22 June 2017
EMA/479764/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Victoza

International non-proprietary name: liraglutide

Procedure No. EMEA/H/C/001026/II/0042

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

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin converting enzyme
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation
AE	adverse event
AJCC	American Joint Committee on Cancer
ANCOVA	analysis of covariance
BMI	body mass index
BNP	brain natriuretic peptide
BPM	beats per minute
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPRD	Clinical Practise Research Datalink
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase-4
EAC	event adjudication committee
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of text
ESRD	end-stage renal disease
EU	European Union
FAS	full analysis set
FDA	U.S. Food & Drug Administration
GCP	good clinical practise
GEP	global expert panel
GLP-1	glucagon-like peptide-1
GLP-1 R	glucagon-like peptide-1 receptor
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HDL	high density lipoprotein
HbA1c	glycosylated haemoglobin
HLGT	high level group term
HR	hazard ratio
hs-CRP	high-sensitive C-reactive protein
ICH	International Conference on Harmonisation
II-6	interleukin-6
LDL	low-density lipoprotein
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome

	Results
LIRA	liraglutide
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
MESI	medical event of special interest
MI	myocardial infarction
MMRM	mixed model repeated measurement
MTC	medullary thyroid carcinoma
NO	nitric oxide
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PAI-1	plasminogen activator inhibitor-1
PBRER	periodic benefit risk evaluation report
PI	product Information
PP	per protocol
PT	preferred term
PSUR	periodic Safety Update Report
PYO	patient year of observation
RMP	risk management plan
RR	rate ratio
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
S.C.	subcutaneous
SGLT-2	sodium-dependent glucose transporter two
SMQ	Standardised MedDRA query
SOC	system organ class
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TNF-alpha	tumor necrosis factor alpha
TZD	thiazolidinediones
UACR	urinary albumin-to-creatinine ratio
UAP	unstable angina pectoris
UK	United Kingdom
UKPDS	UK prospective Diabetes Study
ULN	upper limit normal
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 25 October 2016 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, IIIA and IIIB

Modification of the diabetes mellitus indication for Victoza to include prevention of major adverse cardiovascular events (MACE); as a consequence, sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 6.5 of the SmPC are updated to add warnings and update the safety information based on the findings of the LEADER (EX2211-3748) clinical study results, which constitutes the data set for the application. The Package Leaflet and Labelling (sections 17 and 18) are updated in accordance. Updates to the liraglutide RMP based on the LEADER study results are also proposed: RMP Version 27 was submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0176/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

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: Johann Lodewijk Hillege Co-Rapporteur: Hanne Lomholt Larsen

Timetable	Actual dates
Submission date	25 October 2016
Start of procedure:	26 November 2016
CHMP Rapporteur Assessment Report	20 February 2017
CHMP Co-Rapporteur Assessment Report	17 January 2017
PRAC Rapporteur Assessment Report	1 February 2017
PRAC members comments	N/A
PRAC Outcome	9 February 2017
CHMP members comments	13 February 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 February 2017
Request for supplementary information (RSI)	23 February 2017
CHMP Rapporteur Assessment Report	18 April 2017
PRAC Rapporteur Assessment Report	19 April 2017
PRAC members comments	26 April 2017
PRAC Outcome	5 May 2017
CHMP members comments	08 May 2017
Updated CHMP Rapporteur Assessment Report	11 May 2017
Request for supplementary information (RSI)	18 May 2017
PRAC Rapporteur Assessment Report	29 May 2017
PRAC members comments	31 May 2017
Updated PRAC Rapporteur Assessment Report	7 June 2017
CHMP Rapporteur Assessment Report	7 June 2017
PRAC Outcome	9 June 2017
CHMP members comments	12 June 2017
Updated CHMP Rapporteur Assessment Report	15 June 2017
Opinion	22 June 2017

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.

Subjects with T2DM often have other risk factors for cardiovascular disease such as advanced age, smoking, obesity, hypertension and high levels of blood lipids. Large reductions in cardiovascular complications have been observed if multiple risk factors are treated simultaneously. Consequently, standard of care guidelines recommend lifestyle interventions such as cessation of smoking, diet and exercise as well as treatment with antidiabetic, antihypertensive and lipid lowering drugs with the aim of achieving recommended goals for body weight, blood glucose, blood pressure, cholesterol and triglycerides. Furthermore, treatment with antiplatelet agents such as aspirin at low doses is recommended to reduce the risk of thrombotic events. However, even with use of these standards of care therapies, the risk of cardiovascular disease in subjects with diabetes remains to be more than double that in subjects without diabetes. Hence, there is an unmet medical need for additional therapies which may further reduce the risk of cardiovascular complications in patients with T2DM.

Drug profile and target indication

Liraglutide (Arg34Lys26-(N-ε-(γ-Glu (N-α-hexadecanoyl)))-GLP-1[7-37]) is a once-daily human GLP-1 analogue in which lysine at position 34 has been replaced with arginine, and palmitic acid has been attached via a glutamoyl spacer to lysine at position 26. Liraglutide binds to and activates the GLP-1 receptor and thereby stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. In addition, liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake. Unlike native GLP-1, liraglutide has a pharmacokinetic and pharmacodynamic profile that makes it suitable for once daily administration.

Liraglutide received marketing authorisation in the EU in 2009 and in the US in 2010 and is currently approved in > 100 countries worldwide. In the EU, Victoza 1.2 mg and 1.8 mg/day is indicated for the treatment of adults with T2DM to achieve glycaemic control as 1) monotherapy in patients intolerant to or contraindicated for metformin, as well as 2) in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control. In the US, Victoza 1.8 mg/day is indicated as second-line therapy (monotherapy or combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.

In addition, liraglutide 3.0 mg for weight management (Saxenda) received marketing authorisation in the US in 2014 and in the EU in 2015 and is now approved in major markets (Australia, Brazil, Canada, Israel, Mexico, Russia, Chile and the United Arab Emirates).

In this application, it is proposed to extend the indication to reflect the reduced risk of MACE in subjects with T2DM at high risk of cardiovascular disease. In addition, it is proposed to extend the

existing T2DM indication to unrestricted monotherapy, to extend the use in combination with insulin, to remove limitations for use in special populations. Changes are based on the results from the LEADER trial (trial 3748).

2.2. Non-clinical aspects

2.2.1. Introduction

Two pharmacodynamic studies were performed to support the new indication, prevention of Major Adverse Cardiovascular Events (MACE) in adults with type 2 diabetes mellitus. Also literature was provided to support the role of liraglutide in the attenuation of atherosclerosis.

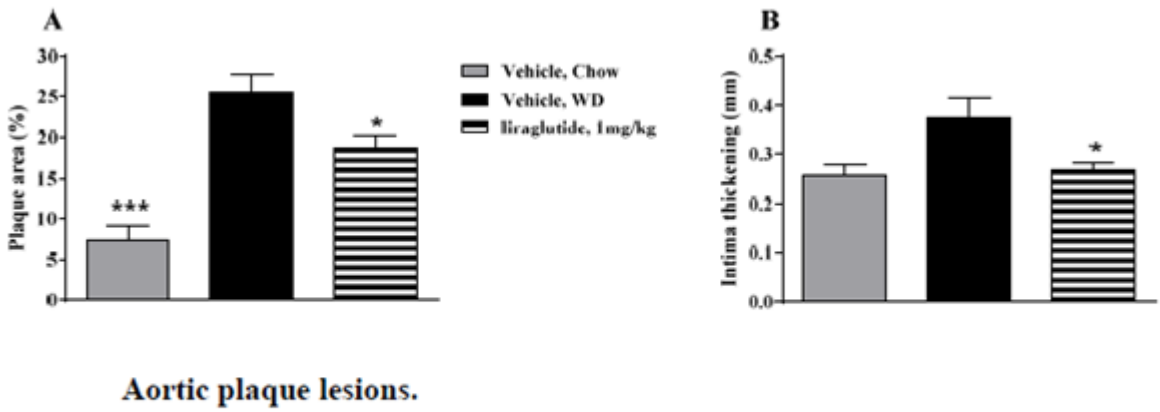
2.2.2. Pharmacology

Primary pharmacodynamic studies

Effect on atherosclerotic plaques in ApoE knock-out mice treated with liraglutide (study GuRa140701)
The effect of liraglutide on the progression and regression of atherosclerosis was investigated. ApoE knock-out (KO) mice were used because it is a well characterized animal model developing atherosclerotic lesions in large extent. The study was divided in 3 sub-studies:

In study Gura140701, female mice were treated with vehicle + chow diet (n=5), vehicle + western diet (WD) (n=15) or liraglutide + western diet (n=14, liraglutide s.c. at 1 mg/kg/day) for 15 weeks. Investigated parameters were body weight, ultra sound imaging of the aorta, and “en face” analysis of the aorta.

Liraglutide prevented aortic plaque progression resulting in a plaque area of 18.8±1.5 % compared to a plaque area in the vehicle + western diet control group of 25.3±2.2 % (p<0.01). In addition, liraglutide treatment significantly prevented further aorta intima thickening (vehicle: 0.38±0.04 mm vs. liraglutide: 0.27±0.01 mm; p<0.01) (see figure 1). Body weight increased in the group treated with vehicle + western diet. This increase was largely prevented by liraglutide.

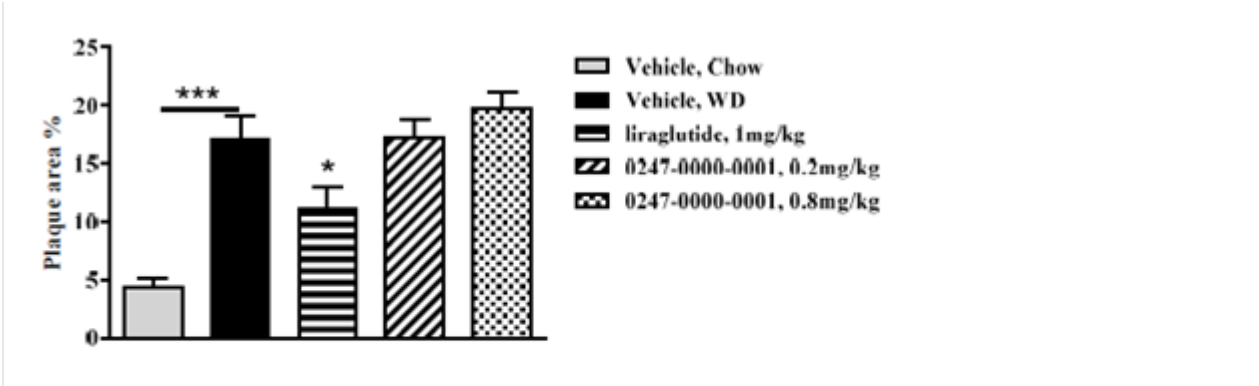


Aortic plaque lesions.

Plaque lesion area (A) and intima thickening by ultra sound imaging (B). Data are mean±SEM, n=5-14. *p<0.05, ***p<0.0001 vs Vehicle, WD.

In study 141101, female mice were treated with vehicle + chow diet (n=6), vehicle + western diet (n=13), liraglutide + western diet (n=14, liraglutide s.c. at 1 mg/kg/day), or an anti-obesity active comparator (proprietary compound under development) at 0.2 or 0.8 mg/kg/day + western diet (n=14 or 15 resp.) for 12 weeks. Investigated parameters were body weight, ultra sound imaging of the aorta, "en face" analysis of the aorta, plasma concentrations of triglycerides and total cholesterol.

Liraglutide prevented aortic plaque progression resulting in a plaque area of 11.1±1.9 % compared to a plaque area in the vehicle + western diet control group of 17.1±1.9 % ($p<0.01$). The body weight active comparator did not result in any reduction of plaque lesion area at both doses (see figure 3). Plasma total cholesterol was increased by the western diet to a similar extent in both vehicle- and liraglutide-treated groups. Liraglutide had no significant effect on total cholesterol compared to vehicle. In the group treated with low dose of active comparator, the increase in cholesterol was significantly higher than in the liraglutide- and vehicle + western diet treated groups, while in the high dose treated group the increase was comparable to these groups. Triglycerides were not significantly affected by diet or treatment, except that the level was lower in the liraglutide-treated group compared to controls at the 8 week time point (but not at 2 or 14 weeks). Body weight increased in the group treated with vehicle + western diet (by 22%). The liraglutide group gained 3%. The body weight active comparator induced 5% weight loss for both doses.



Aortic plaque lesions as assessed by the "en face" method

Data are mean ± SEM, n=5-15, One Way ANOVA, Dunnett's post-hoc analysis for comparison between groups, *$p<0.05$; ***$p<0.0001$ vs. Vehicle, WD

In study 131001, female mice were fed on western diet for 10 weeks and then changed to standard chow and treated s.c. with liraglutide at 0.3 mg/kg/day twice daily (n=14) or vehicle (n=17) for 6 weeks. There was also a group fed only on standard chow and then treated with vehicle (n=8). Investigated parameters were body weight, ultra sound imaging of the aorta, "en face" analysis of the aorta, plasma concentrations of triglycerides, total cholesterol, HDL-, LDL- and VLDL-cholesterol, plasma concentrations of liraglutide, and nanostring gene expression analysis on aortic tissue (genes representing pathways of cardiometabolic diseases specifically comprising markers for inflammatory responses (e.g. immune cell activation and trafficking), cardiovascular disease (e.g. atherosclerosis signalling), organismal injury (e.g. cell death and survival) and connective tissue disorders e.g. (cellular growth and proliferation).

Body weight was increased in both groups fed on western diet. When treatment was initiated and the western diet groups were changed to chow diet, body weight decreased in both groups, but the decrease was larger in the liraglutide-treated group. In the terminal blood sample, plasma TG levels, total cholesterol, LDL-cholesterol and VLDL-cholesterol were all significantly lowered by liraglutide,

whereas HDL-cholesterol was significantly increased when comparing to the group fed on western diet and treated with vehicle (see table below).

Table 4 Plasma lipid levels at termination

Group	Triglyceride, mM	Total Cholesterol, mM	HDL-cholesterol, mM	LDL-cholesterol, mM	VLDL-cholesterol, mM
1. vehicle (Chow-Chow)	1.3±0.1	9.4±0.4	0.14±0.03	4.2±0.2	5.0± 0.3
2. vehicle (WD-Chow)	1.4±0.1	9.3±0.3	0.20±0.02	4.9±0.2	4.2±0.2
3. liraglutide (WD-chow)	0.9±0.1***	6.4±0.2***	0.40±0.05**	3.4±0.1***	2.7±0.2***

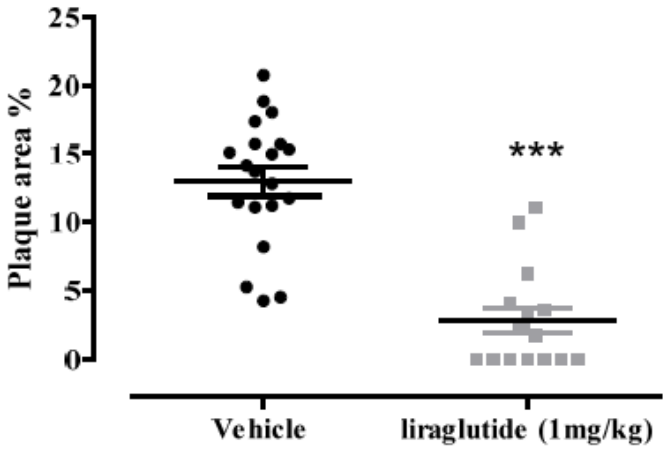
Data are mean±SEM, n=8-17, ***p<0.0001, **p<0.001 Students t-test (gr 2 vs gr 3)

There was a significantly higher aortic plaque lesion area in the control group fed on western diet compared to the control group fed on chow diet, but aortic arch plaque area was not reduced with liraglutide treatment, although there was a small trend towards a reduction. Plasma concentration of liraglutide at termination was 88 ± 12 nM (mean±SEM). Liraglutide had effects on expression of several genes, such as Ccr2 and Thy1 (both decreased, involved in inflammatory processes related to leukocyte recruitment and adhesion), Ptgir (decreased, involved in lipid signalling), and Lep (decreased, hormone leptin, plays a role in satiety [Genetics Home Reference: https://ghr.nlm.nih.gov/gene]).

Effect on atherosclerotic plaques in LDL receptor knock-out mice treated with liraglutide (study GuRa141102)

The effect of liraglutide for the prevention of atherosclerosis was investigated in LDL-receptor knockout (LDLr KO) mice. The LDLr KO mouse is used because it is a well characterized animal model developing atherosclerotic lesions in large extent. Male mice on western diet were treated s.c. with vehicle or liraglutide at 1 mg/kg/day for 17 weeks. Investigated parameters were body weight, “en face” analysis of the aorta, plasma concentrations of triglycerides, total cholesterol, HDL-, LDL- and VLDL-cholesterol, and nanostring gene expression analysis on aortic tissue (genes representing pathways of cardiometabolic diseases specifically comprising markers for inflammatory responses (e.g. immune cell activation and trafficking), cardiovascular disease (e.g. atherosclerosis signalling), organismal injury (e.g. cell death and survival) and connective tissue disorders e.g. (cellular growth and proliferation).

Treatment with liraglutide induced a significant attenuation of aortic plaque lesion development as compared to vehicle control (vehicle: 13±1.0% vs. liraglutide: 2.8±0.9%; p<0.0001) (see figure below). Notably 7 out of 15 animals had no plaque lesions after liraglutide treatment.



Aortic plaque lesions.

Data are mean±SEM, n=15-20. ***p<0.0001 vs Vehicle

Plasma triglycerides, total cholesterol, VLDL-cholesterol and LDL-cholesterol were significantly decreased and plasma HDL was significantly increased at the end of treatment with liraglutide (see table below, except for total cholesterol for which the result was only presented in graph).

Table 2.3.2.1 Plasma triglycerides and lipoproteins at termination in LDL-receptor knock-out mice

Group	Triglycerides (mM)	HDL-cholesterol (mM)	LDL-cholesterol (mM)	VLDL-cholesterol (mM)
vehicle + WD	11.5 ± 0.7	1.9 ± 0.2	36.3 ± 18.3	25.9 ± 2.2
liraglutide (1 mg/kg/day) + WD	7.1 ± 1.0	3.5 ± 0.2	18.3 ± 2.1	9.6 ± 2.4

WD=western diet

Body weight was increased to a significantly higher extent in the vehicle-treated group (by 65%) than in the liraglutide-treated group (by 17%).

Increased expression in liraglutide-treated animals was found for the following genes: Acat1, Acta2, Cav1, Cav2, F3, Insr, Irs1, Kitlg, Pdgfd, Tagln, among which the insulin receptor (Insr) and insulin-receptor substrate-1 (Irs1). Decreased expression was found for: Cd68, Ctss, Il1rn, Il6, Mmp12, Mmp13, Msr1, Lcn2, Saa3, Spp1, among which pathways related to leukocyte recruitment (Il1rn, Il6) and osteopontin (Spp1) of which increased plasma levels have been associated with coronary atherosclerosis and cardiovascular disease. See further the table below.

