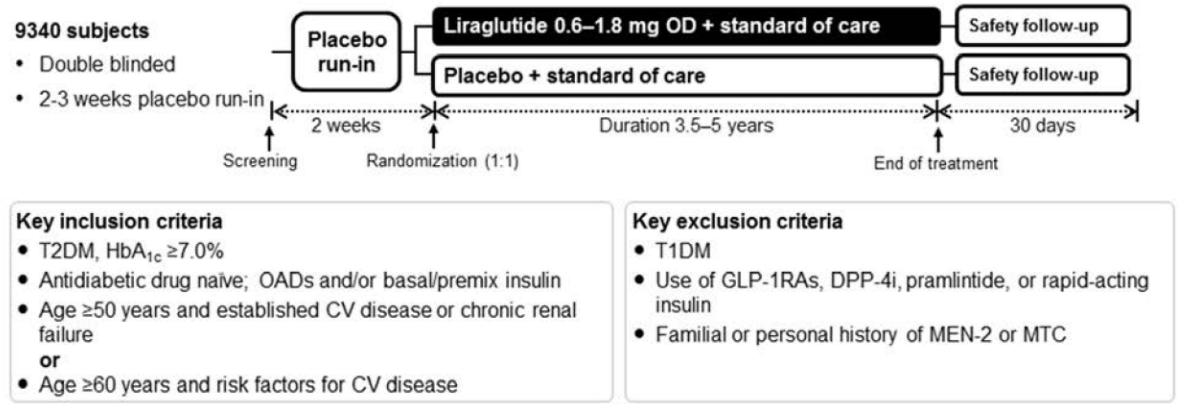
Methods

Trial 3748 was a long-term, multi-centre, multi-national, randomised, double-blind, placebo-controlled trial performed to determine the effect and safety of liraglutide *versus* placebo on cardiovascular outcomes. Both liraglutide and placebo were used in addition to standard of care therapy.

The duration of trial 3748 was driven by both number of MACEs and by time. Thus, trial 3748 ended once all subjects had had a minimum treatment period of 42 months (plus a follow-up period of 30 days), and once at least 611 EAC-confirmed MACEs were recorded. The minimum period of 42 months was defined in order to provide data on long-term exposure to liraglutide and allow assessments of relevant safety parameters of interest. Trial 3748 included a recruitment period of 18 months, resulting in a maximum treatment period of 60 months.

A schematic presentation of the key features of trial 3748, including trial design and population is provided in Figure 1.

Figure 1 Design of trial 3748



Abbreviations: CV: cardiovascular; DPP-4i: dipeptidyl peptidase-4 inhibitor; GLP-1RAs: glucagon-like peptide-1 receptor agonists; HbA_{1c}: glycaeted haemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid carcinoma; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus

Study participants

Main inclusion criteria were male or female subjects with T2DM with a HbA1c ≥ 7.0% at screening who were antidiabetic drug naïve or treated with one or more oral antidiabetic drugs or treated with human NPH insulin or long-acting insulin analogue or premixed insulin, alone or in combination with OAD(s) aged:

- ≥50 years with at least one of the following criteria: prior myocardial infarction; prior stroke or prior transient ischaemic attack (TIA); prior coronary, carotid or peripheral arterial revascularisation; >50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries; documented history of symptomatic coronary heart disease, or unstable angina with electrocardiogram (ECG) changes, documented asymptomatic cardiac ischemia; chronic heart failure NYHA class II-III; chronic renal failure (eGFR < 60 mL/min/1.73m^2 per MDRD or < 60 mL/min per Cockroft-Gault formula).

OR

- ≥60 years with at least one of the following criteria: microalbuminuria or proteinuria; hypertension and left ventricular hypertrophy by ECG or imaging; left ventricular systolic or diastolic dysfunction by imaging; ankle/brachial index <0.9.

Main exclusion criteria were diagnosis of T1DM, use of a GLP-1 receptor agonist or any DPP-4 inhibitor within the 3 months prior to screening or use of insulin other than the products stated in the inclusion criteria, an acute coronary or cerebrovascular event in the previous 14 days, planned coronary, carotid or peripheral artery revascularisation, chronic heart failure NYHA class IV, continuous renal replacement therapy, severe medical disorders or family or personal history of multiple endocrine neoplasia type 2, familial medullary thyroid carcinoma or non-familial medullary thyroid carcinoma.

Additional subjects with estimated glomerular filtration rate (eGFR) (as per MDRD) < 30 mL/min/1.73m^2 at screening were excluded once a target number of 220 subjects with eGFR < 30 mL/min/1.73m^2 had been randomised.

Treatments

The intended treatment dose for liraglutide was 1.8 mg/day, the maximum daily dose allowed according to the product information. The dose level of liraglutide or placebo was escalated from an initial dose of 0.6 mg/day (during the first week), with weekly dose escalation steps of 0.6 mg to the target dose level of 1.8 mg/day. The dose could be reduced (to 1.2 or 0.6 mg/day) at any time at the discretion of the investigator. Subjects were allowed to go on and off treatment during the trial, if decided by the investigator.

To ensure that all subjects in both treatment groups were optimally treated and to eliminate other factors influencing the results of the trial, investigators were encouraged to administer best-practice standard of care treatment in addition to trial product.

Objectives

The primary objective of trial 3748 was to assess the effect of liraglutide compared to placebo in addition to standard of care for at least 3.5 years and up to 5 years on the incidence of cardiovascular events in adults with T2DM and at high risk of cardiovascular events. The secondary objective was to assess the safety and effectiveness with regards to clinically important events or other surrogate parameters of treatment with liraglutide compared to placebo on top of standard of care. Furthermore, the trial was designed to include a sufficient number of subjects with moderate or severe renal impairment, to be able to explore the safety and effectiveness of liraglutide in these subgroups of subjects.

Outcomes / endpoints

The ***primary endpoint*** was the time from randomisation to first occurrence of a composite cardiovascular outcome (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The following ***secondary time-to-event endpoints*** were used as supportive endpoints for the primary objective:

- time from randomisation to first occurrence of an expanded composite cardiovascular outcome, defined as either cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, hospitalisation for unstable angina pectoris, or hospitalisation for heart failure
- time from randomisation to all-cause death
- time from randomisation to non-cardiovascular death
- time from randomisation to each individual component of the expanded composite cardiovascular outcome

In addition, a number of time-to-event endpoints were used as supportive endpoints for the secondary objectives. These included time from randomisation to first occurrence of a composite microvascular outcome (related to retinopathy and nephropathy).

Furthermore, to explore the difference in risk between liraglutide and placebo for progression of renal damage, in subjects with moderate renal failure at screening defined as eGFR 30 - < 60 mL/min/1.73 m^2 per MDRD time from randomisation to first occurrence of a second composite nephropathy outcome was analysed.

Statistical methods

Analysis sets

The following analysis sets were defined in the statistical analysis plan (SAP), prior to un-blinding, and in accordance with ICH E9:

- Full analysis set (FAS) included all randomised subjects. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle, and subjects contributed to the evaluation 'as randomised'.
- Per Protocol (PP) analysis set included all subjects who took at least one dose of the investigational product and these subjects were considered exposed until the accumulated number of days off investigational drugs exceeded 120 days.

Primary analysis

The primary endpoint was:

- Time from randomisation to first occurrence of a composite cardiovascular endpoint (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

In the FAS, observation time was defined as the duration from the date of randomisation to date of last contact with the subject. The primary analysis was conducted for the FAS using the Cox regression model (including treatment group as factor) to estimate the hazard ratio (liraglutide/placebo) and the 2-sided 95% confidence interval (CI). Non-inferiority of liraglutide versus placebo was considered confirmed, if the upper limit of the two-sided 95% CI for the hazard ratio was below 1.3 or if the p-value for the one-sided test of H0: HR ≥1.3 against Ha: HR <1.3 was less than 2.5%. If non-inferiority was established a test for superiority was to be performed. Superiority of liraglutide was confirmed, if the upper limit of the two-sided 95% CI for the hazard ratio was below 1.0 or if the p-value for the one-sided test of H0: HR ≥1.0 against Ha: HR <1.0 was less than 2.5% (or equivalent to 5% two-sided test).

Sensitivity analyses of primary endpoint and exploratory analyses of treatment differences within subgroups

- The primary analysis was repeated on the PP analysis set. Furthermore, as subjects could go on and off treatment, sensitivity analyses were performed for events occurring on randomised treatment +1 day and for events occurring on randomised treatment + 30 days.
- Exploratory analyses of the primary endpoint were performed in several subgroups including cardiovascular risk and renal function. The effect (main effect and interaction with treatment) was explored by adding these to the original Cox model. Hazard ratios and 2-sided 95% CIs were calculated for each subgroup.

Analysis of secondary endpoints

All secondary time-to-event endpoints were analysed by Cox regression models using the FAS (with treatment as factor) to estimate the hazard ratios and 2-sided 95% CIs.

Secondary analyses for effectiveness:

For HbA1c, body weight, blood pressure and lipids, change from baseline to the 3-year assessment, and change from baseline to end of treatment were analysed using a repeated normal mixed model for change from baseline with treatment, antidiabetic therapy at baseline, region, and sex as factors, and corresponding baseline value and age at baseline as covariates, with all effects nested within visit. An unstructured covariance matrix was used. The analysis at 3 years reflected the time of the last available measurement for the entire trial population. For subjects who were insulin-naïve at baseline, an analysis

of time to first use of insulin was performed using a Cox regression with treatment group as factor. The Cox regression model was used to estimate the hazard ratio (liraglutide/placebo) and the two-sided 95% CI. Subjects who did not initiate insulin were censored following the principle applied in the primary analysis.

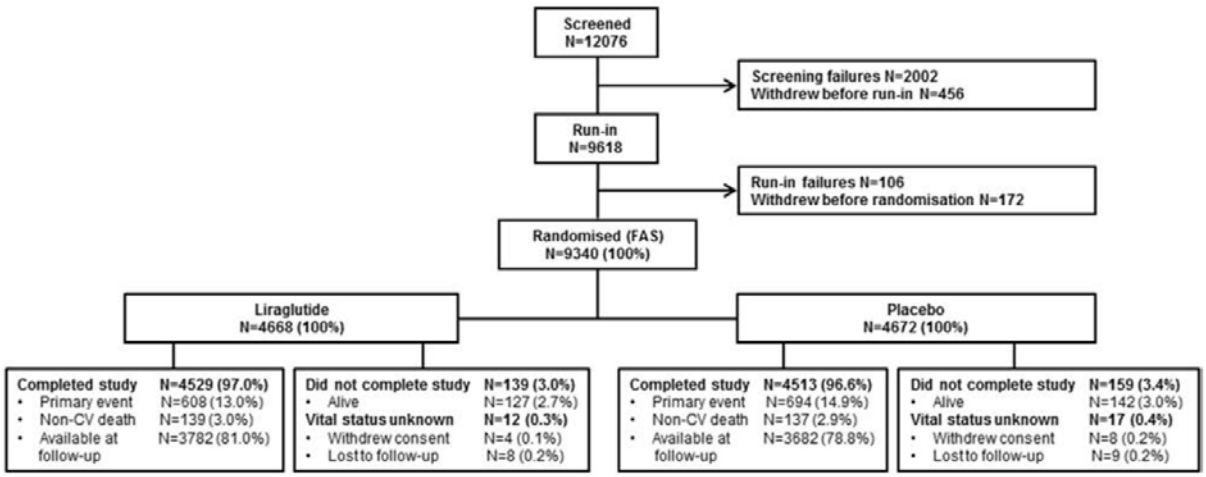
The type I error was not protected beyond the primary endpoint. The secondary endpoints are considered supportive.

Results

Participant flow

A schematic representation of the trial 3748 subject disposition is provided in Figure 2.

Figure 2 Subjects disposition of Trial 3748



Abbreviations: CV: cardiovascular; FAS: full analysis set, N: number of subjects.

Of the 12076 subjects screened, 9340 subjects were randomised 1:1 to either liraglutide or placebo treatment (all randomised subjects were included in the full analysis set (FAS).

To address the primary endpoint related to MACE a completer definition was established. A completer was defined as a subject who either had a primary event (MACE) or died due to non-cardiovascular causes, or with whom direct contact was established at or after the planned follow-up visit. Strict procedures were set up to collect information on subjects who were potentially lost to follow-up, in order to achieve information on vital status at trial closure. At the end of the trial it was determined that ~97% of subjects were completers and > 99% were either completers or had known vital status in both treatment groups, demonstrating a high degree of subject retention in the trial.

Baseline data

Demographics and baseline characteristics were well-balanced between subjects randomised to liraglutide and placebo.

Among all randomised subjects, the mean age was 64.3 years, mean body mass index (BMI) was 32.5 kg/m^2, and 64.3% of the trial population were men. The mean duration of T2DM was 12.8 years and the mean HbA1c was 8.7%. Most subjects were White (77.5%), 8.3% of subjects were Black or African American and 10% of subjects were Asian.

At screening, 81.3% of the subjects were ≥50 years with established cardiovascular disease (of these 24.7% had chronic kidney failure) and 18.7% of the subjects were ≥60 years with only risk factors for cardiovascular disease. A total of 30.1% of all randomised subjects had a history of myocardial infarction (MI), 8.4% had a history of unstable angina (UAP) and 14% had chronic heart failure characterised as NYHA class II or III at screening. At trial entry, mean estimated glomerular filtration rate (eGFR) per MDRD was 80.4 ml/min/1.73m^2 and 23.1% of all randomised subjects had moderate or severe renal impairment. At screening 40.7% of subjects had diabetic nephropathy, 20.1% had diabetic retinopathy, and 34.6% had diabetic neuropathy based on medical history.

Demographics and baseline characteristics in subgroups

Demographics and baseline characteristics were evaluated in a number of subgroups: subgroups according to age, renal function, heart failure status (NYHA class) and use of pre-mix insulin at baseline. In these subgroups analyses of effectiveness were conducted.

Concomitant medication

Overall, use of cardiovascular medication was well-balanced between the two treatment groups at baseline, with only minor differences between treatment groups. The majority of subjects were treated with antihypertensive therapy (most often beta-blockers and ACE inhibitors), lipid-lowering agents (such as statins) and/or platelet aggregation inhibitors (such as acetylsalicylic acid). The proportion of subjects who initiated treatment with cardiovascular medication during the trial was generally lower in the liraglutide group compared to the placebo group across most drug classes.

Overall, use of antidiabetic medication at baseline was well-balanced between the two treatment groups. Metformin was the most commonly used antidiabetic medication at baseline (by 76.5% of all randomised subjects), while SUs were used by 50.7% and any insulin (most commonly long-acting agents) was used by 44.6% of subjects. Of the total trial population, 3.9% were antidiabetic drug naïve at baseline. A lower proportion of subjects in the liraglutide group initiated additional glucose-lowering therapy during the trial and a higher proportion remained insulin-naïve throughout the trial compared to the placebo group. A minor proportion of subjects initiated treatment with GLP-1 RAs or DPP-4 inhibitors although this was not allowed according to the protocol. These subjects were to discontinue treatment with trial product. Trial product could be resumed following a wash-out period if disallowed medication was discontinued.

Table 1 Antidiabetic medication at baseline - FAS

	Lira			Placebo			Total		
	N	PYE	(%)	N	PYE	(%)	N	PYE	(%)
Number of subjects	4668			4672			9340		
Blood glucose lowering drugs (excluding insulin) at baseline	4113	15268	(88.1)	4129	15449	(88.4)	8242	30717	(88.2)
Metformin	3540	9528	(75.8)	3604	9631	(77.1)	7144	19159	(76.5)
SU	2370	4481	(50.8)	2363	4696	(50.6)	4733	9177	(50.7)
Alpha glucosidase inhibitors	139	289	(3.0)	123	265	(2.6)	262	554	(2.8)
TZD	296	649	(6.3)	279	548	(6.0)	575	1196	(6.2)
DPP4 inhibitors	4	5	(<0.1)	2	5	(<0.1)	6	10	(<0.1)
GLP1 receptor agonist	0	0	(0.0)	2	4	(<0.1)	2	4	(<0.1)
SGLT2 inhibitors	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)
Glinides	178	317	(3.8)	172	296	(3.7)	350	613	(3.7)
Other	0	0	(0.0)	1	4	(<0.1)	1	4	(<0.1)
Insulin treatment at baseline	2038	2755	(43.7)	2131	2785	(45.6)	4169	5540	(44.6)
Premix	445	659	(9.5)	463	650	(9.9)	908	1309	(9.7)
Short acting	42	59	(0.9)	26	48	(0.6)	68	107	(0.7)
Intermediate acting	547	619	(11.7)	600	682	(12.8)	1147	1301	(12.3)
Long acting	1041	1391	(22.3)	1077	1401	(23.1)	2118	2792	(22.7)
Other insulins	23	26	(0.5)	14	4	(0.3)	37	30	(0.4)
Insulin naive	2630	10175	(56.3)	2541	9771	(54.4)	5171	19945	(55.4)

N: Number of subjects, %: Proportion of subjects, PYE: Patient years of exposure, SU: Sulphonylurea, TZD: Thiazolidinedione, DPP4: Dipeptidyl peptidase-4, NPH: Neutral Protamine Hagedorn, GLP1: Glucagon-like peptide-1, SGLT-2: Sodium-Dependent Glucose Transporter Two, FAS: full analysis set.82 subjects have missing initiation drug date, these are assumed to be on treatment at baseline, A treatment in the insulin category is included if the subject has initiated the treatment before randomisation, Blood glucose lowering drugs are counted if the treatment is active at time of randomisation.

Outcomes and estimation

Primary endpoint: 3-point MACE

The primary composite cardiovascular endpoint was time from randomisation to first MACE consisting of cardiovascular death, non-fatal stroke and non-fatal MI (including silent MI).

A total of 1302 first EAC-confirmed MACEs were reported in trial 3748 (608 in the liraglutide group and 694 in the placebo group).

In the primary Cox analysis of time to first EAC-confirmed MACE, the estimated hazard ratio (liraglutide vs placebo) of 0.87 $[0.78; 0.97]_{95\% CI}$ was statistically significant and in favour of liraglutide, corresponding to an estimated risk reduction of 13%. Since non-inferiority was confirmed in the pre-specified hierarchy, superiority was then tested and as the upper limit of the 95% CI was below 1.0 superiority was also established of liraglutide vs placebo; with one-sided p-values (α-level: 0.025) for non-inferiority and superiority of $p < 0.001$ and $p = 0.005$, respectively.

All three components of the primary endpoint appeared to contribute to the reduction in first MACE observed with liraglutide (Table 2). In both treatment groups, almost half of the events contributing to the primary endpoint were non-fatal MIs.

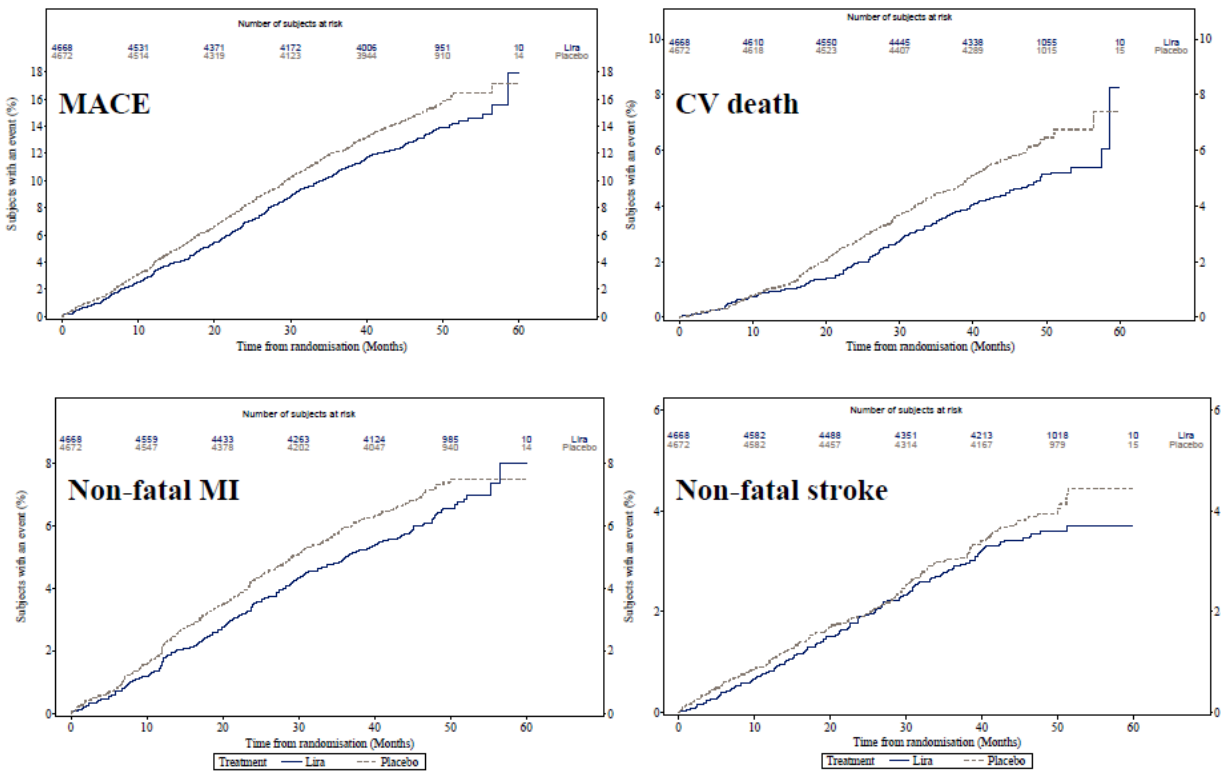
In the corresponding Kaplan-Meier plot (Figure 3), the development in EAC-confirmed first MACE over time is shown. The estimated risk of experiencing a MACE within any certain time from randomisation was lower for liraglutide compared to placebo. Similarly, favourable treatment differences were observed in the time to first event analysis of the individual components of MACE, with a generally lower risk for liraglutide throughout the trial (Figure 3).

In accordance with the results based on first EAC-confirmed MACE, the total number of EAC-confirmed MACEs (first events and recurrent events) and the rate of such events were lower in the liraglutide group (735 events/4.12 events per 100 PYO) than in the placebo group (870 events/4.90 events per 100 PYO). Again all three components of the endpoint contributed to the treatment difference observed for all MACEs (Table 2).

Table 2 First and All EAC-confirmed MACE - FAS

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
FAS	4668				4672			
PYO	17822				17741			
First EAC-confirmed MACE								
EAC confirmed MACE	608	(13.0)	608	3.41	694	(14.9)	694	3.91
Cardiovascular death	181	(3.9)	181	1.02	227	(4.9)	227	1.28
Non-fatal MI	275	(5.9)	275	1.54	304	(6.5)	304	1.71
Non-fatal stroke	152	(3.3)	152	0.85	163	(3.5)	163	0.92
All index events (first and recurrent)EAC-confirmed								
EAC confirmed MACE	608	(13.0)	735	4.12	694	(14.9)	870	4.90
Cardiovascular death	219	(4.7)	219	1.23	278	(6.0)	278	1.57
Non-fatal MI	281	(6.0)	342	1.92	317	(6.8)	393	2.22
Non-fatal stroke	159	(3.4)	174	0.98	177	(3.8)	199	1.12

Figure 3 Kaplan-Meier plot of time to first EAC-confirmed MACE and individual components hereof – FAS



Note: The y-axes are adjusted to the proportion of subjects with events for each of the individual endpoints.

MACE is a composite of cardiovascular death, non-fatal MI and non-fatal stroke. Plots for time to first event for the individual components of MACE include all first events within the individual components regardless of whether these contribute to the time to first MACE analysis.

