28 April 2016
EMA/CHMP/351673/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Victoza

International non-proprietary name: liraglutide

Procedure No. EMEA/H/C/001026/II/0038

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

Δ	change from baseline
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
BL	baseline
BMI	body mass index
BW	body weight
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
Cr_{CL}	creatinine clearance
CT	computerised tomography
CTR	clinical trial report
DPP-4	dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ETD	estimated treatment difference
EU	European Union
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSG	fasting serum glucose
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
HbA_{1c}	glycosylated haemoglobin
Hypo	hypoglycaemia
ITT	intent-to-treat
LEAD	Liraglutide Efficacy and Action in Diabetes
LEAN	Liraglutide Efficacy and Action in NASH
Lira	liraglutide
LOCF	last observation carried forward
MAA	marketing authorisation application
MACE	major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MMRM	mixed model for repeated measurements
^{1}H-MRS	magnetic resonance spectroscopy
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NYHA	New York Heart Association
OAD	oral antidiabetic drug
PBO	placebo

PG	plasma glucose
p.o.	*per os*
PP	per-protocol
PSUR	periodic safety update report
PYE	patient years of exposure
RMP	risk management plan
SAE	serious adverse event
SMPG	self-measured plasma glucose
s.c.	subcutaneous(ly)
SD	standard deviation
SGLT-2	sodium-glucose cotransporter 2
SMPG	self-measured plasma glucose
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal
U.S.	United States of America
WM	weight management

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 7 December 2015 an application for a variation.

The following variation was requested:

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

Extension of Indication to include second-line monotherapy in type II diabetes for Victoza; additionally, the MAH updated information related to hepatic impairment. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC are updated with new efficacy and safety information. The Package Leaflet is updated in accordance. Furthermore, the Marketing authorisation holder (MAH) took the opportunity to align the PI with the latest QRD template version 9.1.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0318/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0318/2014 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 and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	7 December 2015
Start of procedure:	3 January 2016
CHMP Rapporteur Assessment Report	18 February 2016
PRAC Rapporteur Assessment Report	18 February 2016
PRAC members comments	9 March 2016
PRAC Outcome	17 March 2016
CHMP members comments	21 March 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 March 2016
Request for supplementary information (RSI)	1 April 2016
CHMP Rapporteur Assessment Report	13 April 2016
PRAC Rapporteur Assessment Report	13 April 2016
CHMP members comments	18 April 2016
Opinion	28 April 2016

2. Scientific discussion

2.1. Introduction

The purpose of this submission is two-fold:

- To extend the current indication for Victoza (liraglutide) to include monotherapy use "when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications"
- To update the current text in the Victoza product information concerning patients with hepatic impairment to state that "no dose adjustment is required for patients with hepatic impairment"

To support these label updates, data from clinical trials with Victoza as well as data from post-marketing sources are included herein. These data have been previously reviewed by the CHMP and no new clinical trial data are included in this submission.

The marketing authorisation for Victoza was originally granted in June 2009. The marketing authorisation application included data from a large, randomised, double-blind, 52-week pivotal phase 3a monotherapy trial (NN2211-1573) comparing liraglutide against the active comparator glimepiride. However, a monotherapy indication for Victoza was not granted at the time of the approval. The main reasons cited by the CHMP for non-approval of the monotherapy indication included the lack of long-term efficacy and safety data for Victoza and the lack of data on the use of Victoza in sensitive populations contraindicated for metformin (e.g., patients with renal or hepatic impairment, recent myocardial infarction or heart failure). A head-to-head comparison of liraglutide monotherapy against metformin monotherapy in a pivotal phase 3a trial was also lacking.

In the six years since Victoza marketing authorisation approval, long-term efficacy and safety data have been collected in clinical trials as well as in the post-marketing setting. In addition to the reduction in HbA_{1c} with a low risk of hypoglycaemia, Victoza has also been shown to improve body weight and systolic blood pressure (MAA Module 2.5, Clinical Overview). In the past few years, several new incretin-based therapies (i.e., DPP-4 inhibitors and GLP-1 receptor agonists) have been approved, providing additional medical/scientific data (including long-term cardiovascular outcome trial data) for these classes of drugs in the management of T2DM.[i,ii,iii,iv,v,vi,vii,viii,ix,x,xi,xii]

More data and argumentation on the benefit/risk of Victoza in sensitive populations have also become available since 2009. A dedicated trial (NN2211-3916) demonstrated that liraglutide treatment was efficacious in subjects with T2DM and moderate renal impairment and did not raise any safety concerns.[xiii] A meta-analysis of intermediate and long-term Victoza trials that included subjects with NYHA class I and II heart failure showed no increase in cardiovascular risk with liraglutide vs. active comparators (metformin, glimepiride, rosiglitazone and insulin glargine) or placebo (EMEA/H/C/001026/II/0024).[xiv]

Liraglutide is metabolised in a manner similar to large proteins (i.e., catabolised by widely distributed proteolytic enzymes) without a specific organ having been identified as a major route of elimination.[xv] The elimination of liraglutide is therefore unlikely to be influenced by changes in hepatic function. A trial (NN2211-1328) examining single dose pharmacokinetics of liraglutide in patients with hepatic impairment showed that liraglutide exposure was decreased by 13−23% in patients with mild-to-moderate and by 44% in patients with severe impairment (Trial 1328 [M 5.3.3.3]). No safety concerns were raised during the trial; liraglutide was well tolerated in all hepatic impairment groups.

The ADA/EASD position statement on the management of hyperglycaemia in T2DM advocates early optimisation of glycaemic control and an individualised approach to treatment.[xvi,xvii] In alignment with these recommendations, several therapeutic drugs in the GLP-1 receptor agonist, DPP-4 inhibitor and SGLT-2 inhibitor classes recently received marketing approvals that included second-line (restricted) monotherapy indications for patients contraindicated/intolerant to metformin (e.g. Eperzan (EPAR 2014), Trulicity (EPAR 2014)).

Outside the EU, Victoza is approved as first-line monotherapy for T2DM in several countries (including Colombia, Mexico, Russia, South Africa, New Zealand, and Brazil) or as second-line monotherapy (U.S. only). No postmarketing safety issues relating to the use of Victoza in monotherapy have been identified by the marketing authorisation holder.

The following data are included in this submission to address: the initial (2009) CHMP concerns regarding the use of Victoza in monotherapy; the CHMP T2DM drug development guideline requirements; the proposed text concerning patients with hepatic impairment for the Victoza product information.

Monotherapy data from the **pivotal phase 3a NN2211-1573** trial evaluating non-inferiority of liraglutide (doses up to 1.8 mg) against the active comparator glimepiride after 52 weeks of treatment (Trial 1573)

Supportive monotherapy data from **three dose-ranging phase 2 trials** with liraglutide:

- Trial NN2211-1571 (a 14-week trial evaluating the efficacy/safety of liraglutide doses up to 1.9 mg against placebo); Trial 1571
- Trial NN2211-1310 (a 12-week trial evaluating the efficacy/safety of liraglutide doses up to 0.75 mg against placebo); Trial 1310
- Trial NN2211-2072 (a 12-week trial evaluating the efficacy/safety of liraglutide doses up to 0.75 mg against metformin); Trial 2072

References to the overall consistent efficacy and safety of liraglutide across the clinical trials have been included together with the positive conclusion of the **EU renewal assessment** during which these data were reviewed; EMEA/H/C/001026/R/025; MAA Module 2.5, Clinical Overview

Brief summary of data demonstrating efficacious and safe **use of Victoza in sensitive populations**:

- Renal impairment
    - Data from Trial 1329 examining single dose pharmacokinetics of liraglutide in subjects with various degrees of renal impairment; Trial 1329
    - Data from Trial NN2211-3916 evaluating the efficacy and safety of liraglutide in subjects with T2DM and moderate renal impairment;[xiii,xviii,xix] Trial 3916; EMEA/H/C/001026/II/0028
    - Results of the pooled analysis of patient-level data of LEAD 1−6 trials evaluating the efficacy and safety of liraglutide in mild renal impairment[xx]
- Hepatic impairment:
    - Description of metabolism and elimination of liraglutide (Victoza Summary of Product Characteristics, Section 5.2)
    - Results of Trial 1328 examining single dose pharmacokinetics and safety of liraglutide in subjects with various degrees of liver impairment; Trial 1328 (M 5.3.3.3)
    - Results of the patient-level meta-analysis of LEAD 1−6 trials, focusing on the safety of 26-week liraglutide treatment on liver parameters in subjects with baseline ALT >ULN to <2.5 times ULN[xxi]

- Results of the LEAD-2 substudy examining the liver-to-spleen attenuation ratio, assessed by CT, during treatment with three doses of liraglutide vs. glimepiride or placebo[xxii]
- Results of the phase 2 trial examining the efficacy and safety of 48 weeks of treatment with liraglutide 1.8 mg vs. placebo in subjects with biopsy-confirmed NASH, with or without T2DM[xxiii,xxiv]
- Results of a study examining the efficacy of liraglutide 1.2 mg in reducing liver fat after 6 months of treatment, as assessed by ^{1}H-MRS, in patients with T2DM with or without hepatic steatosis[xxv]
- Description of the safety evaluation of liraglutide 3.0 mg (Saxenda) in patients with hepatic impairment enrolled in the phase 3 trials of the weight management programme
- The basis for the recommendations for patients with T2DM and hepatic impairment in the product labels of recently approved GLP-1 receptor agonists albiglutide and dulaglutide is discussed; Eperzan EPAR 2014; Trulicity EPAR 2014
- The same argumentation is used for seeking a second-line (restricted) monotherapy indication based on the efficacy/safety profile of Victoza in patients with hepatic impairment as well as for not requiring a dose adjustment in patients with hepatic impairment

- Cardiovascular disease
  - A *post hoc* meta-analysis of intermediate and long-term phase clinical trials (ranging from 26 to 100 weeks) in subjects with T2DM examining the incidence of MACE (various definitions) with liraglutide versus active comparators and placebo. Subjects with NYHA class I and II heart failure were included in these trials; EMEA/H/C/001026/II/0024
  - A pre-specified pooled analysis of 27 trials from the T2DM and weight management clinical development programmes (including five phase 2/3 weight management trials with liraglutide doses up to 3.0 mg) examining the incidence of adjudicated MACE with liraglutide versus comparator (pooled active and placebo)[xxvi]

A brief summary of significant **updates to the Victoza safety profile** since market authorisation

Clinical trials conducted with liraglutide (Victoza) in the T2DM development programme are identified by the project number NN2211 followed by a unique 4-digit trial ID number. Throughout the next sections, these clinical trials will be referred to as 'Trial xxxx' where 'xxxx' is the unique 4-digit number.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

No new clinical data have been submitted in this application. For extensive description of the studies discussed, reference is made to earlier EPARs.

GCP

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

Table 1. Tabular overview of clinical studies referenced in this application

Trial ID **Country** **Type of study** **Type of Subjects** **Treatment duration**	**Design**	**Test Drugs**	**Numbers randomised**
NN2211-1310 DK, NO, SE, GB Efficacy and Safety Type 2 12 weeks	Multi-centre, multi-national randomised, double-blind (open-label glimepiride), parallel-group trial. Placebo and active control(glimepiride)	Liraglutide: Once daily s.c. doses of 0.045 ,0.225, 0.45 ,0.60, or 0.75mg. Glimepiride: Once daily p.o dose of 1-4mg	190 (127/63); Lira 0.045 mg: 26; Lira 0.225 mg: 24; Lira 0.45 mg: 27; Lira 0.60 mg: 30; Lira 0.75 mg: 28; Glimepiride:26 ; Pbo: 29
NN2211-1571 DK, FR, NL, SK Efficacy and Safety Type 2 and healthy 14 weeks	Multi-centre, multi-national randomised, double-blind, placebo controlled, parallel group trial	Liraglutide: Once daily s.c. doses of 0.65, 1.25 or 1.9 mg	Type 2: 163(99/64) Healthy: 12 (9/3) (not dosed); Lira 0.65 mg: 40; Lira 1.25 mg: 42; Lira 1.90 mg: 41; Pbo: 40
NN2211-3916 FR, GB, PL, RU, UA, US Efficacy and Safety Type 2 diabetes and moderate renal impairment 26 weeks	Multi-center, multinational, double-blind, two-armed, parallel-group trial Placebo control	Liraglutide: 6mg/mL 1.8mg s.c., once-daily; dose-escalated for 3-4 weeks in weekly increments of 0.6mg	279; Lira: 140 ; Pbo: 139
NN2211-1573 US, MX Efficacy, safety and population PK Type 2 52 weeks	Multi-centre, randomised, double-blind, parallel-group trial Active control (glimepiride)	Liraglutide: Once daily s.c. doses of 1.2 mg or 1.8 mg (titrated in weekly steps of 0.6 mg) Glimepiride: Once daily p.o. 8 mg/day	745 (371/374); Lira 1.2 mg: 251; Lira 1.8 mg: 246; Glimepiride: 248
NN2211-2072 US Efficacy and Safety Type 2, obese 12 weeks	Multi-centre, randomised, double-blind, parallel-group trial Active control (metformin)	Liraglutide: Once daily s.c. doses of 0.045, 0.225, 0.45, 0.60, or 0.75mg. Metformin: b.i.d. p.o., 1g/day	210 (84/126); Lira 0.045 mg: 37; Lira 0.225 mg: 35; Lira 0.45 mg: 33; Lira 0.60 mg: 34; Lira 0.75 mg: 37; Metformin: 34
NN2211-1328 PL PK Healthy, with normal	Single-centre, open-label, parallel-group trial	Single s.c. dose of 0.75 mg liraglutide	24 (14/10) divided in 4 groups according to hepatic function (healthy: 19; type 2

hepatic function or hepatic impairment Single dose			diabetes: 5)
NN2211-1329 NZ PK Healthy, with normal renal function or renal impairment Single dose	Single-centre, open-label, parallel-group trial	Single s.c. dose of 0.75 mg liraglutide	30 (22/8) divided in 5 groups according to renal function (healthy: 27; type 2 diabetes: 3)

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Phase 2 Trial 1571

Trial design and methods

The primary objective of this monotherapy trial was to assess and compare the efficacy of three doses of liraglutide vs. placebo on glycaemic control (as assessed by HbA_{1c}). Secondary objectives included assessments of other glycaemic control parameters, cardiometabolic parameters, beta-cell function and safety/tolerability.