Table 2.3.2.2 Genes of which the expression was increased or decreased by liraglutide in LDL-receptor knock-out mice

Gene	Codes for	Involved in	Source
Genes of which expression is increased			
Acat1	Acetyl-CoA acetyltransferase 1	Breaking down proteins and fats from the diet	https://ghr.nlm.nih.gov/gene/ACAT1
Acta2	Actin.alpha2	Part of the actin protein family, which is found in smooth muscle cells	https://ghr.nlm.nih.gov/gene/ACTA2
Cav1	Caveolin 1	Main component of the caveolae in plasma membranes, in endocytosis	http://www.genecards.org/cgi-bin/carddisp.pl?gene=CAV1
Cav2	Caveolin 2	Major component of caveolae, and involved in essential cellular functions, including signal transduction, lipid metabolism, cellular growth control and apoptosis. This protein may function as a tumor suppressor.	http://www.genecards.org/cgi-bin/carddisp.pl?gene=CAV2
F3	Coagulation factor III	Initiation of the blood coagulation cascades	http://www.genecards.org/cgi-bin/carddisp.pl?gene=F3
Insr	Insulin receptor	Insulin receptor	study GuRa141102
Irs1	Insulin-receptor substrate-1	Insulin signalling	http://www.genecards.org/cgi-bin/carddisp.pl?gene=IRS1
Kitlg	KIT ligand	Required in hematopoiesis	http://www.genecards.org/cgi-bin/carddisp.pl?gene=KITLG
Pdgfd	Platelet derived growth factor D	Member of the platelet-derived growth factor family. The four members of this family are mitogenic factors for cells of mesenchymal origin.	http://www.genecards.org/cgi-bin/carddisp.pl?gene=PDGFD
Tagln	Transgelin	Transformation and shape-change sensitive actin cross-linking/gelling protein found in fibroblasts and smooth muscle	http://www.genecards.org/cgi-bin/carddisp.pl?gene=TAGLN
Genes of which expression is decreased			
Cd68	CD68 molecule	Transmembrane glycoprotein that is highly expressed by monocytes and tissue macrophages	http://www.genecards.org/cgi-bin/carddisp.pl?gene=CD68
Ctss	Cathepsin S	Lysosomal proteinase that may participate in the degradation of antigenic proteins to peptides for presentation on MHC class II molecules.	http://www.genecards.org/cgi-bin/carddisp.pl?gene=CTSS

Gene	Codes for	Involved in	Source
Il1rn	Interleukin 1 receptor antagonist	leukocyte recruitment	study GuRa141102
Il6	Interleukin 6	leukocyte recruitment	study GuRa141102
Mmp12	Matrix metallopeptidase 12	Breakdown of extracellular matrix in normal physiological processes as well as in disease processes	http://www.genecards.org/cgi-bin/carddisp.pl?gene=MMP12
Mmp13	Matrix metallopeptidase 13	Breakdown of extracellular matrix in normal physiological processes as well as in disease processes	http://www.genecards.org/cgi-bin/carddisp.pl?gene=MMP13
Msr1	Macrophage scavenger receptor 1	Macrophage-specific integral membrane glycoprotein. It has been implicated in macrophage-associated physiological and pathological processes including atherosclerosis.	https://ghr.nlm.nih.gov/gene/MSR1
Lcn2	Lipocalin 2	Multiple cellular processes, including maintenance of skin homeostasis, and suppression of invasiveness and metastasis	http://www.genecards.org/cgi-bin/carddisp.pl?gene=LCN2
Saa3	Serum amyloid A3	Member of a family of apolipoproteins associated with HDL in plasma and which are expressed in response to inflammatory stimuli.	https://en.wikipedia.org/wiki/Serum_amyloid_A
Spp1	Secreted phosphoprotein 1 or osteopontin	Attachment of osteoclasts to the mineralized bone matrix and also a cytokine that upregulates expression of interferon-gamma and interleukin-12	http://www.genecards.org/cgi-bin/carddisp.pl?gene=SPP1

Literature data

Evidence of beneficial effects of GLP-1R agonists on cardiovascular outcomes has been reported in the literature. Studies in mice have demonstrated that GLP-1R agonists including liraglutide attenuated the development of atherosclerosis in several different strains of mice. Signs of reduction of inflammation and reduced lipid accumulation were observed in murine heart and blood vessels. Anti-inflammatory effects of GLP-1R agonists were also demonstrated in vitro in human aortic endothelial cells (Drucker et al, 2016). In mice treated with liraglutide followed by induction of myocardial infarction, survival was increased and infarct size was reduced in liraglutide-treated mice (Hossein et al, 2009). Also in

other pre-clinical studies, treatment of rodents with GLP-1R agonists prior to induction of ischemia produces robust cardioprotection. However, administration of exendin-4 to mice after the onset of myocardial infarction did not modify infarct size or survival (Ussher et al, 2014).

2.2.3. Ecotoxicity / environmental risk assessment

No environmental risk assessment was performed because liraglutide is composed of a peptide consisting of natural amino acids and a natural fatty acid (palmitic acid) and as such expected to be readily biodegradable. 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 liraglutide.

2.2.4. Discussion on non-clinical aspects

Liraglutide prevented aortic plaque progression in mice when given simultaneously with western diet and caused reductions in blood lipids in two out of three studies. Prevention of aortic plaque progression is supported by effects on genes which may indicate a reduced risk for atherosclerosis including decreased expression of genes for leukocyte recruitment (Il1rn, Il6) and genes involved in inflammation (Msr1, Saa3 and Spp1). Liraglutide had no effect on plaque size of already established plaque in a study in ApoE knock-out mice where liraglutide treatment was initiated after a period of western diet feeding. A cardioprotective effect of liraglutide or GLP-1R agonists when administered before induction of myocardial infarction, has also been reported in the literature. These observations indicate that liraglutide may be effective in the prevention of aortic plaque progression but that it is not expected to be effective to cure already established atherosclerosis. This was supported by the observation in the literature that administration of exendin-4 to mice after the onset of myocardial infarction did not modify infarct size or survival (Ussher et al, 2014). The currently submitted studies support that liraglutide can play a role in the prevention of atherosclerosis. However, they do not support the claimed new indication in the targeted patient population. This patient population consists for the major part of patients who already experienced a cardiovascular event and who most certainly will have already established atherosclerosis. Sub-study in mice BidR131001 of study GuRa140701 showed that liraglutide is not effective in curing already established plaque. There is therefore insufficient evidence that these results are relevant to support the mechanism of the claimed reduction in MACE. Considering the fact that there is insufficient evidence that these results support the indication, the proposed addition to section 5.1 of the SmPC (see section 2.7) is not endorsed.

2.2.5. Conclusion on the non-clinical aspects

The data which are provided support that liraglutide can play a role in the prevention of atherosclerosis, but that it is not expected to cure existing atherosclerosis. There is therefore insufficient evidence that these results are relevant to support the mechanism of action in the claimed reduction in MACE.
Considering the above data, liraglutide is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

In this dossier, the results of the cardiovascular outcome trial are presented. No PK data were collected. The design of the trial is discussed below under clinical efficacy.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

2.4. Clinical efficacy

In this application, a single clinical trial was submitted (LEADER, trial 3748). This trial is discussed below and summarised in Error! Reference source not found..

2.4.1. Main study: cardiovascular outcome trial (3748)

Methods

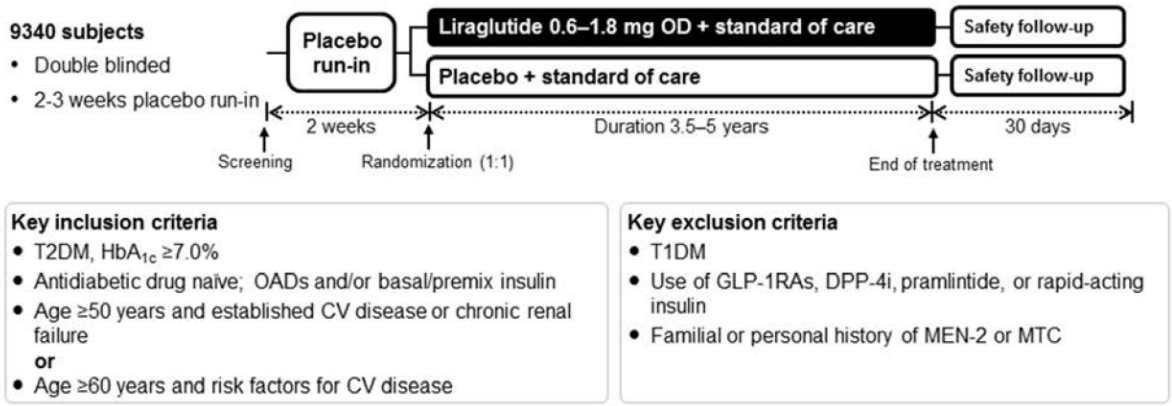
Design

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 to ensure scientific rigour of the comparison.

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.

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**.



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

Figure 1 Design of trial 3748

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; history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with electrocardiogram (ECG) changes, asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo; chronic heart failure NYHA class II-III; chronic renal failure, having clinically reached a stage corresponding to a glomerular filtration rate < 60 mL/min/1.73m2 per Modification of Diet in Renal Disease (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 such as end stage liver disease, organ transplants or malignant neoplasms requiring chemotherapy, surgery, radiation or palliative therapy in the previous 5 years (with the exception of intraepithelial squamous cell carcinoma or basal cell skin cancer) 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. A Global Expert Panel (GEP) provided written recommendations on standard of care treatment to all investigators including recommendations for management of hyperglycaemia and treatment of blood pressure and blood lipids according to the following targets: 1) HbA1c <7% individualised for the individual subject; 2) blood pressure 130/80 mmHg; and 3) LDL <100 mg/dL (<70 mg/dL in subjects with previous cardiovascular events). Subjects with an HbA1c < 8.0% were recommended to perform a 20% reduction of the basal/premixed insulin dose and discontinuation of SUs was to be considered to reduce the risk of hypoglycaemia upon initiation of trial product. Subjects initiating basal insulin were recommended to start on a basal insulin dose of 10 U/day and an algorithm for titration was provided. Statins were recommended for all subjects and aspirin (or clopidogrel) for subjects with prior cardiovascular events.

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.

Sample size

The required sample size was estimated based on time to first MACE using a log rank test for/on the full analysis set (FAS) (including all randomised subjects) and the assumptions of 1) an estimated primary outcome event rate of 1.8% per year for both the liraglutide and the placebo group; 2) uniform enrolment over 1.5 year with a maximum follow-up of 5 years (including the accrual period); 3) a non-inferiority margin versus placebo of 1.3 for the upper limit of the 2-sided 95% confidence interval; 4) a total drop-out rate (subjects lost to follow-up or withdrawn from the trial) of 10%; 5) 90% power to reject the null hypothesis that the hazard ratio is > 1.3.

Under the above assumptions, 8754 subjects were to be randomised. The expected number of events to obtain the 90% power was 611.

Randomisation

Subjects were randomised 1:1 to once-daily liraglutide 1.8 mg or placebo as add-on to their standard of care.
The trial was designed to include a sufficient number of subjects with moderate and severe renal impairment, to be able to assess the effect of liraglutide in these subgroups. According to the protocol, the trial should include 220 subjects with severe renal impairment (defined as eGFR<30 mL/min/1.73 m^2). To ensure this, subjects were stratified through the randomisation procedure according to eGFR (eGFR<30 mL/min/1.73 m^2 vs eGFR≥30 mL/min/1.73 m^2). After having randomised the planned 220 subjects, no additional subjects with eGFR<30 mL/min/1.73 m^2 were included.

Blinding (masking)

The trial was double-blinded. The blinding was maintained until the code-break for database lock and release of the data for statistical analysis. The code-break was performed 02 February 2016. The data were loaded into the clinical database between 02 and 05 February 2016 and locked 05 February 2016. There were no changes to any data between code break and database lock.

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.

Other analyses related to safety

A post hoc analysis of time to first occurrence of a neoplasm was conducted using a Cox regression model with treatment as factor. Descriptive statistics for non-adjudicated safety areas of interest and assessment of SAEs and non-serious MESIs were based on investigator-reported events using pre-defined MedDRA searches (MedDRA version 18.0).

Information related to hypoglycaemia was based on self-measured plasma glucose (SMPG) measurements transferred to the hypoglycaemia form. The number of severe and confirmed hypoglycaemic episodes were analysed using a negative binomial regression model with a log-link function and the logarithm of the observation time as offset. The model included treatment, sex, region and antidiabetic therapy at baseline as factors, and age at baseline as covariate.

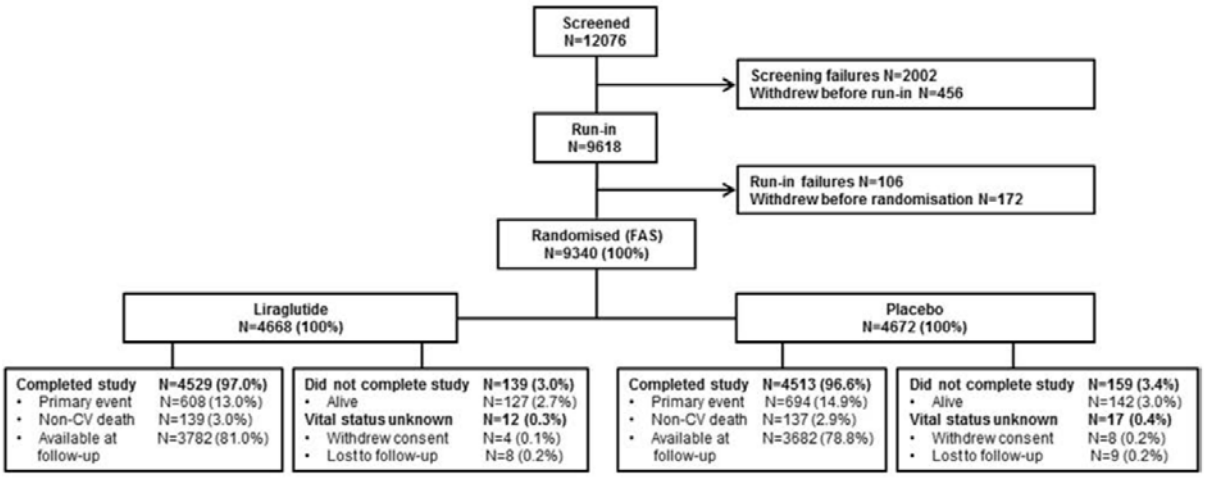
Assessment of adverse events leading to permanent discontinuation of trial products was based on the investigator ticking this off on the adverse event form. Change in heart rate and eGFR (as per MDRD and CKD-EPI at screening) from baseline to the 3-year visit was analysed using a repeated normal mixed model as for the secondary analyses for effectiveness.

Laboratory data, including anti-liraglutide antibodies, and changes in ECG were analysed using descriptive statistics.

Results

Participant flow

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



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

Figure 2 Subjects disposition of Trial 3748

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.

Recruitment

The trial was a multi-centre trial conducted in 410 sites in 32 countries in Europe, North America, (US, Canada), Asia (China, Taiwan, Korea, India), and the Rest of the world (Brazil, Mexico, Australia, South Africa, Turkey, Russian Federation, United Arab Emirates). The first patient was enrolled on 31 Aug 2010. The last on-site visit of a patient took place on 17 Dec 2015.

Conduct of the study

The trial was conducted according to the original trial protocol dated 29 April 2010 and its revisions. There were a total of 39 substantial amendments to the protocol of which 5 were global and 34 were local. The local amendments mostly concerned updates of administrative nature. The 5 global amendments were all issued after FPFV. One of those concerned a broadening of inclusion criteria to allow subjects on premixed insulin to be eligible. All were submitted to CHMP and considered acceptable.

In total, 111 subjects were randomised in error due to violation of one or more inclusion, exclusion or randomisation criteria. Approximately 48% of subjects randomised in error were in the liraglutide group and 52% were in the placebo group. The most common reasons for randomisation in error were violations of the inclusion criterion #3 (CVD risk factors) (27%), exclusion criterion #3 (use of disallowed medication; insulin) (27%), exclusion criterion #2 (use of disallowed medication; GLP-1 RA /pramlintide /DPP-4 inhibitor) (16%) and exclusion criterion #12 (malignant neoplasm) (14%).

Baseline data

Demographics and baseline characteristics of subjects are shown in **Table 1**. 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.

The 3748 trial population represented a population at very high risk of cardiovascular disease. 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 (**Table 1**). 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.

Table 1 Selected demographics and baseline characteristics of subjects in trial 3748[a]

	Liraglutide (N=4668)	Placebo (N=4672)	Total (N=9340)
Sex			
Male	3011 (64.5)	2992 (64.0)	6003 (64.3)
Female	1657 (35.5)	1680 (36.0)	3337 (35.7)
Age (years)	64.2 ± 7.2	64.4 ± 7.2	64.3 ± 7.2
Duration of diabetes (years)	12.8 ± 8.0	12.9 ± 8.1	12.8 ± 8.0
HbA1c (%)	8.7 ± 1.6	8.7 ± 1.5	8.7 ± 1.5
Body weight (kg)	91.9 ± 21.2	91.6 ± 20.8	91.7 ± 21.0
BMI (kg/m^2)	32.5 ± 6.3	32.5 ± 6.3	32.5 ± 6.3
Systolic blood pressure (mmHg)	135.9 ± 17.8	135.9 ± 17.7	135.9 ± 17.7
Diastolic blood pressure (mmHg)	77.2 ± 10.3	77.0 ± 10.1	77.1 ± 10.2
Heart rate (bpm)	72.7 ± 11.3	72.5 ± 11.4	72.6 ± 11.4
eGFR ($ml/min/1.73m^2$) (MDRD)	80.2 ± 27.5	80.6 ± 27.2	80.4 ± 27.4
LDL cholesterol (mmol/L)	2.3 ± 0.9	2.3 ± 0.9	2.3 ± 0.9
Geographic region[b]			
Europe	1639 (35.1)	1657 (35.5)	3296 (35.3)
North America	1401 (30.0)	1446 (31.0)	2847 (30.5)
Asia	360 (7.7)	351 (7.5)	711 (7.6)
Rest of the world	1268 (27.2)	1218 (26.1)	2486 (26.6)
Ethnicity			
Hispanic or Latino	580 (12.4)	554 (11.9)	1134 (12.1)
Not Hispanic or Latino	4088 (87.6)	4118 (88.1)	8206 (87.9)
Race			
White	3616 (77.5)	3622 (77.5)	7238 (77.5)
Black or African American	370 (7.9)	407 (8.7)	777 (8.3)
Asian	471 (10.1)	465 (10.0)	936 (10.0)
Other	202 (4.3)	168 (3.6)	370 (4.0)
Cardiovascular history at screening			
Subjects ≥50 years with established CV disease	3831 (82.1)	3767 (80.6)	7598 (81.3)
Subjects ≥60 years with risk factors for CV disease	837 (17.9)	905 (19.4)	1742 (18.7)
Renal function (MDRD)			
Normal renal function	1620 (34.7)	1655 (35.4)	3275 (35.1)
Mild renal impairment	1932 (41.4)	1975 (42.3)	3907 (41.8)
Moderate renal impairment	999 (21.4)	935 (20.0)	1934 (20.7)
Severe renal impairment	117 (2.5)	107 (2.3)	224 (2.4)
Heart failure			
NYHA class I	179 (3.8)	169 (3.6)	348 (3.7)
NYHA class II	545 (11.7)	546 (11.7)	1091 (11.7)
NYHA class III	108 (2.3)	106 (2.3)	214 (2.3)

Abbreviations: FAS: full analysis set; N: number of subjects; BMI: body mass index; BPM: beats per minute; CV: cardiovascular; eGFR; estimated Glomerular Filtration Rate; HbA1c: glycosylated haemoglobin; MDRD: Modification of Diet in Renal Disease; NYHA: New York Heart Association.

[a] Values are means ± standard deviations or number of subjects (% of either subjects in the liraglutide group or placebo group).

[b] Geographic region is defined as Europe, North America (US, Canada), Asia (China, Taiwan, Korea, India), and the

Rest of the world (Brazil, Mexico, Australia, South Africa, Turkey, Russian Federation, United Arab Emirates).