Abbreviations: CV: cardiovascular; EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide; MACE: major adverse cardiovascular event; MI: myocardial infarction

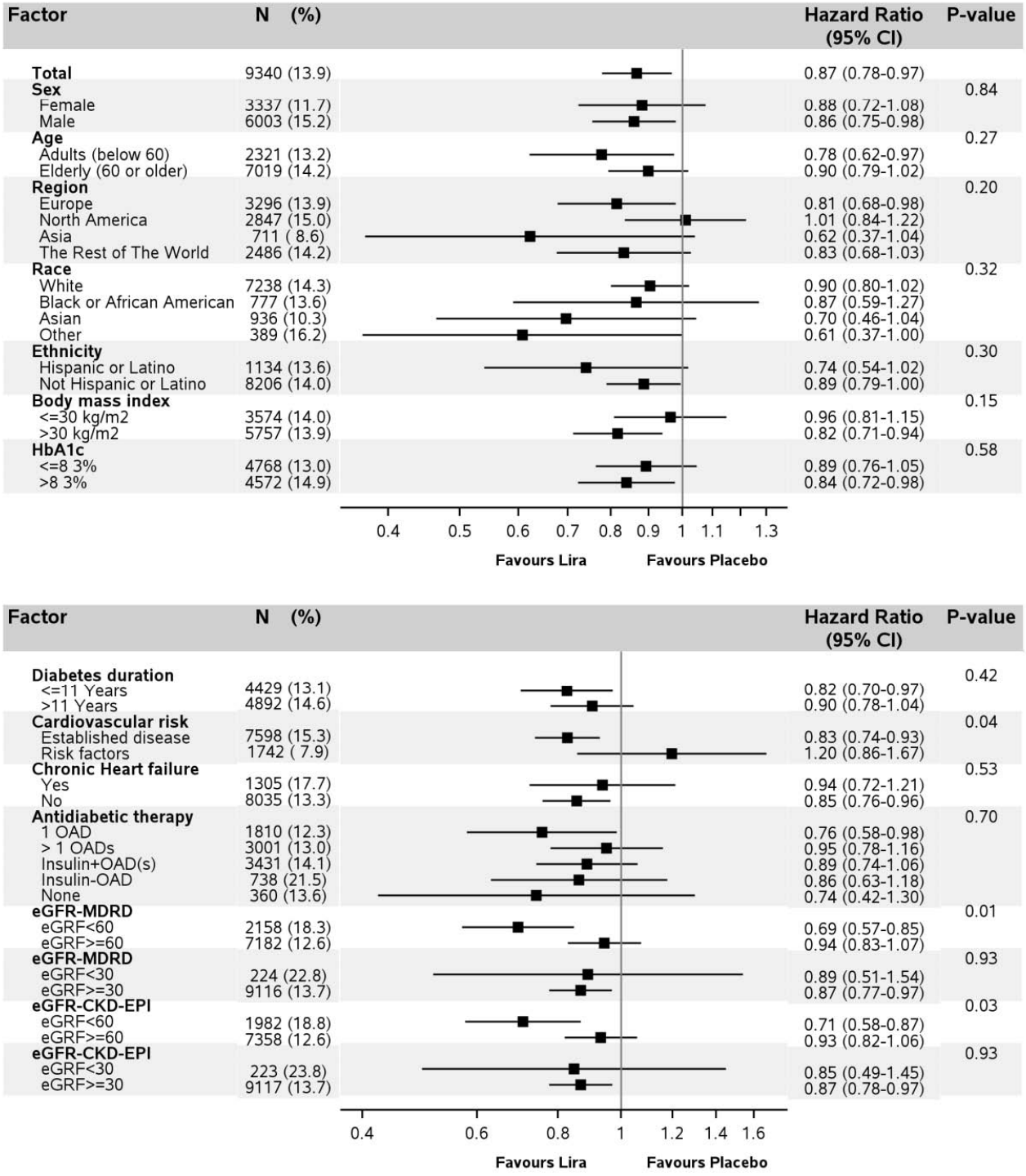
A series of pre-specified sensitivity analyses of the primary endpoint were made. These included one analysis adjusted for additional covariates, one adjusted for additional covariates and random country effects or stratification for severe renal disease. All of these pre-specified analyses were consistent with the primary analysis supporting the robustness of the results for the primary endpoint.

In general, no differences were observed in demographics and baseline characteristic in subjects with MACE between the two treatment groups. Similarly, there were no major differences in the use of cardiovascular medications at baseline or initiated during the trial for subjects with EAC-confirmed MACE between the two treatment groups.

Subgroup analyses of the primary endpoint

Pre-specified exploratory analyses were performed to evaluate the consistency of the treatment effect between liraglutide and placebo in time to *first* MACE across multiple subgroups. Interpretation of these should be made with caution as the study was not powered to detect small or moderate differences in treatment effect between subgroups and because adjustments for multiplicity were not made. The benefit observed with liraglutide *versus* placebo was generally consistent across the majority of the pre-defined subgroups including sex, age, BMI, race, ethnicity, HbA1c, diabetes duration, heart failure status, and antidiabetic therapy (including antidiabetic drug naïve subjects); (Figure 4).

Figure 4 Forest plot of treatment contrast according to subgroups - FAS



Note: Chronic heart failure: NYHA class II or III at baseline. Age, body mass index, HbA1c, diabetes duration, cardiovascular risk, antidiabetic therapy and eGFR values are from baseline. The p-value is from the test statistic for testing the interaction between treatment and factor.

Abbreviations: %: proportion in % of subjects with a first MACE between randomisation and follow-up date;

CI: confidence interval; CKD-EPI: chronic kidney disease epidemiology collaboration equation; eGFR: estimated glomerular filtration rate; FAS: full analysis set; N: number of subjects; Lira: liraglutide; MACE: major adverse cardiovascular event; MDRD: modification of diet in renal disease formula; OAD: oral antidiabetic drug

The two individual subgroup analyses where the hazard ratios were above 1 were in subjects from Region North America (hazard ratio 1.01) and in subjects' ≥60 years of age with risk factors for cardiovascular disease (hazard ratio 1.20), see Figure 4. In both analyses the lower bound of the 95% CI was below

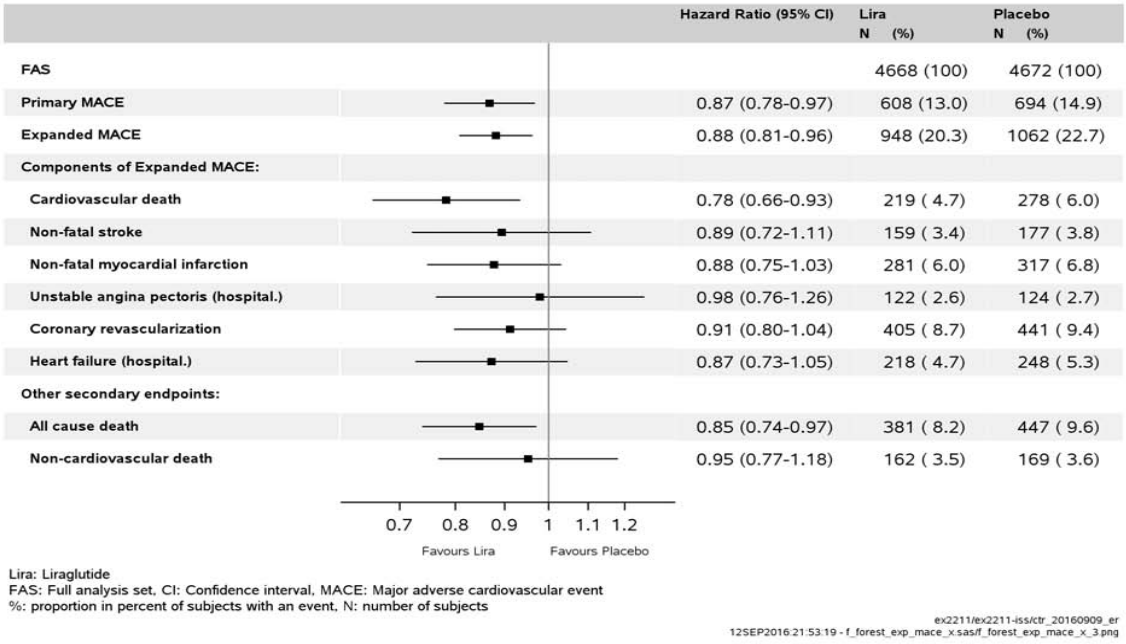
0.87 (i.e. including the HR for the primary analysis). The interaction analyses did not give evidence of a potential difference in treatment effects between regions (p=0.20), whereas a potential difference in treatment effect between cardiovascular risk subgroups was indicated (p=0.04), albeit the risk for false significance (type 1 error) as a result of multiple testing should be kept in mind.

A favourable effect of liraglutide was also observed across subgroups by **renal function** with point estimates consistently < 1 (Figure 4). The benefit of liraglutide compared to placebo, appeared to be more pronounced in subjects with moderate or severe renal impairment at baseline compared to subjects with normal renal function or mild renal impairment, based on eGFR calculations per MDRD or CKD-EPI.

Secondary endpoint: expanded MACE

In line with the results for the primary MACE analysis, the estimated risk of experiencing an expanded MACE was reduced by 12% (HR: 0.88 [0.81; 0.96]95%CI) with liraglutide compared to placebo confirming the cardio-protective effect of liraglutide (Figure 5). All components of expanded MACE appeared to contribute to the reduced risk although the hazard ratio for hospitalisation for UAP was just below 1. A consistent pattern was observed when all events of expanded MACE were considered, including both first and recurrent events, i.e., the number and rate of events was lower with liraglutide (1721 events, 9.66 events per 100 PYO) compared to placebo (1958 events, 11.04 events per 100 PYO).

Figure 5 Forest plot of treatment contrast for components of first EAC confirmed expanded MACE, MACE and death.



Note: For the time to first event of any individual component of expanded MACE, all first events are included regardless of whether these contribute to the time to first event analysis of the composite endpoint.

Abbreviations: %: proportion of subjects with an event; CI: confidence interval; Comp: components; FAS: full analysis set; Hospital: hospitalisation; MACE: major adverse cardiovascular event; N: number of subjects

MACE by heart rate

An increase in estimated mean heart rate of approximately 3 bpm was observed in the liraglutide group in trial 3748. Furthermore, categorical increases in heart rate of ≥ 10 bpm at visit 6 (month 6) were observed in a higher proportion of subjects in the liraglutide group (31%) compared to those in the placebo group (16%). Exploratory *post hoc* Cox analyses of time to first EAC-confirmed MACE and time to first hospitalisation for heart failure by categorical heart rate change at month 6 were performed. As the increase in heart rate with liraglutide occurs rapidly after treatment initiation, the analysis was based on

the first available assessment of heart rate change post baseline which was at month 6. In both analyses, the results were consistent between the categorical heart rate change subgroups < 10 bpm and ≥ 10 bpm, and the proportion of subjects with a first MACE was consistently lower in the liraglutide group compared to the placebo group (First MACE in subjects with Chg in HR <10 bmp: Lira 11.7% and placebo 13.7%; First MACE in subjects with Chg in HR ≥10 bmp: Lira 12.5% and placebo 13.6%). Furthermore, no imbalance was seen in adverse events of arrhythmia as reported by the investigators.

Secondary endpoint: all-cause death and non-cardiovascular death

In trial 3748, the estimated risk of all-cause death was reduced by 15% in the liraglutide group compared to the placebo group (HR: 0.85 [0.74; 0.97]95%CI); see Figure 5. The difference was primarily driven by the lower frequency of cardiovascular deaths. The robustness was supported by a post hoc 'on-treatment' analysis of time to all-cause death and a post hoc tipping point analysis evaluating the potential impact of missing data.

A reduction was also observed for the estimated risk of non-cardiovascular death with liraglutide compared to placebo (HR: 0.95 [0.77; 1.18]95%CI) (Figure 5). The most frequently reported causes of non-cardiovascular deaths were 'malignancy' and 'infection (including sepsis)' with no evident differences between the treatment groups.

Microvascular endpoints

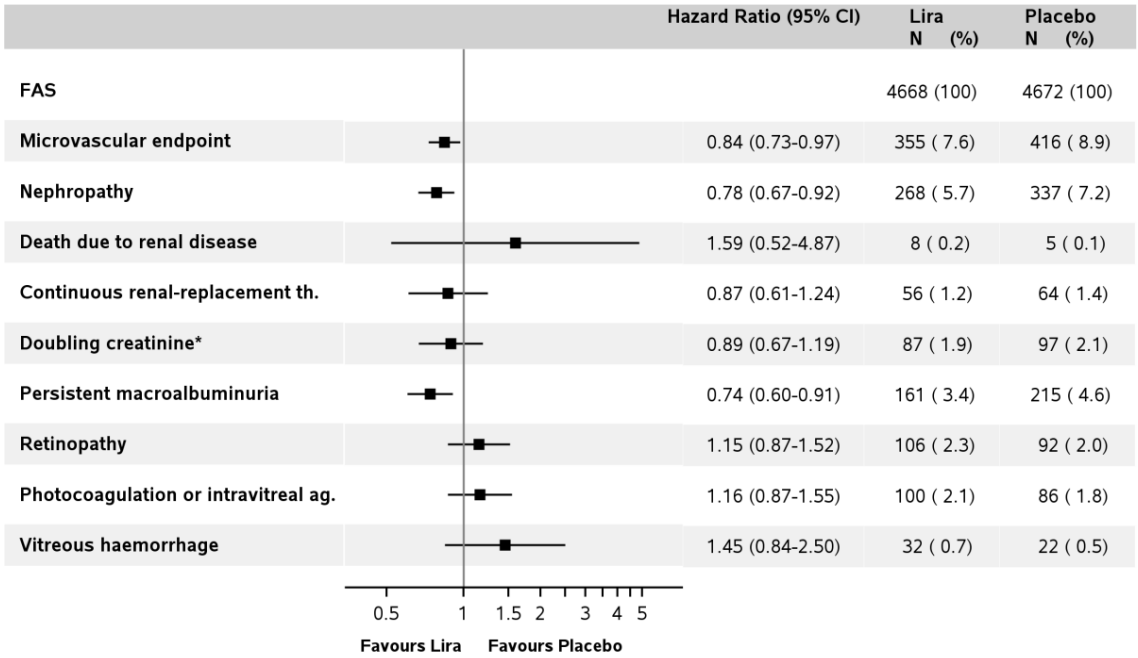
The pre-specified secondary endpoint 'time to first occurrence of a microvascular event' counted first events of any of the 7 components of the microvascular composite (see Figure 6 for components). A single EAC-confirmed event could concomitantly fulfil more than one criterion defining either nephropathy or retinopathy events, thus, an event could count in more than one of the analyses of the individual components of the microvascular composite.

The results of the main pre-specified time-to-event analyses for the microvascular composite and its components are summarised in Figure 6.

The Cox analysis of 'time to first occurrence of a microvascular event' resulted in an estimated hazard ratio (liraglutide *versus* placebo) of 0.84 $[0.73; 0.97]_{95\%CI}$, corresponding to a 16% reduction in the risk of microvascular events in the liraglutide group compared to the placebo group. The results were supported by a pre-specified sensitivity analysis that adjusted for additional covariates and a *post hoc* PP analysis. The difference between the treatment groups was driven by the nephropathy composite, with an estimated hazard ratio (liraglutide *versus* placebo) of 0.78 $[0.67; 0.92]_{95\%CI}$, corresponding to a 22% reduction in the risk of nephropathy events. The estimated hazard ratio for the retinopathy composite was 1.15 $[0.87; 1.52]_{95\%CI}$.

In accordance with the results for the microvascular endpoint based on first events, the number and rate of EAC-confirmed microvascular events overall (first events and recurrent events) were lower in the liraglutide group than in the placebo group.

Figure 6 Forest plot of the microvascular composite endpoint and its components



Note: Doubling creatinine*: persistent doubling of serum creatinine and eGFR ≤45 mL/min/1.73m^2 per MDRD; Continuous renal-replacement th(erapy): need for continuous renal replacement therapy; Photocoagulation or intravitreal ag(ents): need for retinal photocoagulation or treatment with intravitreal agents. Only 1 subject (in the placebo group) had 1 EAC-confirmed event of 'development of diabetes-related blindness' (Trial 3748 [M5.3.5.1], Table 11-11), therefore, the analysis of the component 'development of diabetes-related blindness' is not included in the figure.

Abbreviations: %: proportion of subjects with an event; CI: confidence interval; FAS: full analysis set; Lira: liraglutide; N: number of subjects; eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease.

Glycaemic control

Trial 3748 includes a number of sensitive subject populations for which there is currently no or limited clinical experience with liraglutide. In addition to subjects at high cardiovascular risk, this includes elderly subjects, subjects with severe renal impairment, subjects with heart failure (NYHA class I-III) and subjects treated with pre-mix insulin at baseline.

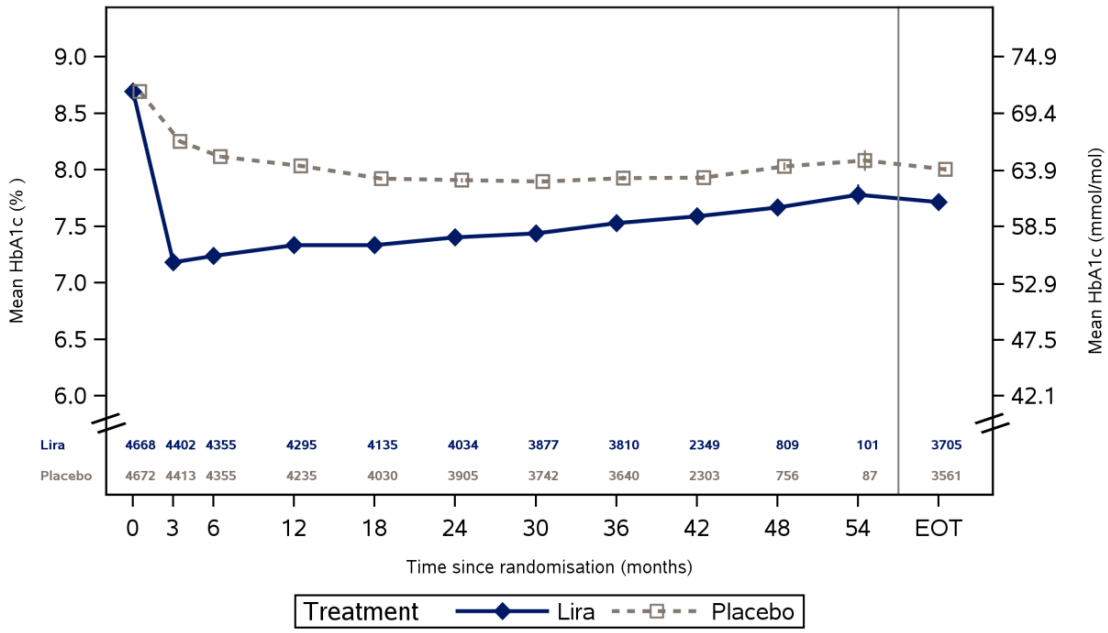
HbA1c

In trial 3748, the mean baseline HbA_{1c} was 8.7% in both treatment groups. In the liraglutide group, a substantial reduction in HbA_{1c} was seen at 3 months, followed by a small, gradual increase throughout the rest of the trial (Figure 7, Table 3). In spite of the recommendations to optimise glycaemic control for all subjects, the placebo group did not achieve the same level of control on standard of care therapy and this was especially apparent during the first part of the trial where after the difference between the treatment groups diminished.

The reduction in HbA_{1c} was significantly greater with liraglutide than with placebo after 3 years of treatment (-1.16% *versus* -0.77%; estimated treatment difference of -0.4% $[-0.45; -0.34]_{95\% CI}$); and the difference was maintained at end of treatment (-0.3% $[-0.35; -0.23]_{95\% CI}$).

Proportions of subjects in the liraglutide group achieving targets for HbA1c of <7%, 7.5% or 8% were in line with these results and were larger than those in the placebo group.

Figure 7 Estimated mean HbA1c over time – FAS



Note: Estimated data. The numbers are the number of subjects with an observed value who contributed to the analysis. Error bars: +/- standard error (mean). Vertical grey line separates last scheduled and end-of-treatment visit.
Abbreviations: EOT: end of treatment; FAS: full analysis set; HbA_{1c}: glycosylated haemoglobin; Lira: liraglutide.

Table 3 Endpoints related to effectiveness: Change from baseline to 3 years – MMRM – FAS

	Change from baseline (estimated means)		Treatment contrast: Lira vs placebo	
	Lira	**Placebo**	**ETD**	**95% CI**
HbA1c (%)	-1.161	-0.765	-0.396	[-0.453; -0.338]
Body weight (kg)	-2.736	-0.472	-2.264	[-2.539; -1.990]
SBP (mmHg)	-1.444	-0.245	-1.199	[-1.916; -0.483]
DBP (mmHg)	-0.787	-1.374	0.587	[0.187; 0.987]
	Ratio to baseline (estimated means)		**Treatment contrast: Lira vs placebo**	
	Lira	**Placebo**	**ETR**	**95% CI**
Total cholesterol (mmol/L)	0.990	1.002	0.988	[0.979; 0.997]
HDL cholesterol (mmol/L)	1.032	1.022	1.009	[1.002; 1.017]
LDL cholesterol (mmol/L)	0.974	0.998	0.977	[0.962; 0.992]
Triglycerides (mmol/L)	0.961	0.975	0.985	[0.968; 1.003]

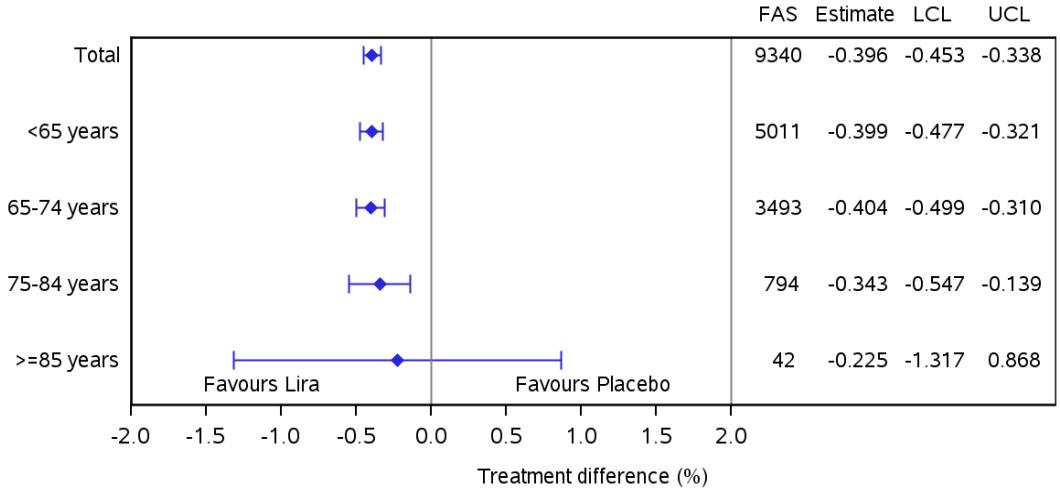
CI: confidence interval; DBP: diastolic blood pressure; ETD: estimated treatment difference; ETR: estimated treatment ratio;

FAS: full analysis set; Lira: liraglutide; SBP: systolic blood pressure. MMRM: mixed model for repeated measures.

HbA1c in sub-populations

The beneficial effect of liraglutide on glycaemic control, as evaluated by $HbA_{1c,}$ was consistent across age groups, baseline renal function, and heart failure status according to NYHA classification (see Figure 8, Figure 9 and Figure 10). Furthermore, the estimated difference in HbA_{1c} with liraglutide *versus* placebo was similar across the different subgroups.