In this randomised, double-blind, multi-centre, multi-national phase 2 trial, subjects with T2DM previously treated with either diet or OAD monotherapy were randomised 1:1:1:1 to 14 weeks of monotherapy with either s.c. liraglutide (0.65, 1.25 or 1.9 mg/day) or s.c. placebo. The doses of liraglutide investigated in this dose-ranging phase 2 trial helped to guide dose selection for the phase 3 clinical development programme. The trial doses differ from the maintenance doses evaluated in the phase 3 programme and subsequently approved for marketed use as Victoza(1.2 and 1.8 mg).

The primary endpoint was change in HbA_{1c} from baseline after 14 weeks of treatment. The primary and continuous secondary efficacy endpoints (e.g., FPG and body weight) were analysed using an ANOVA model, with treatment and previous anti-diabetic treatment (diet or monotherapy) as explanatory variables and baseline parameter value as a covariate. In this approach, missing data were imputed using the LOCF method. To evaluate the impact of early trial withdrawal, additional repeated measurements analyses were conducted for the primary and secondary efficacy endpoints, which used all available post-baseline measurements for a given parameter.

Of the total 165 randomised subjects, 163 were exposed to trial products and 140 subjects (86%) completed the trial. Trial withdrawal was more common in the placebo group (27.5% of subjects) compared to the liraglutide groups (14.6%, 7.1% and 12.5% of subjects withdrew in the liraglutide 1.9 mg, 1.25 mg and 0.65 mg groups, respectively). The reason behind the higher attrition rate in the placebo group was 'ineffective therapy' (17.5% of subjects). The ITT analysis set (defined as all randomised subjects exposed to ≥1 dose of the trial product) contained a total of 163 subjects.

The four treatment arms were well matched with respect to baseline characteristics except for the male/female ratio, which was generally higher in the active treatment groups (male subjects: 55−73%)

than in the placebo group (male subjects: 48%). Mean subject age ranged 53.8−57.7 years across the four treatment groups. Most subjects were White (98−100%). Mean diabetes duration ranged 5.5−6.9 years; 17−23% of subjects were previously treated with diet while the rest were treated with OAD monotherapy (i.e., sulphonylurea, repaglinide or metformin).

Overview of primary and selected secondary endpoints

In all three liraglutide groups, mean HbA_{1c} decreased by week 8 and remained relatively stable thereafter until week 14 (Figure 1). Throughout the treatment period, the decrease was more pronounced in the liraglutide 1.9 mg and 1.25 mg groups compared to the 0.65 mg group. A gradual increase in mean HbA_{1c} was seen during 14 weeks of treatment with placebo. After 14 weeks of treatment, the change in HbA_{1c} was statistically significantly different between each liraglutide dose group and placebo (Table 2).

Consistent with the results seen for HbA_{1c}, FPG decreased from baseline in all liraglutide groups but increased in the placebo group after 14 weeks of treatment. At the end of treatment, the change in FPG was statistically significantly different between each liraglutide dose group and placebo (Table 2).

A reduction in body weight from baseline was seen in all four treatment groups. The treatment difference between liraglutide and placebo was statistically significant only for the highest liraglutide dose group (1.9 mg); (Table 2).

The repeated measurements analyses of changes in HbA_{1c}, FPG and body weight after 14 weeks of treatment produced results similar to those obtained with the ANOVA analyses.

Figure 1. Mean change from baseline in HbA_{1c} by treatment – ITT population

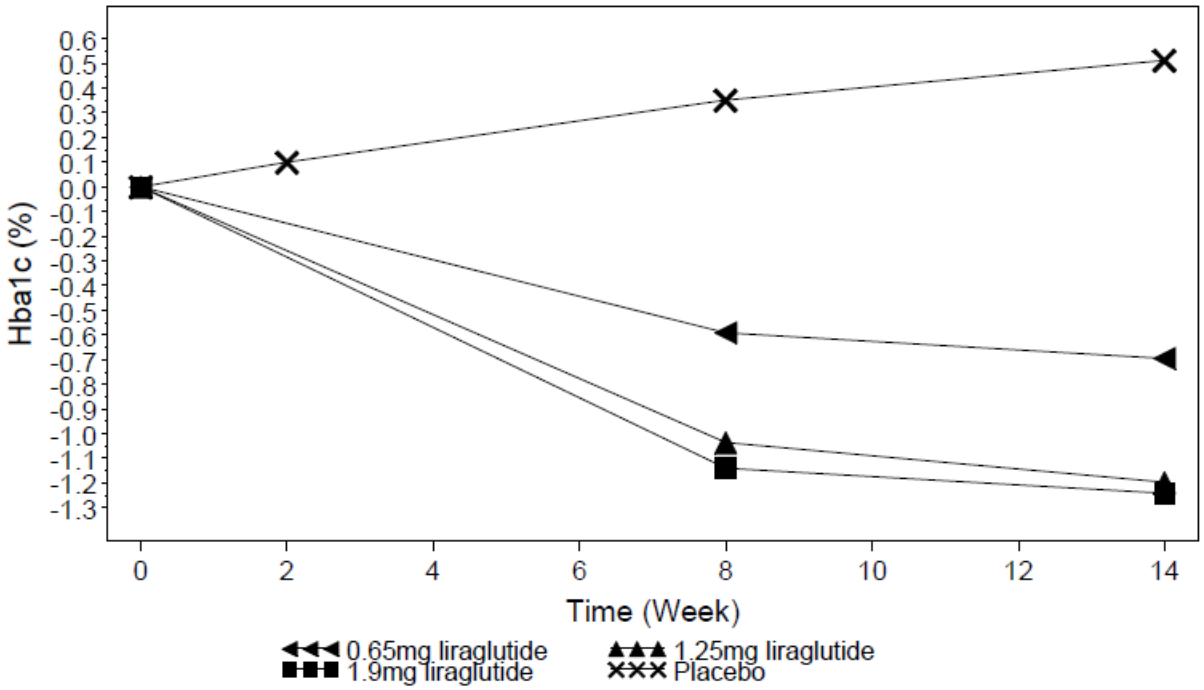


Table 2. Trial 1571 - summary of results for the primary and selected pre-specified secondary endpoints after 14 weeks of treatment – ITT population

Endpoint	Lira 1.9 mg	Lira 1.25 mg	Lira 0.65 mg	Placebo
	N=41	N=42	N=40	N=40
HbA_{1c} (%)				
Baseline	8.48	8.34	8.14	8.20
Δ	-1.45	-1.40	-0.98	0.29
ETD	-1.74	-1.69	-1.27	
(95% CI)	[-2.18;-1.29]	[-2.13;-1.24]	[-1.72;-0.82]	
p-value	<0.0001	<0.0001	<0.0001	
FPG (mmol/L)				
Baseline	12.31	11.93	11.28	11.28
Δ	-3.10	-3.13	-2.43	0.27
ETD	-3.37	-3.40	-2.70	
(95% CI)	[-4.36;-2.38]	[-4.37;-2.43]	[-3.67;-1.72]	
p-value	<0.0001	<0.0001	<0.0001	
Body weight (kg)				
Baseline	88.8	90.4	85.7	86.8
Δ	-2.99	-2.46	-1.52	-1.77
ETD	-1.21	-0.69	0.25	
(95% CI)	[-2.36;-0.06]	[-1.83; 0.46]	[-0.90; 1.41]	
p-value	0.0390	0.2403	0.6643	

Δ=LS mean change from baseline to week 14. All ETD and p-values are between liraglutide and placebo from the ANOVA analysis (LOCF)
Abbreviations: CI = confidence interval; ETD = estimated treatment difference; FPG = fasting plasma glucose; ITT = intention to treat; lira = liraglutide; LS mean = least square mean

No safety issues were raised during the trial. In line with previous observations, the most frequent AEs in the liraglutide groups were of gastrointestinal nature (nausea, diarrhoea and constipation). The safety profile of liraglutide doses up to 1.9 mg in this trial was consistent with the drug safety profile observed across the T2DM development programme.

Phase 2 Trial 1310

Trial design and methods

The primary objective of this monotherapy trial was to establish the dose-response relationship on glycaemic control of five dose levels of liraglutide (referred to in the CTR as NNC 90-1170) and placebo. Secondary trial objectives focused on the comparison of efficacy and safety of liraglutide against glimepiride and the assessment of liraglutide's safety profile.

In this randomised, double-blind, multi-centre, parallel group, placebo-controlled trial with an open-label active comparator arm, subjects with T2DM previously treated with either diet or OAD monotherapy were randomised 1:1:1:1:1:1:1 to 12 weeks of monotherapy with either s.c. liraglutide (0.045, 0.225, 0.45, 0.60 or 0.75 mg), s.c. placebo or p.o. glimepiride. The doses of liraglutide investigated in this dose-ranging phase 2 trial helped to guide dose selection for the phase 3 clinical development programme. The trial doses were relevantly lower than the maintenance doses evaluated in the phase 3 programme and subsequently approved for marketed use as Victoza(1.2 and 1.8 mg).

The primary endpoint (change in HbA_{1c} after 12 weeks of treatment) as well as most continuous secondary endpoints were analysed using a repeated measurements ANOVA, with treatment, visit, and centre as fixed effects and the interaction term (i.e., baseline parameter value by visit) as a covariate.

A total of 193 subjects were randomised into the seven treatment groups and 190 were exposed to treatment. In total, 168 (88%) of subjects completed the trial. The proportion of subject withdrawals was similar between the liraglutide and placebo groups; no subjects withdrew from the glimepiride group. The ITT analysis set (defined as all randomised subjects exposed to ≥1 dose of the trial product) contained a total of 190 subjects.

There were no major differences in baseline characteristics between the treatment groups. Approximately two thirds of subjects in each group were males. Mean age ranged approximately 53−58 years across the groups. Most subjects were Caucasian (96−100% across groups). The majority of subjects were previously treated with OADs (54−93% across groups), while the rest were treated with diet. Mean duration of diabetes ranged 3.4−6.1 years.

As this trial is included here to support the findings of Trial 1571, only the comparison of liraglutide against placebo is discussed below. Also, efficacy data for the two highest doses of liraglutide (0.60 and 0.75 mg) are presented.

Overview of primary and selected pre-specified secondary endpoints

From a baseline of approximately 7.4% in the liraglutide 0.75 mg, 0.60 mg and placebo groups, mean HbA_{1c} decreased in both liraglutide groups, but remained relatively unchanged in the placebo group after 12 weeks of treatment (Table 3 and Figure 2). The changes in HbA_{1c} after 12 weeks of treatment were statistically significantly different between either dose of liraglutide and placebo.

After one week of treatment, reductions in mean FSG levels were seen in the liraglutide 0.75 mg and liraglutide 0.60 mg groups (Figure 2). These reductions were generally sustained up to 12 weeks of treatment. In contrast, FSG remained relatively unchanged during 12 weeks of treatment with placebo. The changes in FSG after 12 weeks of treatment were statistically significantly different between either dose of liraglutide and placebo (Table 3).

No safety issues were raised during the trial. The safety profile of liraglutide doses up to 0.75 mg in this trial was consistent with the drug safety profile observed across the T2DM development programme.

Figure 2. Mean FSG by time and treatment – ITT population

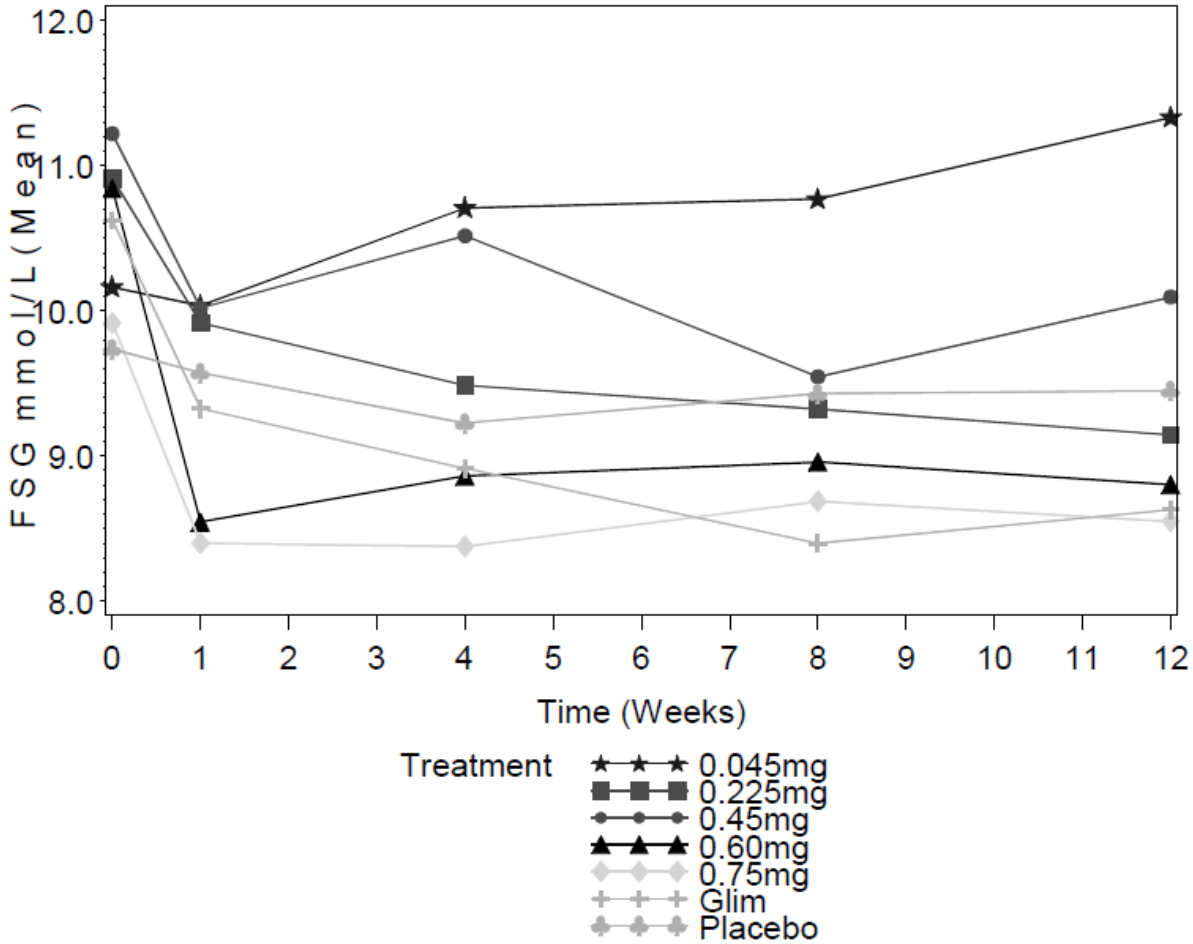


Table 3. Trial 1310 - summary of primary and selected pre-specified secondary endpoints – ITT population