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.

Furthermore, in support of the subgroup analyses of the primary endpoint (time to first MACE) demographics and baseline characteristics were evaluated for the cardiovascular risk subgroups, the various regions (North America, Europe, Asia and the Rest of the World) as well as the US and non-US populations. The following section provides an overview of the distribution of these variables in the specific subgroups.

Age

Across the age groups (< 65 yrs, 65-74 yrs, 75-84 yrs, ≥ 85 yrs) SBP tended to increase with increasing age (134 to ~137 mm Hg), while DBP and eGFR tended to decrease with increasing age (79 to 73 mm Hg; 87 to ~53 mL/min/1.73 m^2). HbA1c was highest in the youngest age group (8.9 to ~8.6%), while T2DM duration increased with increasing age (11 to ~17 years). Overall, the two treatment groups were well balanced across the 4 age groups; however some differences appeared in subjects >85 years due to the very low number of subjects.

Renal function

Across subgroups by renal function (no impairment, mild, moderate and severe impairment), SBP tended to increase (135 to 139 mm Hg), while DBP tended to decrease (78 to 75 mm Hg). HbA1c was highest in subjects with no renal impairment (8.9 to 8.7%), while T2DM duration increased with decreasing renal function (11 to 17 yrs). Overall, only minor differences were seen in baseline characteristics and demographics between the two treatment groups across the 4 subgroups by renal function.

Heart failure status

Overall, baseline characteristics and demographics were similar across the subgroups by heart failure status (no heart failure, NYHA class I, II and III). Only minor differences were seen between the two treatment groups across the 4 subgroups.

Subjects using pre-mix insulin

Baseline characteristics and demographics in subjects using pre-mix insulin at baseline and at least the following 26 weeks and in the remaining subjects (subjects not using pre-mix at baseline or discontinuing use of pre-mix within the first 26 weeks) were evaluated. Subjects using pre-mix insulin at baseline had a higher BMI compared to subjects not using pre-mix insulin at baseline (34 vs 32 kg/m^2), a longer duration of T2DM (17 vs 12 yrs) and a lower eGFR (75 vs 81 mL/min/1.73 m^2). Apart from that, no major differences in baseline characteristics and demographics were observed between the subgroups. Only minor differences were seen between the two treatment groups across subgroups by use of pre-mix insulin.

'Established cardiovascular disease' vs 'risk factors for cardiovascular disease'

In the pre-specified subgroup analysis of 'time to first MACE' for subjects aged ≥60 and with only risk factors for cardiovascular disease' the hazard ratio (liraglutide/placebo) was >1 (see Outcomes and

estimation below). To further characterise this result, baseline characteristics and demographics were evaluated in these two subgroups.

Minor differences in baseline characteristics and demographics were seen between the subgroups, mainly reflecting the differences in inclusion criteria in the two subgroups: SBP, DBP and total cholesterol were slightly higher in subjects with 'risk factors for cardiovascular disease', while eGFR was lower in subjects with 'established cardiovascular disease'. Only minor differences were seen between the two treatment groups across the subgroups.

Region

In the pre-specified analysis of 'time to first MACE' for region North America the hazard ratio (liraglutide/placebo) was >1) (see Outcomes and estimation below). To further characterise this result, baseline characteristics and demographics were evaluated across the regions of North America, Europe, Asia and the Rest of the World (**Table 2**). BMI was highest in North America (34.5 kg/m^2) and lowest in Asia (26.7 kg/m^2). SBP was lowest in North America and Asia (~132 mm Hg), and highest in Europe (139 mm Hg), while DBP was lowest in North America (74 mm Hg). Only minor differences in demographics and baseline characteristics were seen between the two treatment groups across the subgroups by region.

Table 2 Demographics and baseline characteristics by region – FAS

	North America		**Europe**		**Asia**		**Rest of the World**	
	Lira	Placebo	Lira	Placebo	Lira	Placebo	Lira	Placebo
N	1401	1446	1639	1657	360	351	1268	1218
Age (years)	64.5	64.7	64.8	65.2	62.6	62.3	63.5	63.5
Sex (% F/M)	34.4/65.6	34.8/65.2	30.0/70.0	29.8/70.2	33.3/66.7	33.3/66.7	44.4/55.6	46.6/53.4
BMI (kg/m^2)	34.5	34.4	32.9	32.6	26.6	26.8	31.5	31.6
SBP (mmHg)	131.9	132.2	139.1	139.6	131.7	130.2	137.4	136.9
DBP (mmHg)	74.0	74.0	78.6	78.4	76.9	76.5	79.1	78.7
Tot chol (mmol/L)	4.3	4.3	4.4	4.4	4.1	4.1	4.7	4.6
T2DM duration (years)	13.6	13.5	11.8	12.0	13.2	13.2	13.1	13.2
HbA_{1c} (%)	8.8	8.7	8.4	8.3	9.1	8.9	9.1	9.0
eGFR (mL/min/1.73 m^2)	76.5	77.3	81.4	81.6	81.7	83.9	82.3	82.2

US and non-US population

In the pre-specified analysis of 'time to first MACE' for region North America, the hazard ratio (liraglutide/placebo) was >1 (see Outcomes and estimation below). The vast majority of the subjects from region North America were from the US (88% [2847 subjects from North America and 2514 subjects from the US]. To further characterise the result of the MACE subgroup analysis, baseline characteristics and demographics were evaluated for the US and non-US populations. Overall, the US population was comparable to the non-US population in the trial; however, US subjects had a higher baseline BMI (34.5 vs 31.8 kg/m^2), lower SBP (132 vs 137 mm Hg) and DBP (74 vs 78 mm Hg) and slightly lower eGFR (76.8 vs 81.7 mL/min/1.73 m^2) compared to subjects from non-US. Only minor differences in demographics and baseline characteristics were seen between the two treatment groups across the 2 subgroups.

Concomitant medication

Overall, use of cardiovascular medication was well-balanced between the two treatment groups at baseline, with only minor differences between treatment groups (**Table 3**). Consistent with the high cardiovascular risk profile of the trial population, 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 (**Table 4**). 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 3 Concomitant cardiovascular medication at baseline and initiated after baseline-summary - FAS

	Baseline				After baseline			
	Lira		Placebo		Lira		Placebo	
	N	%	N	%	N	%	N	%
Number of subjects	4668		4672		4668		4672	
Antihypertensive therapy	4329	(92.7)	4303	(92.1)	1452	(31.1)	1584	(33.9)
Beta blockers	2652	(56.8)	2529	(54.1)	445	(9.5)	486	(10.4)
Calcium channel blockers	1538	(32.9)	1479	(31.7)	465	(10.0)	557	(11.9)
ACE inhibitors	2417	(51.8)	2350	(50.3)	331	(7.1)	375	(8.0)
Angiotensin receptor blockers	1488	(31.9)	1486	(31.8)	368	(7.9)	456	(9.8)
Renin inhibitors	42	(0.9)	40	(0.9)	5	(0.5)	9	(0.2)
Others	468	(10.0)	454	(9.7)	274	(5.9)	309	(6.6)
Diuretics	1953	(41.8)	1953	(41.8)	851	(18.2)	1025	(21.9)
Loop diuretics	824	(17.7)	837	(17.9)	484	(10.4)	572	(12.2)
Thiazides	829	(17.8)	788	(16.9)	216	(4.6)	293	(6.3)
Thiazide-like diuretics	325	(7.0)	355	(7.6)	125	(2.7)	156	(3.3)
Aldosterone antagonists	254	(5.4)	251	(5.4)	236	(5.1)	238	(5.1)
Lipid lowering drugs	3564	(76.3)	3515	(75.2)	667	(14.3)	738	(15.8)
Statins	3405	(72.9)	3336	(71.4)	439	(9.4)	520	(11.1)
Ezetimibe	165	(3.5)	169	(3.6)	68	(1.5)	73	(1.6)
Fibrates	412	(8.8)	432	(9.2)	172	(3.7)	164	(3.5)
Niacin	95	(2.0)	95	(2.0)	22	(0.5)	31	(0.7)
Other lipid lowering drugs	8	(0.2)	14	(0.3)	15	(0.3)	16	(0.3)
Platelet aggregation inhibitors	3205	(68.7)	3121	(66.8)	701	(15.0)	773	(16.5)
Acetylsalicylic acid (ASA)	2977	(63.8)	2899	(62.1)	378	(8.1)	423	(9.1)
Clopidogrel, Ticlopidine, Prasugrel, Ticegrelor	720	(15.4)	745	(15.9)	387	(8.3)	416	(8.9)
Anti-thrombotic medication	314	(6.7)	327	(7.0)	601	(12.9)	615	(13.2)
Vitamin K antagonists	295	(6.3)	301	(6.4)	174	(3.7)	193	(4.1)
Direct thrombin inhibitors	17	(0.4)	12	(0.3)	49	(1.0)	45	(1.0)
Direct factor Xa inhibitors	0	(0.0)	1	(<0.1)	78	(1.7)	95	(2.0)
Heparin group	5	(0.1)	14	(0.3)	402	(8.6)	393	(8.4)

Table 4 Concomitant antidiabetic medication at baseline and initiated after baseline- summary - FAS

	Baseline				After baseline[a]			
	Lira		Placebo		Lira		Placebo	
	N	%	N	%	N	%	N	%
Number of subjects	4668		4672		4668		4672	
Blood glucose lowering drugs (excluding insulin)	4113	(88.1)	4129	(88.4)	1012	(21.7)	1358	(29.1)
Metformin	3540	(75.8)	3604	(77.1)	249	(5.3)	299	(6.4)
SU	2370	(50.8)	2363	(50.6)	349	(7.5)	505	(10.8)
Alpha glucosidase inhibitors	139	(3.0)	123	(2.6)	83	(1.8)	146	(3.1)
TZD	296	(6.3)	279	(6.0)	99	(2.1)	160	(3.4)
DPP-4 inhibitors	4	(<0.1)	2	(<0.1)	149	(3.2)	170	(3.6)
GLP-1 receptor agonist	0	(0.0)	2	(<0.1)	87	(1.9)	139	(3.0)
SGLT2 inhibitors	0	(0.0)	0	(0.0)	100	(2.1)	130	(2.8)
Glinides	178	(3.8)	172	(3.7)	85	(1.8)	137	(2.9)
Other	0	(0.0)	1	(<0.1)	0	(0.0)	1	(<0.1)
Insulin treatment	2038	(43.7)	2131	(45.6)	1346	(28.8)	2019	(43.2)
Premix	445	(9.5)	463	(9.9)	282	(6.0)	440	9.42)
Short acting	42	(0.9)	26	(0.6)	586	(12.6)	915	(19.6)
Intermediate acting	547	(11.7)	600	(12.8)	273	(5.8)	386	(8.3)
Long acting	1041	(22.3)	1077	(23.1)	619	(13.3)	940	(20.1)
Other insulins	23	(0.5)	14	(0.3)	31	(0.7)	43	(0.9)
Insulin naive[b]	2630	(56.3)	2541	(54.4)	1830	(39.2)	1343	(28.7)

[a] A subject was excluded if the subject was treated at baseline with the same medication, [b] subjects who remained insulin naïve during the trial
Abbreviations: %: proportion of subjects; DPP4: dipeptidyl peptidase-4; FAS: full analysis set; GLP1: glucagon-like peptide-1; Lira: liraglutide; N: number of subjects, SGLT-2: sodium-dependent glucose transporter two; SU: sulphonylurea; TZD: thiazolidinedione

Numbers analysed

In accordance with the SAP, the FAS included all randomised subjects, regardless whether or not the subject received investigational products during the trial. The FAS consisted of 4668 subjects in the liraglutide group and 4672 subjects in the placebo group. The PP population was a subset of the FAS but events were excluded when the accumulated days of no exposure to investigational product exceeded 120 days. The PP analysis was only used as a sensitivity analyses for the primary endpoint. No safety analysis set was defined as safety was assessed using the above mentioned analysis sets.

Outcomes and estimation

Summary of main study

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 5 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	Comparison		Liraglutide vs placebo	

estimate per comparison	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

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. This corresponds to an estimated 13% reduction in risk of experiencing a first MACE with liraglutide compared to placebo. Thus, trial 3748 met the safety objective by ruling out the 1.3 risk margin as per FDA guideline. 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 5**). In both treatment groups, almost half of the events contributing to the primary endpoint were non-fatal MIs.

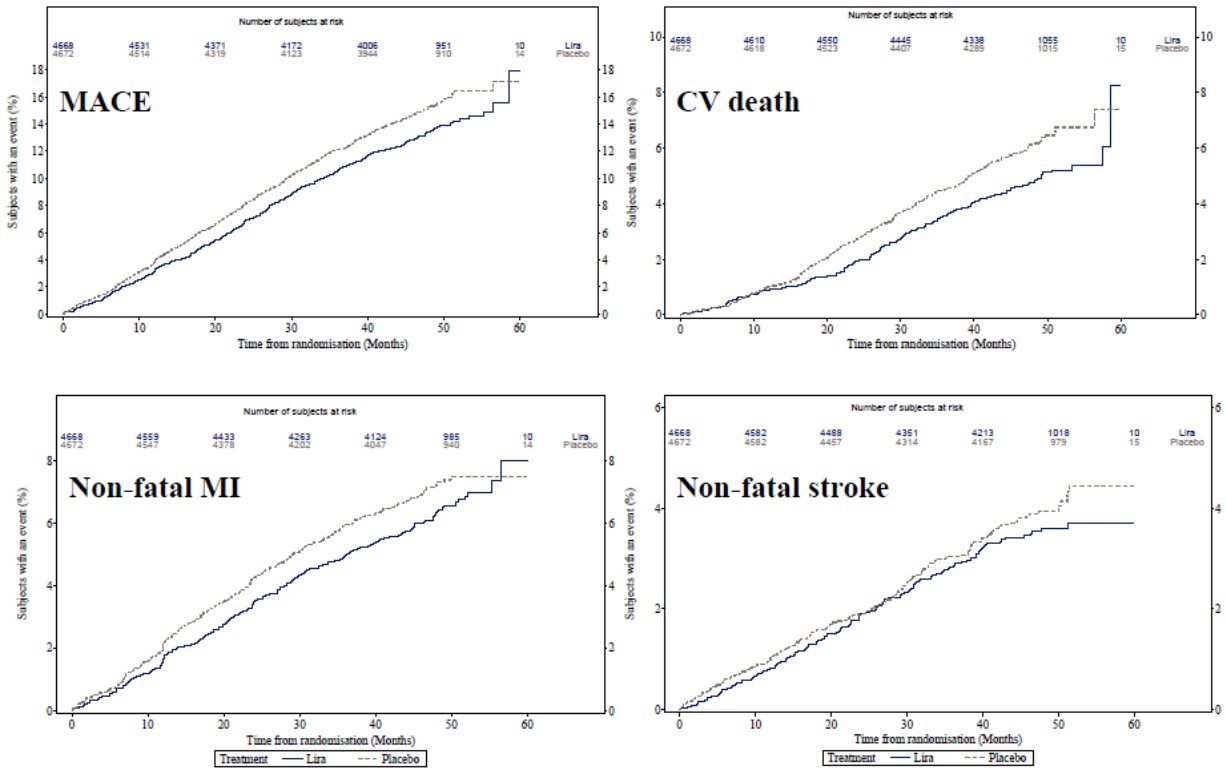
In the corresponding Kaplan-Meier plot (**Figure 3**), the development in EAC-confirmed first MACE over time is shown. The estimated risk of experiencing a MACE within any certain time from randomisation was lower for liraglutide compared to placebo. Similarly, favourable treatment differences were

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 5**).

Table 6 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

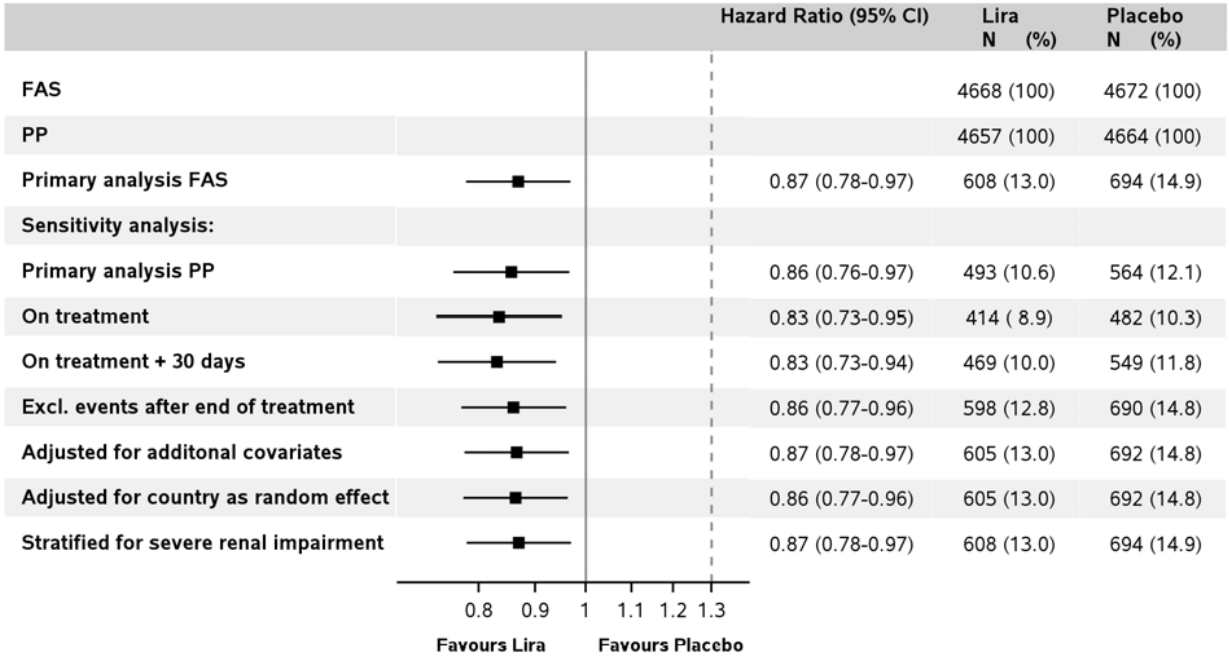


Note: The y-axes are adjusted to the proportion of subjects with events for each of the individual endpoints. MACE is a composite of cardiovascular death, non-fatal MI and non-fatal stroke. Plots for time to first event for the individual components of MACE include all first events within the individual 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

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

Sensitivity analyses of the primary endpoint

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 (**Figure 4**).



FAS: full analysis set, PP: per protocol set, CI: confidence interval.
%: proportion in percent of subjects with an event. N: number of subjects.
Additional covariates: Sex, region, smoking history at baseline (never/prior/current), prior cardiovascular events at baseline (yes/no), antidiabetic therapy at baseline, age at baseline, diabetes duration at baseline, calculated eGFR-MDRD, where eGFR-MDRD is the estimated glomerular filtration rate using the modification of diet in renal disease formula.

ex2211/ex2211-3748/ctr_20160811_er
12AUG2016:20:08:24 - e_forest_primary_sensitivity.sas/ID14201470_e_forest_primary_sensitivity.png

Figure 4 Forest plot of primary analysis and sensitivity analyses

Furthermore, 4 of the pre-specified sensitivity analyses were related to exposure to trial product. Of these, the PP analysis included all subjects who took at least one dose of the trial product, but excluded all first MACEs with onset date after the accumulated number of days of no exposure to trial product exceeded 120 days; the 'on-treatment' sensitivity analysis included all first MACEs occurring while on randomised treatment (+ 1 day), and the 'on-treatment + 30 days' sensitivity analysis included all first MACEs occurring while on randomised treatment + 30 days. Finally, one sensitivity analysis excluded all events that occurred after the end-of-treatment visit (visit 15). Importantly, both 'on-treatment' analyses including either first MACEs in subjects 'on-treatment' (+ 1 day) or in subjects 'on-treatment + 30 days' (i.e. no later than 30 days into an off-treatment period) provided a lower treatment estimate (liraglutide vs placebo) for the hazard ratios (0.83 in both analyses) compared to the primary analysis (hazard ratio: 0.87; **Figure 4**), supporting an effect of liraglutide treatment on the primary endpoint.