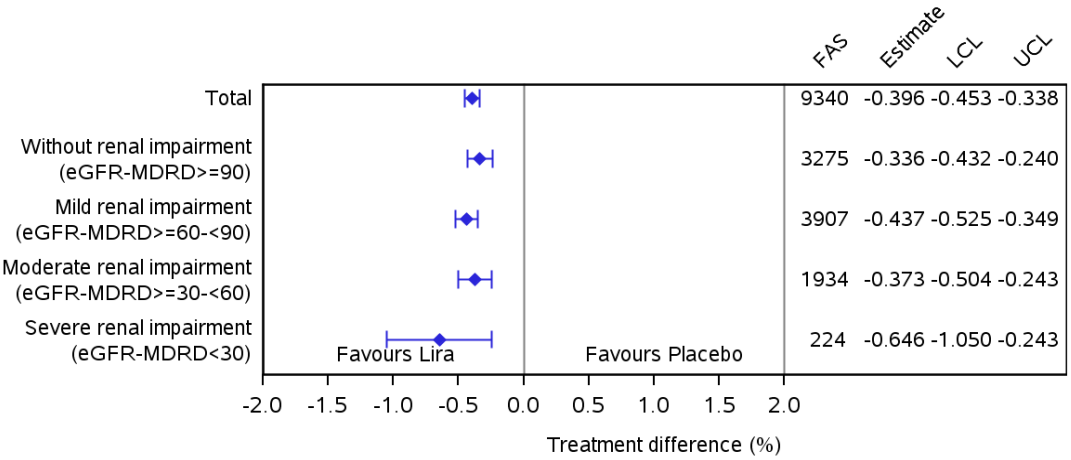
Figure 8 HbA1c - change from baseline to 3-year visit (visit 11) by age group - forest plot - MMRM – FAS



Note: Treatment differences are estimated using MMRM with an unstructured covariance matrix. Treatment, sex, region and antidiabetic therapy at baseline are included as fixed effects and baseline HbA_{1c} and age as covariates, all nested within visit. For the analyses per subgroup, the model also includes subgroup and the interaction between treatment and subgroup, both nested within visit.

Abbreviations: FAS: full analysis set; HbA_{1c}: glycosylated haemoglobin; Lira: liraglutide; LCL: lower 95% confidence limit; MMRM: mixed model for repeated measurements; UCL: upper 95% confidence limit.

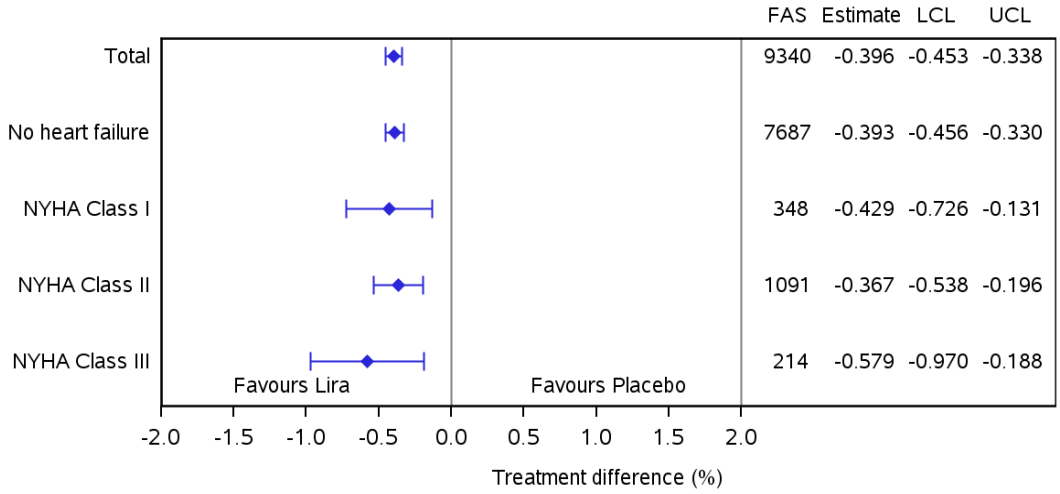
Figure 9 HbA1c - change from baseline to 3-year visit (visit 11) by baseline renal function - forest plot - MMRM – FAS



Note: Treatment differences are estimated using MMRM with an unstructured covariance matrix. Treatment, sex, region and antidiabetic therapy at baseline are included as fixed effects and baseline HbA_{1c} and age as covariates, all nested within visit. For the analyses per subgroup, the model also includes subgroup and the interaction between treatment and subgroup, both nested within visit.

Abbreviations: eGFR: estimated glomerular filtration rate using the modification of diet in renal disease formula; FAS: full analysis set; HbA_{1c}: glycosylated haemoglobin; Lira: liraglutide; LCL: lower 95% confidence limit; MMRM: mixed model for repeated measurements; UCL: upper 95% confidence limit.

Figure 10 HbA1c - change from baseline to 3-year visit (visit 11) by NYHA class at screening - forest plot - MMRM – FAS



Note: Treatment differences are estimated using MMRM with an unstructured covariance matrix. Treatment, sex, region and antidiabetic therapy at baseline are all included as fixed effects and baseline HbA_{1c} and age as covariates, all nested within visit. For the analyses per subgroup, the model also includes subgroup and the interaction between treatment and subgroup, both nested within visit.

Abbreviations: FAS: full analysis set; HbA_{1c}: glycosylated haemoglobin; Lira: liraglutide; LCL: lower 95% confidence limit; MMRM: mixed model for repeated measurements; NYHA: New York Heart Association; UCL: upper 95% confidence limit.

Initiation of insulin and other antidiabetic therapies

At baseline, 56.3% of subjects in the liraglutide group and 54.4% of subjects in the placebo group were insulin-naïve. During the trial, insulin was prescribed by the investigators as part of the recommended standard of care antidiabetic therapy to ensure improved glycaemic control. Insulin was initiated by a larger proportion of subjects in the placebo group than in the liraglutide group (43.2 vs 28.8% for placebo and liraglutide, respectively). A similar pattern was observed with respect to initiation of any new OAD (29.1 vs 21.7% for placebo and liraglutide, respectively) and initiation of insulin or any new OAD, respectively.

Other efficacy endpoints

A reduction in **body weight** was observed in the liraglutide group compared to the placebo group at 3 years (-2.7kg vs -0.5kg). The difference was sustained throughout the trial.

A greater reduction in **systolic blood pressure** was seen in the liraglutide group compared to the placebo group at 3 years (-1.44 vs -0.25 mm Hg), while for diastolic blood pressure a smaller reduction was observed in the liraglutide group (-0.79 vs -1.37 mm Hg).

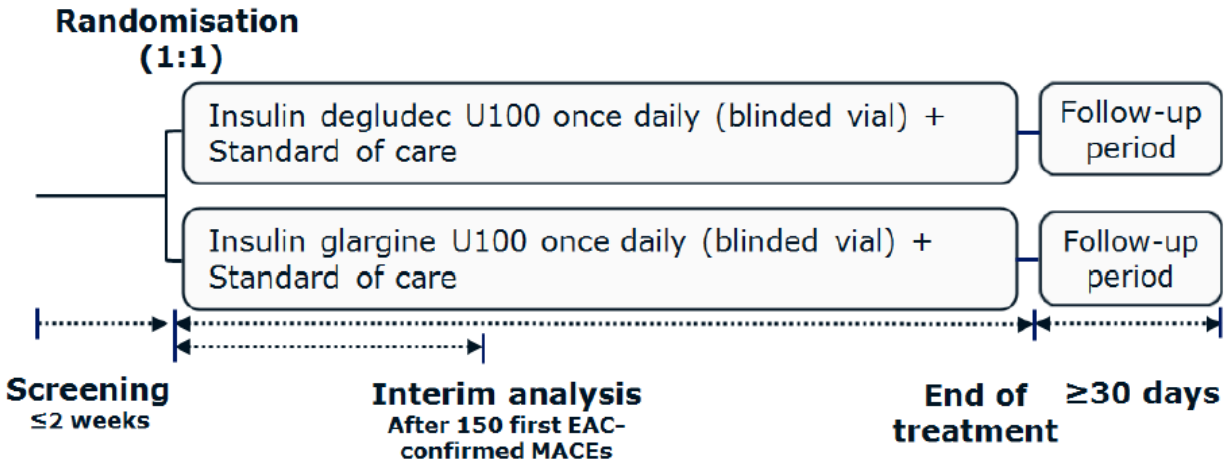
Increases were observed for **total cholesterol, LDL cholesterol and HDL cholesterol**, while the level of **triglycerides** was comparable between the treatment groups. The increases in TC and LDL were smaller for liraglutide as compared to placebo, while the increase in HDL was somewhat larger for liraglutide.

DEVOTE: A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events

Methods

DEVOTE was a long-term, multi-centre, multi-national, randomised, double-blind, parallel-group, treat-to-target, controlled trial performed to confirm the cardiovascular safety of IDeg compared to IGlar when added to standard of care, in male and female subjects with T2DM at high risk of cardiovascular events. The trial design is shown schematically in Figure 11.

Figure 11 Trial design: Randomised, controlled, double-blind, parallel-group trial



Abbreviations: U100: 100 units/mL; EAC: event adjudication committee; MACE: major adverse cardiovascular event.

The trial was event-driven and continued until a pre-specified number of 633 first EAC-confirmed 3-component MACE (henceforth referred to as MACE) comprising cardiovascular death, non-fatal myocardial infarction or non-fatal stroke were accrued.

Study participants

It was planned to randomise at least 7500 male and female subjects aged ≥50 years with established cardiovascular disease or chronic kidney disease and subjects aged ≥60 years with risk factors for cardiovascular disease. Key inclusion and exclusion criteria are listed in Table 4.

Table 4 Key inclusion and exclusion criteria

Inclusion criteria
Subjects with T2DM
Age ≥50 years at screening with established cardiovascular disease or chronic kidney disease *or*
Age ≥60 years at screening with predefined cardiovascular risk factors
HbA_{1c} ≥7.0 % *or* HbA_{1c} <7.0 % and current insulin treatment corresponding to ≥20 units/day of basal insulin
Use of one or more oral or injectable antidiabetic agent(s)
Exclusion criteria
Acute coronary or cerebrovascular event in the previous 60 days
Planned coronary, carotid or peripheral artery revascularisation
Chronic heart failure NYHA class IV
Current haemodialysis or peritoneal dialysis or eGFR <30 mL/min/1.73 m^2 per CKD-EPI
End stage liver disease
Current or past (within the last 5 years) malignant neoplasms (except basal cell and squamous cell skin carcinoma)
Abbreviations: T2DM: type 2 diabetes mellitus; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; HbA_{1c}: glycated haemoglobin; NYHA: New York Heart Association.

Treatments

Basal insulin

All subjects could continue their pre-trial antidiabetic therapy except for the basal insulin component (if any) which was to be replaced by the IMPs i.e. IDeg or IGlar, (administered OD between dinner and bedtime).

Insulin-naïve subjects initiated basal insulin at a dose of 10 units OD. Subjects receiving basal insulin OD were to be switched unit-to-unit from their previous basal insulin dose. Subjects receiving twice daily (or more) basal insulin were to be switched to an OD regimen and the pre-trial total basal insulin dose was to be reduced by 20–30%. No maximum insulin dose was specified as insulin doses were titrated according to individual plasma glucose values.

Bolus insulin

Subjects on pre-trial bolus insulin continued their therapy or switched to an equivalent dose of insulin aspart (IAsp) dispensed free of charge together with the IMP.

Bolus insulin was initiated at the discretion of the investigator at a dose of 4 units per relevant meal.

Switch from previous premixed/biphasic insulin regimen

For subjects receiving premixed/biphasic insulin OD, the basal component was to be calculated and switched unit-to-unit to IMP OD. The bolus insulin component was to be calculated and switched unit-to-unit to IAsp and given at the most appropriate meal at the investigator's discretion. For subjects previously receiving premixed/biphasic insulin twice daily (or more), the total basal component was to be calculated, reduced by 20–30% and switched to IMP OD. The bolus component was to be calculated and switched to IAsp and dosed with the most appropriate meals at the investigator's discretion.

Insulin dose titration

A treat-to-target trial design was employed for glycaemic control. To ensure treatment uniformity between the sites, as well as to ensure that subjects received optimal treatment, titration algorithms were developed specifying recommended dose adjustments at different plasma glucose levels, using the same glycaemic targets as in the phase 3a clinical programme.

Concomitant medications

Continued use and intensification with bolus insulin and other antidiabetic treatments was allowed during the course of the trial. Additional concomitant medications to treat serious adverse events and cardiovascular-related diseases were also permitted. Cardiovascular diseases and risk factors were to be treated according to local standard of care at the investigators' discretion.

Objectives

The primary objective of the trial was to confirm the cardiovascular safety of IDeg compared to that of IGlar. The secondary objectives were to assess the efficacy of IDeg on markers of glycaemic control and to assess safety on other parameters in subjects with T2DM at high risk of cardiovascular events.

Outcomes / endpoints

Primary endpoint

- Time from randomisation to first occurrence of an EAC-confirmed 3-component major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction, or nonfatal stroke.

Confirmatory secondary endpoints

- Number of EAC-confirmed severe hypoglycaemic episodes
- Occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject (yes/no)

Secondary efficacy endpoints

- Change from baseline to last assessment in: HbA1c, FPG, IMP dose, bolus insulin dose and total insulin dose
- Other assessments (after baseline): pre-breakfast SMPG, 8-point SMPG profiles (during one day and across visits) and mean of 8-point SMPG profile

Statistical methods

Analysis sets

All analyses and data presentations are based on the FAS population with the exception of one sensitivity analysis of the primary endpoint that used the PP. The FAS included all randomised subjects. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects were to contribute to the evaluation "as randomised".

Primary analysis

The primary endpoint (time from randomisation to first occurrence of EAC-confirmed 3-component MACE) was analysed using a Cox proportional hazard regression with treatment as factor. The HR and the corresponding two-sided 95% confidence interval were estimated. Non-inferiority of IDeg to IGlar was considered confirmed if the upper limit of the two-sided 95% confidence interval for the HR was below 1.3. Where a cardiovascular death was linked to an earlier fatal MI or stroke, the subject contributed to the analysis with time to the cardiovascular death. If a subject did not experience any MACE, the time was censored at the subject's individual end-trial date. Sensitivity analyses were performed for the primary analysis, which included on-treatment and tipping point analyses, adjustments for baseline covariates, and where the primary analysis was repeated for the per-protocol analysis set.

Secondary confirmatory analyses

Provided that non-inferiority was confirmed for primary endpoint, the secondary confirmatory endpoint, 'Number of EAC-confirmed severe hypoglycaemic episodes' was analysed using a negative binomial regression model with log-link function and the logarithm of the observation time as offset. The model included treatment as a fixed factor. Superiority of IDeg to IGlar was considered confirmed if the upper limit of the two-sided 95% confidence interval for the rate ratio (RR [IDeg/IGlar]) was below 1.0.

Provided that superiority of the number of EAC-confirmed severe hypoglycaemic episodes was confirmed for IDeg vs IGlar, the secondary confirmatory endpoint, 'Occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject' was analysed using a logistic regression model, including treatment as a fixed factor. Superiority of IDeg to IGlar was considered confirmed if the upper limit of the two-sided 95% confidence interval for the odds ratio (OR [IDeg/IGlar]) was below 1.0.

Sensitivity analyses were performed for the secondary confirmatory analyses, which included on-treatment and tipping point analyses (both secondary confirmatory analyses) and where the analysis of

'number of EAC-confirmed severe hypoglycaemic episodes' was repeated with adjustment for baseline covariates, adjustment for baseline insulin treatment, and a truncation of the maximum number of severe hypoglycaemic episodes at 3 episodes per subject.

Other secondary analyses

Time from randomisation to first occurrence of an EAC-confirmed 4-point MACE (cardiovascular death, non-fatal stroke, non-fatal MI and UAP requiring hospitalisation) as well the individual components of the 4-point MACE were analysed using the same Cox regression model as the primary analysis.

The treatment ratio between mean insulin doses at the 24 month visit was analysed using a mixed model for repeated measures (MMRM) within subjects using an unstructured residual covariance matrix among visits at 3, 6, 9, 12, 15, 18, 21 and 24 months of the study. Interactions between visit and treatment and with log("baseline" dose) were included as fixed effects. Baseline dose was the first basal insulin dose reported by investigator for analyses of basal dose, whereas it was the total dose at visit 3 (Week 1) for analyses of total insulin dose.

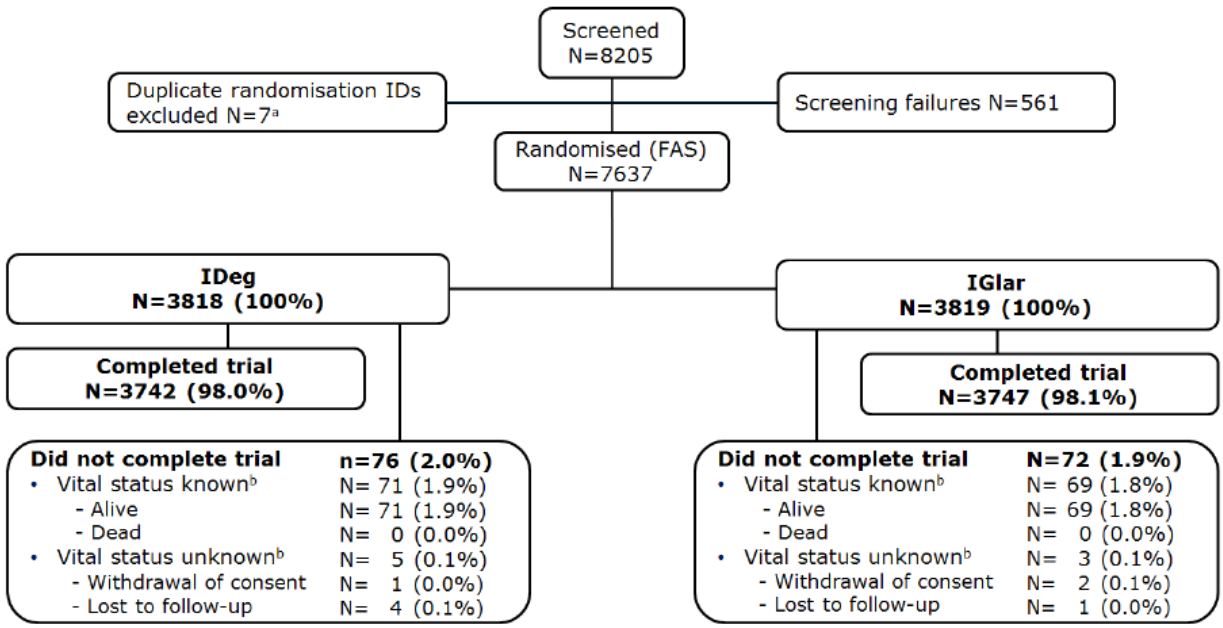
Two post hoc analyses were made where 1) change from baseline in HbA1c after 24 months and, 2) change from baseline in FPG after 24 months were analysed using an MMRM model within subjects using an unstructured residual covariance matrix among visits at 3, 6, 9, 12 and 24 months. Interaction between visit and treatment, and interaction between visit and baseline were included as fixed effects.

Results

Participant flow

An overview of subject disposition by treatment group is provided in Figure 12.

Figure 12 Subject disposition



Note: Completed trial: follow-up visit completed or died during trial. [a]7644 subjects randomised in total; 7 subjects were randomised at 2 different sites; [b]status during trial closure: from the first subject's follow-up visit (29 June 2016) to the actual last patient last visit (16 October 2016).

Abbreviation: N: number of subjects.

Of the 8205 subjects screened, 7637 subjects were randomised (1:1) to treatment with IDeg (3818 subjects) or IGlar (3819 subjects). Of the randomised subjects, 99.7% were exposed to treatment and more than 98% of subjects completed the trial (follow-up visit completed or died during trial). Primary outcome or vital status at end of trial was available for 99.9 % of participants randomised to IDeg and IGlar.

Baseline data

Demographics and baseline characteristics

Demographic and baseline characteristics were well matched between subjects randomised to IDeg and IGlar. The overall mean age at baseline was 65.0 years and a total of 62.6% of the trial population were men. The trial population had a mean BMI at 33.6 kg/m^2, ranging from 17.4 to 68.4 kg/m^2. The mean HbA1c was 8.4% and the mean duration of diabetes was 16.4 years. The mean baseline FPG was 9.5 mmol/L (171.65 mg/dL). Nearly 70% of the total population were recruited from sites in North America.

At baseline 35.4% of subjects had moderate renal impairment and 2.8% of subjects had severe renal impairment. The mean eGFR at baseline was 68 mL/min/1.73 m^2 and 37.4% had an eGFR less than 60 mL/min/1.73 m^2. Known severe renal impairment was an exclusion criterion for the trial; but current renal function was not known at the screening visit for all subjects.

Moreover, 2.6% of subjects had hepatic impairment at baseline.

Demographics and baseline characteristics in subgroups

Demographics and baseline and diabetes characteristics were similar between IDeg and IGlar within subgroups defined by age (<65, ≥ 65, <75 or ≥75 years) as well as within subgroups defined by renal function (normal, mild impairment, moderate impairment and severe impairment).

Medical history and concomitant illnesses

Of the 7637 subjects randomised, 85.2% were aged ≥ 50 years with established cardiovascular disease or chronic kidney disease while 14.5 % were aged ≥ 60 years with risk factors for cardiovascular disease at baseline. The remaining 23 subjects (0.3%) had unknown cardiovascular disease risk at baseline.

The use of cardiovascular and antidiabetic medication was well balanced between the two treatment groups at baseline. The majority of subjects were treated with cardiovascular medications at baseline, 93.1% of subjects were on antihypertensive therapy and 82.2% were on lipid lowering drugs. Approximately 84% of subjects were treated with insulin at baseline and in addition to insulin, the most frequent antidiabetic medications at baseline were metformin (59.8% of subjects), followed by sulphonylureas (29.2% of subjects). Approximately 8% of subjects were treated with GLP1-RA at baseline.

The number of subjects starting new cardiovascular and antidiabetic medication exclusively after baseline was similar across treatment groups.

Outcomes and estimation

Primary endpoint and confirmatory secondary endpoints

The outcome of the primary endpoint and the two confirmatory secondary endpoints is summarised in (Table 5).

Table 5 Confirmatory statistical analyses - FAS

	Endpoint	Estimated			
		Ratio	95% CI	p-value	Conclusion
Primary	Time from randomisation to 1st EAC-confirmed MACE	0.908	[0.781; 1.055]	<0.001	Non-inferiority confirmed
Confirmatory secondary	I) Number of EAC-confirmed severe hypoglycaemic episode	0.601	[0.476; 0.759]	<0.001	Superiority confirmed
	II) EAC confirmed severe hypoglycaemic episode (yes/no)	0.729	[0.600; 0.886]	<0.001	Superiority confirmed

Note: Ratio: Hazard ratio (HR) (IDeg vs IGlar) based on Cox regression with investigational medicinal product as factor for primary analysis, rate ratio (RR) (IDeg vs IGlar) based on negative binomial regression with log-link function and log(duration of observation time) as offset for 1st confirmatory secondary analysis, and odds ratio (OR) (IDeg vs IGlar) based on logistic (binomial) regression for 2nd confirmatory secondary analysis. p-value: Refers to one-sided test of HR >= 1.3 (against Ha: HR<1.3) for primary analysis, one-sided test of RR >= 1.0 (against Ha: RR<1.0) for 1st confirmatory secondary analysis, and one-sided test of OR >= 1.0 (against Ha: OR<1.0) for 2nd confirmatory secondary analysis.