Endpoint	Lira 0.75 mg N=28	Lira 0.60 mg N=30	Placebo N=29
HbA_{1c} (%)			
Baseline	7.4	7.4	7.4
Week 12	6.93	6.98	7.68
ETD (95% CI)	-0.75 [-1.11;-0.39]	-0.70 [-1.06;-0.34]	
p-value	<0.0001	0.0002	
FSG (mmol/L)			
Baseline	9.9	10.8	9.7
Week 12	8.94	8.62	10.76
ETD (95% CI)	-1.82 [-2.80;-0.84]	-2.14 [-3.12;-1.16]	
p-value	0.0003	<0.0001	

Mean values are shown at baseline; mean estimates from the repeated measures analysis are shown at week 12. All ETD are between liraglutide and placebo.
Abbreviations: CI = confidence interval; ETD = estimated treatment difference; FSG = fasting serum glucose; ITT = intention to treat; lira = liraglutide

Phase 2 Trial 2072

Trial design and methods

This was a 12-week, randomised, multi-center, double-blind, parallel-group, double-dummy trial which investigated the dose-response, efficacy, and safety of five doses of liraglutide in subjects with obesity and T2DM who were previously treated with oral hypoglycaemic monotherapy. The trial had an initial screening visit and a four-week metformin run-in period. Subjects were then randomised to receive once daily dosing of liraglutide (0.75 mg, 0.60 mg, 0.45 mg, 0.225 mg, or 0.045 mg s.c.) or metformin 1000 mg p.o. twice daily for 12 weeks. Subjects received liraglutide placebo or metformin placebo to maintain blinding. The doses of liraglutide investigated in this dose-ranging phase 2 trial helped to guide dose selection for the phase 3 clinical development programme. The trial doses differ relevantly from the maintenance doses evaluated in the phase 3 programme and subsequently approved for marketed use as Victoza(1.2 and 1.8 mg).

The primary objective of the trial was to determine the dose-response relationship for body weight of five escalating doses of liraglutide. Secondary objectives included the determination of dose-response with respect to glycaemic parameters (e.g., HbA_{1c} and FPG) and an assessment of safety/tolerability. Continuous efficacy endpoints were analysed using an ANCOVA with treatment (all six arms) effect and corresponding baseline value as a covariate. The PP analysis set (all randomised subjects who received the trial products and had efficacy data at week 12) was the main analysis set used for efficacy endpoint analyses.

Overview of selected secondary endpoints

No statistically significant differences in HbA_{1c} or FPG after 12 weeks of treatment were found between liraglutide and metformin groups at the three highest liraglutide dose levels (0.75 mg, 0.60 mg, and 0.45 mg); (Table 4). No safety issues were raised during the trial. The safety profile of liraglutide doses up to 0.75 mg in this trial was consistent with the drug safety profile observed across the T2DM development programme.

Table 4. Trial 2072 - summary of selected pre-specified secondary endpoints – PP analysis set

Endpoint	Lira 0.75 mg N=32	Lira 0.60 mg N=31[a]	Lira 0.45 mg N=27[b]	Metformin N=29
HbA_{1c} (%)				
Baseline	6.88	6.94	7.01	6.77
Week 12	7.18	7.10	7.19	6.86
LSmean change from BL	0.292	0.160	0.228	0.073
p-value	0.358	0.719	0.534	
FPG (mg/dL)				
Baseline	144.0	145.4	151.9	147.9
Week 12	159.6	145.6	160.9	143.9
LSmean change from BL	14.489	-0.597	10.265	-4.39
p-value	0.050	0.696	0.136	

Observed mean values are shown at baseline and week 12; LS mean change from baseline at week 12 and p-values are from the ANCOVA model. All p-values are between liraglutide and metformin. [a]For FPG, N=30; [b]For FPG, N=29
Abbreviations: BL = baseline; CI = confidence interval; ETD = estimated treatment difference; FPG = fasting plasma glucose; lira = liraglutide; PP = per protocol

2.4.2. Main study

Pivotal Phase 3a Trial 1573 (LEAD-3)

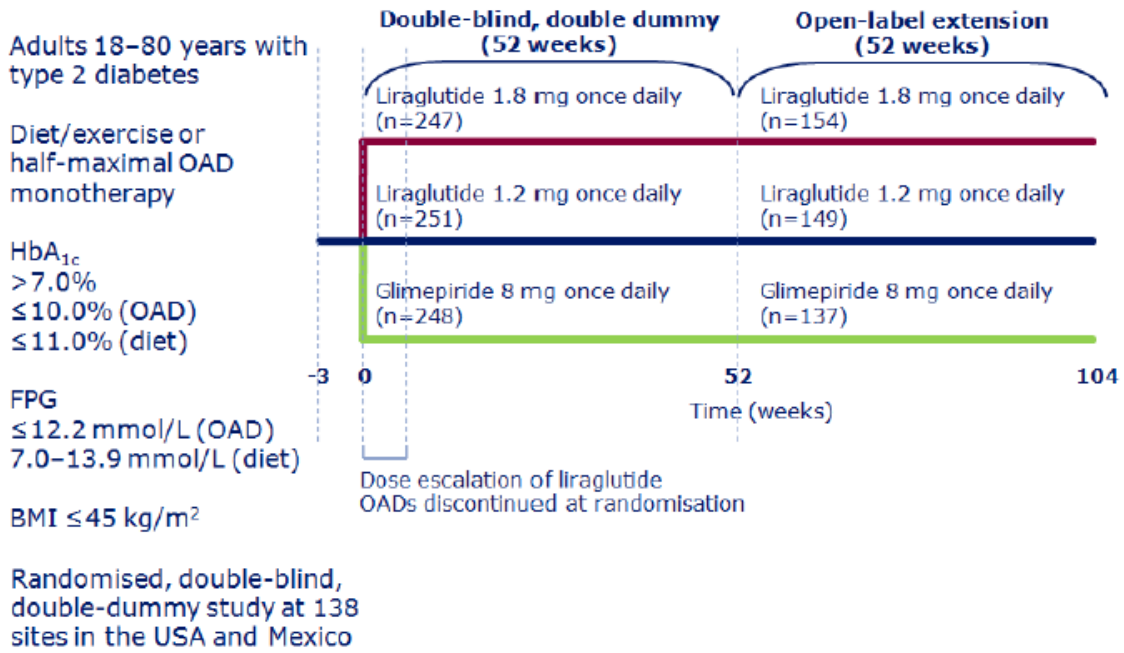
Trial NN2211-1573 was a dedicated monotherapy trial undertaken as part of the pivotal phase 3a development programme for liraglutide in T2DM and was included in the initial MAA.

The purpose of NN2211-1573 was to obtain long-term data on the efficacy and safety of monotherapy with liraglutide in comparison to the sulphonylurea glimepiride. Glimepiride monotherapy is indicated for first-line therapy and is widely used to treat patients with T2DM. The dose of glimepiride was the maximum FDA-approved therapeutic dose at the time of the trial and was considered to be the maximum therapeutic dose for glycaemic control.

Trial design

In this multicentre, double-blind, double-dummy, randomised, parallel-group, active-controlled trial conducted in the U.S. and Mexico, subjects with T2DM previously treated with diet/exercise or with not more than half-maximal OAD monotherapy for at least 2 months were randomised in a 1:1:1 manner to receive liraglutide 1.2 mg, liraglutide 1.8 mg or glimepiride 8 mg treatment for 52 weeks (Figure 3). The 52-week double-blind period was followed by a 52-week open-label extension period, which will not be discussed further here. Liraglutide was started at the once-daily dose of 0.6 mg (s.c. injection) during the first week and the dose was escalated in weekly increments of 0.6 mg to either 1.2 mg or 1.8 mg. Glimepiride was started at a daily dose of 2 mg (p.o.) during the first week and the dose was escalated weekly by 2 mg to a final dose of 8 mg. Placebo products were administered concurrently in a manner mimicking the titration of active compounds to ensure blinding. Subjects were stratified with respect to baseline diabetes treatment (diet/exercise treated vs. OAD monotherapy) and participation in a trial substudy (not discussed further here).

Figure 3. Trial design and key inclusion criteria of Trial 1573, a 52-week double blind trial with a 52-week open-label extension



BMI, body mass index; FPG, fasting plasma glucose; OAD, oral antidiabetic drug

The primary objective of this trial was to assess and compare the efficacy of liraglutide monotherapy versus glimepiride monotherapy on glycaemic control (as assessed by change in HbA_{1c}) after 52 weeks. The primary endpoint was the change in HbA_{1c} from baseline at week 52. Secondary objectives included an assessment/comparison of body weight, beta-cell function parameters, cardiometabolic parameters, incidence of hypoglycaemic episodes and safety/tolerability parameters between the three treatment groups.

Statistical Methods

Sample size

Samples size calculation was based on the following assumptions for the primary endpoint (change from baseline to week 52 in HbA_{1c}): a non-inferiority margin of 0.4%-point and a SD of 1.2%. Assuming a subject dropout of 30%, 234 subjects needed to be enrolled in each treatment arm and 163 subjects needed to complete treatment in each arm in order to have an 85% power to detect a treatment difference between liraglutide and glimepiride at alpha 0.05. This samples size was also judged to be sufficient to detect a difference between liraglutide and glimepiride with respect to body weight (3% of difference in percent change from baseline).

Analysis sets

The ITT and safety analyses sets were identical in this trial and comprised all randomised subjects who were exposed to at least one dose of the trial product.

In addition, the PP analysis set was used for the analysis of the primary endpoint and comprised all exposed subjects who completed the 52-week treatment period with an evaluable HbA_{1c} measurement at weeks 0 and 52. The subjects in the analysis set also had to comply with the following:

- Meet these inclusion criteria: 1) informed consent before any trial-related activities, 2) subjects diagnosed with T2DM and treated with OAD(s) for at least 2 months and 3) inclusion criterion defining limits of HbA_{1c}. For inclusion criterion regarding HbA_{1c} level at screening, an extended range of ± 0.25% was allowed.
- Not meet any withdrawal criteria and meet all randomisation criteria (an extended range of ±0.5 mmol/L was allowed for the FPG randomisation criterion)

Analyses of efficacy and safety endpoints

Consistent with the primary hypothesis of non-inferiority between liraglutide and glimepiride in terms of glycaemic control after 52 weeks of treatment, the primary endpoint of change in HbA_{1c} after 52 weeks was first tested for non-inferiority and then for superiority as a one-sided hypothesis with a significance level of 2.5%.

The change from baseline in HbA_{1c} (%) was analysed using an ANCOVA model with treatment, country and previous anti-diabetic treatment (strata) as fixed effects and baseline HbA_{1c} value as a covariate. The primary endpoint was analysed for both the ITT and the PP set; for comparison of superiority, the PP analysis was considered to be supportive. Post-baseline missing values were imputed using the LOCF approach in the ITT analysis.

Non-inferiority of liraglutide to glimepiride was to be concluded if the upper bound of the 95% CI for the difference between treatments was below 0.4%; superiority was to be concluded if the upper bound of

the 95% CI was below 0%. To protect against the family-wise type I error, a hierarchical testing scheme was used:

- Initially, non-inferiority of liraglutide 1.8 mg compared to glimepiride was tested. Superiority of liraglutide 1.8 mg over glimepiride was only tested after non-inferiority has been confirmed
- Once non-inferiority of the 1.8 mg dose to glimepiride was confirmed, then non-inferiority of the 1.2 mg dose was evaluated. Superiority of the 1.2 mg dose over glimepiride was only tested if both doses were non-inferior to glimepiride and the 1.8 mg dose was superior

Continuous secondary efficacy endpoints were analysed with an ANCOVA model similar to that used for the analysis of the primary endpoint, with the baseline value of the parameter in question as a covariate. Missing values were imputed using the LOCF approach.

HbA_{1c} target responder endpoints were analysed by logistic regression with treatment as a fixed effect and baseline HbA_{1c} value as a covariate. Missing values were imputed using the LOCF approach.

Hypoglycaemic episodes were analysed using a generalised linear model, assuming that the number of hypoglycaemic episodes per subject follows a negative-binomial distribution. The model included treatment and country as fixed effects.

Adverse events were summarised using descriptive statistics.

Subject Disposition

A total of 746 subjects were randomised in this trial (Table 5). Overall, one subject (in the liraglutide 1.8 mg group) was not exposed to treatment and was therefore excluded from the ITT analysis set. The percentages of subjects who completed the 52-week trial were higher in the liraglutide treatment groups (liraglutide 1.8 mg: 70.0%, liraglutide 1.2 mg: 64.5%) compared to the glimepiride treatment group (61.3%). The primary reasons for trial withdrawal in the liraglutide treatment groups were ‘other’ reasons and ‘adverse events’. In the glimepiride treatment group, the primary reasons for trial withdrawal were ‘other’ reasons and ‘ineffective therapy’.