A *post hoc* analysis including events up until last drug date + 30 days (i.e. also counting events during drug holidays) provided a result (estimated hazard ratio: 0.86 $[0.77, 0.96]_{95\%\ CI}$) similar to the primary analysis and the pre-specified 'on-treatment' analyses (i.e. on randomised treatment), again confirming the robustness of the results for the primary analysis.

Two *post hoc* tipping point analyses were undertaken to evaluate the potential impact of missing data on the result of the primary analysis. The first analysis assumed that the 12 subjects in the liraglutide group with unknown vital status at follow-up died from cardiovascular death the day after the last contact, while the 17 subjects in the placebo group were assumed to be alive. This resulted in an estimated hazard ratio of 0.89 $[0.79; 0.99]_{95\%CI}$. In the second analysis, all non-completers in the liraglutide group (i.e., subjects who were alive at follow-up plus subjects without vital status at follow-up) were added in a step-wise fashion, starting with the non-completers who left the trial earliest

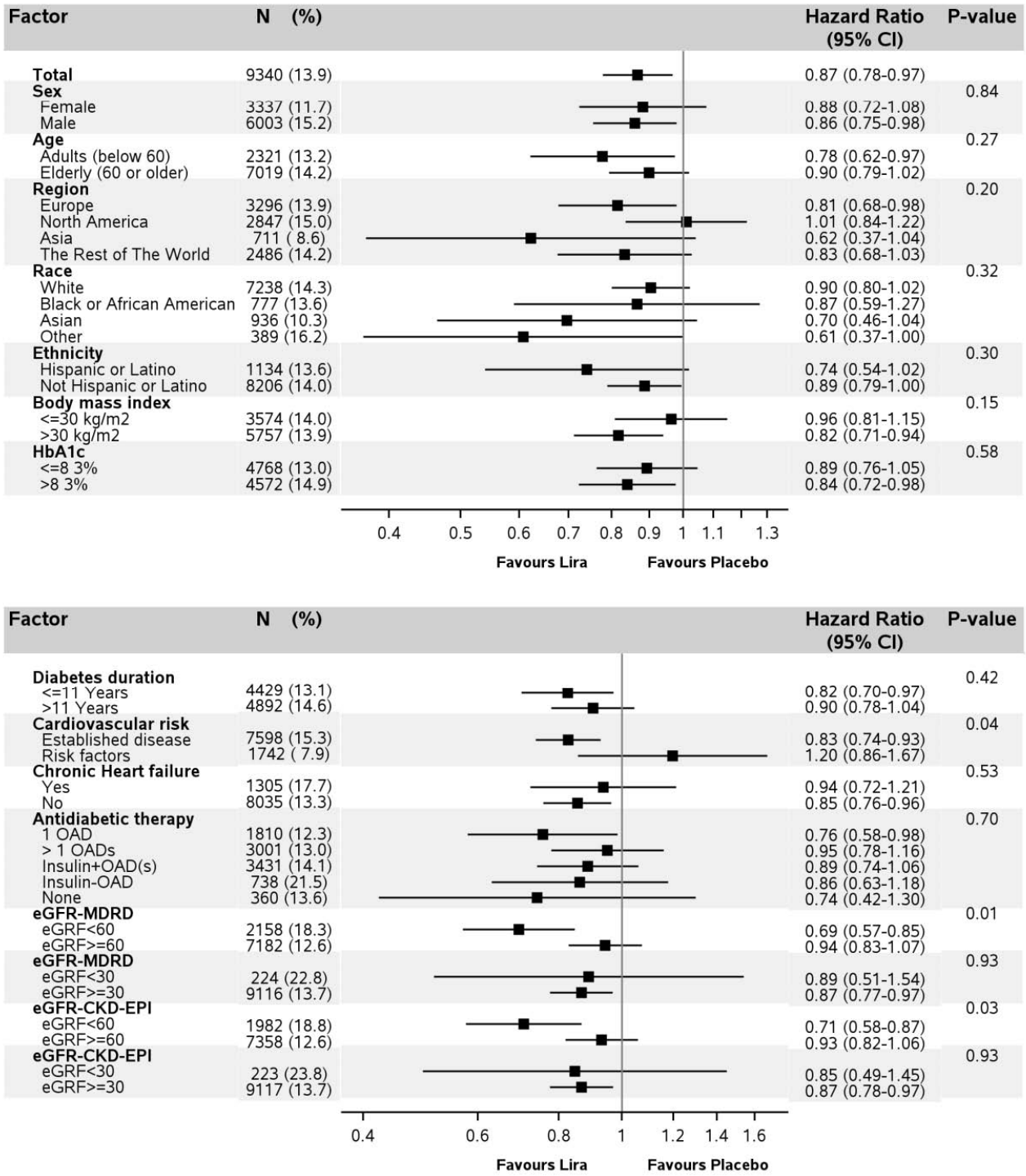
(counting from randomisation), under the assumption that they had had a non-fatal MI or a non-fatal stroke the day after the last contact. In this analysis, 21 of 139 subjects in the liraglutide group (15%) would need to have experienced an event *versus* none of the 159 subjects in the placebo group before superiority was lost (HR: 0.90 $[0.81; 1.00]_{95\%CI}$). Thus, both tipping point analyses further supported the robustness of the results for the primary endpoint.

In the pre-planned analysis for the primary endpoint of MACE, all deaths with 'cause unknown' were included as cardiovascular deaths. A *post hoc* analysis excluding deaths with unknown cause provided similar results as the primary analysis (HR: 0.87 $[0.77, 0.97]_{95\%CI}$) and thus demonstrated that the potential uncertainties related to the adjudication of death with cause 'unknown' did not impact the results.

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 5**). However, a few of the subgroups appeared to show different patterns and are discussed below.



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

Figure 5 Forest plot of treatment contrast according to subgroups - FAS

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 5**. 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.

The potential differential effect between **cardiovascular risk subgroups** could not be explained by differences in other subject characteristics, concomitant medication or exposure to trial drug between the two subgroups. In addition, *post hoc* 'on-treatment' sensitivity analyses in subjects ≥60 years with only risk factors for cardiovascular disease did not show an increased hazard ratio compared to the primary subgroup analysis, as would be expected if treatment with liraglutide was associated with cardiovascular harm in this subgroup. Further, there was no evidence that the treatment effect of liraglutide for changes in HbA1c, body weight and SBP differed between the cardiovascular risk subgroups. Moreover, the difference in hazard ratios observed for first MACE between the cardiovascular risk subgroups could not be explained by a potential heterogeneous treatment effect across the covariates included in a *post hoc* sensitivity analysis using a backward elimination technique.

Exploratory *post hoc* analyses by medical history of MACE (specified as non-fatal MI or non-fatal stroke) were performed to investigate whether the observed difference between the cardiovascular risk subgroups was driven by differences related to previous occurrence of MACE. These analyses resulted in hazard ratios favouring liraglutide, both for subjects with a history of MACE (0.84 $[0.72; 0.97]_{95\% CI}$) and for subjects without a previous MACE (0.89 $[0.76; 1.05]_{95\% CI}$), thus supporting benefits of liraglutide in both primary and secondary prevention of cardiovascular disease.

Consequently, the most plausible explanation for the observed difference is believed to be related to uncertainties associated with the estimate, as the subgroup of subjects aged ≥60 years with only risk factors for cardiovascular disease accounted for a relatively small proportion of the total trial population (~20%) and MACEs (~10%) observed in the trial.

No statistically significant interaction was observed between treatment and **region** as reflected by the test for heterogeneity (p=0.20), (**Figure 5**). However, while the hazard ratio for subjects in regions outside North America was similar to or lower than the hazard ratio for the primary analyses in the overall FAS, a hazard ratio of 1.01 $[0.84; 1.22]_{95\%CI}$ was observed for subjects in **North America**, albeit the 95% CI for the hazard ratio covered the point estimate for the primary analysis. A number of *post hoc* analyses were conducted for subjects in the US, the largest country in the region comprising 88% of the population in North America, to investigate this further. The difference in the point estimate could not be explained by differences in demographic factors or concomitant medication between US and non-US subjects, and remained unchanged after adjustment for relevant covariates. Furthermore, the higher point estimate in North America did not appear to be attributable to differences in treatment responses between the US and non-US populations with respect to changes in effectiveness parameters (HbA1c, body weight and SBP), albeit the treatment difference for mean HbA1c appeared to decrease more over time in the US population in line with the decrease in exposure to trial drug. The most likely explanation for the observed difference was related to a lower exposure to trial drug in the US population compared to other regions. The mean proportion of time on trial drug was lower in the US (0.73%) than in the non-US population (0.87%) due to a higher proportion of subjects with off-drug periods in both treatment arms. *Post hoc* sensitivity analyses accounting for differences in exposure such as the PP analysis as well as analyses of subjects 'on-treatment' and 'on-treatment + 30 days' favoured liraglutide and provided point estimates < 1 in line with those observed on FAS for the overall population (HR: 0.94 $[0.75; 1.17]_{95\% CI}$, HR: 0.89 $[0.69; 1.14]_{95\% CI}$, and HR 0.89 $[0.70; 1.12]_{95\% CI}$), respectively. Similarly, the Kaplan-Meier curves prepared for US subjects 'on-

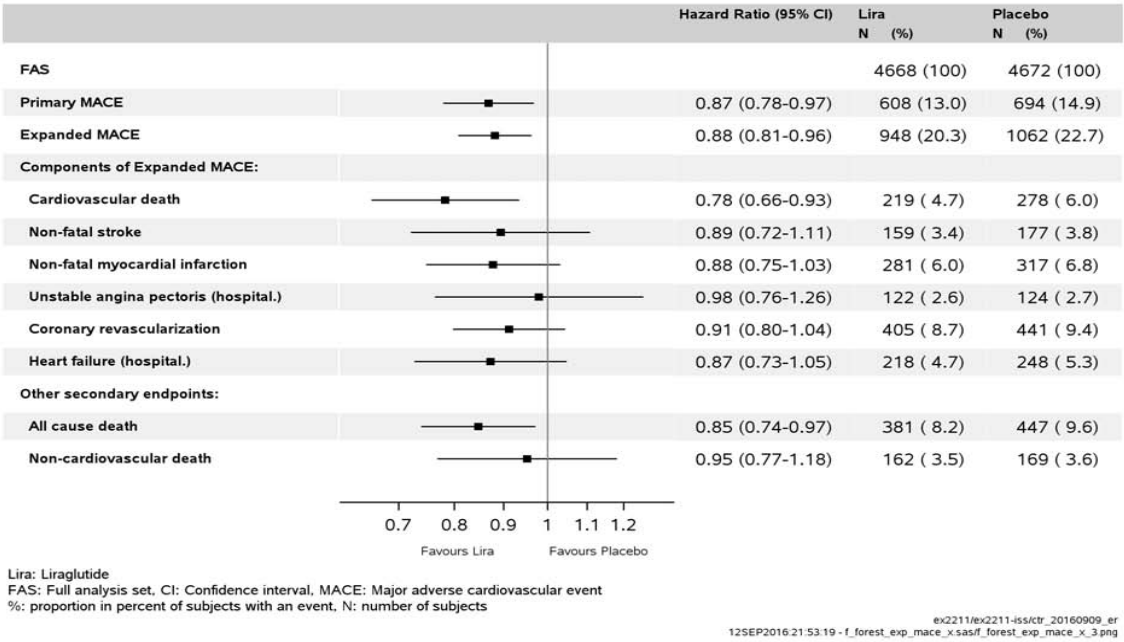
treatment+30 days' resembled that for the overall population with a clear separation of the curves for liraglutide and placebo.

The lower exposure to trial drug in the US was not explained by a higher rate of permanent discontinuations due to adverse events with liraglutide in US *versus* non-US subjects. Exposure to trial drug over time was observed for the two treatment groups, suggesting that this was not caused by tolerability issues with liraglutide. Considering that the estimated hazard ratios for the on-treatment analyses mirrored that for the overall population and that the test for interaction between treatment and region was not statistically significant, there is no strong evidence supporting a difference in treatment response between the US and the non-US population. This is supported by the favourable effects of liraglutide compared to placebo in the pre-specified subgroup analyses reflecting characteristics of the US population including: subjects with a BMI >30 kg/m^2, Black or African Americans, and Hispanic or Latino subjects (**Figure 5**).

A favourable effect of liraglutide was also observed across subgroups by **renal function** with point estimates consistently < 1 (**Figure 5**). 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.

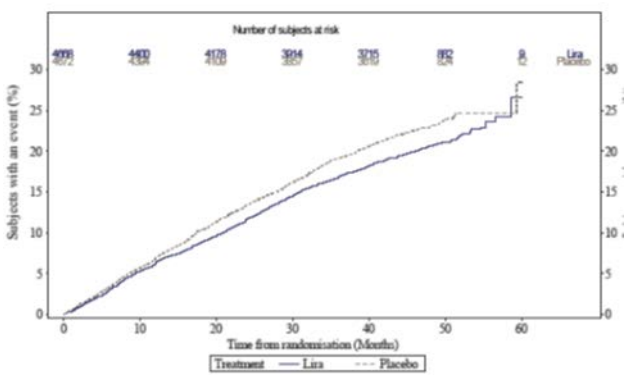
Secondary endpoint: expanded MACE

As a broader definition of MACE may be more sensitive to detect potentially harmful cardiovascular effects, an analysis of time to first EAC-confirmed expanded MACE was conducted, including the composite MACE endpoint used for the primary analysis as well as hospitalisation for UAP, coronary revascularisation and hospitalisation for heart failure. 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 6**). Similarly, the Kaplan-Meier plot resembled the plot for time to first MACE (**Figure 7**). 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).

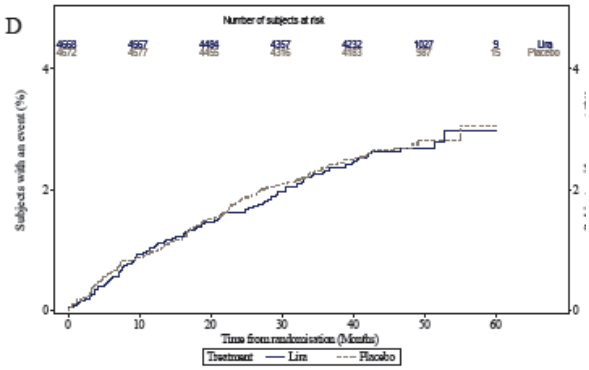


Note: For the time to first event of any individual component of expanded MACE, all first events are included regardless of whether these contribute to the time to first event analysis of the composite endpoint.
Abbreviations: %: proportion of subjects with an event; CI: confidence interval; Comp: components; FAS: full analysis set; Hospital: hospitalisation; MACE: major adverse cardiovascular event; N: number of subjects

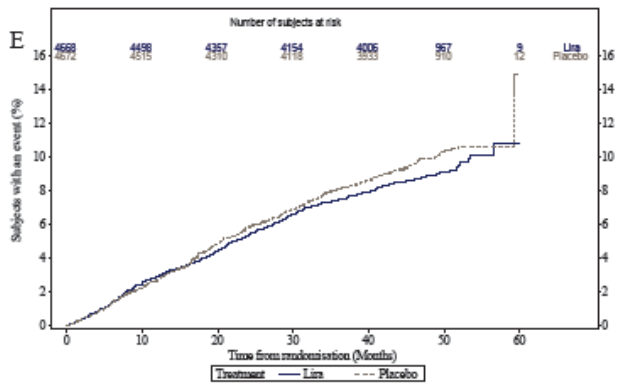
Figure 6 Forest plot of treatment contrast for components of first EAC confirmed expanded MACE, MACE and death.



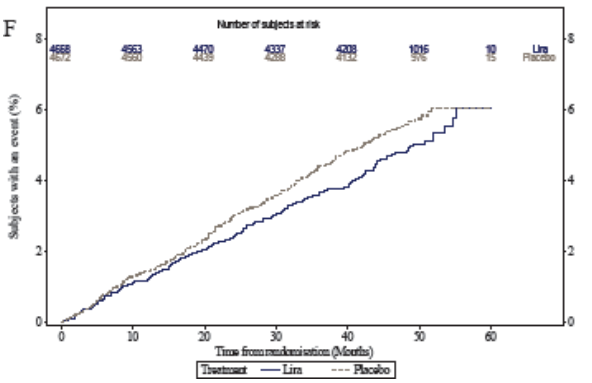
Expanded MACE



Hospitalisation for unstable angina pectoris



Coronary revascularisation



Hospitalisation for Heart Failure

Figure 7 Kaplan-Meier plots – time to first EAC-confirmed cardiovascular endpoint: Expanded MACE, Hospitalisation for unstable angina pectoris, Coronary revascularisation and Hospitalisation for Heart Failure

Individual components of expanded MACE

Cardiovascular death

EAC-confirmed cardiovascular deaths were reported less frequently in the liraglutide group compared to the placebo group (4.7% vs 6.0%)(**Table 5**). The estimated hazard ratio (liraglutide vs placebo) of 0.78 ([0.66; 0.93]95% CI) from the Cox analysis of time to EAC-confirmed cardiovascular death was statistically significant and in favour of liraglutide, corresponding to an estimated 22% risk reduction with liraglutide compared to placebo (**Figure 6**). In the Kaplan-Meier plot, the estimated risk of cardiovascular death within any certain time from randomisation was generally lower for liraglutide group compared to the placebo group (**Figure 3**).

A *post hoc* 'on treatment' (+ 1 day) analysis, including subjects who died from cardiovascular causes (EAC-confirmed) while on randomised treatment were in line with the pre-specified analysis of all subjects who died due to a cardiovascular death (HR 0.74 [0.56; 0.96]).

Non-fatal MI

First events of EAC-confirmed non-fatal MI (acute MIs including silent MIs) were reported less frequently in the liraglutide group compared to the placebo group (6.0% vs 6.8%). The estimated hazard ratio (liraglutide vs placebo) from the Cox analysis was in favour of liraglutide 0.88 ([0.75; 1.03]95% CI) (**Figure 6**). In the Kaplan-Meier plot, the estimated risk of experiencing non-fatal MI within any certain time from randomisation was generally lower for the liraglutide group compared to the placebo group (**Figure 3**).

In accordance with the results from the time to first event analysis, the rate of all EAC-confirmed non-fatal MIs from randomisation to follow up (including recurrent events) was also lower in the liraglutide group compared to the placebo group (1.92 vs 2.22 events per 100 PYO).

The majority of all EAC-confirmed MIs (including recurrent, fatal and non-fatal MIs) were symptomatic (liraglutide: 82.7%; placebo: 81.7%) and non-STEMIs (liraglutide: 86.6%; placebo: 90.7%), with only minor differences between treatment groups noted across sub-categories. Furthermore the majority were categorised as type 1 (spontaneous) MIs in both treatment groups (liraglutide: 78.0%; placebo: 77.0%). Silent MIs were reported in less than 20% of cases in both treatment groups (liraglutide: 17.3%; placebo: 18.3%).