Abbreviations: CI: Confidence interval for estimated ratio; EAC: Event adjudication committee; FAS: full analysis set; MACE: Major adverse cardiovascular event.

Time to first EAC-confirmed MACE

The primary endpoint was the time from randomisation to first occurrence of EAC-confirmed MACE.

A total of 681 first EAC-confirmed MACEs were reported in the trial, of which 325 occurred with IDeg and 356 with IGlar (Table 6). The primary analysis of time to first EAC-confirmed MACE resulted in an estimated HR of 0.91 [0.78; 1.06]95% CI for IDeg relative to IGlar (Figure 13). The upper bound of the 95% CI was below 1.3, thus confirming non-inferiority of IDeg relative to IGlar with respect to cardiovascular safety.

The distribution of the individual components of EAC-confirmed MACE was also similar between the two treatment groups. Of the total number of first EAC-confirmed MACE events, non-fatal myocardial infarction contributed with 45%, cardiovascular death with 34% and non-fatal stroke with 21%.

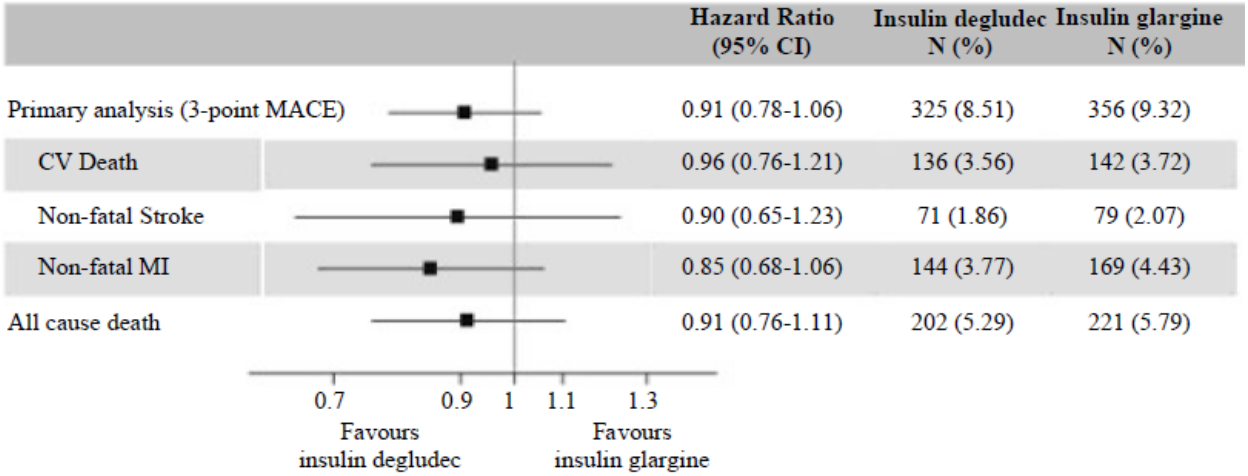
Table 6 First EAC-confirmed MACE - summary - FAS

	IDeg			IGlar		
	N	(%)	R	N	(%)	R
Number of subjects	3818			3819		
PYO	7568			7558		
First EAC-confirmed MACE	325	(8.5)	4.29	356	(9.3)	4.71
Myocardial infarction (non-fatal)	143	(3.7)	1.89	163	(4.3)	2.16
Stroke (non-fatal)	68	(1.8)	0.90	74	(1.9)	0.98
Cardiovascular death*	114	(3.0)	1.51	119	(3.1)	1.57

Note: *Cardiovascular death includes 66 subjects with undetermined cause of death. No subject experienced more than one EAC-confirmed MACE on the day of the first occurrence of an MACE.

Abbreviations: EAC: event adjudication committee; MACE: major adverse cardiovascular event, N: number of subjects; PYO: patient-years of observation; R: event rate per 100 PYO; %: percentage of subjects.

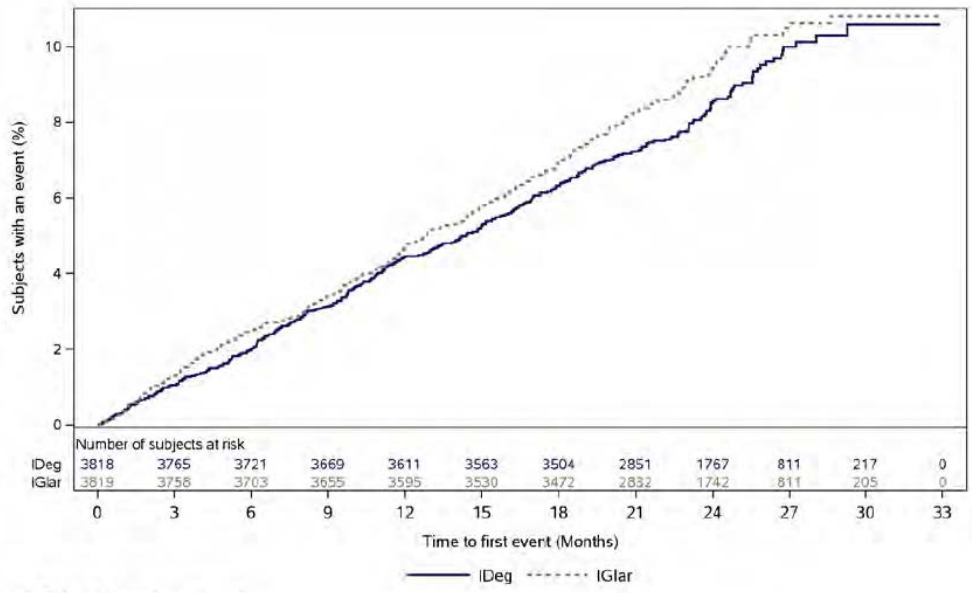
Figure 13 Forest plot of treatment contrast for components of first EAC-confirmed MACE and all-cause death – FAS



Abbreviations: %: proportion in percent of subjects with an event; CV: cardiovascular; CI: confidence interval; FAS: full analysis set; MACE: major adverse cardiovascular event; MI: myocardial infarction; N: number of subjects

First EAC-confirmed MACEs occurred evenly throughout the trial period as assessed from time of randomisation (Figure 14).

Figure 14 Time to first-EAC-confirmed MACE - Kaplan-Meier plot - FAS



Abbreviations: EAC: event adjudication committee; MACE: major adverse cardiovascular event.

Multiple sensitivity analyses were pre-specified in order to assess the robustness of the primary analysis results. The results of the sensitivity analyses were consistent with the result from the primary analysis.

Number of EAC-confirmed severe hypoglycaemic episodes (confirmatory secondary endpoint [I])

The first confirmatory endpoint related to severe hypoglycaemia in the confirmatory testing hierarchy (confirmatory secondary endpoint [I]) was number of EAC-confirmed severe hypoglycaemic episodes.

A total of 280 severe hypoglycaemic episodes were confirmed for the IDeg group vs 472 for the IGlar group (Table 7). The corresponding confirmatory secondary analysis resulted in an estimated RR of 0.60

[0.48; 0.76]95% CI (p<0.001) for IDeg relative to IGlar, thus confirming superiority of IDeg relative to IGlar with respect to number of EAC-confirmed severe hypoglycaemic episodes.

Table 7 EAC-confirmed severe hypoglycaemic episodes - summary - FAS

	IDeg				IGlar			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	3818				3819			
PYO	7568				7558			
EAC confirmed events*	187	(4.9)	280	3.70	252	(6.6)	472	6.25

Note: * EAC-confirmed severe hypoglycaemic episodes defined according to ADA. Episodes with EAC onset date during trial are included.

Abbreviations: ADA: American diabetes association; E: Number of events; EAC: Event adjudication committee; N: Number of subjects; PYO: Patient years of observation; R: Event rate per 100 PYO; %: Percentage of subjects relative to the number of randomised subjects.

Various sensitivity analyses were pre-specified in order to assess the robustness of the confirmatory secondary analysis results. The results of the sensitivity analyses were consistent with the results from the confirmatory secondary analysis.

Occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject - confirmatory secondary endpoint (II)

The second confirmatory endpoint related to severe hypoglycaemia in the confirmatory testing hierarchy (confirmatory secondary endpoint [II]) was occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject.

A total of 187 (4.9%) subjects in the IDeg group and 252 (6.6%) subjects in the IGlar group experienced at least one EAC-confirmed severe hypoglycaemic episode (Table 7). The corresponding confirmatory secondary analysis resulted in an estimated OR of 0.73 $[0.60; 0.89]_{95\%}$ CI (p=0.001) for IDeg relative to IGlar , thus confirming superiority of IDeg in relation to IGlar with respect to the occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject.

Sensitivity analyses were pre-specified in order to assess the robustness of the confirmatory secondary analysis results. The results of the sensitivity analyses were consistent with the results from the confirmatory secondary analysis.

Other secondary endpoints

Change in HbA1c from baseline

At baseline, mean HbA1c was 8.4% in both treatment groups. Mean HbA1c levels in both treatment groups decreased during the initial 3 months and remained relatively constant thereafter. At month 24, mean HbA1c had decreased to 7.5% in both treatment groups, corresponding to a mean change from baseline of approximately 0.9%-point.

Change in FPG from baseline

At baseline, mean FPG was 9.4 mmol/L (169.8 mg/dL) in the IDeg group and 9.6 mmol/L (173.5 mg/dL) in the IGlar group. In both treatment groups, mean FPG levels decreased during the first 12 months of the trial, whereafter the levels were maintained up to month 24. At month 24, mean FPG was 7.1 mmol/L (128.3 mg/dL) in the IDeg group compared to 7.5 mmol/L (135.8 mg/dL) in the IGlar group, corresponding to a mean decrease of 2.2 mmol/L (39.9 mg/dL) with IDeg and 1.9 mmol/L (34.9 mg/dL) with IGlar.

Self-measured plasma glucose measurements

Pre-breakfast SMPG

A similar reduction in pre-breakfast SMPG was observed between the IDeg and IGlar treatment groups. In both treatment groups, pre-breakfast SMPG decreased steadily during the initial 6 months of treatment followed by lower but continuous improvements throughout the remaining treatment period. At month 24, the mean lowest pre-breakfast SMPG value was 5.4 mmol/L (97.1 mg/dL) in the IDeg group and 5.3 mmol/L (95.8 mg/dL) in the IGlar group.

8-point SMPG profiles

There were no major differences between the IDeg and IGlar groups in the 8-point SMPG profile over one day at month 12, month 24 and at the end-treatment visit. A similar decrease in the mean of the 8-point SMPG profile from month 12 to month 24 was observed in both treatment groups.

Insulin dose

IMP dose

Analysis of the basal insulin dose at month 24 showed an estimated treatment ratio of 1.038, corresponding to a small (by 3.8%) but statistically significantly higher basal insulin dose for the IDeg group compared to the IGlar group. Analysis with adjustment for additional baseline covariates showed a similar result.

Bolus insulin dose

There were no major differences in bolus insulin dose between the IDeg and IGlar groups at baseline, month 24 and at the last observed value (representing the dose at the last scheduled visit prior to the end-treatment visit).

Total insulin dose

Analysis of the total insulin dose at month 24 showed a non-significant estimated treatment ratio of 1.001 between IDeg and IGlar. Analysis with adjustment for additional baseline covariates showed a similar result.

Comparison of efficacy results in subgroups

The consistency in treatment effect on glycaemic control was explored across subgroups by age and renal function.

HbA1c by age group

At baseline, a total of 3955 trial subjects were aged ≥65 years, which amounted to 51.8% of the total trial population, and 819 (10.7%) subjects were aged ≥75 years, thus ensuring significant exposure in geriatric subjects. The mean change in HbA1c between IDeg and IGlar was similar across age groups defined by age <65, ≥65, <75, and ≥75 years at baseline.

HbA1c by renal function

A significant proportion of subjects had varying degrees of renal impairment, with more than a third of the trial population having moderate or severe renal impairment. There were no major differences in HbA1c reduction between the IDeg and IGlar groups in patients with severe, moderate and mild renal impairment. Furthermore, the change in HbA1c in patients with renal impairment was comparable to that seen in patients with normal renal function.

MACE across intrinsic and extrinsic factor subgroups

The consistency in the treatment effect for the primary endpoint was explored across a range of intrinsic and extrinsic factor subgroups. The results of the subgroup analyses were in alignment with the result of the primary analysis.

Time to first EAC-confirmed MACE analyses for clinically relevant subgroups are presented in Table 8.

Table 8 Time to first EAC-confirmed MACE by selected subgroups

Subgroup	Hazard Ratio (95% CI)	IDeg N (%[a])	IGlar N (%[a])
Sex			
Female	0.76 (0.59; 0.99)	99 (6.96)	131 (9.12)
Male	0.99 (0.83; 1.20)	226 (9.43)	225 (9.45)
Age			
<65 years	0.84 (0.67; 1.05)	140 (7.63)	167 (9.04)
≥65 years	0.97 (0.79; 1.19)	185 (9.33)	189 (9.58)
Diabetes duration			
≤15 years	0.95 (0.76; 1.18)	149 (8.20)	166 (8.63)
> 15 years	0.87 (0.71; 1.07)	176 (8.80)	190 (10.03)
Cardiovascular risk group			
Established CVD/CKD	0.89 (0.76; 1.02)	293 (8.97)	325 (10.02)
Risk factors for CVD	1.03 (0.62; 1.72)	29 (5.39)	30 (5.29)
HbA_{1c} at baseline			
< 8.0%	0.89 (0.70; 1.13)	121 (7.18)	141 (8.08)
≥ 8.0%	0.91 (0.75; 1.07)	200 (9.58)	212 (10.44)
Previous insulin regimen			
Basal bolus	0.80 (0.66; 0.98)	172 (9.77)	210 (11.97)
Basal only	1.10 (0.84; 1.43)	111 (7.63)	101 (7.01)
Insulin naïve	0.96 (0.63; 1.46)	42 (6.95)	45 (7.21)

Note: [a]percentage of subjects with first EAC-confirmed MACE, relative to the number of randomised subjects;
N: number of subjects with a first EAC-confirmed MACE during the trial
Abbreviations: CI: confidence interval; CVD: cardiovascular disease; CKD: chronic kidney disease; EAC: event adjudication committee; HbA_{1C}: glycated haemoglobin; MACE: major adverse cardiovascular event

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9 Summary of Efficacy for trial 3748

Title:	**LEADER Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results. A long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events**		
Study identifier	EudraCT number – 2009-012201-19 EX2211-3748		
Design	LEADER was a long-term, multi-centre, multi-national, randomised, double-blind, placebo-controlled trial in males and females with T2DM and high risk of cardiovascular disease. Liraglutide and placebo were administered in addition to standard of care therapy (determined at the investigator's discretion), with the option of adding glucose-lowering or cardiovascular medication to achieve (individualised) guideline targets for glycaemic control, blood pressure and lipids. In addition recommendations for life style interventions and antiplatelet therapy were issued. The trial consisted of a screening visit followed by a 2 to 3-week run-in period during which eligible subjects received placebo. Subjects who met the randomisation criteria and could adhere to the injection regimen were randomised (1:1) to liraglutide or placebo for a treatment period of 42 to 60 months and a 30-day post-treatment follow-up period. Subjects were scheduled to attend the sites 1, 3 and 6 months after randomisation and then every 6 months. The duration of the trial was driven by both number of MACEs and by time. Thus, trial 3748 ended once all subjects had had a minimum treatment period of 42 months (plus a follow-up period of 30 days), and once at least 611 EAC-confirmed MACEs were recorded. The minimum period of 42 months was defined in order to provide data on long-term exposure to liraglutide and allow assessments of relevant safety parameters of interest. Trial 3748 included a recruitment period of 18 months, resulting in a maximum treatment period of 60 months. An external, independent event adjudication committee (EAC) was constituted for this trial to perform ongoing adjudication and assessment of potential major adverse cardiovascular events (MACEs), deaths and predefined medical events of special interest (MESIs) in a blinded manner. An independent, external Data Monitoring Committee (DMC) was constituted for the trial to oversee safety and perform ongoing safety surveillance at pre-defined time points as well as ad hoc. The DMC had access to unblinded data. A Steering Committee (StC) comprised of academic members (11) and employees of the sponsor (4) provided scientific and academic leadership for the trial.		
	Duration of main phase:		42 – 60 months (driven by events and time)
	Duration of Run-in phase:		2 - 3 weeks
	Duration of Follow-up:		30 days after treatment
Hypothesis	Non-inferiority, if reached superiority		
Treatments groups	Liraglutide		Liraglutide 1.8 mg, N = 4668
	Placebo		Placebo, N = 4672
Endpoints	Primary endpoint	MACE-3	Time from randomisation to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke
	Key secondary endpoint	Expanded MACE	MACE-3 or hospitalisation for unstable angina pectoris, coronary revascularisation and hospitalisation for heart failure
	Other secondary endpoints	Individual components of expanded MACE	Time from randomisation to first occurrence of each individual component of the expanded composite cardiovascular endpoint
		All-cause death	Time from randomisation to all-cause death.
		Non-CV death	Time from randomisation to non-cardiovascular death

		Composite microvascular endpoint	Time from randomisation to first occurrence of nephropathy events or diabetic retinopathy events
		Components of composite microvascular endpoint	Time from randomisation to first occurrence of a composite nephropathy endpoint and time to first occurrence of a composite retinopathy endpoint
Trial dates	31 Aug 2010 - 17 Dec 2015 Database lock on 05 February 2016		
Results and Analysis			

Analysis description	**Primary Analysis**				
Population		Intent to treat, Full analysis set (FAS)(all randomised subjects)			
Time point		Observation time was the duration from the date of randomisation to date of last contact with the subject (30 days after planned last dose of the investigational product).			
Descriptive statistics	Treatment group			Liraglutide	Placebo
		Number of subjects		4668	4672
	MACE-3	N (%)		608 (13.0)	694 (14.9)
		Event rate/100py		3.41	3.91
	Expanded MACE	N (%)		948 (20.3)	1062 (22.7)
		Event rate/100py		5.32	5.99
	CV death	N (%)		219 (4.7)	278 (6.0)
		Event rate/100py		1.23	1.57
	Non-fatal MI	N (%)		281 (6.0)	317 (6.8)
		Event rate/100py		1.58	1.79
	Non-fatal stroke	N (%)		159 (3.4)	177 (3.8)
		Event rate/100py		0.89	1.00
	Hosp-UAP	N (%)		122 (2.6)	124 (2.7)
		Event rate/100py		0.68	0.70
	Cor. Revasc.	N (%)		405 (8.7)	441 (9.4)
		Event rate/100py		2.27	2.49
	Hosp.-HF	N (%)		218 (4.7)	248 (5.3)
		Event rate/100py		1.22	1.40
	All cause death	N (%)		381 (8.2)	447 (9.6)
		Event rate/100py		2.14	2.52
	Non-CV death	N (%)		162 (3.5)	169 (3.6)
		Event rate/100py		0.91	0.95
	Nephropathy	N (%)		268 (5.7)	337 (7.2)
		Event rate/100py		1.68	2.08
	Retinopathy	N (%)		106 (2.3)	92 (2.0)
		Event rate/100py		0.73	0.59
Effect estimate per comparison	Comparison		Liraglutide vs placebo		
	Primary endpoint	MACE-3	HR		0.87
			95% CI		0.78;0.97
			P-value (HR<1.3 one-sided)		<0.01
			P-value (HR=1.0 two-sided)		0.011
	Secondary endpoint	Expanded MACE	HR		0.88
			95% CI		0.81;0.96
			P-value (HR=1.0 two-sided)		0.005
	Other secondary endpoints	CV death	HR		0.78
			95% CI		0.66;0.93
			P-value (HR=1.0 two-sided)		0.007
		Non-fatal MI	HR		0.88
			95% CI		0.75;1.03
		Non-fatal stroke	HR		0.89
			95% CI		0.72;1.11

		Hosp.-UAP	HR	0.98
			95% CI	0.76;1.26
		Cor. Revasc.	HR	0.91
			95% CI	0.80;1.04
		Hosp.-HF	HR	0.87
			95% CI	0.73;1.05
		All cause death	HR	0.85
			95% CI	0.74;0.97
		Non-CV death	HR	0.95
			95% CI	0.77;1.18
		Nephropathy	HR	0.78
			95% CI	0.67;0.92
		Retinopathy	HR	1.15
			95% CI	0.87;1.52

Table 10 Summary of Efficacy for trial 4080

Title:	**DEVOTE: A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events**		
Study identifier	EudraCT number - 2013-002371-17 EX1250-4080		
Design	This trial was a long-term, multi-centre, multi-national, randomised, double blind, parallel group, controlled trial conducted to confirm the cardiovascular safety of IDeg compared to IGlar when added to standard of care in male and female subjects with T2DM at high risk of cardiovascular events. The trial was event-driven and trial closure was initiated when it was secured that the pre-specified number of first EAC-confirmed major cardiovascular adverse events (MACEs) (633 events) would be accrued. MACE was a 3-component endpoint composed of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Up to 2.8 years (driven by events and time) not applicable 30 days after treatment
Hypothesis	Non-inferiority		
Treatments groups	Insulin degludec (IDeg)		N=3818
	Insulin glargine (IGlar)		N=3819
Endpoints and definitions	Primary endpoint	MACE	Time from randomisation to first occurrence of an EAC-confirmed 3-component major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke
	Secondary confirmatory endpoint (I)	Number of severe hypo-glycaemia episodes	Number of EAC-confirmed severe hypoglycaemic episodes
	Secondary confirmatory endpoint (II)	Occurrence of severe hypo-glycaemia episodes within a subject	Occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject (yes/no)
	Secondary endpoint	HbA1c	Change from baseline in HbA1c
Database lock	31 October 2016		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population	Intent to treat, Full analysis set (FAS)(all randomised subjects)			
Time point	Observation time was the time from randomisation until the individual end of trial date.			
Descriptive statistics and estimate variability	Treatment group		IDeg	IGlar
		Number of subjects	3818	3819
	MACE	N (%)	325 (8.5)	356 (9.3)
		Event rate/100py	4.29	4.71
	Number of severe hypo-glycaemia episodes	Number of events	280	472
	Occurrence of severe hypo-glycaemia episodes within a subject	N (%)	187 (4.9)	252 (6.6)
		Event rate/100py	3.70	6.25
	HbA1c	%	-0.86	-0.87

Effect estimate per comparison	Comparison		IDeg vs IGlar
	Primary endpoint: MACE	HR	0.91
		95% CI	0.78; 1.06
		P-value	<P-value>
	Secondary confirmatory endpoint (I): Number of severe hypo-glycaemia episodes	RR	0.60
		95% CI	0.48; 0.76
		P-value	p<0.001
	Secondary confirmatory endpoint (II): Occurrence of severe hypo-glycaemia episodes within a subject	OR	0.73
		95% CI	0.60; 0.89
		P-value	p=0.001
	Secondary endpoint: HbA1c	% (IDeg-IGlar)	0.008
		95% CI	-0.050; 0.066
		P-value	0.779

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Trial 3748

Trial 3748 (LEADER) was a long-term, multi-centre, multi-national, randomised, double-blind, placebo-controlled trial performed to determine the effect on cardiovascular outcomes and safety of liraglutide versus placebo. Both liraglutide and placebo were used in addition to standard of care therapy to ensure scientific rigour of the comparison.