Table 5. Subject disposition

	Lira1.8 N (%)	Lira1.2 N (%)	Glimepiride N (%)	All N (%)
Randomised	247 (100.0)	251 (100.0)	248 (100.0)	746 (100.0)
Exposed	246 (99.6)	251 (100.0)	248 (100.0)	745 (99.9)
Withdrawn	74 (30.0)	89 (35.5)	96 (38.7)	259 (34.7)
Adverse Events	18 (7.3)	25 (10.0)	15 (6.0)	58 (7.8)
Ineffective therapy	9 (3.6)	15 (6.0)	25 (10.1)	49 (6.6)
Non-compliance with protocol	11 (4.5)	11 (4.4)	5 (2.0)	27 (3.6)
Other	36 (14.6)	38 (15.1)	51 (20.6)	125 (16.8)
Completers	173 (70.0)	162 (64.5)	152 (61.3)	487 (65.3)
Safety Analysis Set	246 (99.6)	251 (100.0)	248 (100.0)	745 (99.9)
ITT Analysis Set	246 (99.6)	251 (100.0)	248 (100.0)	745 (99.9)
PP Analysis Set	154 (62.3)	142 (56.6)	130 (52.4)	426 (57.1)

Subject 277001 was randomised to 1.8mg liraglutide treatment, and discontinued from study due tonon-compliance without receiving any study drug. This subject was added to the “withdrawn” class.

Exposure

The number of subjects and exposure to trial products is summarised in Table 6. Consistent with the higher withdrawal in the glimepiride group, total exposure and duration of treatment were shorter in the glimepiride group compared to both liraglutide groups.

Table 6. Summary of exposure – ITT population

	Lira1.8	Lira1.2	Glimepiride
Duration of Treatment (days)			
N	246	251	248
Mean (SD)	289.2 (128.4)	279.6 (130.8)	273.7 (126.1)
Median	362.0	362.0	360.0
Min ; Max	2.0 ; 390.0	1.0 ; 383.0	3.0 ; 387.0
Total exposure in subject years *	194.8	192.2	185.9

* One subject year equals 365.25 days.

Demographics and other baseline characteristics

Screening/baseline demographics and characteristics were generally comparable between the three treatment groups (Table 7). In total, ~50% of trial subjects were male and the mean subject age was 53.0 years. The majority of randomised subjects were White (77.5%) and of non-Hispanic or Latino ethnicity (65.0%). Mean BMI was in the obese range (33.1 kg/m^2). At baseline, approximately one-third of the subjects had been previously treated for T2DM with diet/exercise and the rest with OAD monotherapy. The average duration of diabetes was 5.4 years.

Table 7. Screening and baseline characteristics of all randomised subjects

	Lira1.8	Lira1.2	Glimepiride	All Randomised
All Randomised Subjects	247	251	248	746
Sex, N (%)				
Male	121 (48.99)	117 (46.61)	133 (53.63)	371 (49.73)
Female	126 (51.01)	134 (53.39)	115 (46.37)	375 (50.27)
Age (years)				
Mean (SD)	52.0 (10.8)	53.7 (11.0)	53.4 (10.9)	53.0 (10.9)
Min ; Max	22.0 ; 79.0	26.0 ; 78.0	19.0 ; 77.0	19.0 ; 79.0
Ethnicity, N (%)				
Hispanic or Latino	87 (35.22)	81 (32.27)	93 (37.50)	261 (34.99)
Not Hispanic or Latino	160 (64.78)	170 (67.73)	155 (62.50)	485 (65.01)
Race, N (%)				
White	186 (75.30)	200 (79.68)	192 (77.42)	578 (77.48)
Black or African Amer	30 (12.15)	34 (13.55)	30 (12.10)	94 (12.60)
Native Hawaiian/Pacific Isl	2 (0.81)	0 (0.00)	0 (0.00)	2 (0.27)
American Indian- Alaska Nat	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Asian	12 (4.86)	5 (1.99)	9 (3.63)	26 (3.49)
Other	17 (6.88)	12 (4.78)	17 (6.85)	46 (6.17)
Screening BMI (kg/m^2)				
Mean (SD)	32.8 (6.3)	33.2 (5.6)	33.2 (5.6)	33.1 (5.8)
Min ; Max	20.8 ; 45.5	20.9 ; 47.1	21.1 ; 46.9	20.8 ; 47.1
Duration of Diabetes (years)				
Mean (SD)	5.3 (5.1)	5.2 (5.5)	5.6 (5.1)	5.4 (5.3)
Min ; Max	0.2 ; 25.7	0.2 ; 40.3	0.2 ; 35.6	0.2 ; 40.3
Previous Anti-diabetic Treatment, N (%)				
Diet/Exercise	87 (35.22)	91 (36.25)	94 (37.90)	272 (36.46)
Monotherapy	160 (64.78)	160 (63.75)	154 (62.10)	474 (63.54)
Baseline HbA1c (%)				
Mean (SD)	8.19 (1.08)	8.18 (1.05)	8.23 (1.06)	8.20 (1.07)
Min ; Max	6.20 ; 11.50	5.90 ; 11.70	4.90 ; 11.20	4.90 ;11.70
Baseline weight (kg)				
Mean (SD)	92.6 (20.7)	92.1 (19.0)	93.3 (19.0)	92.6 (19.6)
Min ; Max	49.9 ; 163.3	50.3 ; 154.0	46.7 ; 159.2	46.7 ;163.3
Baseline FPG (mmol/L)				
Mean (SD)	9.5 (2.6)	9.3 (2.6)	9.5 (2.6)	9.5 (2.6)
Min ; Max	4.5 ; 20.5	4.9 ; 18.2	3.9 ; 22.9	3.9 ; 22.9

BMI: body mass index, FPG: fasting plasma glucose, SD: standard deviation
All parameters are presented at screening except for HbA_{1c}, weight and FPG, for which baseline values (at randomisation/week 0) are provided.

Efficacy endpoints

HbA_{1c} – primary endpoint

Mean HbA_{1c} levels decreased during the initial 8 weeks of treatment and remained relatively stable thereafter in all three treatment groups up to week 52 (Figure 4). Throughout the treatment period, the reduction in HbA_{1c} was more pronounced in the liraglutide groups than in the glimepiride group.

From a baseline of approximately 8.2% in each treatment group, mean HbA_{1c} decreased by 1.14% with liraglutide 1.8 mg, 0.84% with liraglutide 1.2 mg and by 0.51% with glimepiride after 52 weeks of treatment (Table 8). ITT analysis results demonstrated that treatment with either dose of liraglutide (1.2 or 1.8 mg) was superior to treatment with glimepiride, and there was also a significantly greater decrease in HbA_{1c} values for liraglutide 1.8 mg compared to liraglutide 1.2 mg. PP analysis' results were similar to those seen in the ITT analysis.

Figure 4. Mean HbA_{1c} (%) over time by treatment, LOCF for post-baseline visits – ITT population

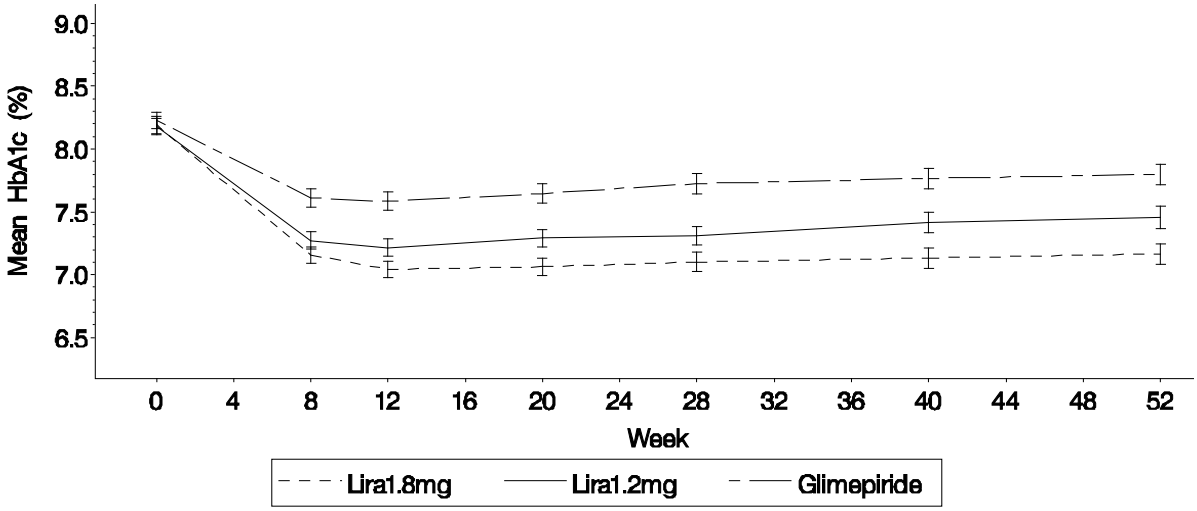


Table 8. ANCOVA of primary endpoint - change in HbA_{1c} (%) – ITT population

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

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

Percentage of subjects achieving HbA_{1c} <7% (secondary endpoint)

After 52 weeks of treatment, greater proportions of subjects treated with liraglutide 1.8 mg or 1.2 mg reached the ADA/EASD HbA_{1c} < 7% target compared to subjects treated with glimepiride (50.9%, 42.8% and 27.8%, respectively); (Table 9). The odds of reaching the above-mentioned glycaemic target were statistically significantly higher with liraglutide treatment (both doses) than glimepiride treatment.

Table 9. Logistic regression analysis of subjects reaching HbA_{1c} < 7% LOCF – ITT population

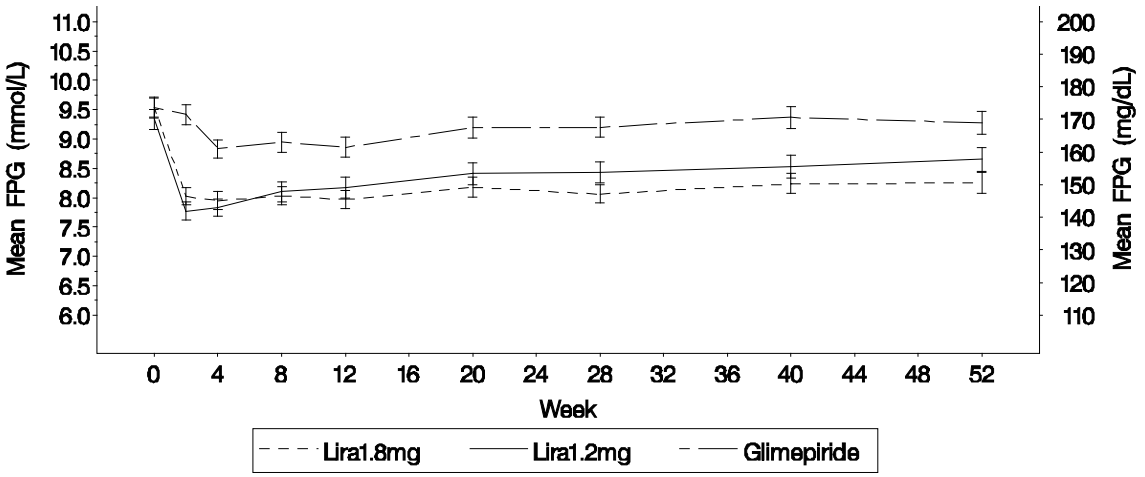
	Comparison at End of Treatment				
Treatment / Comparison	N	n	%	95% CI	P-value
Proportions					
Lira1.8mg	234	119	50.9	[44.3 ; 57.4]	
Lira1.2mg	236	101	42.8	[36.4 ; 49.4]	
Glimepiride	241	67	27.8	[22.2 ; 33.9]	
Odds Ratio					
Lira1.8mg - Glimepiride			2.92	[1.94 ; 4.39]	<.0001
Lira1.2mg - Glimepiride			2.01	[1.34 ; 3.02]	0.0007
Lira1.8mg - Lira1.2mg			1.45	[0.98 ; 2.14]	0.0629

N = Number of subjects with non-missing HbA1c value at the end of treatment, LOCF
n = Number of subjects reaching HbA1c < 7% at the end of treatment, LOCF
Odds Ratio is from Logistic Regression with treatment as a fixed effect and baseline HbA1c value as a covariate.

Fasting plasma glucose (secondary endpoint)

Mean FPG levels decreased during the initial 2−4 weeks of treatment and remained relatively stable thereafter in all three treatment groups up to week 52 (Figure 5). Throughout the 52-week treatment period, the reduction in FPG was more pronounced in both liraglutide groups compared to the glimepiride group.

Figure 5. Plot of mean FPG over time by treatment – ITT population



From a baseline of approximately 9.4 mmol/L across the three groups, mean FPG decreased by 1.42 mmol/L with liraglutide 1.8 mg, 0.84 mmol/L with liraglutide 1.2 mg and 0.29 mmol/L with glimepiride after 52 weeks of treatment (Table 10). The reduction in mean FPG was statistically significantly greater with either dose of liraglutide (1.8 or 1.2 mg) compared with glimepiride. In addition, the decrease in FPG was statistically significantly greater with liraglutide 1.8 mg than liraglutide 1.2 mg.