Non-fatal stroke

First events of EAC-confirmed non-fatal stroke were reported less frequently in the liraglutide group compared to the placebo group (3.4% vs 3.8%). The estimated hazard ratio (liraglutide vs placebo) of 0.89 ([0.72; 1.11]95% CI) from the Cox analysis was in favour of liraglutide (**Figure 6**).

In the Kaplan-Meier plot the estimated risk of experiencing non-fatal stroke within any certain time from randomisation was generally lower for the liraglutide group compared to the placebo group (**Figure 3**). In accordance with the results from the time to first event analysis, the rate of all EAC-confirmed non-fatal strokes from randomisation to follow up (including recurrent events) was also lower in the liraglutide group compared to the placebo group (0.98 vs 1.12 events per 100 PYO).

The majority of all EAC-confirmed strokes (fatal and non-fatal) were ischaemic in both treatment groups (liraglutide: 84.7%; placebo: 83.0%).

Hospitalisation for unstable angina pectoris

First events of EAC-confirmed hospitalisation for UAP were reported at similar frequency in the liraglutide group and the placebo group (2.6% vs 2.7%). The estimated hazard ratio from the Cox analysis was just below 1 (0.98 [0.76; 1.26]95% CI) (**Figure 6**), and in the Kaplan-Meier plot no difference in the estimated risk was apparent throughout the trial (**Figure 7**).

In accordance with the results from the time to first event analysis, the rate of all EAC-confirmed hospitalisation for UAP events from randomisation to follow up (including recurrent events) was similar in the two treatment groups (0.79 vs 0.79 events per 100 PYO).

Coronary revascularisation

First events of EAC-confirmed coronary revascularisation were reported less frequently in the liraglutide group compared to the placebo group (8.7% vs 9.4%). The estimated hazard ratio (liraglutide vs placebo) of 0.91 ([0.80; 1.04]95% CI) from the Cox analysis was in favour of liraglutide

(**Figure 6**). In the corresponding Kaplan-Meier plot, the estimated risk of experiencing coronary revascularisation within any certain time from randomisation was generally lower in the liraglutide group compared to the placebo group (**Figure 7**).

In accordance with the results from the time to first event analysis, the rate of all EAC-confirmed coronary revascularisation from randomisation to follow up (including recurrent events) was lower in the liraglutide group compared to the placebo group (2.82 vs 3.15 events per 100 PYO).

Hospitalisation for heart failure

First events of EAC-confirmed hospitalisation for heart failure were reported at a lower frequency in the liraglutide group compared to the placebo group (4.7% vs 5.3%). The estimated hazard ratio (liraglutide vs placebo) of (0.87 [0.73; 1.05]95% CI) from the Cox analysis of time to EAC-confirmed hospitalisation for heart failure was in favour of liraglutide (**Figure 6**). In the Kaplan-Meier plot, the estimated risk of experiencing hospitalisation for heart failure within any certain time from randomisation was generally lower in the liraglutide group compared to the placebo group (**Figure 7**). A *post hoc* 'on-treatment' (+ 1 day) Cox analysis of time to first EAC-confirmed hospitalisation for heart failure on randomised treatment provided similar results (estimated hazard ratio: 0.85 [0.69; 1.05]95% CI) as the pre-specified analysis for first events.

In accordance with the results from the time to first event analysis, the rate of all events of EAC-confirmed hospitalisation for heart failure (including recurrent events) was also lower in the liraglutide group compared to the placebo group (1.92 vs 2.19 events per 100 PYO).

A *post hoc* analysis of time to *first* EAC-confirmed hospitalisation for heart failure or all cause death was performed to ensure that potential fatal cases of heart failure were taken into account. This showed an estimated risk reduction of 13% (HR: 0.87 [0.77; 0.97]95%CI with liraglutide compared to placebo substantiating that liraglutide was not associated with an increased risk of hospitalisation for heart failure.

MACE by heart rate

In line with observations from the liraglutide for T2DM development programme, 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 compared to those in the placebo group (Assessor: Liraglutide 31% vs Placebo 16%). 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. Therefore, 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. Hence, in addition to the overall results on MACE and expanded MACE, these data further support that the increase in resting heart rate was not associated with adverse cardiovascular outcomes, including arrhythmias.

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 6**. The difference was primarily driven by the lower frequency of cardiovascular deaths. A post hoc 'on-treatment' analysis of time to all-cause death showed a lower estimated hazard ratio compared to the pre-defined Cox analysis (HR: 0.72 [0.57; 0.91]95%CI), supporting a favourable treatment effect of liraglutide on all-cause mortality. The robustness was further supported by 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 6**). 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

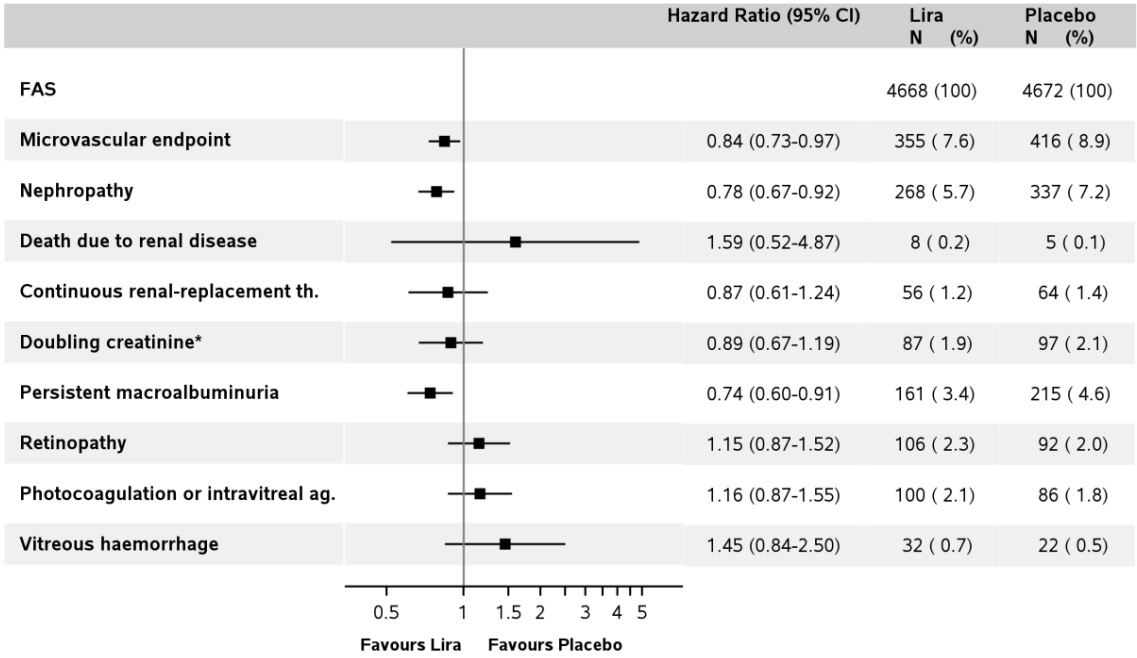
Microvascular safety was evaluated using pre-specified composite microvascular, nephropathy and retinopathy endpoints. The microvascular composite comprised the components of the nephropathy composite (with 4 components: new onset of persistent macroalbuminuria, persistent doubling of serum creatinine and eGFR $\leq$ 45 mL/min/1.73 m^2 per MDRD, need for continuous renal replacement therapy, and death due to renal disease) and retinopathy composite (with 3 components: need for retinal photocoagulation or treatment with intravitreal agents, vitreous haemorrhage, and diabetes-related blindness).

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. 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 8**.

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.



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.

Figure 8 Forest plot of the microvascular composite endpoint and its components

Nephropathy

This risk reduction in nephropathy was mainly driven by an estimated 26% risk reduction for the component 'new onset of persistent macroalbuminuria' (HR: 0.74 [0.60; 0.91]$_{95\%CI}$), but also the components 'persistent doubling of serum creatinine and eGFR ≤45 mL/min/1.73m^2 per MDRD' (HR: 0.89 [0.67; 1.19]$_{95\%CI}$) and 'need for continuous renal replacement therapy' (HR: 0.87 [0.61; 1.24]$_{95\%CI}$) contributed. The analysis of the component 'death due to renal disease', based on few subjects (liraglutide: 8 subjects; placebo: 5 subjects), resulted in an estimated hazard ratio of 1.59 [0.52; 4.87]$_{95\%CI}$.

The pathophysiology behind diabetic nephropathy is complex and the time course of the disease is variable. From the earliest stages of microalbuminuria, it usually takes 10-20 years to develop end-stage renal disease (ESRD). The relatively short duration of trial 3748 in the context of renal disease progression (median observation time was 3.84 years), together with the fact that the majority (approximately 77%) of the subjects had normal renal function or only mild renal impairment at baseline, may explain that the risk reduction in the nephropathy composite was mainly driven by the component 'new onset of persistent macroalbuminuria'. Albuminuria is seen as predictive for the prognosis of progression of kidney disease and the risk of ESRD correlates with increasing UACR. Therefore, the estimated risk reduction with liraglutide relative to placebo for 'new onset of persistent macroalbuminuria' in trial 3748 may be considered clinically relevant.

Risk reductions of the 4-component composite were also observed in post-hoc analyses conducted in subgroups with different stages of renal impairment. In addition, the pre-specified analysis of a narrow

3-component composite (without persistent macroalbinuria) conducted in subjects with moderate renal impairment resulted in an estimated hazard ration of 0.73 [0.50; 1.07]$_{95\% CI}$. These results indicate that liraglutide may have a renoprotective effect beyond the beneficial effect demonstrated for 'new onset of persistent macroalbuminuria' in the total trial population. Furthermore, the results indicate that liraglutide may be safely used across subgroups of subjects with varying degrees of renal impairment and/or microalbuminuria.

The positive outcomes for nephropathy were supported by results on serum creatinine (used to calculate eGFR) and UACR. The differences between the treatment groups in serum creatinine and eGFR (as assessed using the ratio to baseline at the 3-year visit, MMRM) were small (1% - 2%), suggesting less renal deterioration in the liraglutide group than in the placebo group.

Furthermore, the increase in UACR over the course of the trial observed in both treatment groups was lower in the liraglutide group than in the placebo group, with an estimated treatment ratio to baseline at the 3-year visit of 0.81 [0.76; 0.86]$_{95\% CI}$). A beneficial effect of liraglutide treatment on UACR has been observed in other trials, including a trial conducted in subjects with T2DM and moderate renal impairment.

Retinopathy

The estimated hazard ratio of the time-to-event analysis for the retinopathy composite disfavoured liraglutide (HR: 1.15 [0.87; 1.52]$_{95\%CI}$). The analyses of the components 'treatment with photocoagulation or intravitreal agents' and 'vitreous haemorrhage' each resulted in hazard ratio point estimates >1 (liraglutide *versus* placebo, HR: 1.16 [0.87, 1.55]$_{95\%CI}$ and HR: 1.45 [0.84, 2.50]$_{95\%CI}$, respectively), whereas for 'development of diabetes-related blindness', only 1 subject in the placebo group had 1 EAC-confirmed event thereby precluding a meaningful analysis.

A limitation in the evaluation of retinopathy events was that standardised and systematic assessments of the eyes, such as fundoscopy or fundus photography at baseline or during the trial were not specified in the protocol, resulting in potential variability in the identification of retinopathy events by the investigators. The components of the retinopathy composite were, furthermore, highly interdependent in that the majority of the events that fulfilled the criterion 'vitreous haemorrhage' concomitantly fulfilled the criterion 'treatment with photocoagulation or intravitreal agents', reflecting the clinical practice of treating vitreous haemorrhage with photocoagulation or intravitreal agents.

To investigate the treatment effect of liraglutide *versus* placebo on 'need for retinal photocoagulation or treatment with intravitreal agents' without concomitant 'vitreous haemorrhage', a *post hoc* time-to-event analysis was performed. In this analysis, events concomitantly fulfilling the criteria 'need for retinal photocoagulation or treatment with intravitreal agents' and 'vitreous haemorrhage' were excluded. The Cox analysis resulted in a hazard ratio of 1.02 [0.74; 1.41]$_{95\% CI}$, indicating that the observed imbalance in retinopathy events was driven by events of 'vitreous haemorrhage'.

Additional exploratory analyses in subjects with 'vitreous haemorrhage' events, including time-to-event analyses in subgroups of subjects and an investigation of the time course of HbA_{1c} reduction, did not reveal any patterns that could further explain the imbalance in the component 'vitreous haemorrhage'.

Thus, the difference between the treatment groups in retinopathy events was driven by an imbalance in a small number of subjects with 'vitreous haemorrhage' events (32 subjects *versus* 22 subjects in the liraglutide and placebo groups, respectively).

Glycaemic control

Trial 3748 was designed as a dedicated CVOT and therefore 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. Trial 3748 provides robust information on long-term effectiveness following 3-5 years of treatment as well as important information on the use of liraglutide in the above mentioned sub-populations.

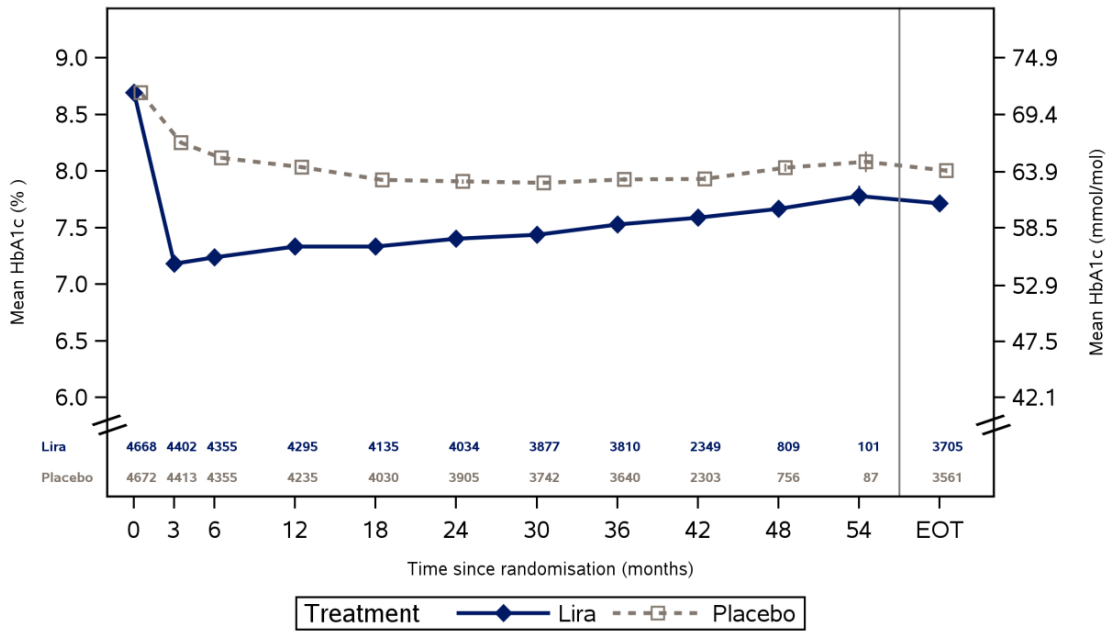
HbA1c

Liraglutide has been shown to result in consistent and clinically relevant reductions in HbA_{1c} based on clinical trials in the T2DM development programme. In trial 3748, the mean baseline HbA_{1c} was 8.7% in both treatment groups reflecting sub-optimal glycaemia and no upper inclusion limit for HbA_{1c} at trial entry. Investigators were instructed to follow recommendations from the GEP on standard of care treatment for antidiabetic therapy throughout the treatment period, with the aim of achieving similar glycaemic control in the two treatment groups based on individualised HbA_{1c} targets.

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 9**, **Table 6**).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 difference in glycaemic control may partly reflect the vulnerable trial population, for which higher glycaemic targets may have been considered appropriate by the investigators. Furthermore, the treatment options for subjects in the placebo group were limited by the fact that use of incretin-based therapies was not allowed.

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% $[-0.35; -0.23]_{95\% CI}$). Thus, liraglutide was shown to be efficacious compared to placebo, both in addition to standard of care therapy, and to have a sustained effect on glycaemic control up to 5 years.

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.



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.

Figure 9 Estimated mean HbA_{1c} over time – FAS

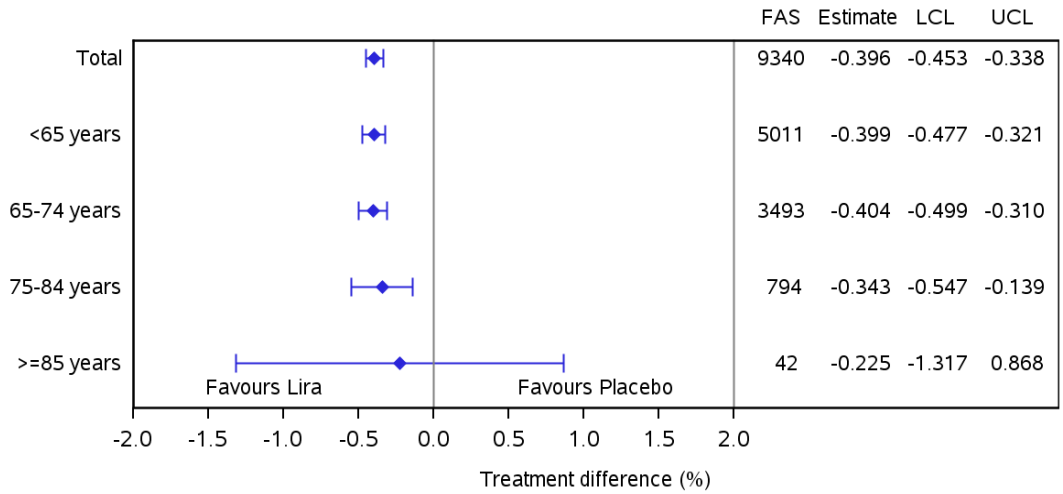
Table 7 Endpoints related to effectiveness: Change from baseline to 3 years – MMRM – FAS

	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.

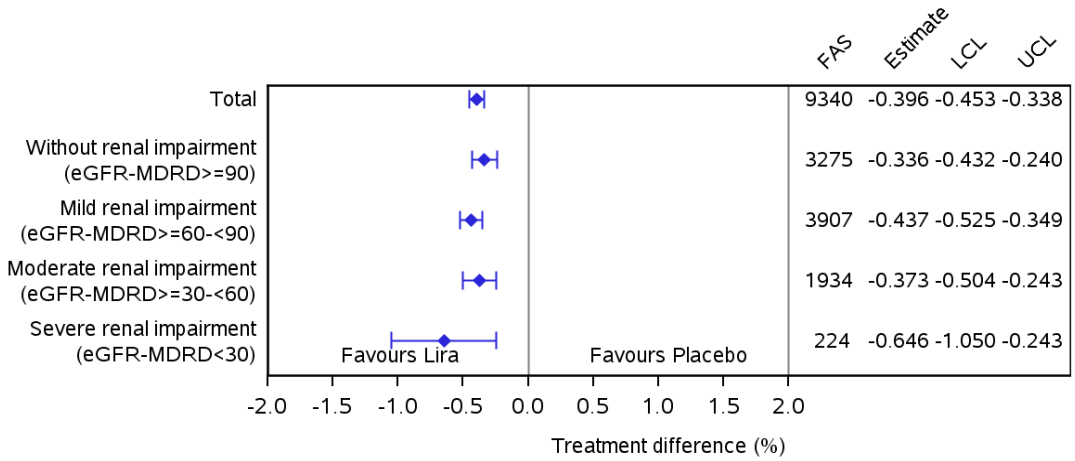
HbA1c in sub-populations

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 supporting the effect of liraglutide and the applicability of the data from trial 3748 across a broad population of subjects with T2DM (see **Figure 10**, **Figure 11** and **Figure 12**). Furthermore, the estimated difference in HbA_{1c} with liraglutide *versus* placebo was similar across the different subgroups. Thus, reductions in HbA_{1c} 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 HbA_{1c} 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.