The protocol of the study and the amendments to the protocol were agreed by CHMP. MACE-3 was the primary endpoint for the LEADER trial, in accordance with the EMA guidance (Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)). An expanded MACE, including hospitalisation for unstable angina, coronary revascularisation and hospitalisation for heart failure in addition to MACE-3, was a secondary outcome measure. These are also acceptable outcome measures. MACE-3 was assessed for both non-inferiority and superiority.

Inclusion criteria allowed for a population with T2DM at very high risk for CV events, as patients were included ≥50 years with "established cardiovascular disease", or ≥60 years with only "risk factors for

cardiovascular disease". Most subjects that were actually included were from Europe (35%) or North America (30%) and had a mean age of 64 years. The number of European subjects is considered sufficient and is representative for the European T2DM population with documented atherosclerotic disease. In total 45% of subjects were on insulin treatment at baseline, out of which 35% used intermediate or long acting insulin. This subpopulation could be of relevance for the current application.

The statistical analysis plan has been discussed and was considered acceptable by CHMP before trial completion. The analysis sets are considered acceptable. There are no concerns regarding randomisation or blinding or group differences in baseline characteristics. An analysis excluding the 111 protocol violations indicated that the primary endpoint was not affected by these protocol violations.

Trial 4080

The DEVOTE trial was a long-term, randomised, double-blind, parallel-group, treat-to-target, controlled trial with the aim of confirming the cardiovascular safety of insulin degludec (IDeg). The study design, including primary and secondary objectives and endpoints, was adequate. Insulin glargine (IGlar) was chosen as comparator which is endorsed, since CV safety data is available showing that IGlar does not alter the risk of CV events compared to standard-of-care.

The key inclusion and exclusion criteria aimed at recruiting patients at high risk of CV events. Notably, patients with eGFR < 30 were to be excluded. The demographic and baseline characteristics were as expected for a T2DM population at high CV risk. The majority of patients included were patients aged ≥ 50 years with established cardiovascular disease or chronic kidney disease. As expected the vast majority of patients were treated with cardiovascular medications at baseline. A high proportion of patients used basal insulin at baseline, in line with a long duration of diabetes at inclusion. Only about 8% of subjects were treated with GLP1-RA at baseline, thus the subpopulation most relevant to this application is verylimited. There were no imbalances between treatment groups.

Patients were randomised to treatment with either IDeg or IGlar. The trial was double-blinded. Adequate treatment algorithms were in place for the adjustment of both basal and bolus insulin doses to ensure uniformity between sites when titrating to target.

The statistical methods applied were adequate as were the sample size calculations. The analysis sets are agreed with. As this was a non-inferiority trial, the sensitivity analysis of the primary endpoint that used the PP set is of special interest.

Three amendments were made to the protocol, none of which are considered to affect the outcome or interpretation of the data. The MAH has accounted for the important protocol deviations. The subject-level protocol deviations were similarly distributed between the IDeg and IGlar groups, overall, as well as within each category and subcategory. The study was well conducted and the protocol deviations are not considered to have an overall impact on trial conduct, subject safety or data integrity.

Efficacy data and additional analyses

In the following, focus is on the data of relevance for the current application.

Trial 3748

The primary endpoint **(MACE-3)** showed superiority of liraglutide over placebo. All three components of MACE-3 appeared to contribute to the reduction, most notably CV-death (HR 0.78). Sensitivity analyses confirmed the results of the primary analysis. Kaplan-Meier plots of time to first EAC-confirmed events showed that differences in MACE and its components were observable from week 10-20 onwards.

Other secondary endpoints were all-cause death and non-cardiovascular death. All-cause death was reduced by liraglutide treatment, while only a favourable trend was observed for non-CV death. Thus, the reduction in all-cause death was mainly due to a reduction in CV-death.

To explore the possibility that censoring due to non-CV death influenced the primary analysis, post hoc analyses were performed of the time to all-cause death, MI and stroke and of the time to CV death, MI and stroke adjusted for non-CV death. The results of these analyses were similar to the primary analysis. Furthermore, no difference was observed in an analysis of time to non-CV death censoring for CV death, MI and stroke. Therefore it is unlikely that the primary analysis is biased by censoring for non-CV death.

Exploratory analyses of the primary endpoint were performed in subgroups of sex, age, BMI, HbA1c, duration of diabetes, race, ethnicity, cardiovascular risk group, heart failure (NYHA class I-III), severe and moderate renal failure and antidiabetic medication at baseline. Results for most subgroups were consistent with the overall effect on MACE, but there were 2 subgroups that showed a hazard ratio above 1. First, although no statistically significant interaction was found between treatment and **region**, for **Region North America** hazard ration was above 1. There were baseline differences between US and European participants. Results for Europe, the most relevant region for this application, were consistent with the overall effects on MACE: HR 0.81 (0.68-0.98) for liraglutide vs placebo. Second, the hazard ratio was above 1 for subjects aged >60 with only one cardiovascular risk factor for CV. A number of post-hoc analyses were performed for the **cardiovascular risk groups**. These did not reveal an explanation for the observed difference. The difference might be due to uncertainties associated with the estimate, as the subgroup of subjects aged ≥60 years with only risk factors for CV disease accounted for a relatively small proportion of the total trial population (~20%) and MACEs (~10%) observed in the trial.

The subgroup relevant to this application is patients on concomitant treatment with liraglutide and basal insulin, preferably IDeg. In total 45% of subjects were on insulin treatment at baseline. Only 23% of the study population was treated with a combination of long-acting insulin (insulin glargine or insulin detemir) and liraglutide. The subgroups included in the prespecified analysis were patients on insulin+OADs and patients on insulin only. For both these groups the point estimate for MACE-3 was below 1 but the confidence interval includes 1 for both subgroups. The MAH has provided a subgroup analysis which includes all patients on concomitant liraglutide and basal insulin therapy. Analysis of time to first EAC-confirmed MACE resulted in an estimated HR of 0.82 [0.66; 1.03]95%CI for liraglutide relative to placebo. However, no patient in the LEADER trial was exposed to the combination of liraglutide and insulin degludec.

Exploratory analyses according to **heart failure** (yes/no) indicated similar results in favour of liraglutide as overall effect on MACE. However, analyses according to heart failure class revealed slightly different results. There were no notable differences between treatment groups with respect to the distribution of EAC-confirmed expanded MACE, deaths, AEs (SAEs and non-serious MESIs) or hypoglycaemic episodes across the subgroups for HF status; however, there was a numerical increase in non-fatal MI, non-fatal stroke and HF hospitalisations in patients with NYHA III at baseline. This is considered a chance finding related to the low number of patients (lira: 108 pbo: 106) and expanded MACE events (lira: 82 pbo: 75) in the group with NYHA III at baseline.

In the LEADER trial, liraglutide or placebo was added to standard care. At baseline, some imbalances were present in use of **cardiovascular medication**. Sensitivity analyses showed that HRs were similar to the primary HR, and thus it is unlikely that primary results are biased by differences in cardiovascular medication. An interaction was observed for treatment and **renal function**: liraglutide performed better with respect to MACE in subjects with moderate to severe renal impairment (eGFR<60) as compared to subjects with normal renal function or mildly reduced renal function (eGFR>60). A beneficial effect was however observed in all subgroups of renal function with the exception of patients with eGFR 75-<90

ml/min/1.73 m^2. No specific pattern is observed and, there is no obvious pharmacokinetic or pharmacodynamic reason to believe that the effect should differ based solely on renal function.

Until now the therapeutic experience with liraglutide in patients with severe renal impairment was limited. In this study experience has been extended with 224 patients (117 liraglutide, 107 placebo).

Mean HbA1c at baseline was rather high: 8.7%. Subgroup analyses showed that there was no interaction with treatment effect and HbA1c.

In line with observations from the liraglutide for T2DM development programme, an increase in estimated mean **heart rate** was observed in the liraglutide group in trial 3748. It has been suggested that small increases in resting heart rate may be associated with an increased oxygen demand, which may result in heart failure, MACE, or even increased mortality. The exploratory *post hoc* analyses performed, showed results consistent with the primary analysis. Furthermore, no imbalance was seen in adverse events of arrhythmia as reported by the investigators. Hence according to these data, the increase in resting heart rate was not associated with adverse cardiovascular outcomes, including arrhythmias.

Microvascular safety was evaluated using composite microvascular, nephropathy and retinopathy endpoints. A positive effect, in favour of liraglutide, was observed for the composite microvascular endpoint, showing a reduction in the risk of microvascular effects events in the liraglutide group compared to the placebo group: 355/4668 (7.6%) events in the liraglutide group versus 416/4672 (8.9%) in the placebo group (HR 0.84 [0.73-0.97] $_{95\%CI}$). The difference between the treatment groups was driven by the nephropathy composite with an estimated hazard ratio (liraglutide *versus* placebo) of 0.78 [0.67; 0.92]$_{95\%CI}$, corresponding to a 22% reduction in the risk of nephropathy events (liraglutide 268/4668 (5.7%) events, placebo 337/4672 (7.2%) events). The reduction in nephropathy was mainly due to a reduction in persistent macroalbuminuria.

In contrast, no reduction in retinopathy was seen: liraglutide 106/4668 (2.3%) events vs placebo 92/4672 (2.0%) events. The imbalance in the retinopathy composite was due to an imbalance in vitreous haemorrhage (32 vs 22 subjects in the liraglutide group vs placebo; total events liraglutide: 32 subjects, 44 events, 0.25 events/100 PYO *versus* placebo: 22 subjects, 23 events, 0.13 events/PYO), (HR 1.45 [0.84; 2.50]). The MAH considers a causal relationship with liraglutide treatment unlikely, as the incidence of vitreous haemorrhage events was low, and there was no signal in non-clinical and clinical trials with liraglutide. The increase was appearing within the first 16 weeks of treatment. In patients with type 1 diabetes an association is reported between rapid glucose lowering and worsening of retinopathy. If this association is applicable to the effects of liraglutide, this would be reassuring. In type 1 diabetes, the early worsening of retinopathy is transient, largely resolving after 1 to 2 years, and there is clear evidence of benefit from glucose lowering in the following years. The fact that the increased risk of retinopathy with liraglutide does not decrease in the course of the 5 year trial is worrisome and suggests that other mechanisms than rapid glucose lowering may play a role. For semaglutide, another GLP-1 RA, also an increase of diabetic retinopathy was observed, according to published data.[1] Therefore, it is possible that there is a class effect. No firm conclusions are possible from the LEADER trial due to the low number of events. No signal was detected in other clinical trials with liraglutide, although it should be remarked that retinopathy was not actively looked for. Retinopathy will be monitored in the PSURs for liraglutide.

Glycaemic control, measured by HbA1c, was evaluated for the total study population and for a number of subgroups. HbA1c target was <7%. For the total study population, the reduction in HbA_{1c} was greater with liraglutide than with placebo after 3 years of treatment (-1.16% *versus* -0.77%; estimated

1 Marso SP et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016; 375:1834-1844

treatment difference of -0.4% [-0.45; -0.34]$_{95\% CI}$); and the difference was maintained at end of treatment (-0.3% [-0.35; -0.23]$_{95\% CI}$).

Although investigators were instructed to provide standard of care treatment for antidiabetic therapy throughout the treatment period, the placebo group did not achieve the same level of control. This may be partly explained by the fact that the treatment options for subjects in the placebo group were limited by the fact that use of incretin-based therapies was not allowed.

The results were consistent across the subgroups of age, renal function, NYHA classes and use of premix insulin at baseline, and the estimated difference in HbA1c vs placebo was similar across subgroups. Thus, reductions in HbA1c with liraglutide versus placebo were observed in sub-populations, for which there are currently limited therapeutic experience with liraglutide, including subjects aged ≥75 years, subjects with severe renal impairment and subjects with heart failure according to NYHA class I, II and III. Liraglutide was also associated with similar reductions in HbA1c in subjects treated with or without pre-mix insulin at baseline and the following 26 weeks confirming the effectiveness of liraglutide in combination with pre mix insulin.

Other efficacy endpoints were initiation of insulin and antidiabetic therapies, body weight, SBP and DBP. These were all in favour of liraglutide.

In both treatment groups small increases were observed for total cholesterol, LDL cholesterol and HDL cholesterol, while the level of triglycerides was comparable between treatment groups. The increases in TC and LDL were smaller for liraglutide as compared to placebo, while the increase in HDL was somewhat larger for liraglutide. It is not agreed with the MAH that results are in favour of liraglutide. It is better to say that, compared to placebo; results for liraglutide are less negative.

The **mechanism** behind the cardiovascular benefit with liraglutide is unclear. The MAH suggest a direct effect of liraglutide on MACE. However, liraglutide was associated with statistically significantly reductions in established cardiovascular risk factors such as HbA_{1c}, SBP, body weight and LDL cholesterol compared to placebo. These benefits might contribute to the observed effect on MACE. Further, it is of importance that a significantly higher proportion of patients in the placebo group during the study initiated antidiabetic medications, including SUs, TZDs and insulin, compared to patients in the liraglutide group. Both SUs and TZDs have been associated with an increased risk of cardiovascular harm. In fact analysis excluding patients using SUs or TZDs at baseline only showed a borderline significant results of liraglutide on MACE (HR: 0.86, 95%CI: 0.73, 1.00). Although, it is acknowledged that previous data suggest that liraglutide also has a direct effect on the atherosclerotic process, a direct effect of liraglutide on cardiovascular death is not evident from the LEADER trial. More insight in the mode of action would be important to optimize use of liraglutide in subgroups.

At present, it must be concluded that the mechanism behind the beneficial cardiovascular effect of liraglutide remains largely unknown and further non-clinical and clinical studies are needed to elucidate the mechanism.

Trial 4080

Non-inferiority with regards to the primary endpoint was shown for IDeg vs IGlar (HR 0.91 [0.78; 1.06]$_{95\%}$ CI). The outcome was robust and supported by the sensitivity analyses, including the analysis in the PP set. Events occurred evenly distributed over time for both treatments and the three components of MACE (non-fatal MI, non-fatal stroke and CV-death) were equally distributed for both treatments.

The first confirmatory secondary endpoint (number of EAC-confirmed hypoglycaemic episodes) showed that IDeg was superior to IGlar (RR 0.60 [0.48; 0.76]$_{95\%}$ CI ($p<0.001$)). The second confirmatory secondary endpoint (occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject) also showed that IDeg was superior to IGlar with a reduced risk of experiencing hypoglycaemia

(OR 0.73 [0.60; 0.89]$_{95\%}$ CI (p=0.001)). The results for both endpoints were supported by the sensitivity analyses performed and are deemed robust.

Other antidiabetic treatments, including bolus insulin, were allowed during the course of the trial without restrictions. Cardiovascular diseases and risk factors were to be treated according to local standard of care. There were no imbalances between treatment groups with regards to medications initiated after study entry.

There was no difference in the change in HbA1c from baseline between treatments. This is as expected provided that both treatments were titrated to target. A post-hoc analysis showed no difference between treatments. There was a slightly more pronounced decrease in FPG with IDeg compared to IGlar. There were no differences between treatments in the pre-breakfast SMPG or 8-point SMPG profiles. Thus the difference observed in FPG was not confirmed by the SMPG.

At 24 months, slightly higher doses of IDeg were observed compared to IGlar, however at the last visit before EOT, no difference was observed. There were no major differences in bolus doses or total insulin dose between groups.

Known severe renal impairment was an exclusion criterion but the MAH states that current renal function was not known at screening visit for all patients. Subjects who were non-compliant with any of the eligibility criteria were not to be randomised. However, if there were no safety concerns, treatment with trial products could be continued or resumed at the discretion of the investigator after consulting the sponsor's global medical expert. This resulted in the inclusion of 214 patients with eGFR<30 (2.8%), equally distributed between the two treatment groups (108 patients in the IDeg group and 106 patients in the IGlar group).

There was no difference in the treatment effect in terms of HbA1c reduction between IDeg and IGlar in the subgroups by age or renal function.

2.4.3. Conclusions on the clinical efficacy

The LEADER trial was a well-designed and well-conducted CV outcome trial which showed superiority of liraglutide over placebo in the primary endpoint of 3-point MACE. The results were mainly driven by a decrease in CV-death. Secondary endpoints showed a reduction in expanded MACE, with (non-significant) decreases in non-fatal MI, non-fatal stroke, hospitalisation for heart failure and coronary revascularisation. No effects on hospitalisation due to UAP were observed. Furthermore, a reduction in nephropathy was observed with liraglutide treatment. No firm conclusions can be drawn with respect to retinopathy for which an imbalance in favour of placebo was observed.

The data from the DEVOTE trial show that IDeg did not alter the relative risk for CV disease and CV mortality when compared to IGlar since non-inferiority could be established. IGlar has previously been shown not to alter the relative risk for CV disease and CV mortality when compared to standard of care.

In the clinical program supporting the MAA, IDeg was shown to have a lower risk of hypoglycaemia compared to IGlar in patients with T2DM. This was confirmed in this study where the number of severe hypoglycaemias as well as the risk of experience a severe hypoglycaemia was significantly lower with IDeg than with IGlar.

Both studies contribute with important data on the cardiovascular safety for each of the two components of IDegLira; however extrapolation of these outcomes to the combination has not been justified. Therefore the proposed reference to the effect on cardiovascular events in section 4.1 is not accepted nor is the inclusion of study data in section 5.1.

Nevertheless, the LEADER trial contributes with important data on the liraglutide component of IDegLira, e.g. information on the use in special populations and conditions, that have been reflected in the SmPC.

2.5. Clinical safety

Introduction

With the current application, safety data from two large cardiovascular outcome studies have been submitted. In these studies the effect on cardiovascular safety of the monocomponents (liraglutide and IDeg, respectively) of Xultophy (IDegLira) was investigated. Thus no data on the combination has been provided. The safety data has resulted in changes both to the product information and RMPs for the monocomponents. Some of these changes may also be relevant for the combination why these data are presented in the following.

Trial 3748

The most frequently reported AEs with the current indication of Victoza (liraglutide) are gastrointestinal adverse events (nausea and diarrhoea, vomiting, constipation, abdominal pain, and dyspepsia). Headache and nasopharyngitis are also common. Furthermore, hypoglycaemia is common, and very common when liraglutide is used in combination with a sulfonylurea.

In trial 3748, only SAEs (serious adverse events) and MESIs (medical event of special interest) were systematically collected and the present evaluation is based on these events only. The selective and targeted approach to safety data collection was in line with the FDA guidance on safety data collection in late stage premarket and post-approval clinical investigations. No additional safety concerns were identified based on review of non-serious AEs not systematically collected (i.e., non-serious, non-MESI events).

CV outcomes form the primary endpoint of this trial and are therefore described in the efficacy section of this document. Microvascular endpoints, although defined as safety endpoints in the protocol, are also discussed in the efficacy section above.

MESIs discussed in this section are: neoplasms and calcitonin, thyroid disease, pancreatitis, acute gallstone disease, hypoglycaemia and immunogenicity.

In addition, safety in specific populations is discussed.

Trial 4080

As the safety profiles of IDeg and IGlar are well characterised and the trial was designed to evaluate cardiovascular outcomes data, a selective and targeted approach was used to collect safety data. The most important and common AE with insulin treatment is hypoglycaemia.

The following types of events were systematically collected: all SAEs, episodes of severe hypoglycaemia, AEs leading to permanent discontinuation of investigational product, medication errors leading to an SAE and adverse events related to technical complaints. Data on neoplasms was also collected and was subject to external classification.

CV outcomes form the primary endpoint of this trial and are therefore described in the efficacy section of this document. Hypoglycaemia constituted the confirmatory secondary endpoints and is also briefly discussed in the efficacy section but some additional data is discussed in this section. Data on neoplasms is also presented.

In addition, safety in specific populations is discussed.

Patient exposure

Trial 3748

The median time of observation in the trial was 3.84 years (including follow-up period) and the total median exposure time to the trial product was 3.52 years. The total mean proportion of time on trial product was 83%. In the liraglutide group slightly more subjects had one or more drug holidays (accumulated days off drug) compared to subjects in the placebo group (Table 11). Overall, 85% of the total liraglutide exposure in the trial was to the 1.8 mg/day dose.

More than 70% of total subjects were exposed for 90% or more of the observation time (as assessed by the PYE/PYO ratio) indicating that the majority of subjects continued treatment with trial product during the trial period. A smaller fraction of subjects (~ 6% in both arms) were exposed for less than 10% of the observation time, indicating that they discontinued during the initial phase of the trial.

Table 11 Exposure – FAS

	Lira	Placebo	Total
Number of subjects (N)	4668	4672	9340
Total years in trial (PYO)	17822	17741	35563
Median years of observation including follow-up period	3.84	3.84	3.84
Total years in trial excluding follow-up period	17341	17282	34623
Median years of observation excluding follow-up period	3.75	3.75	3.75
Total years of exposure to trial drug	14502	14157	28659
Subjects with one or more drug holidays, N (%) (exposed and alive subjects at follow up)	1687 (36.1)	1584 (33.9)	3271 (35.0)
Median years of exposure to trial drug	3.52	3.51	3.52
Mean proportion of time on trial drug	0.84	0.82	0.83
Median proportion of time on trial drug	1.00	1.00	1.00

FAS: full analysis set, N: Number of subjects, %: Proportion of subjects, Years in trial are calculated from randomisation date to last contact (phone or visit), PYO: patient years of observation. Exposure is calculated from first drug date to last drug date or last visit date (whichever comes first) - only time periods with a dose. If last drug date is missing it is substituted with withdrawal date.

Trial 4080

Observation time for each subject was defined as the time from randomisation to last visit, last EAC-confirmed MACE or death before last patient last visit, whichever came first.

The total number of patient years of observation (PYO) in the trial was 15125 years, with a median observation time of 1.99 years. The total number of patient years of exposure (PYE) to investigational trial product was 13522 years with a median of 1.83 years. A similar distribution of observation time and exposure time was seen between treatment groups (IDeg vs IGlar) (Table 12). Treatment pauses and the ≥30-day safety follow-up period from the end of treatment visit to the follow-up visit were included as observation time (PYO) but not as exposure time (PYE). Hence, the total exposure time (PYE) was less

than the total observation time (PYO). In total, 85.2% of subjects were exposed for ≥90% of the planned exposure time.

Table 12 Exposure and observation time – FAS

	IDeg	IGlar	Total
Number of subjects	3818	3819	7637
PYO (years)			
N	3818	3819	7637
Total	7568	7558	15125
Mean (SD)	1.98 (0.38)	1.98 (0.39)	1.98 (0.38)
Median	1.99	1.99	1.99
Min ; Max	0.00; 2.75	0.00; 2.75	0.00; 2.75
PYE (years)			
N	3818	3819	7637
Total	6792	6730	13522
Mean (SD)	1.78 (0.49)	1.76 (0.52)	1.77 (0.51)
Median	1.84	1.83	1.83
Min ; Max	0.00; 2.64	0.00; 2.64	0.00; 2.64
Planned exposure time (years)			
N	3818	3819	7637
Total	7255	7245	14499
Mean (SD)	1.90 (0.37)	1.90 (0.37)	1.90 (0.37)
Median	1.91	1.91	1.91
Min ; Max	0.00; 2.66	0.00; 2.75	0.00; 2.75
PYE/(planned exposure time) (%)			
N	3818	3819	7637
Mean (SD)	93.57 (18.60)	92.73 (20.15)	93.15 (19.39)
Median	99.84	99.84	99.84
Min ; Max	0.00; 100.00	0.00; 100.00	0.00; 100.00

Note: Exposure is defined as duration in trial excluding periods off-treatment with investigational product; planned exposure time is PYO excluding follow-up period.

Abbreviations: PYO: patient years of observation; PYE: patient years of exposure; N: number of subjects; SD: standard deviation

Adverse events

Trial 3748

The overall adverse event profile with liraglutide in trial 3748 resembled that observed in the clinical development programme for with T2DM, albeit the incidence of especially deaths and cardiovascular events was higher, reflecting a population at very high risk of cardiovascular disease.