Table 10. ANCOVA of change in FPG (mmol/L) at end of study, LOCF

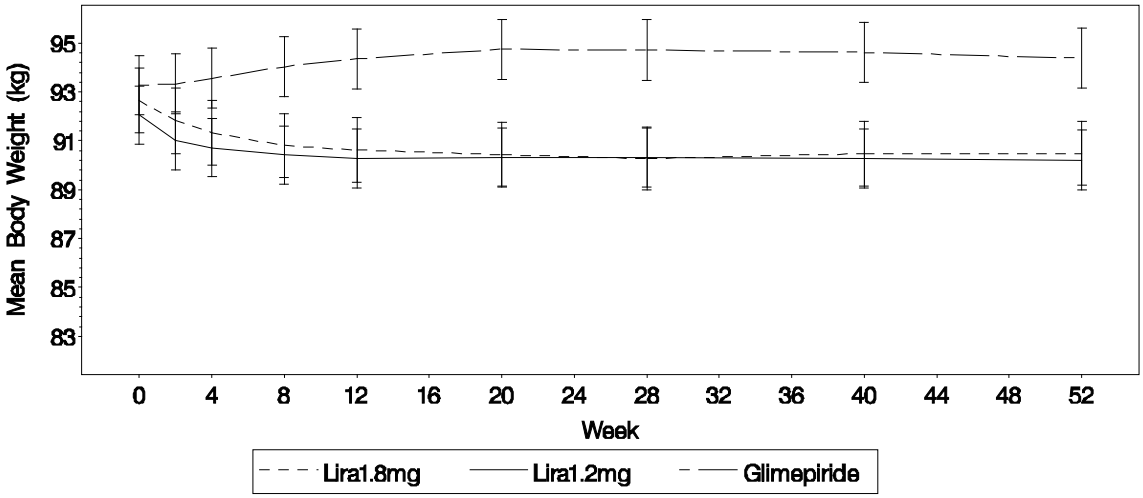
Treatment / Comparison	Estimates			P-value
Least Square Means	N	Mean	SE	
Lira1.8mg	230	-1.420	0.194	
Lira1.2mg	234	-0.844	0.194	
Glimepiride	242	-0.294	0.185	
Estimated Treatment Differences	LSMean	95% CI		
Lira1.8mg - Glimepiride	-1.126	[-1.615 ; -0.636]		<.0001
Lira1.2mg - Glimepiride	-0.551	[-1.039 ; -0.063]		0.0270
Lira1.8mg - Lira1.2mg	-0.575	[-1.068 ; -0.082]		0.0223

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

Body weight (key secondary endpoint)

In both liraglutide groups, mean body weight decreased during the initial 8 weeks of treatment and remained relatively stable thereafter up to week 52 (Figure 6). In the glimepiride group, a modest increase in body weight was seen during the initial 12 weeks of treatment, followed by parameter stabilisation up to week 52.

Figure 6. Mean body weight over time by treatment, LOCF for post-baseline visits – ITT population



From a baseline of 92−93 kg across the three groups, mean body weight decreased by 2.45 kg with liraglutide 1.8 mg, 2.05 kg with liraglutide 1.2 mg and increased by 1.12 kg with glimepiride after 52 weeks of treatment (Table 11).

Table 11. ANCOVA of change in body weight (kg) – ITT population

Treatment / Comparison	Estimates			P-value
Least Square Means	N	Mean	SE	
Lira1.8mg	240	-2.454	0.282	
Lira1.2mg	245	-2.048	0.281	
Glimepiride	248	1.123	0.269	
Estimated Treatment Differences	LSMean	95% CI		
Lira1.8mg - Glimepiride	-3.577	[-4.281 ; -2.873]		<.0001
Lira1.2mg - Glimepiride	-3.171	[-3.872 ; -2.471]		<.0001
Lira1.8mg - Lira1.2mg	-0.406	[-1.111 ; 0.299]		0.2584

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

2.4.3. Clinical studies in special populations

Renal impairment

Single-dose pharmacokinetics of liraglutide (Victoza) were evaluated in subjects with varying degrees of renal impairment (classified based on estimated Cr_{CL}) in Trial 1329: mild (> 50 - ≤80 mL/min), moderate (> 30− ≤ 50 mL/min), severe (≤ 30 mL/min), end-stage renal disease (requiring dialysis). Compared to subjects with normal renal function, liraglutide exposure (AUC) in subjects with mild, moderate and severe renal impairment or end stage renal disease was lower by 33%, 14%, 27% and 26%, respectively.

Since the submission of the Victoza MAA a pooled patient-level analysis of the six phase 3 LEAD trials in subjects with T2DM evaluating the effect of mild renal impairment on the efficacy/safety of liraglutide and a dedicated clinical trial (3916) evaluating the efficacy and safety of liraglutide in subjects with T2DM and moderate renal impairment have become available.

The pooled patient-level analysis of the LEAD programme showed that mild renal impairment (Cr_{CL}: 60 – ≤89 mL/min as determined by the Cockcroft-Gault equation) had no relevant effect on the efficacy and safety of liraglutide at doses up to 1.8 mg.

Trial 3916 data were submitted to the CHMP in June 2014 and supported a label update of liraglutide's use in patients with T2DM and moderate renal impairment (EMEA/H/C/001026/II/0028). This was a randomised, double-blind, two-armed, parallel-group, multicentre, multinational trial evaluating and comparing the efficacy and safety of liraglutide 1.8 mg against placebo over 26 weeks of treatment in subjects with T2DM and moderate renal impairment (eGFR 30 - 59 mL/min/1.73m^2 per MDRD formula) inadequately controlled with OAD(s) and/or basal or premix insulin. The trial excluded subjects with NYHA class IV, but permitted the enrolment of subjects with NYHA class ≤3. The primary objective of the trial was to confirm the superiority of liraglutide vs. placebo, both as add on to existing OAD and/or insulin therapy, on glycaemic control after 26 weeks of treatment. Consistent with this objective, the primary endpoint was change in HbA_{1c} from baseline to week 26. Secondary trial objectives included an evaluation and comparison of the effect of liraglutide vs. placebo after 26 weeks of treatment on safety/tolerability and cardiovascular risk factors.

A total of 279 subjects were randomised to treatment with liraglutide (140) or placebo (139), 277 were exposed to trial products (2 subjects in the placebo group were not exposed) and 210 (~75% in both groups) completed the trial. A brief overview of subject baseline characteristics is shown in Table 12. Trial subjects were generally older and frailer compared to subjects in other trials of the Victoza development programme. Mean age was approximately 67 years and duration of diabetes was approximately 15 years. Approximately 50% of trial subjects had a history of cardiac disorders and 2 subjects with NYHA class III heart failure were enrolled in the trial. Diabetic complications such as nephropathy, neuropathy and retinopathy were present in approximately 45−58% of trial subjects, while one-third of subjects had macro-angiopathy.

Table 12. Trial 3916 - baseline subject characteristics

BASELINE	**Lira 1.8 mg (N=140)**	**Placebo (N=137)**
Age, yrs, mean (SD)	68.0 (8.3)	66.3 (8.0)
Diabetes duration, yrs, mean (SD)	15.86 (8.86)	14.17 (7.52)
No insulin ± OAD, %	45.0	44.5
Basal insulin ± OAD, %	20.7	17.5
Premix insulin ± OAD, %	34.3	38.0
HbA_{1c}, %, mean (SD)	8.08 (0.79)	8.00 (0.85)
BW, kg, mean (SD)	93.6 (17.4)	95.6 (17.7)
BMI, kg/m^2, mean (SD)	33.4 (5.4)	34.5 (5.4)
Albumin:creatinine ratio (mg/mmol) (SD)	44.3 (96.3)	41.8 (93.7)
eGFR (MDRD) mean (SD) (mL/min/1.73 m^2)	46.6 (10.3)	46.9 (11.7)

Treatment with liraglutide was superior to treatment with placebo in terms of reductions from baseline in HbA_{1c} after 26 weeks of treatment. In addition, liraglutide produced greater improvements compared to placebo in other measures of glycaemic control (FPG, 7-point SMPG, HbA_{1c} target response) and selected cardiovascular risk factors (including body weight and BMI) (Table 13).

Treatment with liraglutide had no notable effect on renal function compared to treatment with placebo. The overall incidence of AEs was higher in this trial compared to that seen in other trials in the Victoza development programme, but consistent with the frailer population included. The AEs reported in this trial were similar in nature to those generally observed in the Victoza development programme; no unexpected safety or tolerability issues relating to the treatment of patients with moderate renal impairment with liraglutide were identified.

Table 13. Trial 3916 - selected efficacy and safety endpoint results

ENDPOINT	Lira 1.8 mg	Placebo	ETD or ETR (95% CI) p-value
HbA_{1c}, %, change from BL, mean	-1.05	-0.38	-0.66 (-0.90; -0.43) p<0.0001
Achieved HbA_{1c} <7%	52.8%	19.5%	4.64 (2.54; 8.46) p<0.0001
Achieved A1c <7% and no weight gain and no minor/severe hypo	27.9%	8.5%	4.14 (2.20; 7.80) p<0.0001
Experienced a hypo episode	5.7%	10.9%	0.50 (0.23; 1.08) p=0.0760
BW, kg, change from BL, mean	-2.41	-1.09	-1.32 (-2.24; -0.40) p=0.0052
Albumin:creatinine, ratio to BL, mean	0.87	1.05	0.83 (0.62; 1.10) p=0.1856
eGFR (MDRD), ratio to BL, mean	0.99	1.01	0.98 (0.94; 1.02) p=0.3575

The primary and continuous secondary endpoints were analysed using MMRM with treatment, country, stratification groups as factors and baseline parameter value (log transformed if not normally distributed) as a covariate, all nested within week. Responder endpoints were analysed by logistic regression model with treatment, country and product of renal function category and background diabetes treatment category as fixed effects and baseline HbA_{1c} value as a covariate. BL = baseline; BW = body weight; BMI = body mass index; eGRF = estimated glomerular filtration rate; ETD = estimated treatment difference; ETR = estimated treatment ratio; HbA_{1c} = glycosylated haemoglobin; lira = liraglutide; MMRM = mixed model for repeated measurements; OAD = oral antidiabetic drug; yrs = years

Post hoc analyses showed that HbA_{1c} reductions after 26 weeks of treatment with liraglutide 1.8 mg were similar in magnitude between eGFR subgroups corresponding to Stage 3a CKD (45−59 mL/min/1.73m^2) and Stage 3b CKD (30 - <45 mL/min/1.73m^2) or between the age subgroups of 18−64 years, 65−74 years, ≥75 years (Table 14 and Table 15).[xviii,xix] The reductions in HbA_{1c} were larger with liraglutide vs. placebo across the eGFR subgroups and across the age subgroups.

Table 14. Trial 3916 - efficacy and safety of liraglutide 1.8 mg vs. placebo across eGRF subgroups

Stage CKD (eGFR Subgroup)	Stage 3 CKD (30-59 mL/min/1.73 m^2)		Stage 3b CKD (30-<45 mL/min/1.73 m^2)		Stage 3a CKD (45-59 mL/min/1.73 m^2)	
Treatment Group	**Lira n=140**	**PBO n=137**	**Lira n=61**	**PBO n=59**	**Lira n=79**	**PBO n=78**
HbA_{1c}, BL, mean % (SD)	8.08 (0.79)	8.00 (0.85)	8.09 (0.81)	8.06 (0.92)	8.07 (0.78)	7.95 (0.80)
Change from BL at Week 26, estimated means	-1.05	-0.38	-0.97	-0.40	-1.10	-0.38
Treatment difference, p-value	-0.66; p<0.0001		-0.57; p=0.0022		-0.72; p<0.0001	
Subgroup by treatment interaction	na		p=0.4897			
AE, % subjects	76.4	68.6	77.0	78.0	75.9	61.5
SAE, % subjects	10.0	10.9	14.8	15.3	6.3	7.7
GI AE, % subjects	35.7	17.5	32.8	20.3	38.0	15.4
Confirmed hypo,% subjects	10.7	16.8	13.1	15.3	8.9	17.9

eGFR=estimated glomerular filtration rate; na=not applicable; BL=baseline; AE=adverse event; SAE=serious adverse event; GI=gastrointestinal; hypo=hypoglycaemia

Table 15. Trial 3916 - efficacy and safety of liraglutide 1.8 mg vs. placebo across age subgroups

Age Subgroup	**18-64 yr**		**65-74 yr**		**≥75 yr**	
Treatment Group	**Lira n=38**	**PBO n=55**	**Lira n=72**	**PBO n=66**	**Lira n=30**	**PBO n=16**
HbA_{1c}, BL, mean %	8.15	8.09	8.13	7.94	7.87	7.97
(SD)	(0.79)	(0.87)	(0.79)	(0.85)	(0.79)	(0.83)
Change from BL at Week 26, estimated means	-1.04	-0.31	-0.92	-0.40	-1.37	-0.59
Treatment difference, estimated; p-value	-0.72; p=0.0005		-0.52; p=0.0031		-0.78; p=0.0135	
Subgroup by treatment interaction	p=0.8392					
AE, % subjects	73.7	69.1	75.0	72.7	83.3	50.0
SAE, % subjects	10.5	3.6	9.7	15.2	10.0	18.8
GI AE, % subjects	36.8	14.5	31.9	16.7	43.3	31.3
Confirmed hypo, % subjects	10.5	10.9	12.5	22.7	6.7	12.5

BL=baseline; SD=standard deviation; AE=adverse event; SAE=serious adverse event; GI AE=gastrointestinal adverse event; hypo=hypoglycaemia

Hepatic impairment

Liraglutide is metabolised in a similar manner to large proteins, without a specific organ having been identified as a major route of elimination. Liraglutide is fully metabolised in the body by cleavage into small peptide fragments and amino acids, a process that involves neutral endopeptidase and DPP-4 enzymes.

Single-dose pharmacokinetics of liraglutide were evaluated in subjects with varying degrees of hepatic impairment (based on Child-Pugh classification score) in Trial 1328: mild (5−6 score, N=6), moderate (7−9 score, N=6), severe (>9 score, N=6). Compared to subjects with normal hepatic function (N=6), liraglutide exposure (AUC) was lower by 13−23% in subjects with mild-to-moderate hepatic impairment and by 44% in subjects with severe hepatic impairment (Trial 1328). No clear association was seen between the unbound fraction of liraglutide and different degrees of hepatic impairment. No safety concerns were raised during the trial; a single dose of liraglutide was well tolerated by all hepatic impairment groups.

The safety experience with liraglutide in patients with liver abnormalities is discussed in (safety) section 2.5.2.

Cardiovascular disease

No specific data regarding efficacy in cardiovascular disease are discussed.