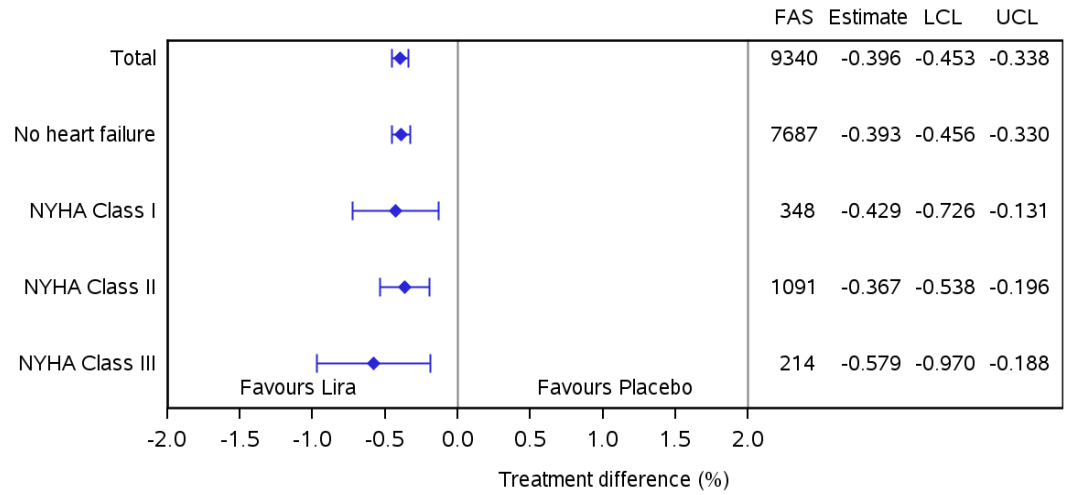
Note: Treatment differences are estimated using MMRM with an unstructured covariance matrix. Treatment, sex, region and antidiabetic therapy at baseline are included as fixed effects and baseline HbA_{1c} and age as covariates, all nested within visit. For the analyses per subgroup, the model also includes 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 10 HbA_{1c} - 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: 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 11 HbA_{1c} - 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 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.

Figure 12 HbA_{1c} - change from baseline to 3-year visit (visit 11) by NYHA class at screening - forest plot - MMRM – FAS

Initiation of insulin and other antidiabetic therapies

The long-term effect of liraglutide on HbA_{1c} was further substantiated by analyses of initiation of glucose-lowering drugs, including insulin, during the trial. At baseline, 56.3% of subjects in the liraglutide group and 54.4% of subjects in the placebo group were insulin-naïve (**Table 4**). 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.
Taken together, trial 3748 showed that treatment with liraglutide reduced the need for addition of insulin and other antidiabetic drugs during a period of up to 5 years.

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.

2.4.2. Discussion on clinical efficacy

Design and conduct of the clinical study

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. The primary objective of CV outcome trials in type 2 diabetes mellitus is to exclude a harmful effect on cardiovascular events and mortality. MACE-3 was the primary endpoint for the LEADER trial, which is the preferred endpoint for safety according to 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, 111 subjects were randomised in error due to violation of one or more inclusion, exclusion or randomisation criteria. The most common reasons for randomisation in error were violations of the inclusion criterion for CVD risk factors, use of disallowed medication and exclusion criterion for

malignant neoplasm. An analysis excluding the 111 protocol violations indicated that the primary endpoint was not affected by these protocol violations.

Based on the assumption of a 1.8% primary outcome event rate, a non-inferiority margin of 1.3, 10% drop-out rate and 90% power, the required sample size was 8754 with 611 expected events. A total of 1302 first EAC-confirmed MACEs were eventually reported in trial 3748, with event rates of 3.4% and 3.9% in the liraglutide and placebo groups respectively.

Subjects were randomised 1:1 to once-daily liraglutide 1.8 mg or placebo as add-on to their standard of care. The trial was designed to include a sufficient number of subjects with moderate and severe renal impairment, to be able to assess the effect of liraglutide in these subgroups. According to the protocol, the trial should include 220 subjects with severe renal impairment (defined as eGFR<30 mL/min/1.73 m^2). To ensure this, subjects were stratified through the randomisation procedure according to eGFR (eGFR<30 mL/min/1.73 m^2 vs eGFR≥30 mL/min/1.73 m^2). There are no concerns regarding randomisation or blinding or group differences in baseline characteristics.

The statistical analysis plan has been discussed and was considered acceptable by CHMP before trial completion. The analysis sets are considered acceptable. The primary analysis of time to MACE-3 was conducted in the full analysis set using Cox regression model. If non-inferiority with a NI margin of 1.3 for HR was confirmed, a test for superiority could be performed. The primary analysis in the full analysis set was supported by an analysis in the per protocol set, which is considered of importance for a non-inferiority trial. Sensitivity analyses included an on treatment analysis and a COX regression model including additional baseline covariates. The secondary time to event analyses were performed in the same way as the primary analysis. Linear secondary endpoints were analysed using a repeated normal mixed model.

According to the Points to consider on application with 1. meta-analyses; 2. one pivotal study (CPMP/EWP/2330/99), the minimum requirement for authorisation is generally one controlled study with statistically compelling and clinically relevant results and it is regulatory practice that evidence from a single pivotal trial is generally required to be stronger than the nominal level used in an application with multiple pivotal trials. In addition, internal and external validity, clinical relevance, data quality and internal consistency should be supportive. The phase-3 results submitted with the original MAA are primarily supportive for safety. While the primary endpoint and the mortality data are considered highly reliable, for exploratory results the effect of chance findings is an important concern.

Efficacy data and additional analyses

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.
Similar results were obtained for **expanded MACE**. Coronary revascularisation and hospitalisation for heart failure were observed less frequently in the liraglutide group, although the differences were not statistically significant. For hospitalisation for UAP no difference vs placebo was seen.
Kaplan-Meier plots of time to first EAC-confirmed events showed that differences in (expanded) 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 difference 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. US participants had a longer history of T2DM, higher body weight, higher baseline HbA1c, and lower SBP and DBP. Furthermore, more subjects were of Black or African American origin and fewer subjects from the US were insulin naïve, fewer used non-insulin antidiabetic medication at baseline whereas more subjects in the US were on lipid lowering drugs and diuretics at baseline compared to subjects outside US. Several post hoc analyses were performed with correction for covariates that could potentially influence the risk of MACE. None of the tested covariates and their interaction with treatment impacted the estimated hazard ratio for first MACE in the US population. Furthermore, the higher point estimate in North America did not appear to be attributable to differences in treatment responses between the US and non-US populations with respect to changes in effectiveness parameters (HbA1c, body weight and SBP). The MAH blames the reduced effect to a lower exposure to trial drug in the US population. This is supported by post hoc sensitivity analysis showing that the effect of liraglutide in MACE in On-treatment (and On treatment+30 days) US patients (On treatment US-population: HR: 0.89 [0.69;1.14] and On treatment+30 days US-population: HR: 0.89 [0.70;1.12]) was similar to the results from the primary analysis (HR: 0.87 [0.78;0.97]). The shorter on-treatment period, which is mostly due to discontinuation of study medication, was not due to an increased frequency of adverse events, but could be related to the difference in healthcare system and health-economics.

It was suggested that body weight might also have influenced results, as pharmacokinetics of liraglutide are influenced by body weight. The MAH presented an analysis MACE and CV death by baseline body weight. Results did not support an association between MACE or cardiovascular death with body weight at baseline or change in body weight due to liraglutide. In addition, a post hoc analysis of treatment contrasts for first MACE according to baseline BMI groups was submitted. There seems to be a trend towards better effect of liraglutide in the higher BMI sub-groups but there is no clear difference when making an across subgroup comparison. As argued by the Applicant, higher BMI is associated with higher risk of cardiovascular disease including MACE. This can at least theoretically explain a better effect among patients with higher BMI.

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.

A total of 360 subjects (3.9%) did not receive glucose lowering drugs at baseline and thus can be considered to be at liraglutide or placebo **monotherapy** during the trial. MACE was in favour of liraglutide (0.74 [0.42-1.30]), although confidence interval was wide, as can be expected with limited numbers.

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 (**Figure 13**).

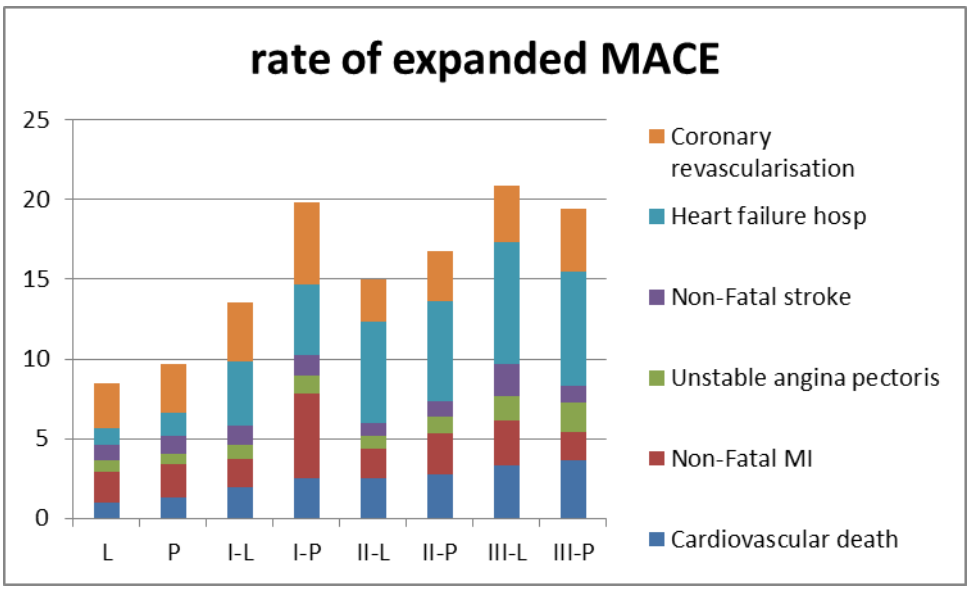


Figure 13 Rate (events/100 patient-years) of expanded MACE by HF class at baseline

In the LEADER trial, liraglutide or placebo was added to standard care. At baseline, **some imbalances were present in use of cardiovascular medication**: 56.8% of patients in the liraglutide group used beta-blockers versus 54.1% in the placebo group; percentages for use of angiotensin-converting–enzyme inhibitors were 51.8% vs. 50.3%, for statins 72.9% vs. 71.4%, and platelet-aggregation inhibitors 68.7% vs. 66.8%. The MAH has performed sensitivity analyses of time to first MACE with each of the 4 cardiovascular medications included as covariates. The results 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). Actually, it appears that there was no significant difference of liraglutide on MACE in the group of patients with normal renal function, and this was further discussed by the Applicant. Across subgroups by renal function point estimates were consistently <1 for liraglutide vs placebo. The subgroup with eGFR<30 contained a limited number of patients and therefore CI's were wide. Nevertheless, the point estimate was in favour of use of liraglutide in these patients. 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. However, this was performed for two classes of HbA1c only (<8.3, ≥8.3%). For external validation of the effects, the MAH is requested to present more detailed analyses according to HbA1c classes of 0.5%. The MAH has performed these analyses. Results do not indicate an association between baseline HbA1c and CV risk reduction with liraglutide.

Similarly, mean estimated glomerular filtration rate (eGFR) per MDRD was rather high: 80.4 ml/min/1.73m^2, especially as the trial also included >200 subjects with severe renal impairment. For external validation of the effects, the MAH was requested to present more detailed analyses according to eGFR classes by 15 ml/min/1.73m^2. These data were presented. A beneficial effect was observed in all subgroups of renal function with the exception of patients with eGFR 75-<90 ml/min/1.73 m^2. It is agreed that 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.

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.

Glycaemic control, measured by HbA1c, was evaluated for the total study population and for a number of subgroups. Investigators were instructed to provide standard of care treatment for

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

antidiabetic therapy throughout the treatment period. 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 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 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.

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.
In response the MAH has discussed possible mechanism behind the beneficial cardiovascular effect of liraglutide. Overall, none of the presented data is convincing but associated with different weaknesses and short-comings. 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.

2.4.3. Conclusions on the clinical efficacy

The LEADER trial was a well-designed and well-conducted CV outcome trial. The study 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. Retinopathy will be monitored in the PSURs.

2.5. Clinical safety

Introduction

The most frequently reported AEs with the current indication of Victoza 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: diabetic foot ulcer, neoplasms and calcitonin, thyroid disease, pancreatitis, acute gallstone disease, hypoglycaemia and immunogenicity.

In addition, safety in specific populations is discussed.

Patient exposure

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 8**). 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 8 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
Median years of exposure to trial drug	3.52	3.51	3.52
Subjects with one or more drug holidays, N (%) (exposed and alive subjects at follow up)	1687 (36.1)	1584 (33.9)	3271 (35.0)
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.

Adverse events

The overall adverse event profile with liraglutide in trial 3748 resembled that observed in the clinical development programme for 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 9**). 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 9 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.

Diabetic foot ulcer

Diabetic foot ulcer has not been evaluated as a safety endpoint in previous clinical trials with liraglutide. The proportion of subjects with events of diabetic foot ulcer and the rate of such events were similar in the two treatment groups (Lira: 3.9%, rate 1.5/100PY; placebo: 4.2%, rate 1.7/100PY). Data on complications to events of diabetic foot ulcers (based on *post hoc* review of individual case narratives by medically qualified personnel) showed that a lower proportion of subjects in the liraglutide group reported diabetic foot ulcer events with subsequent amputation compared to the placebo group (0.9% *versus* 1.4%). Among all foot ulcer events reported, a difference in amputations was mainly observed in the category with the most severe amputations i.e. 'amputation of foot, crus or leg' (liraglutide: 6.2%; placebo: 11.3%).

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 10**). Cox analyses applied *post hoc* showed no statistically significant difference between the treatment groups across these neoplasm categories.

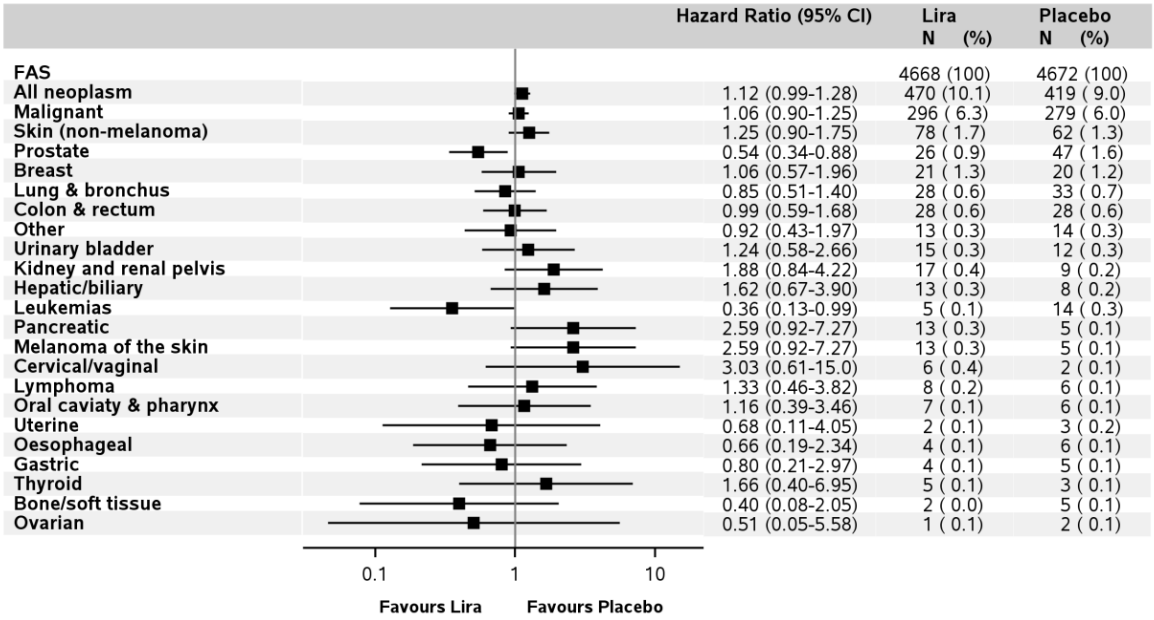
Table 10 EAC-confirmed neoplasm index events including thyroid neoplasms - FAS

	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. As shown in **Figure 14**, 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.



Note: Estimated hazard ratios are derived from the Cox model with treatment as only covariate. Analyses were made *post hoc*.
The forest plot only displays malignant neoplasms for organ/tissue sites of origin for which at least 1 event occurred in each treatment group. The category of 'other' malignant neoplasms included malignant neoplasms not related to any pre-specified organ/tissue of origin. The forest plot is sorted by total proportion of events (sex specific when applicable).
Abbreviations: %: proportion in percent of subjects with an event; CI: confidence interval; EAC: event adjudication committee; FAS: full analysis set; Lira: liraglutide; N: number of subjects.

Figure 14 Distribution of types of EAC-confirmed malignant neoplasms

EAC-confirmed pre-malignant or malignant **skin (non-melanoma) neoplasms** comprised 133 events in 87 subjects in the liraglutide group and 103 events in 70 subjects in the placebo group. A difference between the treatment groups was observed in basal cell carcinomas only, whereas no difference was observed for squamous cell carcinomas. Among subjects with events, a slightly higher proportion of subjects in the liraglutide group as compared to the placebo group had a previous medical history of actinic keratosis, which is known to result from chronic sun exposure. The EAC-confirmed pre-malignant and malignant skin (non-melanoma) neoplasms occurred shortly after randomisation and continued to occur throughout the trial. At the early time point of around month 4, a slightly higher proportion of subjects with events was observed in the liraglutide group as compared to the placebo group. The MAH is of the opinion that a causal relationship between liraglutide and skin (non-melanoma) neoplasms is not likely.

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.

Events of **malignant hepatic or biliary neoplasms** were confirmed for a few subjects, and for more subjects in the liraglutide group (0.3%, 14 events in 13 subjects, 0.08 events per 100 PYO) compared with the placebo group (0.2%, 8 events in 8 subjects, 0.05 events per 100 PYO) (estimated hazard ratio – liraglutide vs placebo: 1.62 $[0.67-3.90]_{95\% CI}$). In the liraglutide group, EAC-confirmed malignant hepatic or biliary neoplasms first occurred shortly after randomisation and accrued throughout the trial. In the placebo group, events first occurred from around month 16 and accrued at a constant rate comparable to that observed for the liraglutide group for the remainder of the trial.

Events of **malignant kidney or renal pelvis neoplasms** were confirmed for a few subjects, and for more subjects in the liraglutide group (0.4%, 17 events in 17 subjects, 0.10 events per 100 PYO) compared with the placebo group (0.2%, 9 events in 9 subjects, 0.05 events per 100 PYO) (estimated hazard ratio – liraglutide vs placebo: 1.88 $[0.84-4.22]_{95\% CI}$). EAC-confirmed malignant kidney or renal pelvis neoplasms first occurred around month 4 in the liraglutide group and around month 8 in the placebo group. In both treatment groups, events accrued at constant and comparable rates throughout the trial.

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 (**Figure 14**). 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.

Figure 15 shows the observed pattern for time to first EAC-confirmed malignant pancreatic neoplasm for the two treatment groups. Events presented shortly after randomisation and accrued at a constant rate throughout the trial in the liraglutide group, suggesting no increased risk of malignant pancreatic neoplasms with liraglutide over time with longer treatment duration.