In general, the proportion of subjects with SAEs and non-serious MESIs and the rates of such events were similar between the treatment groups, whereas the rate of fatal events was lower in the liraglutide group (Table 13). A higher proportion of subjects in the liraglutide group compared to the placebo group had SAEs and non-serious MESIs evaluated as being probably or possibly related to trial product by the investigator and events leading to permanent treatment discontinuation were also more common with liraglutide. These differences were driven by non–serious MESIs and were not apparent when evaluating SAEs separately.

Table 13 SAEs or non-serious MESIs – FAS

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of subjects	4668				4672			
PYO	17822				17741			
All events	2909	(62.3)	9421	52.86	2839	(60.8)	9260	52.20
Serious	2320	(49.7)	6643	37.27	2354	(50.4)	6998	39.45
Fatal	382	(8.2)	500	2.81	447	(9.6)	597	3.37
MESI	2378	(50.9)	5918	33.21	2313	(49.5)	5696	32.11
Severe	1502	(32.2)	3286	18.44	1533	(32.8)	3557	20.05
Product withdrawn permanently	447	(9.6)	623	3.50	340	(7.3)	479	2.70
Probably related to IMP	345	(7.4)	561	3.15	139	(3.0)	175	0.99
Possibly related to IMP	542	(11.6)	851	4.77	413	(8.8)	633	3.57

N: number of subjects, %: proportion of subjects, E: number of events, FAS: full analysis set, IMP: investigational medicinal product, PYO: patient years of observation, R: event rate per 100 patient years of observation, MESI: medical event of special interest as reported by the investigator (serious and non-serious), SAE: serious adverse event.

Neoplasms

Neoplasms including MTC were to be addressed as a post-marketing commitment for Victoza. Furthermore, specific malignancies were addressed in alignment with regulatory concerns raised for the class of incretin-based therapies (pancreatic cancer) and specific imbalances noted during the regulatory review of liraglutide 3.0 mg for weight management (Saxenda; breast and colorectal neoplasms). Finally, neoplasms by insulin use were addressed to provide further insights on previous clinical trial findings with liraglutide in combination with insulin detemir (NN2211-1842).

Neoplasms (overall, benign and malignant)

The proportion of subjects with EAC-confirmed neoplasms in the liraglutide and placebo groups were 10.1% *versus* 9.0% for overall neoplasms, 3.6% *versus* 3.1% for benign neoplasms and 6.3% *versus* 6.0% for malignant neoplasms (Table 14). Cox analyses applied *post hoc* showed no statistically significant difference between the treatment groups across these neoplasm categories.

Table 14 EAC-confirmed neoplasm index events including thyroid neoplasms - FAS

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
FAS	4668				4672			
PYO	17822				17741			
EAC-confirmed neoplasms (0verall)	470	(10.1)	595	3.34	419	(9.0)	528	2.98
Malignant	296	(6.3)	356	2.00	279	(6.0)	326	1.84
Pre-malignant	37	(0.8)	40	0.22	26	(0.6)	30	0.17
Benign	168	(3.6)	196	1.10	145	(3.1)	171	0.96
Unclassified	3	(0.1)	3	0.02	1	(0.0)	1	0.01

%: Proportion of subjects, E: Number of events, EAC: Event adjudication committee, FAS: Full analysis set, Lira: liraglutide, N: Number of subjects, PYO: Patient years of observation, R: Event rate per 100 observation years;
Index events with EAC onset date from randomisation date to follow-up are included.
The index event is the event selected among multiple events if these were assessed and confirmed to be one and the same event.

Of the EAC-confirmed benign neoplasms, benign colorectal neoplasms (discussed further below) were the most common type occurring in both treatment groups. A wide variety of EAC-confirmed malignant neoplasms occurred in both treatment groups including malignant non-melanoma of the skin and malignant breast (women), prostate, lung and colorectal neoplasms which are among the most common

malignancies in the general/T2DM populations. As estimated by *post hoc* Cox analyses (liraglutide *versus* placebo), no statistically significant treatment difference was observed for any specific types of benign neoplasms. For malignant neoplasms, the point estimate for the hazard ratios for the various types were distributed on both sides of the line of unity with a statistically significant treatment difference observed only for malignant prostate neoplasms and leukaemia (both favouring liraglutide). Some of the malignant neoplasm types included only few subjects with confirmed events which are reflected in very broad 95% confidence intervals.

Apart from the predefined malignancy types (i.e., thyroid, pancreatic, breast and colorectal) additional evaluations of other types were applied to identify other potential safety concerns related to liraglutide. Malignancy types which underwent a more in-depth evaluation were: malignant non-melanoma skin neoplasms, melanoma of the skin, hepatic or biliary neoplasms and kidney or renal pelvis neoplasms.

In the following, only data on malignant melanoma, thyroid neoplasms and pancreatic neoplasms is presented.

Malignant melanoma

Number of subjects with EAC-confirmed pre-malignant or malignant melanoma was low: 20 events in 19 subjects in the liraglutide group and 9 events in 9 subjects in the placebo group. As expected, the majority of events occurred at sun-exposed skin areas and in White subjects. Of note, among subjects with an EAC-confirmed pre-malignant or malignant skin melanoma neoplasm, more subjects in the liraglutide group had risk factors such as previous UV exposure and/or a medical history of skin cancer as compared to the placebo group. Events had onset shortly after randomisation and occurred at comparable rates in the two treatment groups until around month 18 into the trial. After this, events continued to accrue at a similar and constant rate in the liraglutide group, whereas, for the placebo group, only 2 additional events occurred at a late stage during the course of the trial. The MAH is of the opinion that a causal relationship between liraglutide and skin melanoma neoplasms is not likely.

Thyroid neoplasms and calcitonin

Events of EAC-confirmed thyroid neoplasms (overall or malignant) occurred at comparable low incidences for the two treatment groups (overall thyroid neoplasms: 0.1% in both treatment groups; malignant thyroid neoplasms: 0.1% in both treatment groups. No cases of MTC, a very rare cancer type in humans, were identified in liraglutide-treated subjects (1 MTC occurred in the placebo group). Consistently, there was no indication of a liraglutide effect on blood calcitonin concentrations (a clinical biomarker for MTC and a potential predictor of C-cell neoplasia at levels ≥50 ng/L). EAC-confirmed thyroid neoplasms of papillary origin (malignant events) were well-balanced between the treatment groups (5 and 4 events, respectively, in the liraglutide and placebo groups.

Pancreatic neoplasms

The incidence of EAC-confirmed pancreatic neoplasms was low in both the liraglutide (0.3%) and the placebo (0.1%) groups. Based on low numbers, EAC-confirmed malignant pancreatic neoplasms occurred disproportionately more in the liraglutide group (13 subjects with 14 events; 0.08 events per 100 PYO) compared to the placebo group (5 subjects with 5 events; 0.03 events per 100 PYO). There was one EAC-confirmed pre-malignant pancreatic neoplasm event occurring in the liraglutide group.

Thyroid disease

In trial 3748, the proportion of subjects with events of thyroid disease was similar in the liraglutide group (4.2%) and in the placebo group (4.1%) and the event rates for the most frequently reported preferred terms (PTs) (‘hypothyroidism’, ‘blood calcitonin increased’ and ‘goitre’) were low and similar between treatment groups.

Although the numbers were low, the proportion of subjects with events of thyroid disease and the rate of such events among subjects with a medical history of thyroid disease were higher in the liraglutide group (7.5%) compared to the placebo group (5.8%). This was also noted in the liraglutide T2DM clinical development programme. The imbalance was driven by events of 'goitre' (liraglutide, 16 events; placebo 6 events), while no imbalances were observed with respect to the proportion of subjects with 'thyroid neoplasm' or 'blood calcitonin elevated' between liraglutide and placebo or in the rates of such events. 'Goitre' events occurred throughout the trial in subjects with a medical history of thyroid disease in the liraglutide group with an approximate constant although slightly higher rate than for the placebo group and with no events reported in the placebo group after approximately 22 months. Thus no new findings were observed for liraglutide and thyroid disease.

Pancreatitis

In trial 3748, the proportion of subjects with EAC-confirmed acute pancreatitis and the rates of such events were comparable between the liraglutide group (0.4%; 0.11 events per 100 PYO) and the placebo group (0.5%; 0.19 events per 100 PYO) and the majority of events were classified as 'mild acute pancreatitis' based on the revised Atlanta classification (Table 15). In addition, in subjects with a medical history of pancreatitis there was no indication of an increased risk of pancreatitis when treated with liraglutide: in the lira-group 2/147 subjects with a history of pancreatitis experienced a new pancreatitis vs 6/120 in the placebo group.

The first events of acute pancreatitis had onset approximately after 6 months in the liraglutide group and after 1 month in the placebo group. In this respect it is of note that drug-induced pancreatitis has been observed to present within the first 3 months of treatment.

Consistent with findings from previous completed clinical trials with liraglutide, the liraglutide group experienced a higher increase in lipase and amylase activity levels during the trial compared to the placebo group. Among subjects with at least one lipase or amylase value ≥1×ULN, ≥2×ULN or ≥3×ULN at any scheduled visit during trial, only a small proportion of subjects had an EAC-confirmed event of acute pancreatitis, with no differences noted between treatment groups. Based on this, the predictive value of isolated elevations of lipase and/or amylase for future development of pancreatitis is considered low.

Data from trial 3748 does not provide further evidence on a potential causal relationship between liraglutide treatment and pancreatitis.

Table 15 EAC-confirmed pancreatitis index events - FAS

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
FAS	4668				4672			
PYO	17822				17735			
Number of events	18	(0.4)	19	0.11	25	(0.5)	33	0.19
Acute pancreatitis	18	(0.4)	19	0.11	23	(0.5)	31	0.17
Chronic pancreatitis	0	(0.0)	0	0.00	2	(0.0)	2	0.01

%: Proportion of subjects, E: Number of events, EAC: Event adjudication committee, FAS: Full analysis set, Lira: liraglutide, N: Number of subjects, PYO: Patient years of observation, R: Event rate per 100 observation years;

Acute gallstone disease

Acute gallstone disease is a well-known risk factor for acute pancreatitis and was therefore evaluated in trial 3748.

The proportion of subjects with events of acute gall stone disease and the rates of such events were higher in the liraglutide group (3.1%; 0.90 events per 100 PYO) than in the placebo group (1.9%, 0.65 events per 100 PYO) and the mean number of events per subject appeared to increase more over time with liraglutide compared to placebo. Among the events reported in both treatment groups, the proportions of SAEs (liraglutide: 76% [124/160 events]; placebo: 79% [91/115 events]) and severe events (liraglutide: 28% [45/160 events]; placebo: 38% [44/115 events]) of acute gallstone disease were not higher in the liraglutide group compared to the placebo group. Furthermore, the proportions of subjects with events leading to hospitalisation at the time of the event (liraglutide: 62.8%; placebo: 62.2%) and/or resulting in cholecystectomy (acute or elective) (liraglutide: 55.9%; placebo: 57.8%) were similar.

When evaluating events of acute gallstone disease by categorical weight loss at year 3 (weight gain; 0-5%, 5-10% and >10% weight loss), there was no indication of a relationship between the magnitude of the weight changes and the development of acute gallstone disease in subjects in the liraglutide group (ratio 0.6 for weight gain and 0.9 for all categories of weight loss). In the placebo group, the proportion of subjects with events of acute gallstone disease increased with increasing weight loss (ratio 0.4 for weight gain, and 0.5, 1.1, and 1.8 for the respective category of weight loss).

The higher rate of acute gallstone disease in the liraglutide group was not associated with an increased risk of acute pancreatitis. Thus, no difference between treatment groups was seen for EAC-confirmed pancreatitis, and the proportion of subjects with pancreatitis and concomitant gallstone disease was not higher in the liraglutide group than in the placebo group.

In conclusion, a causal relationship between liraglutide treatment and acute gallstone disease cannot be excluded although the mechanism behind this remains unknown.

Hypoglycaemia

The overall rates of hypoglycaemic episodes (i.e., confirmed and for overall hypoglycaemia according to the ADA classification) were lower in the liraglutide group compared to the placebo group. A similar pattern was observed for overall nocturnal hypoglycaemia.
The rates of both severe and confirmed hypoglycaemic episodes were lower with liraglutide compared to placebo RR: 0.69 $[0.51; 0.93]_{95\%CI}$ and RR: 0.81 $[0.74; 0.88]_{95\%CI}$, respectively). A similar pattern in favour of liraglutide was also observed for nocturnal severe and nocturnal confirmed hypoglycaemia, RR: 0.56 $[0.29; 1.07]_{95\%CI}$ and RR: 0.62 $[0.54; 0.72]_{95\%CI}$, respectively.

The vast majority of severe hypoglycaemic episodes occurred in subjects treated with insulin, SU/glinides or a combination of these at baseline in both treatment groups (liraglutide: 167 of 178 severe episodes; placebo: 237 of 255 severe episodes). Similarly, the majority of confirmed hypoglycaemic episodes occurred when subjects were treated with insulin, SU/glinides or a combination of these at baseline in both treatment groups (liraglutide: 11128 of 12177 episodes; placebo: 14579 of 15756 episodes). Across these categories of baseline medication, lower rates of hypoglycaemia were observed in the liraglutide group compared to the placebo group.

In conclusion, a treatment difference in the rates of severe and confirmed hypoglycaemic episodes was observed in favour of liraglutide as compared to placebo in combination with standard of care therapy.

Immunogenicity

No new safety concerns related to allergic reactions and injection site reactions were identified in trial 3748. Although based on low numbers, a higher proportion of subjects in the liraglutide group reported allergic reactions and injection site reactions compared to the placebo group (allergic reactions: lira 1.3%, 0.42 events per 100 PY vs placebo 0.9%, 0.27 events per 100 PY; injection site reactions: lira 0.7%, 0.19 events per 100 PY vs placebo 0.3%, 0.07 events per 100 PY).

The proportion of subject with events of immune complex disease was similar in the liraglutide group and in the placebo group (liraglutide: 3 subjects <0.1%; placebo 10 subjects, 0.2%). Thus, the data are not suggestive of a causal relationship between liraglutide and immune complex disease.

Trial 4080

Overall safety

A summary of SAEs and AEs of special interest is provided in (Table 16). For each safety parameter the proportion of subjects reporting an event, the number of reported events and event rate per 100 PYO were similar between the IDeg and IGlar groups.

Table 16 SAEs and AEs of special interest – FAS

	IDeg				IGlar			
	N	%	E	R	N	%	E	R
Number of subjects	3818				3819			
PYO	7568				7558			
Number of events	1488	(39.0)	3381	44.68	1529	(40.0)	3788	50.12
SAEs	1473	(38.6)	3341	44.15	1517	(39.7)	3745	49.55
Severe events	945	(24.8)	1863	24.62	962	(25.2)	1962	25.96
Events related to IMP*								
Probable	48	(1.3)	67	0.89	42	(1.1)	55	0.73
Possible	81	(2.1)	99	1.31	81	(2.1)	98	1.30
Fatal events*	205	(5.4)	276	3.65	220	(5.8)	294	3.89
AEs leading to permanent discontinuation of IMP	200	(5.2)	276	3.65	222	(5.8)	305	4.04
Medication errors leading to SAEs	4	(0.1)	4	0.05	4	(0.1)	4	0.05
AEs related to technical complaints	2	(0.1)	2	0.03	1	(0.0)	1	0.01

Note: Events of special interest include events with medication errors, adverse events related to technical complaints and adverse events leading to discontinuation of trial product excluding subjects resuming treatment; %: percentages; *includes SAEs and AEs of special interest

Abbreviations: AEs: adverse events; IMP: investigational medicinal product; E: number of events; N: number of subjects; PYO: patient years of observation; R: event rate per 100 PYO; SAEs: serious adverse events .

Serious adverse events

The majority of SAEs were of severe or moderate severity and were assessed as unlikely related to IMP by the investigator. No noteworthy differences between the treatment groups were observed with respect to the distribution of SAEs across SOCs and preferred terms. The majority of subjects recovered from the events in both treatment groups, and a similar proportion of subjects had SAEs with fatal outcome in both treatment groups.

Similar number of subjects and number of events were reported as severe SAEs in both treatment groups. Furthermore, no differences between causality, recovery status and discontinuation of IMP were observed in reported severe SAEs between the IDeg and IGlar groups. The distribution of SAEs across SOCs was similar between treatment groups. SOCs with the most frequently reported SAEs were “cardiac disorders”, “infections and infestations” and “nervous system disorders”.

Similar number of subjects and number of events were reported as SAEs leading to dose reduction in both treatment groups. The two most frequently reported PTs leading to dose reduction were hypoglycaemia and hypoglycaemic unconsciousness.

Deaths

A total of 433 deaths were reported for randomised subjects until the database lock date of 31 October 2016. Of these, 423 deaths were determined by the EAC to occur during the trial period. These deaths occurred in 202 (5.3%) subjects randomised to IDeg and 221 (5.8%) subjects randomised to IGlar. The distribution across causes of death was similar between treatment groups. Consistent with the trial population being at high risk of cardiovascular events, approximately half of the deaths were attributed to cardiovascular causes. The EAC was not able to determine the cause of death in 75 cases. In the primary analysis and analysis of cardiovascular death, undetermined cause of death counted as an EAC-confirmed cardiovascular death.

The statistical analysis of time to all-cause death showed no difference between the IDeg and IGlar groups (hazard ratio 0.91 $[0.75; 1.11]_{95\%}$ CI).

Severe hypoglycaemia

A total of 752 events were confirmed by the EAC to be severe hypoglycaemic episodes during the trial period, corresponding to a rate of 4.97 events per 100 PYO, with 3.70 episodes per 100 PYO in the IDeg group and 6.25 episodes per 100 PYO in the IGlar group.

Severe hypoglycaemia was confirmed for 187 (4.9%) subjects in the IDeg group and for 252 (6.6%) subjects in the IGlar group.

Of the subjects with EAC-confirmed events of severe hypoglycaemia, the majority experienced a single episode as opposed to multiple episodes.

Nocturnal severe hypoglycaemia

Of the 752 EAC-confirmed severe hypoglycaemic episodes, 155 episodes were nocturnal, corresponding to a rate of 1.02 events per 100 PYO. In the IDeg group, 24 (8.57%) of the EAC-confirmed hypoglycaemic episodes did not have a time point reported. In the IGlar group, 33 (6.99%) of the EAC-confirmed hypoglycaemic episodes did not have a time point reported. Episodes without time point were not considered in the statistical analysis.

The proportion of subjects with nocturnal severe hypoglycaemia was 1.0% in the IDeg group (0.65 episodes per 100 PYO) and 1.9% in the IGlar group (1.40 episodes per 100 PYO). The rate of nocturnal severe hypoglycaemic episodes was significantly lower for IDeg than for IGlar, with an estimated rate ratio of 0.47 [0.31; 0.73]95% CI ($p<0.001$).

Post hoc on-treatment sensitivity analyses were performed to assess the robustness of the result. The results of the sensitivity analyses were consistent with the results from the main analysis

Neoplasms

In total, 255 events were sent for external classification, of which 253 were assigned a definitive classification outcome of malignant or benign (only 2 events were unclassifiable). The majority of the events were classified as malignant in both treatment groups. The higher proportion of events classified as malignant may be a consequence of more malignant than benign neoplasms meeting the criteria for an SAE.

The overall rate of neoplasms was similar in the IDeg and IGlar groups (1.69 vs 1.68 events per 100 PYO), and the overall rate of malignant neoplasms was 1.32 vs 1.42 events per 100 PYO in the IDeg and IGlar groups, respectively.

Neoplasms classified as malignant were distributed across several primary organ sites, and there were no obvious differences between treatment groups with respect to the distribution of malignant neoplasms across specific primary organ sites.

Laboratory findings

Trial 3748

In trial 3748, no new safety findings related to clinical laboratory parameters, vital signs, (heart rate, SBP, DBP), ECGs and physical examination findings were identified.

Trial 4080

In DEVOTE, no new safety findings related to vital signs (pulse, systolic and diastolic blood pressure) body weight and body mass index findings were identified. No pregnancies were reported for randomised subjects during the trial.

Safety in special populations

Trial 3748

Previously there has been no or limited clinical experience with liraglutide in elderly subjects (≥75 years of age), subjects with severe renal impairment and subjects with heart failure (NYHA class I to III). Therefore the impact of age, renal function and heart failure on the safety profile of liraglutide was evaluated in trial 3748 (NYHA class IV and end-stage renal disease [i.e. current continuous renal replacement therapy] were exclusion criteria in trial 3748). A total of 836 subjects were aged ≥75 years (3074 PYO), a total of 224 subjects had severe renal impairment at baseline (771 PYO) and a total of 1653 subjects had heart failure (NYHA class I to III) (6044 PYO). For all subgroups by age, renal function and heart failure status the following event types were evaluated: EAC-confirmed expanded MACE, deaths, AEs (SAEs and non-serious MESIs) and hypoglycaemic episodes. Furthermore, for subgroups by renal function, EAC-confirmed nephropathy, renal laboratory parameters and the SMQ 'acute renal failure' was evaluated.

Age

The proportion of subjects with EAC-confirmed expanded MACE (including the individual components of expanded MACE) and the rate of such events increased with increasing age in both treatment groups but were similar or lower with liraglutide compared to placebo across all age groups.

As expected the proportion of subjects who died (both EAC-confirmed cardiovascular and non-cardiovascular deaths) tended to increase with higher age in both treatment groups. The proportion of subjects who died tended to be lower in the liraglutide group when compared to the placebo group across age groups.

The proportion of subjects experiencing AEs (SAEs and non-serious MESIs), SAEs and severe events and the rate of such events increased with increasing age in both treatment groups, with no marked differences between treatment groups. The proportion of subjects with AEs leading to permanent discontinuation of trial product and the rate of such events increased with increasing age and tended to be higher in the liraglutide group across all age groups, in line with the pattern observed for the overall population.

Across age groups, there were no unexpected patterns in the distribution of AEs compared to that observed for the overall trial population. The treatment differences in favour of liraglutide observed in the

'cardiovascular events' SOC appeared to be present across the different age groups and were in line with the results seen for EAC-confirmed expanded MACE.

A low number of subjects aged >85 years (liraglutide: 12; placebo: 10) experienced confirmed and/or severe hypoglycaemic episodes, thus further evaluation of these data was not considered appropriate for this subgroup. The rates of both confirmed and severe hypoglycaemia were similar or lower in the liraglutide group compared to the placebo group across age groups, except in the age group of subjects aged 75-84 years in which there was a slightly higher rate of confirmed hypoglycaemic episodes in the liraglutide group compared to the placebo group. However, in that age group the rate of severe hypoglycaemic episodes was similar between the two treatment groups.

Renal function

In trial 3748, a total of 224 subjects with severe renal impairment at baseline were enrolled, with a substantial observation time accumulated in both treatment groups (liraglutide: 117 subjects/ 405 PYO; placebo: 107 subjects/ 366 PYO). There were no notable differences between treatment groups with respect to the distribution of EAC-confirmed expanded MACE, deaths, AEs (SAEs and non-serious MESIs), hypoglycaemic episodes, EAC-confirmed nephropathy events, renal laboratory parameters or acute renal failure across renal subgroups. Specifically, no new safety findings were identified in subjects with severe renal impairment, suggesting that liraglutide was safe to use in this subgroup of subjects.