2.4.4. Post-marketing data

The renewal application for Victoza (EMEA/H/C/001026/R/025) included data from all sources, including clinical trials, post-marketing experience and available literature. The Victoza renewal application included previously submitted data from five large randomised phase 3a (LEAD 1−5) trials that formed the basis of the original marketing authorisation, as well as data from three additional completed large phase 3b trials (LEAD 6, 1860 and 1842); these results are summarised in Table 16.

Table 16. Overall efficacy results from completed phase 3a and b trials within indication (26 weeks data, ITT population, LOCF)

Trial	Victoza is superior to	Δ HbA_{1c} (%) Victoza 1.8 /1.2 mg	% of patients with HbA_{1c} < 7% Victoza 1.8 /1.2 mg	Δ body weight (kg) Victoza 1.8 /1.2 mg	Δ systolic blood pressure (mmHg) Victoza 1.8 /1.2 mg
Phase 3a clinical trials supporting the marketing authorisation					
LEAD 1 + SU	Rosiglitazone	-1.1 / -1.1	42 / 35	-0.2 / 0.3	-2.8 / -2.6
LEAD 2 + Metformin	Non-inferior to glimepiride	-1.0 / -1.0	42 / 35	-2.8 / -2.6	-2.3 / -2.8
LEAD 3§ Monotherapy	Glimepiride	-1.1 / -0.8	51 / 43	-2.5 / -2.1	-3.6 / -2.1
LEAD 4 +Metformin +TZD	Placebo	-1.5 / -1.5	54 / 58	-2.0/ -1.0	-2.5 / -6.7
LEAD 5 +Metformin +SU	Insulin glargine	-1.3 / na	53 / na	-1.8 / na	-4.0 / na
Phase 3b clinical trials					
LEAD 6 +Metformin ±SU	Exenatide	-1.1 / na	54 / na	-3.2 / na	-2.5 / na
NN2211-1860 +Metformin	Sitagliptin	-1.5 / -1.2	55 / 43	-3.4 / -2.9	-0.7 / -0.6
NN2211-1842§ (+ metformin + insulin detemir)	Trial NN2211-1842 investigated the intensification of metformin+Victoza treatment with insulin detemir. This trial demonstrated superior glycaemic control (reduction in HbA_{1c}) of the intensification treatment (metformin+Victoza+insulin detemir) vs.Victoza+metformin.				

Note: HbA_{1c}, body weight and SBP reductions are estimated mean change from baseline to week 26 (or 52 for LEAD 3). §Not approved as an indication in the EU
Abbreviations: Δ = mean change from baseline**;** ITT = intention-to-treat; LOCF = last observation carried forward; mmHG = millimeter of mercury; SBP=systolic blood pressure.

2.4.5. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the current application for restricted monotherapy, the MAH has summarised previously submitted data from one phase 3 trial (1573) and three phase 2 trials (1571, 1310, 2072). These trials have been extensively discussed in the EPAR for the original MAA; this discussion will not be repeated here.

In the original assessment, the dose of 8mg/day glimepiride that was used as a comparator for Trial 1573 was discussed. In Europe usually 4 mg daily (6 mg is the maximum approved dose) is recommended. Therefore, the safety of liraglutide (especially hypoglycaemic events) may be overestimated by this high

dose (see Safety section). A comparison with metformin would have been preferred as metformin is currently the first choice in T2DM. However, from an efficacy point of view, the comparator is acceptable. Many health care professionals will prescribe an SU if metformin is not appropriate.

Of the phase 2 trials, only 1571 employed a dose that is close to the current recommendation in the SmPC. The other trials (1310, 2072) tested a maximum dose of 0.75 mg liraglutide, which makes these trials less relevant.

Efficacy data and additional analyses

Used as monotherapy (trial 1573), liraglutide 1.2 and 1.8 mg was more effective than glimepiride 8 mg daily. Compared to glimepiride, the treatment differences on HbA1c after 52 weeks were -0.623 [-0.826; -0.421] for Lira 1.8 mg and -0.329 [-0.531; -0.127] for Lira1.2 mg. Thus, for both doses, not only non-inferiority but superiority to the chosen active comparator was shown. Most of the decrease in mean HbA_{1c} with liraglutide occurred by week 8.

Based on phase 2 trial 1571, an estimate can be made for performance of liraglutide against placebo. For both dose levels, the end-of-treatment (14 week) difference was close to -1.7 (-2.2; -1.2).

Overall, the trial populations were representative of the general population of patients with T2DM at an early stage of disease progression and for whom monotherapy treatment would be indicated. In current regulatory practice, such data can be used to support an application in a population for which metformin is inappropriate.

Liraglutide treatment also decreased mean FPG/FSG levels. Most of the reduction in mean FPG/FSG with liraglutide occurred after 1−2 weeks of treatment and was maintained up to 52 weeks of treatment (in Trial 1573). Liraglutide treatment at doses ≥1.2 mg also reduced mean body weight by 1−3 kg in Trials 1573 (after 52 weeks) and 1571 (after 14 weeks).

The MAH has also provided some efficacy data on the use of Victoza in sensitive populations (e.g., in patients with renal or hepatic impairment).

Based on liraglutide's mechanism of action, data from the LEAD programme as well as Trials 1329 and 3916, treatment with liraglutide doses up to 1.8 mg was shown to be efficacious in subjects with T2DM and **mild to moderate renal impairment**; no safety concerns were identified. This was assessed and approved in variation EMEA/H/C/001026/II/0028, to extend the use of Victoza in patients with T2DM and moderate renal impairment.

Regarding subjects with **hepatic impairment**, the MAH provided single-dose pharmacokinetics from Trial 1328, which showed that liraglutide exposure was decreased by 13−23% in patients with mild-to-moderate and by 44% in patients with severe impairment. Therefore, the main concern regarding use of Victoza in these patients may be lack of efficacy, for which no further data are discussed. Section 4.2 in the Saxenda label recommends no dose adjustment for patients with mild or moderate hepatic impairment.[xxvii] Saxenda is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment (referencing sections 4.4 and 5.2). Furthermore, Saxenda users are protected against lack of efficacy by a stopping rule, which is not in place for Victoza.

In the recent renewal procedure for Victoza (EMEA/H/C/001026/R/025), no new concerns regarding efficacy (or safety) were identified on the basis of the totality of data.

2.4.6. Conclusions on the clinical efficacy

The MAH has provided adequate data to show efficacy of liraglutide as monotherapy, in subjects for whom metformin is inappropriate. However, no data supporting the efficacy of liraglutide with respect to glycaemic control in hepatic impairment were discussed, while exposure is markedly reduced.

2.5. Clinical safety

2.5.1. Trial 1573

In the context of this application, the description of safety is based upon the active-controlled monotherapy trial 1573.

Exposure data are summarised in Table 6 above.

Adverse events

A treatment-emergent AE was defined as an event that either occurred before randomisation and increased in severity during the treatment period or had an onset date on or after the first day of randomised treatment and no later than 7 days after the last day of treatment. Only treatment-emergent AEs are discussed below.

A summary of AEs in the three treatment groups is presented in Table 17. More subjects reported AEs in the liraglutide groups (liraglutide 1.8 mg: 79.3%, liraglutide 1.2 mg: 82.5%) as compared to the glimepiride group (71.4%). The majority of AEs were mild in severity. The proportions of subjects reporting severe adverse events were similar between the liraglutide 1.8 mg and the glimepiride treatment groups (13.4% and 12.9%, respectively) and higher in the liraglutide 1.2 mg treatment group (17.1%). The majority of AEs in all three treatment groups were assessed as 'unlikely related to trial product' by the investigator. The proportion of subjects with AEs as well as the number of AEs assessed as probably or possibly related to treatment by the investigator was higher in each liraglutide group compared to the glimepiride group.

Table 17. Summary of AEs – safety analysis set

	Lira1.8		Lira1.2		Glimepiride	
	N (%)	E	N (%)	E	N (%)	E
Safety Analysis Set (N)	246		251		248	
All Adverse Events	195 (79.3)	957	207 (82.5)	947	177 (71.4)	705
Serious Adverse Events	8 (3.3)	9	16 (6.4)	18	13 (5.2)	17
Deaths	0 (0.0)	0	0 (0.0)	0	1 (0.4)	1
Relation to Treatment Regimen						
Probable	59 (24.0)	117	55 (21.9)	107	28 (11.3)	44
Possible	105 (42.7)	234	89 (35.5)	198	58 (23.4)	105
Unlikely	163 (66.3)	600	177 (70.5)	639	157 (63.3)	540
NA+	6 (2.4)	6	3 (1.2)	3	11 (4.4)	16
Severity						
Mild	162 (65.9)	491	168 (66.9)	510	138 (55.6)	395
Moderate	139 (56.5)	409	142 (56.6)	368	111 (44.8)	258
Severe	33 (13.4)	57	43 (17.1)	69	32 (12.9)	52
Adverse Events Withdrawals#	23 (9.3)	46	34 (13.5)	69	17 (6.9)	20

N: Number of subjects with adverse events. %: Proportion of subjects in analysis set having adverse event. E: Number of adverse events. + Subjects were not on liraglutide or its placebo treatment when AE starting. # 20 subjects (5 in Lira1.8, 11 in Lira1.2, and 4 in Glimepiride) indicated product withdrawn, but actually either completed the study or dropped out due to reasons other than AE. 4 additional subjects (2 in Lira1.2, and 2 in Glimepiride) who discontinued the study due to non-TEAE are not included.

AEs reported by >5% of subjects in any one treatment group are summarised by system organ class and preferred term in Table 18. The most frequently-reported AEs by preferred term in the liraglutide 1.8 mg and liraglutide 1.2 mg groups were events related to the gastrointestinal system (nausea [29.3% and 27.5% of subjects, respectively] and diarrhoea [18.7% and 15.5% of subjects, respectively]). In general, nausea experienced with liraglutide was transient and declined after the initial several weeks of treatment. In the glimepiride group, the most frequently reported AEs by preferred term were headache (9.3% of subjects) and diarrhoea (8.9% of subjects).

Table 18. AEs (>5%) by system organ class and preferred term – safety analysis set

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

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

Serious adverse events and deaths

One death (due to a motor vehicle accident) was reported in this trial for a subject in the glimepiride treatment group. The proportions of subjects experiencing SAEs were low and similar between treatments (liraglutide 1.8 mg: 3.3% [9 events], liraglutide 1.2 mg: 6.4% [18 events], glimepiride: 5.2% [17 events]). Most of the SAEs were classified as 'unlikely related to treatment' by the investigator. No SAEs were considered to have a 'probable' causality relationship to the trial products, while the following 7 SAEs were considered to have a 'possible' relationship:

- hypoaesthesia (left arm numbness); liraglutide 1.8 mg
- myocardial infarction (liraglutide 1.8 mg)
- appendicitis perforated (liraglutide 1.8 mg)
- gastroenteritis (liraglutide 1.2 mg)
- myocardial infarction (liraglutide 1.2 mg)
- myocardial infarction (glimepiride)

- grand mal convulsion (glimepiride)

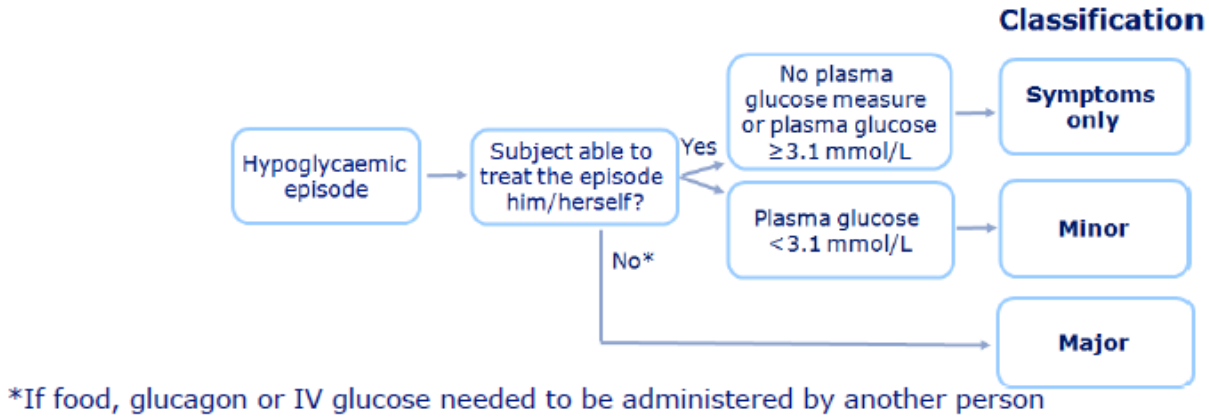
Discontinuations

Across the three treatment groups, a total of 54 subjects discontinued from the trial early due to AEs. The proportion of subjects discontinuing from the trial as well as the number of events leading to discontinuation were higher in the liraglutide groups (liraglutide 1.8 mg: 7.3% [38 events], liraglutide 1.2 mg: 9.2% [50 events]) compared to the glimepiride group (5.2% [15 events]). Subjects in the liraglutide treatment groups who withdrew from the trial early due to AEs, mainly withdrew due to GI AEs.

Hypoglycaemia

When symptoms consistent with hypoglycaemia were present, trial subjects were asked to measure their PG levels. Depending on the severity of the symptoms, availability of PG measurement and PG level, the reported episodes in the clinical trial database were classified as shown below (Figure 7). The same definition of treatment emergence as for AEs was used for hypoglycaemic episodes.

Figure 7. Classification of hypoglycaemic episodes



No major hypoglycaemic episodes were reported during the trial. The percentage of subjects reporting minor hypoglycaemia, as well as the number of episodes, was higher in the glimepiride group than in either liraglutide treatment group (Table 19).

Table 19. Summary of hypoglycaemic episodes – safety analysis set

	Lira1.8			Lira1.2			Glimepiride		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Safety Analysis Set	246			251			248		
Total Exposure (yrs)	195			192			186		
Major	0 (0.0)	0	0.00	0 (0.0)	0	0.00	0 (0.0)	0	0.00
Minor	19 (7.7)	48	0.25	28 (11.2)	58	0.30	60 (24.2)	365	1.96
Symptoms Only	27 (11.0)	72	0.37	37 (14.7)	108	0.56	72 (29.0)	350	1.88
Unclassified	2 (0.8)	2	0.01	4 (1.6)	8	0.04	6 (2.4)	10	0.05

N: Number of subjects having at least one hypoglycaemic episode. %: Proportion of subjects exposed in the treatment period having an episode. E: Number of hypoglycaemic episodes. R: Hypoglycaemic episodes per subject year.