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). Considering the lag time for development of cancer, the relatively early presentation of these advanced cases suggests that these were due to pre-existing malignancy. In terms of risk factors, 1 subject in the liraglutide group had a medical history of chronic pancreatitis.

Based on an analysis of investigator-reported adverse events of malignant pancreatic neoplasms, a total of 5 events (all in the placebo group) were identified as not being confirmed as such events by the EAC subcommittee adjudicating neoplasms. One (1) of these events was confirmed as a malignant lymphoma. The remaining 4 events were all fatal and confirmed as non-cardiovascular deaths by the

EAC subcommittee adjudicating fatal events with the plausible cause of death being malignancy or pancreatic cancer.

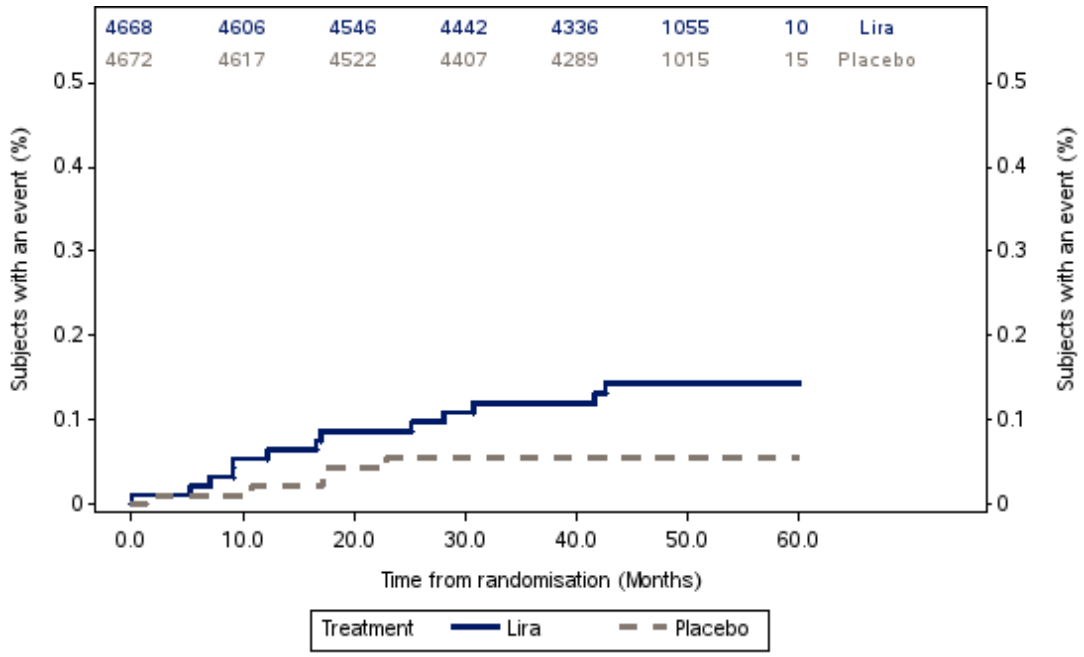


Figure 15 Kaplan-Meier plot of time to first EAC-confirmed malignant pancreatic neoplasm index event – FAS

Breast neoplasms (malignant and pre-malignant)

The incidence of EAC-confirmed breast neoplasms (overall) was comparable between the two treatment groups (liraglutide: 24 events in 24 females [1.4%]; placebo: 22 events in 22 females (1.3%]). In both treatment groups, the majority of the EAC-confirmed breast neoplasms were classified as malignant with no difference between the treatment groups (liraglutide: 21 of 24 events; placebo: 20 of 22 events). The hazard ratio (liraglutide vs placebo) for this event type was 1.06 ($[0.57-1.96]_{95\%\ CI}$) as estimated by a *post hoc* Cox analysis (**Figure 14**). Pre-malignant breast neoplasms accounted for 3 events (in 3 subjects) in the liraglutide group and 1 event (in 1 subject) in the placebo group. Benign breast neoplasms accounted for 1 event (placebo group).

Colorectal neoplasms (malignant, benign and pre-malignant)

EAC-confirmed malignant colorectal neoplasms occurred at comparable incidences (0.6%) for the two treatment groups (**Figure 14**). This is consistent with the lack of GLP-1 R expression in colorectal adenocarcinomas (and in the normal colon except in the myenteric plexus).

Benign events constituted most of the EAC-confirmed colorectal neoplasms in both treatment groups. The proportion of subjects with EAC-confirmed benign colorectal neoplasms was 3.0% and 2.6% in the liraglutide and placebo groups, respectively. The treatment difference seemed to occur at one single time point (at 14 months into the trial) where an increase in the proportion of subjects with events occurred only for the liraglutide group. The prevalence of colorectal adenomas in the background non-diabetes population is high; in a meta-analysis based on 14 studies, the estimated pooled prevalence of colorectal adenomas was 30.2% among subjects of average risk from North America. Therefore any

imbalance in investigations performed in the two treatment groups during the trial could lead to an imbalance in the diagnosis of benign colorectal neoplasms. Considering the well-established gastrointestinal tolerability profile for Victoza, this raises the possibility that gastrointestinal-related side effects in subjects treated with liraglutide may have led to early enhanced detection of benign colorectal neoplasms in this group. In support of this, after month 14 and for the remainder of the trial, events of benign colorectal neoplasms accrued at constant and comparable rates in both treatment groups.

Pre-malignant events were infrequent (3 subjects in the liraglutide group vs 1 in the placebo group). Review of subjects with either EAC-confirmed benign or pre-malignant colorectal neoplasms showed that the majority of the events presented as events of 'low risk for malignant progression' in both treatment groups with more of such events presenting in the liraglutide group compared to the placebo group. In addition, more subjects with events in the liraglutide group compared with the placebo group had a relevant medical history primarily of colon adenomas, and accordingly more subjects with liraglutide had events discovered via colonoscopy performed due to a personal history of colorectal neoplasms.

Neoplasms by insulin use

No notable differences in the pattern of neoplasms (overall or malignant) across subgroups by insulin use (i.e., any insulin use, basal insulin use, or insulin naïve) were observed compared to the total trial population. Data for neoplasms by insulin use did not support an additive or synergetic tumour promoting effect of combination use of liraglutide and any insulin or any basal insulin.

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 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.

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 11**). 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 potantial causal relationship between liraglutide treatment and pancreatitis.

Table 11 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

In trial 3748, hypoglycaemic episodes were reported on a specific hypoglycaemia form and were categorised according to the American Diabetes Association (ADA) classification and to the MAH-definition of confirmed hypoglycaemia: 'severe hypoglycaemia according to the ADA classification and/or an episode with a plasma glucose measurement <3.1 mmol/L (56 mg/dL) with or without symptoms'.

Table 12 provides an overview of hypoglycaemic episodes according to the ADA classification and according to the MAH definition of confirmed 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.

Table 12 Hypoglycaemic episodes by classification – FAS

	Lira				Placebo			
	N	(%)	E	R	N	(%)	E	R
FAS	4668				4672			
PYO	17341				17282			
Hypoglycaemic episodes								
Confirmed	2039	(43.68)	12177	70.2	2130	(45.59)	15756	91.2
ADA	3262	(69.88)	53438	308.2	3177	(68.00)	61937	358.4
Severe	114	(2.44)	178	1.0	153	(3.27)	255	1.5
Documented Symptomatic	2409	(51.61)	26514	152.9	2431	(52.03)	34322	198.6
Asymptomatic	2479	(53.11)	25131	144.9	2360	(50.51)	25823	149.4
Probable Symptomatic	148	(3.17)	300	1.7	148	(3.17)	259	1.5
Relative	433	(9.28)	1315	7.6	429	(9.18)	1278	7.4
Nocturnal hypoglycaemic episodes								
Confirmed	682	(14.61)	2048	11.8	807	(17.27)	3102	17.9
ADA	1279	(27.40)	6755	39.0	1342	(28.72)	8823	51.1
Severe	25	(0.54)	35	0.2	34	(0.73)	55	0.3
Documented Symptomatic	917	(19.64)	4309	24.8	1016	(21.75)	6037	34.9
Asymptomatic	614	(13.15)	2197	12.7	646	(13.83)	2440	14.1
Probable Symptomatic	30	(0.64)	49	0.3	33	(0.71)	73	0.4
Relative	100	(2.14)	165	1.0	109	(2.33)	218	1.3

%: Proportion of subjects, ADA: American Diabetes Association, E: Number of episodes, FAS: Full analysis set, N: Number of subjects, R: Episode rate per 100 observation years
Hypoglycaemic episodes on and after randomisation date and up to visit 15 are included (episodes with a missing date are included).

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.

Antibodies were only measured in US subjects. Less than 1% of subjects in the liraglutide group developed anti-liraglutide antibodies; the antibody response was low (<9 %B/T) and none developed antibodies with *in vitro* neutralising effect against liraglutide. For the subjects who developed anti-

liraglutide antibodies there was no indication of any impact on effectiveness as evaluated by reductions in HbA_{1c}, or on immunogenicity-related AEs.

Safety in special populations

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. An overview of safety by selected intrinsic factor subgroups is shown in **Table 13**.

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 (**Table 13**).

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

The clinical experience with liraglutide has previously been limited in subjects with severe renal impairment. 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 (**Table 14**). 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

Previously there have been no or limited clinical experience with liraglutide in subjects with heart failure NYHA class I, II and III (NYHA class IV was an exclusion criterion in trial 3748). 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.

Table 13 Overview of safety by age subgroups – FAS

	<65 years		65-74 years		75-84 years		≥85 years	
	L	**P**	**L**	**P**	**L**	**P**	**L**	**P**
FAS	2512	2499	1738	1755	401	393	17	25
PYO	9706	9541	6559	6684	1500	1446	57	71
Unit	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**
EAC-confirmed expan. MACE	473/18.8/9.05	503/20.1/10.02	367/21.1/10.22	419/23.9/11.22	104/25.9/11.27	128/32.6/16.26	4/23.5/6.99	12/48.0/23.88
Cardiovascular death	92/3.7/0.95	129/5.2/1.35	93/5.4/1.42	107/6.1/1.60	32/8.0/2.13	34/8.7/2.35	2/11.8/3.49	8/32.0/11.24
All cause death	149/5.9/1.54	187/7.5/1.96	172/9.9/2.62	177/10.1/2.65	54/13.5/3.60	70/17.8/4.84	6/35.3/10.48	13/52.0/18.26
SAEs and non-serious MESIs	1442/57.4/45.89	1412/56.5/45.40	1154/66.4/58.80	1114/63.5/54.27	298/74.3/70.9	292/74.3/86.0	15/88.2/82.1	2184.0/82.9
Confirmed hypoglycaemia	1057/42.08/66.7	1085/43.42/85.9	788/45.34/71.3	856/48.77/102.1	184/45.89/86.9	180/45.80/77.0	10/58.82/103.5	9/36.00/55.6
Severe hypoglycaemia	49/1.95/1.0	65/2.60/1.5	47/2.70/0.9	65/3.70/1.4	16/3.99/1.8	22/5.60/1.7	2/11.76/9.4	1/4.00/1.4
EAC-confirmed nephropathy	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Acute renal failure	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Table 14 Overview of safety by renal function subgroups – FAS

	Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment	
	L	**P**	**L**	**P**	**L**	**P**	**L**	**P**
FAS	1620	1655	1932	1975	999	935	117	107
PYO	6269	6346	7408	7582	3740	3446	405	366
Unit	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**
EAC-confirmed expan. MACE	300/18.5/8.53	315/19.0/9.08	386/20.0/9.71	430/21.8/10.42	223/22.3/10.53	280/29.9/15.47	39/33.3/18.01	37/34.6/16.11
Cardiovascular death	45/2.8/0.72	65/3.9/1.02	94/4.9/1.27	104/5.3/1.37	69/6.9/1.84	92/9.8/2.67	11/9.4/2.71	17/15.9/4.64
All cause death	75/4.6/1.20	104/6.3/1.64	162/8.4/2.19	165/8.4/2.18	119/11.9/3.18	150/16.0/4.35	25/21.4/6.17	28/26.2/7.64
SAEs and non-serious MESIs	895/55.2/43.3	886/53.5/39.0	1206/62.4/51.2	1190/60.3/49.2	704/70.5/65.7	680/72.7/76.8	104/88.9/111.0	83/77.6/112.5
Confirmed hypoglycaemia	576/35.56/53.3	652/39.40/70.2	866/44.82/66.8	901/45.62/87.8	525/52.55/97.3	511/54.65/132.7	72/61.54/143.4	66/61.68/133.7
Severe hypoglycaemia	32/1.98/0.7	34/2.11/0.7	34/1.76/0.6	48/2.43/0.9	41/4.10/2.0	55/5.88/3.5	7/5.98/4.8	15/14.02/7.6
EAC-confirmed nephropathy	53/3.3/0.86	69/4.2/1.10	69/3.6/0.99	112/5.7/1.54	105/10.5/3.24	119/12.7/4.03	41/35.0/12.58	37/34.6/11.74
Acute renal failure	34/2.1/0.6	45/2.7/0.8	78/4.0/1.2	86/4.4/1.2	100/10.0/3.1	108/11.6/3.7	22/18.8/6.9	23/21.5/6.8

Table 15 Overview of safety by NYHA subgroups – FAS

	NYHA I		NYHA II		NYHA III	
	L	**P**	**L**	**P**	**L**	**P**
FAS	179	169	545	546	108	106
PYO	672	626	1982	1984	393	387
Unit	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**	**N / % / R**
EAC-confirmed expan. MACE	52/29.1/13.55	60/35.5/19.80	149/27.3/14.98	174/31.9/16.74	42/38.9/20.87	36/34.0/19.40
Cardiovascular death	13/7.3/1.94	16/9.5/2.55	50/9.2/2.52	54/9.9/2.72	13/12.0/3.31	14/13.2/3.62
All cause death	21/11.7/3.13	22/13.0/3.51	80/14.7/4.04	88/16.1/4.44	18/16.7/4.58	18/17.0/4.66
SAEs and non-serious MESIs	116/64.8/63.1	112/66.3/65.6	338/62.0/64.2	364/66.7/70.1	78/72.2/74.8	67/63.2/68.0
Confirmed hypoglycaemia	91/50.84/85.6	81/47.93/78.1	218/40.00/76.8	237/43.41/86.6	60/55.56/96.4	44/41.51/72.3
Severe hypoglycaemia	7/3.91/1.7	5/2.96/1.0	12/2.20/1.0	33/6.04/2.2	4/3.70/1.3	7/6.60/2.4
EAC-confirmed nephropathy	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Acute renal failure	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Laboratory findings and vital signs

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.

Post marketing experience

From the post-marketing experience, 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).

2.5.1. Discussion on clinical safety

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, diabetic foot ulcer, 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 pancreatic cancer will remain as an Important potential risk in the RMP. 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, 'neoplasm (including melanoma)' is included as an important potential risk in the RMP.

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

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 (lira 16 events, placebo 6 events).

The risk for **pancreatitis** is seen as a potential class-effect of incretin-based therapies. 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 MAH has adjusted the SmPC to include these data from the LEADER trial.

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). The MAH proposes to add cholelithiasis and cholecystitis to section 4.8 of the SmPC, which can be agreed. Somewhat surprisingly, these events were not clearly related to cases of pancreatitis in this trial.

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. The SmPC already includes information regarding hypoglycaemia and the risk when combination with insulin. It is not considered necessary to amend the SmPC. **Diabetic foot ulcer** has not been evaluated as a safety endpoint in previous clinical trials with liraglutide. The proportion of subjects with events of diabetic foot ulcer and the rate of such events were similar in the two treatment groups (Lira: 3.9%, rate 1.5/100PY; placebo: 4.2%, rate 1.7/100PY).

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.

2.5.2. Conclusions on clinical safety

In trial 3748, only SAEs (serious adverse events) and MESIs (medical event of special interest) were systematically collected, and safety in special subgroups. 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. Pancreatic carcinoma was of special interest because of uncertainties of the relation with liraglutide treatment and incretin-based therapies in general raised in the past. Therefore, the increased risk of pancreatic carcinoma in the LEADER trial is of concern.

No difference between treatment groups was seen in the incidence of pancreatitis; however, cholelithiasis was observed more frequently with liraglutide and has been added to section 4.8 of the SmPC.

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.

2.5.3. 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 27.3 is acceptable.

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 27.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• hypoglycaemia in combination with other anti-glycaemic agents • Gastrointestinal AEs • Hyperglycaemia due to discontinuation of insulin • Altered renal function • Allergic reaction • Acute gallstone disease
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Children and adolescents < 18 years • Pregnant and lactating women • Patients with hepatic impairment

Summary of safety concerns	
	• Patients with end-stage renal disease • Congestive heart failure NYHA IV • Off-label use, including abuse due to weight-lowering potential • Drug- drug interaction with warfarin

Pharmacovigilance plan

Ongoing and planned studies in the PhV development plan of liraglutide for glycaemic control

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
MTC registry MTC- 22341 Category 3	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Ongoing	Final report 15 Sep 2026

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypoglycaemia in combination with other anti-glycaemic agents	Dosing recommendations and precautions are included in SmPC Sections 4.2 and 4.4, respectively. In addition, the risk of hypoglycaemia is reflected in Section 4.8 of the SmPC.	None
Gastrointestinal AEs	Dosing recommendations with the objective of improving gastrointestinal tolerability are included in Section 4.2 of the SmPC. Furthermore, Section 4.4 of the SmPC contains precautions and warnings related to the use of Victoza in patients with inflammatory bowel disease and gastroparesis, as well as the risk of Victoza-induced dehydration which may lead to renal impairment/acute renal failure. The risk of gastrointestinal AEs associated with Victoza treatment is addressed in Section 4.8 of the SmPC.	None
Hyperglycaemia due to discontinuation of insulin	A warning that Victoza is not a substitute for insulin is included in Section 4.4 of the SmPC.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Altered renal function	Dosing recommendations for the use of Victoza in patients with renal impairment are included in Section 4.2 of the SmPC. Furthermore, precautions related to the risk of Victoza-induced dehydration which may lead to renal impairment/acute renal failure are implemented in Section 4.4 of the SmPC. The events related to altered renal function and the risk of gastrointestinal AEs associated with Victoza treatment in patients with renal impairment is addressed in Section 4.8 of the SmPC.	None
Allergic reaction	A contraindication related to hypersensitivity to the active substance or any of the excipients is included in Section 4.3 of the SmPC. Furthermore, the risk of allergic reactions associated with Victoza is addressed in Section 4.8 of the SmPC.	None
Acute gallstone disease	The risk of acute gallstone disease associated with liraglutide is addressed in Section 4.8 of the proposed SmPC.	None
Neoplasms (including melanoma)	None	None
Medullary thyroid cancer (C-cell carcinogenicity)	Text on thyroid disease is included in Section 4.4 of the proposed SmPC.	None
Pancreatic cancer	None	None
Children and adolescents <18 years	The lack of data on the use of Victoza in children and adolescents is addressed in Section 4.2 of the SmPC. Additional routine risk minimisation By the legal status of the product; prescription only	None
Pregnant and lactating women	The lack of data supporting the use of Victoza in pregnant and lactating women is reflected in Section 4.6 of the SmPC. Additional routine risk minimisation By the legal status of the product; prescription only	None
Patients with hepatic impairment	Administration of liraglutide in patients with hepatic impairment is addressed in Section 4.2 and 5.2 of the SmPC. Section 4.2 states that no dose adjustment is recommended for patients with mild or moderate hepatic impairment. Victoza is not recommended for use in patients with severe hepatic impairment (see section 5.2).	None
Patients with end-stage renal disease	The lack of data supporting the use of Victoza in patients with end-stage renal disease is addressed in Section 4.2 of the proposed SmPC. Precautions related to the risk of Victoza-induced dehydration which could lead to renal	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	impairment/acute renal failure are implemented in Section 4.4 of the SmPC. The risk of gastrointestinal AEs associated with Victoza treatment in patients with renal impairment is addressed in Section 4.8 of the SmPC.	
Congestive heart failure NYHA IV	A precaution highlighting the lack of data supporting the use of Victoza in patients with congestive heart failure is included in Section 4.4 of the proposed SmPC. The risk of increased heart rate with Victoza is addressed in Section 4.8 of the SmPC.	None
Off-label use including abuse due to weight-lowering potential	The approved indication is described in Section 4.1 of the SmPC. Additional routine risk minimisation By the legal status of the product; prescription only	None
Drug-drug interaction with warfarin	Recommendations for the concomitant use of warfarin and Victoza is included in Section 4.5 of the SmPC.	None

2.7. Update of the Product information

As a consequence of the submission of the LEADER results, the indication in sections 4.1 of the SmPC has been modified. Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC have as well been updated. The Package Leaflet and Labelling (sections 17 and 18) are updated in accordance.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- The changes to the patient leaflet are not significant (ref. Guideline on the readability of the labelling and package leaflet of medicinal products for human use, January 2009)
- a user consultation was made for liraglutide during the marketing authorization application approved in January 2009
- QRD test was performed by EMA as part of the renewal procedure, approved in April 2014.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Liraglutide, as Victoza 1.2 and 1.8 mg/day, is indicated for the treatment of type 2 diabetes mellitus.