Heart failure status

In trial 3748, a total of 1439 subjects with NYHA class I-II were enrolled with a substantial observation time accumulated in both treatment groups (liraglutide: 724 subjects/ 2654 PYO; placebo: 715 subjects/ 2610 PYO) and a total of 214 subjects with NYHA class III were enrolled (liraglutide: 108 subjects/393 PYO; placebo: 106 subjects/387 PYO). There were no notable differences between treatment groups with respect to the distribution of EAC-confirmed expanded MACE, deaths, AEs (SAEs and non-serious MESIs) or hypoglycaemic episodes across the subgroups for heart failure status. No new safety findings were identified in subjects with NYHA class I, II or III, suggesting that liraglutide was safe to use in this subgroup of subjects.

Trial 4080

Previously there has been limited clinical experience with insulin degludec in subjects with hepatic impairment and in subjects with severe renal impairment.

Age

At baseline, a total of 3955 trial subjects were aged ≥65 years, which amounted to 51.8% of the total trial population, and 819 (10.7%) subjects were aged ≥75 years, thus ensuring significant exposure in geriatric subjects. In the reported safety areas results were similar across age groups between IDeg and IGlar.

Renal function

In DEVOTE subjects had varying degrees of renal impairment, with more than a third of the trial population having moderate (35.8%) or severe renal impairment (2.8%). In the reported safety areas results were similar across renal function subgroups between IDeg and IGlar.

Sex

Of the total trial population 37.4% were female and 62.6% were male. The general SAE data were similar across female and male subgroups between IDeg and IGlar.

Hepatic impairment

Patients with hepatic impairment, except for end stage liver disease, could be included in the trial. A total of 196 patients (2.6%) with hepatic impairment (defined as having a score of > 2 on a modified Child-Pugh criteria scale using only bilirubin and albumin values) were included (102 patients in the IDeg group and 94 patients in the IGlar group). The general SAE data were similar across subjects with hepatic impairment and subjects with no hepatic impairment between IDeg and IGlar.

Post marketing experience

Trial 3748

From the post-marketing experience with liraglutide, two pharmacoepidemiology studies are especially relevant for this application. One study utilised the Optum Research Database (an insurance claims database in the US) and the other study utilised the Clinical Practice Research Datalink in the UK (a medical records based set of data; the CPRD study). The objective of the two database studies was to evaluate the safety of liraglutide when used in clinical practice post-marketing. This included an evaluation of a potential relationship between Victoza and MTC, in addition to other predefined outcomes of special interest such as thyroid cancer, pancreatic cancer, acute pancreatitis and neoplasms.

The **Optum Research Database study** was a post-marketing requirement from the FDA (PMR 1583-6) and was included in the liraglutide RMP as a required pharmacovigilance activity (category 3). The study was a 5-year prospective observational cohort safety surveillance study evaluating the safety of liraglutide in routine use and with thyroid cancer and, specifically MTC, as primary outcome. Secondary outcomes included acute pancreatitis and pancreatic cancer (evaluated according to a pre-specified algorithm). Participants were adult (≥18 years) initiators of liraglutide or a comparator between 01 February 2010 and 30 November 2014. A total of 5 comparison cohorts were defined by different antidiabetic therapies (exenatide, metformin, pioglitazone, sulfonylureas and DPP-4 inhibitors) and 3 overall comparison cohorts defined by 1) all comparison treatments, 2) all comparison treatments excluding exenatide, and 3) all comparison treatments excluding other incretin-based treatments. Across the study period there were 35,898 episodes of initiation of liraglutide (initial and subsequent) and nearly all liraglutide initiators (initial and subsequent) (35,197; 98%) were propensity score-matched to a member of the all comparators cohort (493,978 episodes of initiation).

No new safety concerns were identified based on the results from the 5-year safety surveillance study. Furthermore, the results did not indicate any increased risk with respect to pre-specified outcomes (thyroid cancer, pancreatic cancer, acute pancreatitis and a number of other safety outcomes) when comparing liraglutide with other antidiabetic medications in common use.

The Optum Research Database study report was submitted to EMA June 2016 (EMEA/H/C/WS/0943) and to the FDA 15 July 2016.

The **Clinical Practice Research Datalink (CPRD)** study was a post-authorisation measure requested by the CHMP. It was set up as a cohort study of adult subjects in a large primary healthcare database from the UK population (CPRD), using their primary care database (GOLD), the Hospital Episode Statistics (HES) and the National Cancer Data Repository (NCDR). The study evaluated the safety of liraglutide in routine use, was based on an inception cohort design, and compared new users of liraglutide with new users of seven other non-insulin antidiabetic treatments (sulphonylureas, biguanides, acarbose, exenatide, glinides, glitazones, and DPP-4 inhibitors) for several outcomes (neoplasms, thyroid cancer (including medullary [C-cell origin]), pancreatic cancer, acute pancreatitis and macrovascular conditions).

The GOLD database identified about 250,000 patients that fulfilled all of the inclusion and exclusion criteria. Of the patients identified as initiating liraglutide treatment in GOLD, 3432 were eligible for HES

linkage and 894 were eligible for both HES and NCDR linkage. Patients were followed for 3.5 years on average.

The final results did not indicate any increased risk with respect to the specified outcomes of interest for patients treated with Victoza compared to patients treated with comparator products (EMEA/H/C/001026/II/WS784).

Trial 4080

Based on global data (until 31 Dec 2016) for insulin degludec (Tresiba) with an estimated cumulative exposure of 930000 PYE no new safety concerns were raised.

2.5.1. Discussion on clinical safety

Trial 3748

In trial 3748, only SAEs (serious adverse events) and MESIs (medical event of special interest) were systematically collected and the present evaluation is based on these events only. MESIs discussed in this section are: neoplasms and calcitonin, thyroid disease, pancreatitis, acute gallstone disease, hypoglycaemia and immunogenicity.

Overall, the differences in proportion of subjects with **EAC-confirmed neoplasms** between treatment groups were 10.1% *versus* 9.0% for overall neoplasms, 3.6% *versus* 3.1% for benign neoplasms and 6.3% *versus* 6.0% for malignant neoplasms for liraglutide versus placebo.

For some individual neoplasms, the HR was > 1. This was especially true for **pancreatic carcinoma** and **melanoma of the skin**; the 95% CI was 0.92-7.27 for both neoplasms. EAC-confirmed pancreatic cancer was seen in 13 subjects (14 events, 0.3%, rate 0.08 events/100PY) in the liraglutide group vs 5 subjects (5 events, 0.1%, rate 0.03 events/100PY) in the placebo group. The MAH reasons that the relatively early presentation of the (advanced) cases suggest that these were pre-existing malignancies and that the incidence falls within the predicted range for T2DM patients (0.06-14.3 events/100PY). In addition two post-marketing epidemiological studies did not indicate an increased risk for pancreatic cancer. In a recent study of human pancreatic tissue, normal ductal epithelial cells, ductal pancreatic carcinomas, or pancreatic intraepithelial neoplasia 3 did not express GLP-1 R indicating that GLP-1 Rs are unlikely to be related to neoplastic transformation in the pancreas. However, there were already uncertainties whether incretin-based treatments are related to pancreatic neoplasms. These uncertainties have not been removed by the present data. Therefore it was decided that pancreatic cancer will remain as an Important potential risk in the RMP for liraglutide. As there is no change in the situation, a change in the SmPC with regard to mentioning pancreatic carcinoma was not considered necessary.

Malignant melanoma was another neoplasm seen more frequently with liraglutide compared to placebo (20 events in 19 subjects in the liraglutide group vs 9 events in 9 placebo-treated patients). The events occurred at similar rates until month 18, after which events continued to accrue in the liraglutide group, while in the placebo group only 2 additional events occurred. Melanoma was not identified as a risk in earlier trials or in the two epidemiological trials performed post-marketing. However, most trials were of shorter duration than 18 months, and thus a difference could not be detected if it occurs after 18 months. The MAH states that LEADER was not designed nor powered to demonstrate a treatment effect in relation to neoplasm subtypes. For malignant melanoma specifically, risk factors were not systematically collected at baseline, and the skin was not subject to systematic evaluation during the trial. It is agreed with the MAH that there is no acceleration in rate of events, which might have been expected when a tumour promoting effect is present; there was a flattening in the placebo curve. From the data a causal relation can not be confirmed or excluded. However, seen the importance of the disorder monitoring malignant melanoma through routine pharmacovigilance activities, as proposed by the MAH, was considered not

sufficient. Therefore, it was decided that 'neoplasm (including melanoma)' should be included as an important potential risk in the RMP for liraglutide.

Trial data do not support a causal relationship between treatment with liraglutide and the risk of **breast cancer, colorectal neoplasms, or thyroid neoplasms** (all data not shown). Also, combination with insulin did not show an increased risk for the occurrence of neoplasms (data not shown).

Thyroid disease occurred in similar proportions of patients in both treatment groups (lira 4.2%, placebo 4.1%). However, in subjects with a medical history of thyroid disease, the proportion with events of thyroid disease was higher in the liraglutide group (7.5%) than in the placebo group (5.8%). This has also been observed in the liraglutide T2DM clinical development programme. The imbalance was driven by events of goitre (liraglutide 16 events, placebo 6 events).

In 2014, FDA and EMA made an independent review and evaluation of all available data regarding the risk of **pancreatitis** with incretin-based drugs. At that time, the agencies concluded that there was no strong evidence to support a causal relationship, but that pancreatitis should be regarded as a potential risk with these therapies until further data became available. A class labelling was therefore issued for all incretin-based therapies concerning the risk of pancreatitis. Data from trial 3748 did not show a difference in the incidence of pancreatitis between treatment groups. The proportion of subjects with EAC-confirmed acute pancreatitis and the rates of events were comparable between the liraglutide group (0.4%; 0.11 events per 100 PYO) and the placebo group (0.5%; 0.19 events per 100 PYO). The SmPC for liraglutide was amended to include these data from the LEADER trial. Further to this, pancreatitis was removed as an important identified risk from the RMP for liraglutide.

In contrast, **acute gallstone disease** seen as a well-known risk factor for pancreatitis, was observed more frequently in the liraglutide group (3.1%; 0.90 events per 100 PYO) than in the placebo group (1.9%, 0.65 events per 100 PYO). Cholelithiasis and cholecystitis are already included in section 4.8 of the SmPC for IDegLira. Somewhat surprisingly, these events were not clearly related to cases of pancreatitis in this trial. Acute gallstone disease was included as an important identified risk in the RMP for liraglutide.

Data for **hypoglycaemia** were in favour of liraglutide compared to placebo, when added to standard of care. As can be expected, the vast majority of severe or confirmed hypoglycaemic episodes occurred in subjects treated with insulin and/or SU/glinides. Though based on few patients (401 liraglutide-treated patients aged age 75-84 years, 17 liraglutide-treated patients aged age ≥85 years and 25 placebo-treated patients aged age ≥85 years), severe hypoglycaemia was observed with a noticeable higher frequency among liraglutide-treated patients aged age ≥85 years (11.76%) both when compared to liraglutide-treated patients aged 75-84 years (3.99%) and placebo-treated patients aged age ≥85 years (4.00%). However, it concerned only 2 patients, who were also treated with insulin as a confounding factor. No amendments were made to the SmPC for liraglutide.

No new safety concerns related to **allergic reactions and injection site reactions** were identified in trial 3748.

The LEADER trial included a total of 836 subjects were aged ≥75 years (3074 PYO), a total of 224 subjects had severe renal impairment at baseline (771 PYO) and a total of 1653 subjects had heart failure (NYHA class I to III) (6044 PYO), subgroups for which limited experience exists from previous trials.

There were more deaths with increasing **age**, as can be expected. CV-death and all-cause death tended to be lower with liraglutide compared to placebo. There was no difference between treatment groups in the incidence of SAEs and MESIs in the different age classes.

For **renally impaired** patients too, CV-death and all-cause death increased with increasing impairment, but the incidence tended to be lower in the liraglutide group. No difference between treatment groups was seen for SAEs and MESIs.

The same pattern was seen for patients in the different classes of **heart failure**. Although the differences between liraglutide and placebo were small, they were in favour of liraglutide.

Results indicate that liraglutide might be used safely in these patients. The SmPC for liraglutide was updated with regards to the elderly and patients with renal impairment, and similar amendments are proposed for the IDegLira SmPC. This is acceptable, considering that the current recommendations relate to liraglutide and not to IDeg. Based on these data, mild/moderate hepatic impairment, severe renal impairment and congestive heart failure NYHA III was removed as missing information in the liraglutide RMP.

Trial 4080

As the safety profile of both IDeg and IGlar are well characterised, the focus of the safety evaluation in the DEVOTE trial was on CV safety and hypoglycaemias. In addition, events of neoplasms were evaluated.

The trial contributes with a total of 15,125 PYE, which was evenly distributed between the two treatment groups.

The overall reporting pattern of SAEs and AEs of special interest did not differ between treatments and when SAEs were presented by SOC, no differences were observed. The rate of AEs leading to permanent discontinuation of treatment did not differ between groups. Few events were considered probably or possibly related to study medication (0.6% of events for IDeg and 0.8% of events for IGlar). Eight events of medication errors leading to SAEs were reported (four in each group) and three of these events were assessed as related to study medication. The events were due to unintentional overdose or double dosing due to missed dose, resulting in hypoglycaemias. There was no difference observed between treatments neither in the number of deaths (202 for IDeg and 221 for IGlar), nor in the causes of death. The rate of neoplasms did not differ between treatments.

The rate of severe hypoglycaemic events was lower with IDeg than with IGlar, see also efficacy section of the AR. The characteristics of the severe hypoglycaemia events were comparable for IDeg and IGlar, although common symptoms were less frequently reported with IDeg. Notably, unconsciousness and coma was reported at a comparable rate (1.4% and 1.6% for IDeg and IGlar, respectively). Fewer subjects experienced severe hypoglycaemia with IDeg than with IGlar (4.9% and 6.6%, respectively). The majority of patients only experienced a single event. The analysis of time to first EAC-confirmed severe hypoglycaemic episode confirms that hypoglycaemic episodes were less frequent with IDeg throughout the study duration. Nocturnal hypoglycaemias were also analysed and the rate was significantly lower with IDeg than with IGlar (rate ratio 0.47 [0.31; 0.73]95% CI ($p<0.001$)).

There were no apparent differences in the use of other antidiabetic medications that could explain the differences observed in the occurrence of hypoglycaemias. Based on these data, and in accordance with the GVP Module V, hypoglycaemia was removed as an important identified risk from the RMP for IDeg.

There were no differences in changes in clinical laboratory parameters or vital signs between groups. Generally, changes over time were only minor.

The trial included 214 patients with severe renal impairment and 196 patients with hepatic impairment. When the safety data for these patients were compared between the two treatment groups, no differences in the safety profile were observed. Although the number of patients within these groups and exposed to IDeg are limited (108 patients with severe renal impairment and 102 patients with hepatic impairment), the trial provided long-term data of about 2 years without any emergent safety issues.

Therefore “severe renal impairment” and “hepatic impairment” were removed as missing information from the RMP for IDeg.

2.5.1. Conclusions on clinical safety

In both trials, only SAEs (serious adverse events) and MESIs (medical event of special interest) were systematically collected. Both trials also provided data on safety in special subgroups, for which the experience previously has been limited.

With the **LEADER** trial, safety data was provided regarding a number of known safety concerns with the use of liraglutide. Neoplasms were considered as MESI. Overall, there were no significant differences in proportion of subjects with EAC-confirmed neoplasms between treatment groups. Especially data for breast cancer, colorectal neoplasms and thyroid neoplasms did not show an increased risk with liraglutide. However, for pancreatic carcinoma and malignant melanoma, a numerical increase was observed in patients treated with liraglutide. However, no updates were made in the SmPC due to these findings.

No difference between treatment groups was seen in the incidence of pancreatitis; and based on these data and data from observational studies, amendments were made to the SmPC. Cholelithiasis was observed more frequently with liraglutide and was added to section 4.8 of the SmPC for liraglutide.

Results in subgroups of elderly patients, patients with severe renal insufficiency and subjects with heart failure did not reveal significant differences between liraglutide and placebo in safety profile.

No new safety concerns arise from the analysis of the data from the **DEVOTE** trial. The safety profile of IDeg is comparable to that observed with the comparator IGlar, for which there is long clinical experience. The lower rate of hypoglycaemias observed with IDeg compared to IGlar, confirms previous observations in clinical trials. No safety concerns arise with regards to the use of IDeg in patients with hepatic or renal impairment.

The safety data provided by trials 3478 and 4080 are partly of relevance to IDegLira. The warnings regarding pancreatitis and thyroid disease are both based on safety data for liraglutide and the proposed updates to align the SmPC for IDegLira with that of liraglutide is acceptable. Cholelithiasis and cholecystitis is however already included in section 4.8 for IDegLira, thus no updates are needed. The data on hypoglycaemias with IDeg is not relevant to IDegLira, and no updates are proposed.

The restrictions with regards to the use of IDegLira in elderly patients, patients with severe renal insufficiency and subjects with heart failure are also based on safety data for liraglutide, thus the proposed updates to align the SmPC for IDegLira with that of liraglutide are acceptable.

2.5.2. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

- The PRAC considered that the risk management plan version 7.0 is acceptable.
- In addition, it was recommended that with the next RMP update, the MAH should implement the

Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (Rev. 2) with the definition of important risks, as per GVP module V revision 2, on which the list of safety concerns could be shortened.

- The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 7.0 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal disorders • Hypoglycaemia • Immunogenicity (allergic reactions) • Acute gallstone disease
Important potential risks	• Altered renal function • Lack of efficacy due to anti-IDeg antibody formation • Medication errors, including errors with transfer from injectable diabetes therapy • Medullary thyroid cancer • Neoplasms • Pancreatic cancer
Missing information	• Children and adolescents • Congestive heart failure NYHA IV • Drug–drug interactions with warfarin • Patients with severe hepatic impairment • Patients with end-stage renal disease • Pregnant and lactating women • Off-label use in patients with T1DM • Transfer from injectable diabetes therapy (basal insulin)[a]

[a]Xultophy® has not been studied in patients transferring from <20 units or >50 units of insulin.
Abbreviations: IDeg = insulin degludec; NYHA = New York Heart Association; T1DM = type 1 diabetes mellitus.

Pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities.
Routine Pharmacovigilance is considered sufficient to further characterise all safety concerns included in the safety specification of the RMP.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Gastrointestinal disorders	**Text in SmPC** 4.4 Special warnings and precautions for use Dehydration 4.8 Undesirable effects Gastrointestinal adverse reactions	None
Hypoglycaemia	**Text in SmPC** 4.4 Special warnings and precautions for use Hypoglycaemia 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects Hypoglycaemia 4.9 Overdose	None
Immunogenicity (allergic reactions)	**Text in SmPC** 4.3 Contraindications 4.8 Undesirable effects Allergic reactions	None
Acute gallstone disease	**Text in SmPC** 4.8 Undesirable effects	None
Altered renal function	**Text in SmPC** 4.4 Special warnings and precautions for use Dehydration	None
Lack of efficacy due to anti-IDeg antibody formation	**Text in SmPC** 4.4 Special warnings and precautions for use Antibody formation	None
Medication errors, including errors with transfer from injectable diabetes therapy	**Text in SmPC** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 5.1 Pharmacodynamic properties	Educational material for healthcare professionals in the EU, in the form of a brochure (see Annex 11)
Medullary thyroid cancer	**Text in SmPC** 5.3 Preclinical safety	None
Neoplasms	None	None
Pancreatic cancer	None	None
Children and adolescents	**Text in SmPC** 4.1 Therapeutic indication 4.2 Posology and method of administration Paediatric population	None
Congestive heart failure NYHA IV	**Text in SmPC** 4.4 Special warnings and precautions for use Populations not studied	None
Drug–drug interactions with warfarin	**Text in SmPC** 4.5 Interaction with other medicinal products and other forms of interaction	None
Patients with severe hepatic impairment	**Text in SmPC** 4.2 Posology and method of administration Special populations Hepatic impairment	None
Patients with end-stage renal disease	**Text in SmPC** 4.2 Posology and method of administration Special populations Renal impairment	None
Pregnant and lactating women	**Text in SmPC** 4.6 Fertility, pregnancy and lactation Pregnancy Breast-feeding Fertility	None

Off-label use in patients with T1DM	**Text in SmPC** 4.1 Therapeutic indication 4.4 Special warnings and precautions for use	None
Transfer from injectable diabetes therapy (basal insulin)[a]	**Text in SmPC** 4.4 Special warning and precautions for use Populations not studied	None

[a] Xultophy® has not been studied in patients transferring from <20 units or >50 units of insulin.
Abbreviations: IDeg = insulin degludec; NYHA = New York Heart Association; SmPC = Summary of Product Characteristics; T1DM = type 1 diabetes mellitus.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated in order to include the safety information based on cardiovascular outcomes studies conducted a for each of the monocomponents of Xultophy: LEADER (Liraglutide Cardiovascular Outcomes Trial) and DEVOTE (Insulin Degludec Cardiovascular Outcomes Trial). Moreover, information regarding certain safety issues related to liraglutide, including information on special populations, have been included. There were no consequential changes to the PIL.

SmPC section 4.1 has been revised as follows (new text in bold, removed text as strikethrough):

"Xultophy is indicated for the treatment of adults with **insufficiently controlled** type 2 diabetes mellitus to improve glycaemic control **as an adjunct to diet and exercise** ~~in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control~~ **in addition to other oral medicinal products for the treatment of diabetes.** ~~(~~**For study results with respect to combinations, effects on glycaemic control, and the populations studied,** see sections 4.4**, 4.5** and 5.1~~ for available data on the different combinations)~~.".

For the other changes of the SmPC see Attachement.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH, however, the proposed changes to the package leaflet were minimal. No changes of the package leaflet were agreed following the assessment of the variation application.

2.7.2. Additional monitoring

Xultophy remains on the list of medicines under additional monitoring; the fixed ratio combination of liraglutide and insulin degludec has an EURD date of 18/09/2014.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The previously approved indication for Xultophy was:

"*Xultophy is indicated for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations).*"

With this application the MAH had proposed to include reference to the effect of Xultophy on cardiovascular events in section 4.1. The indication was also simplified:

"Xultophy is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus in combination with other medicinal products for the treatment of diabetes. For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1."

Further to this, some other changes to section 4.2, 4.4, 4.8 and 5.1 of the SmPC were proposed.

The therapeutic objectives of treatment for diabetes include both glycaemic glucose control and the prevention of cardiovascular events and microvascular complications.

3.1.2. Available therapies and unmet medical need

T2DM is a progressive metabolic disorder characterised by chronic hyperglycaemia associated with increased risk of long-term micro-and macrovascular complications. Diabetes has been identified as an independent risk factor for cardiovascular disease, which represents the leading cause of morbidity and mortality in subjects with diabetes. Thus, the risk of cardiovascular disease is 2−4 times greater for patients with T2DM compared to the general population, and death from cardiovascular causes is the most common cause of death in patients with T2DM.

Even with use of standard of care therapies to control cardiovascular risk factors, the risk of cardiovascular disease in subjects with diabetes remains to be more than double that in subjects without diabetes. Hence, the cardiovascular safety of antidiabetic drugs is of paramount importance.

3.1.3. Main clinical studies

With this application, the results of two cardiovascular outcome trials are presented. Both studies have been previously assessed by the CHMP, therefore only an abbreviated description of the studies is provided in this assessment report.

- Trial 3748 – LEADER - inclusion of data in the SmPC for Victoza (liraglutide) was approved in July 2017 through procedure EMEA/H/C/001026/II/0042.
- Trial 4080 – DEVOTE - inclusion of data in the SmPC for Tresiba (IDegLira) was approved in Sept 2017 through procedure EMEA/H/C/002498/II/0028.