2.5.2. Clinical safety in special populations

Renal impairment

Overall, there was no clinically-relevant difference in the safety profile of liraglutide vs. placebo across either the eGFR subgroups or the age subgroups based trial 3916 in moderate renal impairment (Table 15).

Hepatic impairment

The safety of 26-week liraglutide treatment and efficacy on liver parameters was assessed in an individual patient data meta-analysis of six large randomised phase 3 trials from the liraglutide T2DM development programme (LEAD 1−6). The meta-analysis provided a descriptive overview of the safety profile of liraglutide in T2DM patients (N=4442) with and without **abnormal blood liver enzymes** prior to treatment (baseline ALT: >ULN to <2.5 times ULN in ~50% of patients). Even though the long-term adverse events remain unknown, this study provided reassurance on the safe short-term use of liraglutide in the presence of mild-to-moderate liver injury (baseline ALT: >ULN to <2.5 times ULN).

In addition, the efficacy and safety of liraglutide 1.8 mg vs. placebo after 48 weeks of treatment was assessed in patients with **biopsy-confirmed NASH**, with or without T2DM, in the Liraglutide Efficacy and Action in NASH (LEAN) randomised, double-blind phase 2 trial. Liraglutide met the primary endpoint of histological clearance of NASH and reduction in the progression of fibrosis. There were no serious AEs in patients treated with liraglutide, which was well tolerated with only 2 (8%) of patients withdrawing from treatment due to drug-related AEs (of a gastrointestinal nature). The liver-to-spleen attenuation ratio was assessed by CT in a substudy of the LEAD-2 trial, which compared three doses of liraglutide (0.6, 1.2, 1.8 mg) against glimepiride 4 mg and placebo, all added to metformin. The ratio increased from baseline (0.10) with liraglutide 1.8 mg, possibly indicating reduced hepatic steatosis. This increased ratio was significantly different from the unchanged ratio in the glimepiride group (p = 0.0451).

A prospective **pilot study** (N=43) examined the effect of liraglutide 1.2 mg on liver fat content after 6 months of treatment in patients with T2DM, with (35 [81.3%]) and without hepatic steatosis as assessed by ^{1}H-MRS. Six months of treatment with liraglutide 1.2 mg resulted in a 33.3% relative reduction in mean liver fat content (from 19.1% to 12.7%, p<0.001), demonstrating liraglutide's efficacy in reducing hepatic steatosis. Liraglutide-induced weight loss appeared to be an important promoter of hepatic fat reduction.

Three out of four phase 3a trials (NN8022-1839, -1922 and -3970) in the liraglutide weight management programme (liraglutide 3.0 mg, Saxenda) had no restriction on the enrolment of subjects with **abnormal liver function tests** (i.e., liver enzyme levels), but did not classify hepatic function according to the Child-Pugh score. An analysis of AEs by ALT and AST levels at baseline (AST or ALT < 75th percentile compared to ≥75th percentile) was performed in the Saxenda MAA. No indication of adverse effects of Saxenda in these patients was seen in the analysis; there were no differences in AE or SAE patterns in patients with low vs. high ALT and AST levels. No safety signal has emerged from the use of Saxenda in subjects with elevated liver enzymes at baseline; treatment with Saxenda was associated with decreases in ALT and AST levels in these subjects.

Cardiovascular disease

The cardiovascular safety of liraglutide with respect to MACE was evaluated in a *post hoc* meta-analysis of intermediate and long-term phase 2 and 3 trials with liraglutide in subjects with T2DM. The inclusion criteria of these trials allowed the enrolment of subjects with NYHA class I and II heart failure. The main

analysis included 13 trials (5,607 subjects, 3,651 of which were exposed to liraglutide) ranging in duration from 26 to 100 weeks and focused on serious MACE (cardiovascular death, myocardial infarction and stroke). No increased risk in serious MACE (incidence ratio 0.75 [95% CI 0.35; 1.63]) was seen with liraglutide vs. comparators (metformin, glimepiride, rosiglitazone, insulin glargine, placebo). The results of MACE analyses conducted in a number of different subject populations and using various MACE definitions (e.g., broad, narrow, custom) were robust and consistent; most of the point estimates for the incidence ratios of MACE with liraglutide were below 1, with the upper bound below 1.8. Additional analyses based on independently *post hoc* adjudicated events provided results consistent with those described above. The limitations of the MACE meta-analysis include its *post hoc* nature, inclusion of low risk patients and duration of included trials (≤100 weeks). The results of this analysis were submitted to the CHMP in the Victoza type 2 variation (EMEA/H/C/001026/II/0024).

Consistent with the above-mentioned findings, no increase in the risk of adjudicated MACE with liraglutide versus comparator (pooled active and placebo) was identified in a pre-specified pooled analysis of 27 trials from the T2DM and weight management clinical development programmes, which included five phase 2/3 weight management trials with liraglutide doses up to 3.0 mg (WM trials: liraglutide: N=3,872; comparator: N=2,036). Based on the total of 69 events, the MACE hazard ratio (95% CI) for liraglutide/comparator was 0.57 [0.35, 0.94].

No safety concerns have been detected in the post-marketing setting (PSUR/PBRER 18 August 2015), providing further reassurance regarding the cardiovascular safety of Victoza.

The cardiovascular safety of liraglutide in subjects with T2DM at high risk for cardiovascular disease is under investigation in the LEADER trial. Trial results will become available in 2016.

2.5.3. Post-marketing data

The recent renewal application for Victoza (EMEA/H/C/001026/R/025) is used as reference source for the post-marketing data. No specific safety issues have emerged from this analysis.

2.5.4. Discussion on clinical safety

For this monotherapy application, the primary source of safety data is the active-controlled monotherapy trial 1573. This trial was assessed in the original MAA for Victoza and above in Section 2.4.2.

In the previous assessment, the dose of 8mg/day glimepiride that was used as a comparator for Trial 1573 was discussed. In Europe usually 4 mg daily (6 mg is the maximum approved dose) is recommended. Therefore, the safety of liraglutide (especially hypoglycaemic events) might be overestimated by this high dose. The percentage of subjects experiencing minor hypoglycaemic episodes during the trial was lower in the 2 liraglutide groups (liraglutide 1.2 mg: 11.2% and liraglutide 1.8 mg, 7.7%) than in the glimepiride group (glimepiride, 24.2%). Although only speculation if based on trial 1573, it seemed unlikely that the difference in hypoglycaemia rates between the 4mg dose and the 8mg dose would have been so large as to reverse the favourable safety profile of liraglutide with regard to hypoglycaemic event compared to glimepiride. The general experience with liraglutide (both from the add-on setting as Victoza and from weight management as Saxenda) confirms that liraglutide is unlikely to cause hypoglycaemias.

More subjects reported AEs in the liraglutide groups compared to glimepiride. Most AEs were mild and related to the gastrointestinal system. This is consistent with the safety profiles of Victoza and also Saxenda. The safety profile is adequately described in the SmPC.

Both hepatic and renal impairment are associated with lower exposures than in healthy subjects. Therefore, the primary concern is efficacy and not safety. Safety of Victoza in renal impairment was recently reviewed in the context of variation EMEA/H/C/001026/II/0028 and appears similar to subjects with normal renal function.

For subjects with hepatic impairment, data are sparse. The MAH references data in subjects with abnormal liver enzymes, which are not considered representative for the hepatically impaired population. The data in NASH patients are discussed referencing abstracts and no separate analysis is discussed for the diabetes patients included.

The cardiovascular meta-analysis was assessed in procedure EMEA/H/C/001026/II/0024. The population studied was relatively young and with a relatively short diabetes duration, without active cardiovascular disease, relatively low-risk cardiovascular subjects. The results from these specific populations could therefore not be extrapolated to patients with longstanding diabetes and at particular high cardiovascular risk as reflected in section 5.1 of the SmPC.

For the GLP-1 agonists as a class, results of the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, in patients with type 2 diabetes and acute coronary syndrome, are reassuring. In this trial, lixisenatide did not increase or decrease the rate of cardiovascular (CV) events compared to placebo.

2.5.5. Conclusions on clinical safety

The Victoza safety profile is adequately described in the current SmPC. Safety data regarding patients with renal impairment have been recently reviewed. Safety data regarding patients with hepatic impairment are sparse; however, because of the lower exposure no major issues are expected.

2.5.6. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

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

The MAH implemented the changes in the RMP as requested by PRAC. The PRAC considered that the risk management plan version 25.1 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 25.1 with the following content:

Safety concerns

Important identified risks	• Hypoglycaemia in combination with other anti-glycaemic agents (T2DM patients only) • Gastrointestinal adverse events • Altered renal function • Allergic reaction • Acute gallstone disease • Pancreatitis
Important potential risks	• Hyperglycaemia due to discontinuation of insulin • Medullary thyroid cancer • Neoplasm (including breast cancer) • Pancreatic cancer • Cardiovascular disorders • Immunogenicity – Anti-liraglutide antibody formation • Immunogenicity – Immune complex disorders
Missing information	• Children and adolescents < 18 years • Pregnant and lactating women • Patients with severe hepatic impairment • Patients with severe renal impairment • Patients with congestive heart failure NYHA III-IV • Patients with a history of major depression or other severe psychiatric disorders • Concomitant use of other weight lowering products • Off-label use

Pharmacovigilance plan

Liraglutide in T2DM:

Study/activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
NN2211-3784, Optum Database study Category 3	Post-marketing safety surveillance to observe the safety profile of liraglutide when used in a real-life setting in the U.S. To describe and monitor the safety profile of liraglutide and compare the incidence of adverse events with other antidiabetic medications commonly in use	Neoplasms (including thyroid cancer, MTC, pancreatic cancer and overall malignant neoplasms), serious hypoglycaemia, acute pancreatitis, acute renal failure, macrovascular conditions, microvascular conditions, thyroid events and hypersensitivity reactions	Ongoing	Final study report August 2016

EX2211-3748 LEADER® Category 3	A long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events.	Cardiovascular disorders, neoplasms, pancreatic cancer, pancreatitis, anti-liraglutide antibody formation, congestive heart failure	Ongoing	Final study report November 2016
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 U.S. and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Ongoing	Final report 15 Sep 2026

Liraglutide in weight management:

Study/activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
EX2211-3748 LEADER® Category 3	A long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events.	Cardiovascular disorders, neoplasms, pancreatic cancer, pancreatitis, anti-liraglutide antibody formation, congestive heart failure,	Ongoing	Final study report November 2016
EX2211-3748 LEADER® Category 3	Collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer in LEADER® (including prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status and age at menopause)	Neoplasms (including breast cancer)	Ongoing	November 2016
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 U.S. and to identify any increase related to the introduction of liraglutide into the marketplace.	Medullary thyroid cancer	Ongoing	Final report 15 Sep 2026

NN2211-3784, Optum Database study Category 3	Post-marketing safety surveillance to observe the safety profile of liraglutide when used in a real-life setting in the U.S. To describe and monitor the safety profile of liraglutide and compare the incidence of adverse events with other antidiabetic medications commonly in use	Neoplasms (including thyroid cancer, MTC, pancreatic cancer and overall malignant neoplasms [including breast cancer]), serious hypoglycaemia, acute pancreatitis, acute renal failure, macrovascular conditions, microvascular conditions, thyroid events and hypersensitivity reactions	Ongoing	Final study report August 2016
NN8022-4246 Category 3	In market utilisation of liraglutide used for weight management in the UK: a study in the CPRD primary care database	Off-label use (Victoza® used for treatment of weight management and Saxenda® not used correctly according to approved label)	Planned	6-month progress report: June 2018 Final study report: December 2019
NN8022-4241 Category 3	In-market utilisation of liraglutide used for weight management in Europe: a retrospective medical record review study	Off-label use (Victoza® used for treatment of weight management and Saxenda® not used correctly according to approved label)	Planned	6-month progress report: November 2017 Final study report: November 2019

NN8022-4192Category 3	To compare the effect of liraglutide 3.0 mg with placebo on postprandial gallbladder dynamics after 12 weeks of treatment in overweight and obese subjects	Acute gallstone disease	Started	Submission of final study report: December 2017

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hypoglycaemia in combination with other anti-glycaemic agents (T2DM patients only)	Text included in Section 4.2, Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Gastrointestinal AEs	Text included in Section 4.2, Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Altered renal function	Text included in Section 4.2, Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Allergic reaction	Text included in Section 4.3, Section 4.8 and listed in Section 4.8 of the SmPC	None
Acute gallstone disease	Text included in Section 4.4, Section 4.8 and listed in Section 4.8 of the SmPC	None
Pancreatitis	Text included in Section 4.4 and listed in Section 4.8 of the SmPC	None
Hyperglycaemia due to discontinuation of insulin (T2DM patients only)	Text included in Section 4.4 of the SmPC	None
Medullary thyroid cancer	Text on thyroid disease including thyroid neoplasms is included in Section 4.4 of the SmPC	None
Neoplasms (including breast cancer)	None proposed	None
Pancreatic cancer	None proposed	None
Cardiovascular disorders	Text included in Section 4.4 and listed in Section 4.8 of the SmPC	None
Immunogenicity – Anti-liraglutide antibody formation	Text included in Section 5.1 of the SmPC	None
Immunogenicity – Immune complex disorders	None proposed	None
Children and adolescents < 18 years	Text included in Section 4.1 and 4.2 of the SmPC	None
Pregnant and lactating women	Text included in Section 4.6 of the SmPC	None
Patients with severe hepatic impairment	Text included in Section 4.2 and Section 4.4 of the SmPC	None

Patients with renal impairment/end-stage renal disease	Text included in Section 4.2 and 4.4 of the SmPC	None
Congestive heart failure NYHA III–IV	Text included in Section 4.4 of the SmPC	None
Major depression or other severe psychiatric disorders	None proposed	None
Concomitant use of other weight lowering drugs	Text included in Section 4.4 of the SmPC	None
Off-label use	Text included in Section 4.1 of the SmPC Text included in patient leaflet.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1 and 5.1 of the SmPC have been updated.