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

In this type 2 variation, the MAH seeks to extend the indication with prevention of Major Adverse Cardiovascular Events (MACE: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus at high cardiovascular risk, as an adjunct to standard of care therapy.

In addition, the MAH proposes to remove the limitation that monotherapy is only allowed in subjects for whom use of metformin is considered inappropriate due to intolerance or contraindications, i.e. first-line monotherapy.

Furthermore, some other changes to section 4.2, 4.4, 4.8 and 5.1 of the SmPC are proposed.

3.1.2. Available therapies and unmet medical need

There are several classes of medicinal products for the treatment of T2DM, with different mechanism of action. All products have been shown to reduce blood glucose level, and to improve HbA1c. However, until recently only metformin had been shown to reduce macrovascular events, albeit only in a single trial with a limited number of subjects. For SUs it has been debated for a long time whether possible adverse cardiovascular effects can be excluded; no CV outcome trials have been performed for SUs. Rosiglitazone, a TZD, has been associated with an increased CV risk. CV-outcome trials for DPP4 inhibitors and lixisenatide, another GLP-1 RA, did not show any CV benefit. Recently, empagliflozin, an SGLT2-inhibitor, has shown to be superior compared to placebo in reducing 3-point MACE in a CV outcome trial.

Based on the extensive therapeutic experience including a well-understood safety profile, metformin is currently recommended as first-line treatment for all patients with T2DM, unless contraindications apply (most notably, GFR < 30 ml/min).

3.1.3. Main clinical study

In support of the application, results of the LEADER trial (3748) were submitted. 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.

3.2. Favourable effects

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 $[0.78; 0.97]_{95\% \text{ CI}}$ was statistically significant and in favour of liraglutide. 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 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 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.

3.3. Uncertainty in the knowledge about favourable effects

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]). No differences were found for "continuous renal replacement therapy" and "doubling creatinine". Number of deaths due to renal disease were 8 and 5 for liraglutide and placebo, respectively. In contrast, the HR for retinopathy was above 1 (HR 1.15[0/87;1.52])(see below).

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 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 including sex, age, BMI, race, ethnicity, HbA1c, diabetes duration, heart failure status, and antidiabetic therapy (including antidiabetic drug naïve subjects). 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**. US participants had a longer history of T2DM, higher body weight, higher baseline HbA1c, and lower SBP and DBP. Furthermore, more subjects were of Black or African American origin and fewer subjects from the US were insulin naïve,

fewer used non-insulin antidiabetic medication at baseline whereas more subjects in the US were on lipid lowering drugs and diuretics at baseline compared to subjects outside US. In addition, the mean proportion of time on trial drug was lower in the US (0.73%) than in the non-US population. The MAH blames the reduced effect to a lower exposure to trial drug in the US population. This is supported by post hoc sensitivity analysis showing that the effect of liraglutide in MACE in On-treatment (and On treatment+30 days) US patients (On treatment US-population: HR: 0.89 [0.69;1.14] and On treatment+30 days US-population: HR: 0.89 [0.70;1.12]) was similar to the results from the primary analysis (HR: 0.87 [0.78;0.97]).

To explore the potential relationship between risk of MACE or cardiovascular death and body weight at baseline, MACE and cardiovascular death were analysed by baseline body weight quartiles and forest plots were made to illustrate first MACE and cardiovascular death across these four groups. The hazard ratio for time to first MACE or cardiovascular death was similar in subjects within the lowest and highest quartiles of baseline body weight. Thus, the results do not support an association between baseline body weight and risk of MACE or cardiovascular death. Furthermore, the tests for interaction between treatment and baseline weight quartiles were not statistically significant. The data on body weight are also supported by the results of the pre-specified analyses of MACE by BMI at baseline.

A number of post-hoc analyses were performed for the **cardiovascular risk groups**. These did not reveal an explanation for the observed difference.

Mean HbA1c at baseline was 8.7%. Subgroup analyses showed that there was no interaction with treatment effect and HbA1c. However, this was performed for two classes of HbA1c only (<8.3, ≥8.3%). For external validation of the effects, more detailed analyses according to a range of HbA1c classes were needed. The MAH has performed these analyses. Results do not indicate an association between baseline HbA1c and CV risk reduction with liraglutide.

Mean estimated glomerular filtration rate (eGFR) per MDRD was 80.4 ml/min/1.73m^2, despite the fact that the trial included >200 subjects with severe renal impairment. For external validation of the effects, more detailed analyses according to a range of eGFR classes were needed. The MAH presented the data. A beneficial effect was observed in all subgroups of renal function with the exception of patients with eGFR 75-<90 ml/min/1.73 m^2. It is agreed that 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.

A total of 360 subjects (3.9%) did not receive glucose lowering drugs at baseline and thus can be considered to be on a liraglutide or placebo **monotherapy** during the trial. MACE was in favour of liraglutide (0.74 [0.42-1.30]), although confidence interval was wide.

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.

In the LEADER trial, liraglutide or placebo was added to standard care. At baseline, some imbalances were present in use of cardiovascular medication: 56.8% of patients in the liraglutide group used beta-blockers versus 54.1% in the placebo group; percentages for use of angiotensin-converting–enzyme inhibitors were 51.8% vs. 50.3%, for statins 72.9% vs. 71.4%, and platelet-aggregation inhibitors 68.7% vs. 66.8%. The MAH has performed sensitivity analyses of time to first MACE with each of the 4 cardiovascular medications included as covariates. The results showed that HRs were similar to the primary HR, and thus it is unlikely that primary results are biased by differences in cardiovascular medication.

In total, 111 subjects were randomised in error due to violation of one or more inclusion, exclusion or randomisation criteria. The most common reasons for randomisation in error were violations of the inclusion criterion for CVD risk factors, use of disallowed medication and exclusion criterion for malignant neoplasm. However, an analysis excluding the 111 protocol violations indicated that the primary endpoint was not affected by these protocol violations.

3.4. Unfavourable effects

The most frequently reported AEs with the current indication of Victoza 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. MESIs discussed are: neoplasms, thyroid disease, pancreatitis, acute gallstone disease, hypoglycaemia, diabetic foot ulcer, 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 (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).

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: lira 70.2 episodes/100PY, placebo 91.2 episodes/100PY; ADA overall lira 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. The SmPC already includes information regarding hypoglycaemia and the risk when combination with insulin. 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.

3.5. Uncertainty in the knowledge about the unfavourable effects

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 (combined malignant and premalignant events). 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 Table

Table 16 Effects Table for liraglutide in the prevention of major cardiovascular events. (data cut-off:

Effect	Short Description	Unit	Lira	Pla	Uncertainties / Strength of evidence
Favourable Effects					
MACE-3	time to first occurrence of cardiovascular death,	% of patients	13.0	14.9	Primary endpoint

Effect	Short Description	Unit	Lira	Pla	Uncertainties / Strength of evidence
	non-fatal myocardial infarction (incl. silent MI) or non-fatal stroke.	with event			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)
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

3.7. Benefit-Risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The LEADER trial was a well-designed and conducted CV outcome trial in patients with very high risk of CV events. Both liraglutide and placebo were added to standard of care for treatment of cardiovascular disease and T2DM. A statistically significant reduction in 3-point MACE was found in the liraglutide group, indicating a 13% decrease in events, which is considered clinically relevant. All three components contributed to the effect, most notably CV death.

Expanded MACE was a secondary endpoint and was also reduced in favour of liraglutide. The reduction of 12% is considered clinically relevant. No difference was seen for the component hospitalisation due to unstable angina pectoris. This component is not as hard an outcome as death, MI or stroke, and therefore less important.

The risk for all-cause death was significantly reduced by 15%, which was driven by a reduction in CV-death with a neutral effect on non-CV death.

These data indicate that liraglutide can reduce 3-point MACE, and especially CV-death in T2DM patients with established CV disease. Until recently, only metformin was considered to have demonstrated a positive effect on macrovascular outcomes; Recently data for empagliflozin (EMEA/H/C/002677/II/0014) has shown a reduction of CV events in T2DM patients with established cardiovascular disease.

This type 2 variation is based on the results of a single, but large pivotal clinical trial.. The primary endpoint and the mortality data are considered reliable; however for exploratory results the effect of chance findings is an important concern. For subjects >60 years with risk factors only, no positive effect on MACE could be detected. Thus there is no full consistency in results.
In addition, the effect of liraglutide seems to be diminished in patients with normal renal function, based on eGFR calculations per MDRD or CKD-EPI.

The trial was designed to achieve optimal treatment in both treatment groups, and investigators were encouraged to administer best-practice standard of care treatment in addition to trial product. For glycaemic control HbA1c target was <7%. During the trial, HbA1c data showed a greater reduction in HbA1c in the liraglutide group compared to placebo. It can be questioned whether encouragement of investigators has been intensive enough. This difference occurred in spite of the fact that in the placebo group treatment for glucose control was intensified more than with liraglutide. In the liraglutide group treatment was accompanied with fewer hypoglycaemic episodes. This might indicate that treatment of subjects in the placebo group was hampered by the risk of hypoglycaemia.

Baseline HbA1c and eGFR were rather high. To clarify whether the possible positive effects of liraglutide are also applicable for subjects with lower values, the MAH was required to perform more detailed analyses over a range of classes of hyperglycaemia and renal impairment. These analyses did not indicate an association between baseline HbA1c or eGFR on the one hand and CV outcomes on the other.

Microvascular events were analysed as exploratory endpoints. The positive effects of liraglutide on nephropathy were mainly due to a reduction in new onset of macroalbuminuria. The risk reduction of 22% is potentially clinically relevant.

However, there was an increase in retinopathy. 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 EAC-confirmed diabetic retinopathy was observed. 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 North America, and in particular the US population, there was no decrease in 3-point MACE. There were some baseline differences and a reduced duration of actual treatment with trial product that might explain the difference in effect between the US population and the European population or the rest of the world. It was suggested that body weight could have influenced results, as pharmacokinetics of liraglutide are affected by body weight, and body weight was higher in the US population. However, analyses by baseline body weight, change in body weight, baseline BMI did not suggest an association with CV outcomes. The most plausible reason seems a lower exposure to trial drug in the US population, due to discontinuation of study drug. For the European patient population, this issue is of less importance, as for Europe the reduction in 3-point MACE was statistically robust and clinically relevant.

A numerical increase was observed 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 (liraglutide: 108 vs. placebo: 106) and expanded MACE events (liraglutide: 82 vs. placebo: 75); in the group with NYHA III at baseline. 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.

A reasonable number of elderly subjects, subjects with severe renal impairment and subjects with more advanced stages of heart failure were included in the study. A positive effect of liraglutide on 3-point MACE was observed for all subgroups, which is clinically relevant. Also, glycaemic control in these subgroups was consistent with the rest of the population. The MAH claimed an unrestricted monotherapy indication. The main reason for a restricted monotherapy indication has been that only metformin had demonstrated a CV benefit in T2DM, in addition to comparably more extensive long-term safety experience. The LEADER trial included only a limited number of subjects (360, 3.9%; 194 on liraglutide) who were drug naïve at baseline. Glycaemic efficacy and effects on MACE were comparable to the overall population, although results were not statistically significant due to the low number of subjects and events. However, the LEADER trial only included individuals at high cardiovascular riskwhich do not adequately represent the target population for a first line indication. Furthermore, the LEADER trial did not show a positive effect on MACE in subjects without established cardiovascular disease, where liraglutide was associated with a *higher* risk, although not statistically significant, for cardiovascular events (HR 1.20 [0.86 – 1.67]). Therefore, experience in the target population for unrestricted monotherapy is very limited, i.e. number of subjects in the monotherapy trial submitted with the MAA (N=251 for liraglutide 1.2 mg, N=246 for liraglutide 1.8 mg), in addition to very limited information on cardiovascular effects..

At baseline, some imbalances between treatment groups were present in the use of cardiovascular medication. There were more users of cardiovascular medication (56.8%) in the liraglutide group, compared to the placebo group (54.1%). However, there were also slightly more patients with established CV disease in the liraglutide group (82.1% vs 80.6% in the placebo group). However, it is unlikely that primary results are biased by differences in cardiovascular medication.

The mechanism behind the cardiovascular benefit with liraglutide is unclear. The MAH suggest a direct effect of Liraglutide on MACE. However, liraglutide has been shown to be 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. The Applicant has discussed possible mechanisms behind the beneficial cardiovascular effect of liraglutide. Overall, none of the presented data is convincing but associated with different weaknesses and short-comings. 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.

Overall, there were no differences between treatment groups in the proportion of subjects with neoplasms. Especially, there were no differences in the incidence of breast cancer, colorectal neoplasms or thyroid neoplasms. These are important data, as neoplasms in general are considered as important potential risks. Questions on breast cancer were raised in the initial application for the use of liraglutide 3.0 mg/day as Saxenda for weight management.

However, a HR >1 was seen for pancreatic cancer. Pancreatic carcinoma was of special interest in this trial because of uncertainties of the relation with liraglutide treatment and incretin-based therapies in general raised in the past. Pancreatic cancer is seen as an important potential risk. The LEADER trial was not designed nor powered to demonstrate a treatment difference in relation to neoplasm subtypes, but these uncertainties about the risk have not been removed. More cases of malignant melanoma were seen with liraglutide compared to placebo. Malignant melanoma has not been identified as a risk in earlier trials or in the two epidemiological studies performed post-marketing. However, in the LEADER trial a difference occurred from month 18. Trials in the past could have been not long enough to reveal a difference. MAH answered 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 cannot be confirmed or excluded. However, considering the importance of the disorder, monitoring malignant melanoma through routine pharmacovigilance activities only, as proposed by the MAH, seems not sufficient and therefore 'neoplasm (including melanoma)' is included as an important potential risk in the RMP.

3.7.2. Balance of the benefits and risks

The pivotal study (EX2211-3748; LEADER) 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.

The indication proposed by the MAH was defining two T2DM populations, one large (T2DM) and one more restricted (patients with T2DM and established cardiovascular disease), aiming at two different goals of treatment (glycaemic control and prevention of cardiovascular events). Important in this regard is the view that the cardiovascular benefit appears to be not only explained by the glucose lowering effect of liraglutide. The MAH has discussed possible mechanisms behind the beneficial cardiovascular effect of liraglutide. Overall, none of the presented data is convincing. Instead, the data were associated with different weaknesses and short-comings. 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.

With regards to the indication claimed by the MAH, the CHMP is of the view that the patient population eligible for treatment with liraglutide should be mentioned, i.e. patients with T2DM, without mentioning any goal of treatment, i.e. neither improvement of glycaemic control, nor prevention of MACE. This means that the wording of the indication will refer to the patient population for whom treatment with liraglutide is intended, i.e. patients with T2DM, and the information on the LEADER study, will be included in section 5.1. The CHMP considers both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality an integral part of the treatment of T2DM, which could best be expressed in a single indication for the treatment of T2DM. Therefore, a separate cardiovascular prevention indication was not considered approvable. However, the CHMP considered the strengthening of the wording of the indication in section 4.1 of the SmPC by deleting “improvement of glycaemic control” from section 4.1 of the SmPC (as this restriction does no longer adequately reflect the demonstrated effects for liraglutide) together with the description of the benefits with liraglutide regarding macrovascular and microvascular events, as assessed in this application, in section 5.1 of the SmPC. The wording “treatment of T2DM” is considered more relevant as it encompasses both glycaemic control and results on clinical outcomes such as CV complications, with a reference to section 5.1 of the SmPC.

With respect to the target population, the CHMP was of the view that the population studied in the LEADER trial (i.e. T2DM patients with high CV risk), is a sub-population of the T2DM population already approved for Victoza. Since both the target population and the treatment effect documented in the LEADER trial were considered to be covered by the overarching “treatment of type 2 diabetes” indication, a separate claim in section 4.1 of the SmPC specific to the prevention of cardiovascular events could not be accepted. All patients that would benefit from the treatment with liraglutide are covered by the indication as worded in the section 4.1 of the SmPC that resulted from this variation procedure.

The MAH also applied for an unrestricted monotherapy. However, the experience with liraglutide in that target population, i.e. newly diagnosed subjects with T2DM in need of a first treatment, is considered very limited, including very limited information on cardiovascular effects. Therefore, an unrestricted monotherapy was not granted.

3.7.3. Additional considerations on the benefit-risk balance

The final wording for the modified indication in SmPC section 4.1 as agreed by the CHMP is as follows (new text shown in bold; removed text as strikethrough):

"Victoza is indicated for **the** treatment of adults with **insufficiently controlled** type 2 diabetes mellitus ~~to achieve glycaemic control~~ as **an adjunct to diet and exercise**~~:~~

- **as** ~~M~~**m**onotherapy ~~When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of~~ **when** metformin is considered inappropriate due to intolerance or contraindications.

~~Combination therapy~~

~~In combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4 and 5.1 for available data on the different combinations).~~

- **in addition to 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."

3.8. Conclusions

The overall B/R of Victoza is positive.

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, IIIA and IIIB

Update of section 4.1 of the SmPC for Victoza based on the findings of the study LEADER (EX2211-3748), which constitutes the data set for the application; sections 4.2, 4.4, 4.7, 4.8, 5.1 and 6.5 of the SmPC are also updated to add warnings and update the safety information based on the findings of the LEADER (EX2211-3748) clinical study results. The Package Leaflet and Labelling (sections 17 and 18) are updated in accordance. Updates to the liraglutide RMP based on the LEADER study results are also proposed: RMP Version 27.3 was agreed.

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

Update of section 4.1 of the SmPC for Victoza based on the findings of the study LEADER (EX2211-3748), which constitutes the data set for the application; sections 4.2, 4.4, 4.7, 4.8, 5.1 and 6.5 of the SmPC are also updated to add warnings and update the safety information based on the findings of the LEADER (EX2211-3748) clinical study results. The Package Leaflet and Labelling (sections 17 and 18) are updated in accordance. Updates to the liraglutide RMP based on the LEADER study results are also proposed: RMP Version 27.3 was agreed.

Summary

Please refer to the published Assessment Report H-1026-II-42-AR.