Both studies were designed to investigate the cardiovascular safety of liraglutide and IDeg, respectively. However, as the data on cardiovascular outcome is relevant for the assessment of the proposed change to the indication, the cardiovascular outcome is presented in the efficacy part of this report.

Trial 3748 was a long-term, multi-centre, multi-national, randomised, double-blind, placebo-controlled trial performed to determine the effect and safety of liraglutide *versus* placebo on cardiovascular outcomes. The trial included 9340 subjects with a very high risk for CV events (> 80% were > 50 years with established CV disease and 18% were >60 years with risk factors for CV disease). Both liraglutide and placebo were used in addition to standard of care therapy to ensure scientific rigour of the comparison. Primary endpoint was time to first occurrence of 3-point MACE. The median time of observation in the trial was 3.84 years (including follow-up period) and the total median exposure time to the trial product was 3.52 years.

Trial 4080 was a randomised, double-blind and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of insulin degludec (IDeg) versus insulin glargine (IGlar, 100 units/mL) in 7,637 patients with type 2 diabetes mellitus at high risk of cardiovascular events. The majority of patients included were patients aged ≥ 50 years with established cardiovascular disease or chronic kidney disease. The primary analysis was time from randomisation to first occurrence of a 3-point MACE. The median time of observation was 1.99 years and the total median exposure time to the trial product was 1.83 years.

3.2. Favourable effects

Trial 3748

A total of 1302 first EAC-confirmed MACEs were reported in trial 3748 (608/4668 [13.0%] in the liraglutide group and 694/4672 [14.9%] in the placebo group). In the primary Cox analysis of time to first EAC-confirmed MACE, the estimated hazard ratio (liraglutide vs placebo) of 0.87 [0.78; 0.97]$_{95\%\ CI}$ was statistically significant and in favour of liraglutide. All three components of MACE-3 contributed to the reduction; most notably CV-death (HR 0.79). Sensitivity analyses confirmed the results of the primary analysis.

Expanded MACE was a secondary endpoint. It consisted of the components of MACE-3 plus hospitalisation for unstable angina pectoris, coronary revascularisation and hospitalisation for heart failure. Estimated hazard ratio (liraglutide vs placebo) for time to expanded MACE was 0.88 (0.81; 0.96).

The risk of all-cause death was reduced (HR 0.85 [0.74; 0.97]); supported by a beneficial trend in non-CV death HR (0.95 [0.77; 1.18]).

The reduction in MACE was substantiated by a series of pre-specified sensitivity analyses. These included several 'on-treatment' analyses, which resulted in lower point estimates consistent with a liraglutide mediated effect.

For **microvascular events** an exploratory composite endpoint was formulated consisting of nephropathy (4 components) and retinopathy (3 components). Treatment with liraglutide resulted in a reduction of the time to first occurrence of the composite microvascular endpoint (HR 0.84 [0.73; 0.970]. Also, a reduction in nephropathy was observed in favour of liraglutide (HR 0.78 [0.67; 0.92). This was primarily driven by "new onset of macroalbuminuria" (HR 0.74 [0.60; 0.91]).

A total of 836 subjects were **aged ≥75 years**, and exploratory analyses were performed according to 4 subgroups of age (<65 years, 65-74 years, 75-84 years, and ≥85 years). The proportion of subjects with EAC-confirmed expanded MACE (including the individual components of expanded MACE) and the rate of

such events increased with increasing age in both treatment groups but were similar or lower with liraglutide compared to placebo across all age groups.

In trial 3748, a total of 224 subjects with **severe renal impairment** at baseline were enrolled. For MACE-3 a treatment interaction was observed for subjects with moderate or severe renal impairment vs subjects with mild or no renal impairment (eGFR < 60 vs eGFR ≥ 60 ml/min/1.73m^2)(p=0.03). The HR of the effect of liraglutide in subjects with eGFR < 60 was 0.71 (0.58; 0.87) vs 0.93 (0.82; 1.06) in subjects with eGFR ≥ 60.

Exploratory analyses were performed according to 4 subgroups of renal function (normal, renal function, or mild, moderate or severe renal impairment) for expanded MACE. There were no notable differences between treatment groups with respect to the distribution of EAC-confirmed expanded MACE and deaths.

A total of 1439 subjects with NYHA class I-II were enrolled (liraglutide: 724 subjects/ 2654 PYO; placebo: 715 subjects/ 2610 PYO) and a total of 214 subjects with NYHA class III were enrolled (liraglutide: 108 subjects/393 PYO; placebo: 106 subjects/387 PYO). There were no notable differences between treatment groups with respect to the distribution of EAC-confirmed expanded MACE, deaths, AEs (SAEs and non-serious MESIs) or hypoglycaemic episodes across the subgroups for HF status; however, there was a numerical increase in non-fatal MI, non-fatal stroke and HF hospitalisations in patients with NYHA III at baseline.

For glycaemic control, the reduction in HbA_{1c} was significantly greater with liraglutide than with placebo after 3 years of treatment (-1.16% *versus* -0.77%; estimated treatment difference of -0.4% [-0.45; -0.34]$_{95\% CI}$); and the difference was maintained at end of treatment (-0.3% [-0.35; -0.23]$_{95\% CI}$). The effect of liraglutide on glycaemic control, as measured by HbA1c, was consistent across age groups (<65, 65-74, 75-84, > 85), baseline renal function (normal, mild, moderate, severe renal impairment), and heart failure status (NYHA class I-III). The improvement in glycaemic control was achieved with lower rates of both severe and confirmed hypoglycaemia as compared to placebo. The effect of liraglutide on HbA_{1c} was accompanied by a reduced likelihood of initiation of other glucose-lowering treatment during the trial, including insulin or any new oral antidiabetics. Liraglutide was associated with a greater reduction in body weight compared to placebo of around 2.3 kg, which was sustained throughout the trial, as well as small but statistically significant reductions in SBP.

Trial 4080

A total of 681 first EAC-confirmed MACEs were reported in trial 4080, of which 325 occurred with IDeg and 356 with IGlar. The primary analysis of time to first EAC-confirmed MACE resulted in an estimated HR of 0.91 [0.78; 1.06]$_{95\%}$ CI for IDeg relative to IGlar. The upper bound of the 95% CI was below 1.3, thus confirming non-inferiority of IDeg relative to IGlar with respect to cardiovascular safety. The outcome was supported by the sensitivity analyses, including the analysis in the PP set. Events occurred evenly distributed overtime for both treatments and the three component of MACE (non-fatal MI, non-fatal stroke and CV-death) were equally distributed for both treatments.

The first confirmatory secondary endpoint (number of EAC-confirmed hypoglycaemic episodes) showed that IDeg was superior to IGlar (RR 0.60 [0.48; 0.76]$_{95\%}$ CI (p<0.001)). The result was supported by the sensitivity analyses performed.

The second confirmatory secondary endpoint (occurrence of at least one EAC-confirmed severe hypoglycaemic episode within a subject) also showed that IDeg was superior to IGlar with a reduced risk of experiencing hypoglycaemia (OR 0.73 [0.60; 0.89]$_{95\%}$ CI (p=0.001)). Again, the result was supported by the sensitivity analyses performed.

There was no difference in the change in HbA1c from baseline between treatments, confirming that patients were titrated to target in both treatment groups.

At 24 months, slightly higher doses of IDeg were observed compared to IGlar, however at the last visit before end-of-trial, no difference was observed. There were no major differences in bolus doses or total insulin dose between groups.

3.3. Uncertainties and limitations about favourable effects

Trial 3478

Exploratory analyses were performed to evaluate the consistency of the treatment effect between liraglutide and placebo in time to *first* MACE across multiple subgroups. The benefit observed with liraglutide *versus* placebo was generally consistent across the majority of the pre-defined subgroups. However, for **Region North America** (HR 1.01 [0.84; 1.22]) and in **subjects' ≥60 years of age with risk factors** for cardiovascular disease (HR 1.20 [0.86; 1.67]) HR was above 1. There were baseline differences between **US and European participants**. In addition, the mean proportion of time on trial drug was lower in the US (0.73%) than in the non-US population. The lower exposure to trial drug in the US population may explain the observed difference. A number of post-hoc analyses were performed for the **cardiovascular risk groups**. These did not reveal an explanation for the observed difference.

3.4. Unfavourable effects

Trial 3478

In trial 3748, only SAEs (serious adverse events) and MESIs (medical event of special interest) were systematically collected and the present evaluation is based on these events only. MESIs discussed are: neoplasms, thyroid disease, pancreatitis, acute gallstone disease, and immunogenicity.

Overall, the proportion of subjects with EAC-confirmed neoplasms was low in both treatment groups (10.1% *versus* 9.0% for overall neoplasms, 3.6% *versus* 3.1% for benign neoplasms and 6.3% *versus* 6.0% for malignant neoplasms for liraglutide versus placebo). Notably, for some individual neoplasms (**pancreatic carcinoma** and **malignant melanoma**) the HR was > 1 (see below).

No clear differences between treatment groups were observed for **breast cancer** (HR 1.06 [0.57; 1.96]), **colorectal neoplasms** (HR 0.99 [0.59; 1.68]), **or thyroid neoplasms** (HR 1.66 [0.40; 6.95]).

Thyroid disease occurred in similar proportions of patients in both treatment groups (liraglutide 4.2%, placebo 4.1%). However, in subjects with a medical history of thyroid disease, the proportion with events of thyroid disease was higher in the liraglutide group (7.5%) than in the placebo group (5.8%). This has also been observed in the liraglutide T2DM clinical development programme. The imbalance was driven by events of goitre (liraglutide 16 events, placebo 6 events).

The proportion of subjects with EAC-confirmed acute **pancreatitis** and the rates of events were comparable between the liraglutide group (0.4%; 0.11 events per 100 PYO) and the placebo group (0.5%; 0.19 events per 100 PYO).

In contrast, **acute gallstone disease**, seen as a well-known risk factor for pancreatitis was observed more frequently in the liraglutide group (3.1%; 0.90 events per 100 PYO) than in the placebo group (1.9%, 0.65 events per 100 PYO). However, no association with pancreatitis events was observed.

The overall rates of **hypoglycaemic episodes** (i.e., confirmed and for overall hypoglycaemia according to the ADA classification) were lower in the liraglutide group compared to the placebo group (confirmed: liraglutide 70.2 episodes/100PY, placebo 91.2 episodes/100PY; ADA overall liraglutide 308.2 episodes/100PY, placebo 358.4 episodes/100PY). A similar pattern was observed for confirmed and overall nocturnal hypoglycaemia. The rates of both severe and confirmed hypoglycaemic episodes were

lower with liraglutide compared to placebo RR: 0.69 [0.51; 0.93]$_{95\%CI}$ and RR: 0.81 [0.74; 0.88]$_{95\%CI}$, respectively. A similar pattern in favour of liraglutide was also observed for nocturnal severe and nocturnal confirmed hypoglycaemia.

Although based on few patients (401 liraglutide-treated patients aged age 75-84 years, 17 liraglutide-treated patients aged age ≥85 years and 25 placebo-treated patients aged age ≥85 years), severe hypoglycaemia was observed with a noticeable higher frequency among liraglutide-treated patients aged age ≥85 years (11.76%) both when compared to liraglutide-treated patients aged 75-84 years (3.99%) and placebo-treated patients aged age ≥85 years (4.00%). However, it concerned only 2 patients, who were also treated with insulin as a confounding factor. For subgroups by age, renal impairment category, and heart failure class, no differences between treatment groups were seen in the incidence of SAEs and MESIs.

Trial 4080

The focus of the safety evaluation in the DEVOTE trial was on CV safety and hypoglycaemias. Only the following types of events were systematically collected: all SAEs, episodes of severe hypoglycaemia, AEs leading to permanent discontinuation of investigational product, medication errors leading to an SAE and adverse events related to technical complaints. Data on neoplasms was also collected and was subject to external classification.

The trial contributes with a total of 15,125 PYO, which were evenly distributed between the two treatment groups.

The observed MACE rate was 5.28 events per 100 PYO, similar in both groups. In the safety evaluation a 4-point MACE, which also included “unstable angina requiring hospitalisation”, was evaluated. The outcome of this evaluation was in line with the primary analysis, thus no difference was observed between treatments. No difference between treatments was observed in events of heart failure requiring hospitalisation. The analysis of MACE in different subgroups was consistent with the primary analysis. There was no difference observed between treatments neither in the number of deaths (202 for IDeg and 221 for IGlar), nor in the causes of death.

The overall reporting pattern of SAEs and AEs of special interest did not differ between treatments and when SAEs were presented by SOC, no differences were observed.

Fewer subjects experienced severe hypoglycaemia with IDeg than with IGlar (4.9% and 6.6%, respectively). The majority of patients only experienced a single event. The analysis of time to first EAC-confirmed severe hypoglycaemic episode confirms that hypoglycaemic episodes were less frequent with IDeg throughout the study duration. Nocturnal hypoglycaemias were also analysed and the rate was significantly lower with IDeg than with IGlar (rate ratio 0.47 [0.31; 0.73]95% CI ($p<0.001$)). There were no apparent differences in the use of other antidiabetic medications that could explain the differences observed in the occurrence of hypoglycaemias.

The trial included 214 patients (2.8%) with severe renal impairment and 196 patients (2.6%) with hepatic impairment. When the safety data for these patients were compared between the two treatment groups, no differences in the safety profile were observed. Although the number of patients within these groups and exposed to IDeg are limited (108 patients with severe renal impairment and 102 patients with hepatic impairment), the trial provides long-term data of about 2 years without any emergent safety issues. “Severe renal impairment” and “hepatic impairment” were deleted as missing information from the RMP for IDeg based on the data provided.

3.5. Uncertainties and limitations about unfavourable effects

Trial 3478

Pancreatic neoplasms were analysed as a MESI. The HR was 2.59 (0.92; 7.27), in favour of placebo. EAC-confirmed pancreatic cancer was seen in 13 subjects (14 events, 0.3%, rate 0.08 events/100PY) in the liraglutide group vs 5 subjects (5 events, 0.1%, rate 0.03 events/100PY) in the placebo group. The majority of the events were ductal adenocarcinomas and advanced at time of diagnosis (i.e., of stage IIA or above; according to the AJCC staging system).

Malignant melanoma occurred in 20 events (19 subjects) in the liraglutide group vs 9 events (9 patients) in the placebo group. The events occurred at similar rates until month 18, after which events continued to accrue in the liraglutide group, while in the placebo group only 2 additional events occurred. Melanoma has not been identified as a risk in earlier trials or in the two epidemiological trials performed post-marketing.

The HR for **retinopathy** was above 1 (HR 1.15[0.87; 1.52]), and this was primarily due to "vitreous haemorrhage". The incidence of vitreous haemorrhage tended to be higher in the liraglutide group, as compared to the placebo group (HR 1.45 [0.84; 2.50]).

3.6. Effects Tables

Table 17 Effects table for liraglutide in the prevention of major cardiovascular events

Effect	Short Description	Unit	Lira	Pla	Uncertainties / Strength of evidence
Favourable Effects					
MACE-3	Time to first occurrence of cardiovascular death, non-fatal myocardial infarction (incl. silent MI) or non-fatal stroke.	% of patients with event	13.0	14.9	Primary endpoint HR 0.87 (0.78;0.97) P (2-sided) = 0.011
Expanded MACE	MACE-3 or hospitalisation for unstable angina pectoris, coronary revascularisation and hospitalisation for heart failure	% of patients with event	20.3	22.7	Secondary endpoint HR 0.88 (0.81;0.96)
CV death	Mortality adjudicated to CV cause	% of patients with event	4.7	6.0	Secondary endpoint HR 0.78 (0.66;0.93)
Non-fatal MI	Time to non-fatal MI	% of patients with event	6.0	6.8	Secondary endpoint HR 0.88 (0.75;1.03)
Non-fatal stroke	Time to non-fatal stroke	% of patients with event	3.4	3.8	Secondary endpoint HR 0.89 (0.72;1.11)
Hosp.-UAP	Adjudicated events of hospitalisation due to unstable angina pectoris	% of patients with event	2.6	2.7	Secondary endpoint HR 0.98 (0.76;1.26)
Cor. Revasc.	Time to coronary revascularisation	% of patients with event	8.7	9.4	Secondary endpoint HR 0.91 (0.80;1.04)

Effect	Short Description	Unit	Lira	Pla	Uncertainties / Strength of evidence
Hosp.-HF	Adjudicated events of hospitalisation due to heart failure	% of patients with event	4.7	5.3	Secondary endpoint HR 0.87 (0.73;1.05)
All cause death	Time from randomisation to all-cause death.	% of patients with event	8.2	9.6	Secondary endpoint HR 0.85 (0.74;0.97)
Non-CV death	Time from randomisation to non-cardiovascular death	% of patients with event	3.5	3.6	Secondary endpoint HR 0.95 (0.77;1.18)
Composite microvascular endpoint	Time from randomisation to first occurrence of nephropathy events or diabetic retinopathy events	% of patients with event	7.6	8.9	Secondary endpoint HR 0.84 (0.73;0.97)
Nephropathy	Time from randomisation to first occurrence of nephropathy events	% of patients with event	5.7	7.2	Secondary endpoint HR 0.78 (0.67;0.92)
Unfavourable Effects					
Retinopathy	Time from randomisation to first occurrence of retinopathy event	% of patients with event	2.3	2.0	Secondary endpoint HR 1.15 (0.87;1.52)
Pancreatic carcinoma	Incidence of EAC-confirmed pancreatic neoplasms	N (%) of patients with event	13 (0.3)	5 (0.1)	Low number of events
Malignant melanoma	Incidence of EAC-confirmed malignant melanoma	N (%) of patients with event	13 (0.3)	5 (0.1)	Low number of events

Table 18 Effects Table for insulin degludec (IDeg) in the prevention of major cardiovascular events (Trial 4080)

Effect	Short description	Unit	IDeg	IGlar	Uncertainties / Strength of evidence
Favourable Effects					
MACE-3	Time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.	% of patients with event	8.5	9.3	Primary endpoint HR 0.91 (0.78;1.06)
CV death	Mortality adjudicated to CV cause	% of patients with event	3.6	3.7	HR 0.96 (0.76;1.21)
Non-fatal stroke	Time to non-fatal stroke	% of patients with event	1.9	2.1	HR 0.90 (0.65;1.23)
Non-fatal MI	Time to non-fatal MI	% of patients with event	3.8	4.4	HR 0.85 (0.68;1.06)
Unfavourable Effects					
Severe hypo-glycaemia	Number of EAC-confirmed severe hypoglycaemia	Number of events	280	472	Confirmatory secondary endpoint (I)

Effect	Short description	Unit	IDeg	IGlar	Uncertainties / Strength of evidence
	episodes				RR 0.60 (0.48;0.76)
Severe hypo-glycaemia	Occurrence of at least one EAC-confirmed severe hypoglycaemia episode within a subject	% of patients with event	4.9	6.6	Confirmatory secondary endpoint (II) OR 0.73 (0.60;0.89)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

T2DM is characterised by chronic hyperglycaemia associated with increased risk of long-term micro-and macrovascular complications. Diabetes has been identified as an independent risk factor for cardiovascular disease and until recently, metformin was the only antidiabetic drug considered to have demonstrated a positive effect on macrovascular outcomes. Even with use of standard of care therapies to control cardiovascular risk factors, the risk of cardiovascular disease in subjects with diabetes remains to be more than double that in subjects without diabetes. Hence, the cardiovascular safety of antidiabetic drugs is of outmost importance.

Both trials submitted with this application were designed to provide data on cardiovascular safety for liraglutide and insulin degludec, respectively.

The LEADER trial was a CV outcome trial in patients with very high risk of CV events. In the recently concluded procedure for liraglutide (EMEA/H/C/001026/II/0042) the CHMP concluded that the LEADER trial has shown benefits on 3-point MACE, expanded MACE, and all-cause death and suggests benefits with respect to nephropathy and hypoglycaemia at the cost of possibly an increased incidence of pancreas carcinoma, malignant melanoma, and retinopathy. The incidence of the carcinomas is that low, that the benefits outweigh the risk. The benefits on glycaemic control have been established previously. Reference to the effects of liraglutide on cardiovascular events was added to the indication.

The DEVOTE trial was also a CV outcome trial in patients at high risk of CV events. In the recently concluded procedure for insulin degludec (EMEA/H/C/002498/II/0028) the CHMP concluded that the data presented showed that IDeg did not alter the relative risk of CV disease and CV mortality when compared to IGlar in a population at high risk of CV events, since non-inferiority could be established. IGlar has previously been shown not to alter the relative risk for CV disease and CV mortality when compared to standard of care. The data from the DEVOTE trial is reflected in section 5.1 of the SmPC for insulin degludec.

With this application, the MAH proposed to include the following wording in the indication "*For study results with respect to combinations, effects on glycaemic control* ***and cardiovascular events****, and the populations studied, see sections 4.4, 4.5 and 5.1.*"

Both studies contribute with important data on the cardiovascular safety for each of the two components of IDegLira, however extrapolation of these outcomes to IDegLira has not been justified. In contrast to oral fixed dose combinations of antidiabetic drugs, IDegLira is titrated from a recommended starting dose of 10 U of IDeg and 0.36 mg of liraglutide to a maximum dose of 50 U of IDeg and 1.8 mg liraglutide. Thus patients on IDegLira may be exposed to (much) lower doses of liraglutide than investigated in the LEADER trial, where 85% of subjects were treated with liraglutide 1.8 mg. This raised concerns in case the effect observed in the LEADER trial is dose dependent.

The possibility of extrapolation of the outcomes would also depend on whether the population studied in the LEADER trial corresponds to the target population for treatment with Xultophy.

Although some data on the cardiovascular effect of concomitant treatment with liraglutide and insulin has been presented further analyses were requested as part of the justification for the claim.

Other changes proposed with this application mainly related to updated safety information concerning liraglutide based on new safety data obtained with trial 3478. These changes were acceptable.

3.7.2. Balance of benefits and risks

The data provided with this application provides important cardiovascular safety information on the monocomponents of Xultophy. These data do not indicate that the individual components carry any increased risk for cardiovascular events.

The MAH considered the results from the LEADER and DEVOTE trials to be relevant also for the target population of Xultophy based on claims that there is an overlap in the patient populations and liraglutide doses in LEADER and the Xultophy phase 3 trials, and on post-hoc analyses of the LEADER and DEVOTE trials in patients using liraglutide in combination with a long-acting insulin.

CHMP acknowledged that there was some, albeit incomplete, overlap between the population included in the LEADER trial and the target population for Xultophy, including with respect to liraglutide doses, even though a lower proportion in the target population for Xultophy is exposed to a daily dose of 1.8 mg compared to the LEADER trial. CHMP considered that evidence of CV safety could be extrapolated to the use of Xultophy since the CVOTs may represent a “worst case scenario” having included high risk patients and a maximal dose of liraglutide. Therefore, inclusion of some results from the LEADER and DEVOTE trials in section 5.1 of the SmPC was found to be adequate by CHMP.

The data is however not sufficient in order to draw any conclusions on beneficial effects on cardiovascular events by Xultophy.

In addition, safety data has been provided concerning certain safety issues related to liraglutide, including information on special populations. These data are relevant to Xultophy and updates to the product information are implemented.

3.8. Conclusions

The overall B/R of Xultophy remains positive and unchanged also taking into account effects on cardiovascular events.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information based on cardiovascular outcomes studies conducted a for each of the monocomponents of Xultophy: LEADER (Liraglutide Cardiovascular Outcomes Trial) and DEVOTE (Insulin Degludec Cardiovascular Outcomes Trial). Section 5.1 was also re-organised to improve reader friendliness.

The RMP version 7.0 has also been approved.

The variation leads to amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Xultophy-H-C-002647-II-0023'.