Additionally, new information with regard to the use of liraglutide in patients with hepatic impairment has been added to the product information (SmPC section 4.2):

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.

and information regarding renally impaired patients has been updated in the section 5.3 of the SmPC:

Liraglutide exposure was reduced in patients with renal impairment compared to individuals with normal renal function. Liraglutide exposure was lowered by 33%, 14%, 27% and ~~28~~ 26% in patients with mild (creatinine clearance, CrCl 50-80 ml/min), moderate (CrCl 30-50 ml/min), and severe (CrCl <30 ml/min) renal impairment and in end stage renal disease requiring dialysis, respectively.

The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template which was accepted by the CHMP.

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

With the current variation, the MAH intends to include restricted monotherapy (in patients for whom metformin is inappropriate) in the indication for Victoza. At the same time, changes are proposed regarding the posology in hepatic impairment. No new data are included in this variation.

Benefits

Beneficial effects

The efficacy of liraglutide monotherapy is primarily shown in the 52-week, glimepiride-controlled trial 1573. In this trial, both doses of liraglutide provided superior reduction of the primary endpoint HbA_{1c} compared to glimepiride (treatment benefit: Lira 1.8 mg -0.623 [-0.826; -0.421]; Lira 1.2 mg -0.329 [-0.531; -0.127]). Also, percentage responders (HbA_{1c} <7) was significantly better than with control.

Based on phase 2 trial 1571, an estimate can be made for performance of liraglutide against placebo. For both dose levels, the end-of-treatment (14 week) difference in $HbA_{1c}$was close to -1.7 (-2.2; -1.2).

Liraglutide treatment also decreased mean FPG/FSG levels. Most of the reduction in mean FPG/FSG with liraglutide occurred after 1−2 weeks of treatment and was maintained up to 52 weeks of treatment (in Trial 1573). Liraglutide treatment at doses ≥1.2 mg also reduced mean body weight by 1−3 kg in Trials 1573 (after 52 weeks) and 1571 (after 14 weeks).

Based on liraglutide's mechanism of action, data from the LEAD programme as well as Trials 1329 and 3916, treatment with liraglutide doses up to 1.8 mg was shown to be efficacious in subjects with T2DM and **mild to moderate renal impairment**. This was assessed and approved in variation EMEA/H/C/001026/II/0028, to extend the use of Victoza in patients with T2DM and moderate renal impairment

Uncertainty in the knowledge about the beneficial effects

The exposure of liraglutide in **hepatic impairment** is documented by the results of single-dose pharmacokinetic trial 1328: Compared to subjects with normal hepatic function (N=6), liraglutide exposure (AUC) was lower by 13−23% in subjects with mild-to-moderate hepatic impairment and by 44% in subjects with severe hepatic impairment. The MAH has discussed safety data in subjects with abnormal liver enzymes and effects on liver fat in subjects with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steato-hepatitis (NASH), but no specific results for glycaemic control.

Risks

Unfavourable effects

The safety profile of liraglutide monotherapy is primarily based on the glimepiride-controlled trial 1573. AEs occurred in more patients than with glimepiride (lira 1.8 mg: 79.3%; lira 1.2 mg: 82.5%; glim: 71.4%). The most frequent AEs were gastro-intestinal (nausea, diarrhoea, constipation, vomiting, flatulence). Serious AEs were comparable between groups (3.3, 6.4 and 5.2% respectively). Withdrawals due to AEs were more frequent with liraglutide (9.3, 13.5 and 6.9% respectively).

The safety profile is in line with combination therapy as already described in Section 4.8 of the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Symptomatic hypoglycaemias were less frequent with liraglutide compared to glimepiride (11.0, 14.7, 29.0%). However, the dose of glimepiride was higher than recommended in Europe, which may have caused excess hypoglycaemias in the control group.

Regarding cardiovascular disease, a *post hoc* meta-analysis of intermediate and long-term phase clinical

trials (ranging from 26 to 100 weeks) in subjects with T2DM examining the incidence of MACE (cardiovascular death, myocardial infarction, stroke) with liraglutide versus active comparators and placebo was provided earlier (EMEA/H/C/001026/II/0024) and its description included in the SmPC. The analysis included 5,607 patients (3,651 exposed to liraglutide) and showed no increase in cardiovascular risk (incidence ratio of 0.75 (95% CI 0.35; 1.63) for the composite endpoint for liraglutide versus all comparators (metformin, glimepiride, rosiglitazone, insulin glargine, placebo). High-risk cardiovascular patients were excluded from the trials and the incidence rates of serious major cardiovascular events in the trials were low (6.02 per 1,000 patient years in liraglutide-treated patients and 10.45 in all-comparator-treated patients).

Effects Table

Table 20. Effects Table for Victoza monotherapy

Effect	Short Description	Unit	Treatment Liraglutide	Control	Uncertainties/ Strength of evidence
Favourable effects					
Trial 1573			52 weeks	Comparator glimepiride	N = 246 to 251 per group
HbA_{1c}	Change from baseline	%	1.2 mg: -0.84 1.8 mg: -1.14	-0.51	P=0.0014 P<0.0001
Responders (All)	Patients achieving HbA_{1c} <7%	%	1.2 mg: 42.8 1.8 mg: 50.9	27.8	P=0.0007 P<0.0001
Weight	Mean change from baseline	kg	1.2 mg: -2.05 1.8 mg: -2.45	+1.12	P<0.0001 P<0.0001
Trial 1571			14 weeks	Comparator placebo	N = 40 to 42 per group
HbA_{1c}	Change from baseline	%	1.25 mg: -1.40 1.9 mg: -1.45	+0.29	P<0.0001 P<0.0001
FPG	Change from baseline	mmol/L	1.25 mg: -3.13 1.9 mg: -3.10	+0.27	P<0.0001 P<0.0001
Weight	Change from baseline	kg	1.25 mg: -2.46 1.9 mg: -2.99	-1.77	P=0.2403 P=0.0390
Unfavourable effects					
Trial 1573				Comparator glimepiride	
All AEs	Patients with any AE	%	1.2 mg: 82.5 1.8 mg: 79.3	71.4	
Serious AEs	Patients with any AE	%	1.2 mg: 6.4 1.8 mg: 3.3	5.2	
AE withdrawals	Patients with withdrawal due to AE	%	1.2 mg: 13.5 1.8 mg: 9.3	6.9	
Hypoglycaemia	Patients with symptomatic hypoglycaemia	%	1.2 mg: 14.7 1.8 mg: 11.0	29.0	Unusually high dose of glimepiride (8 mg) may overestimate hypoglycaemia in control group.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Regarding restricted monotherapy, the efficacy and safety of liraglutide are supported by pivotal trial 1573 (52 weeks, comparator glimepiride) and phase 2 trial 1571 (14 weeks, placebo controlled). Based

on the extensive clinical trial program for Victoza in the add-on setting, the efficacy and safety as determined during the initial application for marketing authorisation has been confirmed by the data obtained post-approval.

There is still uncertainty around the potential risks in patients with advanced cardiac disease (that might have contra-indications for metformin). More information will be provided in the course of 2016, with the results of the LEADER trial. Current, but limited data indicate no specific CV risk for liraglutide and CV risk factors show improvement. Also, patients who are candidates for diabetes monotherapy may have lower CV risk than patients who are candidates for combination therapy.

Benefit-risk balance

The benefit-risk balance for Victoza as restricted monotherapy is positive. The efficacy of Victoza in subjects with hepatic impairment has not been established.

Discussion on the Benefit-Risk Balance

The marketing authorisation for Victoza was originally granted in June 2009. The marketing authorisation application included data from a large, randomised, double-blind, 52-week pivotal phase 3a monotherapy trial (NN2211-1573) comparing liraglutide against the active comparator glimepiride. However, a monotherapy indication for Victoza was not granted at the time of the approval. The main reasons cited by CHMP for non-approval of the monotherapy indication included the lack of long-term efficacy and safety data for Victoza and the lack of data on the use of Victoza in sensitive populations contraindicated for metformin (e.g., patients with renal or hepatic impairment, recent myocardial infarction or heart failure). A head-to-head comparison of liraglutide monotherapy against metformin monotherapy in a pivotal phase 3a trial was also lacking.

Since 2009, the experience with liraglutide and the class of GLP-1 receptor agonists has increased importantly. Liraglutide has a large safety database, especially in the add-on setting. The recent renewal is used as reference source for the post-marketing data. No specific issues have emerged from this analysis.

Regarding a monotherapy indication, requirements for Phase 3 can be distilled from the current diabetes guideline (Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus, CPMP/EWP/1080/00 Rev. 1).

For this assessment regarding monotherapy, the add-on studies from the LEAD program are of limited value. These are not further discussed, but their value in the general knowledge about GLP-1 receptor agonists and in particular liraglutide is acknowledged.

Superiority over placebo in a monotherapy setting has been evaluated in phase 2 only, with trial 1571 meeting the 3-months criterion and investigating liraglutide at a dose that was similar to the proposed dose (1.9 instead of 1.8 mg). The treatment effect on HbA1c was documented as: Liraglutide 1.9 mg: -1.45%; Placebo +0.29%; Thus, the genuine glucose lowering effect of liraglutide in this study was 1.74%. Taking into account that also superiority was achieved in the monotherapy trial with glimepiride, this was considered sufficiently documented for authorisation of an add-on indication. In an evaluation for monotherapy authorisation, the documentation of effect compared to placebo may be weighed more heavily; the limited size of the trial and the different dose are limitations, which in the end do not prevent authorisation.

Trial 1573 was an **active-controlled monotherapy study** of 1 year duration, which was in line with requirements from the guideline. Although the data were obtained outside the EU, extrapolation of the

data to the EU is justifiable as baseline characteristics and demographics of the included patients mostly can be considered representative for a European type 2 diabetes mellitus population. Comparison to another non-hypoglycaemic agent would have been advantageous, which currently is not available, but this is not a firm requirement.

As stated in the guideline, a monotherapy study comparing the test drug to metformin is always needed if an indication for first line (unrestricted) monotherapy is intended. Such a trial is not available, and the MAH did not apply for a first-line monotherapy indication.

A second line monotherapy indication (in patients for whom use of metformin is considered inappropriate) is approvable, in line with other products which have been approved since Victoza's original MAA, where such an indication was approved based on similar data as presented here.

By the initial assessment (in 2009), it was of concern that *"the most essential contraindications for metformin (moderate and severe renal impairment, hepatic impairment, heart failure and recent myocardial infarction) are conditions for which there is limited experience for liraglutide".*

The MAH recently addressed the clinical (efficacy and safety) experiences in use of liraglutide in patients with **renal impairment** in variation EMEA/H/C/001026/II/0028, based on Trial 3916 in patients with T2DM and moderate renal impairment. In this trial, liraglutide was administrated as add-on to existing OAD and/or insulin therapy, but it is still considered sufficient in this (monotherapy) context.

There is currently no recommendation for treatment of patients with **hepatic insufficiency**. The current SmPC states that "the therapeutic experience in patients with all degrees of hepatic impairment is currently too limited to recommend the use in patients with mild, moderate or severe hepatic impairment (see section 5.2)." The MAH refers to Trial 1328, investigating the pharmacokinetics and safety profile after a single dose of liraglutide in subjects with hepatic impairment. In this trial, liraglutide exposure was found to be decreased by 13-23% in patients with mild to moderate hepatic impairment compared to health subjects. Exposure was significantly lower (44%) in patients with severe hepatic impairment. Based on these results the Rapporteur recommended to the MAH to document a clinically relevant effect of liraglutide monotherapy in this subgroup of patients, but no such data were discussed and the MAH only emphasized that the lower exposure is unlikely associated with safety issues. While the MAH points to albiglutide and dulaglutide as a justification for not discussing efficacy data, for these substances, a 44% decrease in exposure was not documented.

Long-term **cardiovascular, safety** of liraglutide is currently supported by a meta-analysis of clinical trial data. Although these results are important, more robust data are expected this year from the company's CV outcome trial (LEADER). It is not clear how much of these data concern monotherapy. This trial will address the safety of liraglutide when used in a patient population with already existing cardiovascular disease (e.g. recent myocardial infarction or heart failure) mimicking the populations with contraindications for use of metformin, the usual first line treatment of T2DM. For the GLP-1 agonists as a class, results of the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, in patients with type 2 diabetes and acute coronary syndrome, are reassuring. In this trial, lixisenatide did not increase or decrease the rate of cardiovascular (CV) events compared to placebo.

Data from the Saxenda program contribute to the overall knowledge about GLP-1 agonists and especially liraglutide. The dossier includes extensive placebo-controlled data. However, these data are obtained at a different dose and in a different population. In occasional cases where weight loss is seen as an essential aspect of therapy, Saxenda may be more suitable than Victoza. Moreover, Saxenda would usually be indicated already in such patients.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus 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 and IIIB

Extension of indication to include monotherapy with liraglutide when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate; additionally, the MAH updated information related to the hepatic and renal impairment. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC have been updated with new efficacy and safety information. The Package Leaflet and RMP (v. 25.1) are updated in accordance. Furthermore, the Marketing authorisation holder (MAH) took the opportunity to align the PI with the QRD template version 9.1.

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

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

Extension of indication to include monotherapy with liraglutide when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate; additionally, the MAH updated information related to the hepatic impairment. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC have been updated with new efficacy and safety information. The Package Leaflet and RMP (v. 25.1) are updated in accordance. Furthermore, the Marketing authorisation holder (MAH) took the opportunity to align the PI with the QRD template version 9.1.

Summary

Please refer to the Scientific Discussion Victoza-H-C-1026-II-38

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[xv] Novo Nordisk Company. Victoza® (Liraglutide), Summary of Product Characteristics. March 2015.

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