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Efficacy and Safety of Liraglutide versus Placebo as Add-on to Glucose Lowering Therapy in Patients with Type 2 Diabetes and Moderate Renal Impairment (LIRA-RENAL): A Randomized Clinical Trial

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Running head: Liraglutide and Moderate Renal Impairment

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Abstract

Objective: Renal impairment in type 2 diabetes limits available glucose-lowering treatment options. This trial was conducted to establish the efficacy and safety of liraglutide as add-on to existing glucose-lowering medications in patients with inadequately controlled type 2 diabetes and moderate renal impairment.

Research Design/Methods: In this 26-week, double-blind trial, 279 patients with HbA_{1c} 7-10%, BMI 20-45 kg/m^2, and moderate renal impairment (eGFR 30-59mL/min/1.73m^2; MDRD) were randomized (1:1) to once-daily liraglutide 1.8 mg (n=140) or placebo (n=139).

Results: The estimated treatment difference in HbA_{1c} from baseline to week 26 was -0.66% [-7.25 mmol/mol] (95%CI -0.90 to -0.43] [-9.82 to -4.69 mmol/mol]; $P<0.0001$). Fasting plasma glucose decreased more with liraglutide (-1.22 mmol/L; [-22.0 mg/dL]) than with placebo (-0.57 mmol/L; [-10.3 mg/dL]) ($P=0.036$). There was a greater reduction in body weight with liraglutide (-2.41 kg) than with placebo (-1.09 kg) ($P=0.0052$). No changes in renal function were observed (eGFR relative ratio to baseline: -1% liraglutide; +1% placebo, estimated treatment ratio (ETR) 0.98, $P=0.36$). The most common adverse events were gastrointestinal side-effects (liraglutide 35.7%, placebo 17.5%). No difference in hypoglycemic episodes was observed between treatment groups (event rate/100 patient-years exposure: liraglutide, 30.47; placebo, 40.08; $P=0.54$). The estimated ratio to baseline for lipase was 1.33 and 0.97 for liraglutide and placebo, respectively (ETR 1.37, $P<0.0001$).

Conclusions: Liraglutide did not affect renal function and demonstrated better glycemic control with no increase in hypoglycemia risk but with higher withdrawals due to GI

adverse events than placebo in patients with type 2 diabetes and moderate renal

impairment.

Type 2 diabetes is the most prevalent cause of chronic kidney disease (CKD) that may

progress to end-stage renal disease (dialysis and/or transplant) Diabetic nephropathy is

the most likely cause of CKD especially associated with suboptimal glycemic control.

Kidney function is categorized, based on estimated glomerular filtration rate (eGFR), (1).

as: normal; mild; moderate; severe; end-stage. Stage 3 CKD (moderate renal

impairment), defined as eGFR 30-59 mL/min/1.73m^2, is further categorized as Stage 3a

(eGFR 45-59 mL/min/1.73m^2) and Stage 3b (30-44 mL/min/1.73m^2) (1). In the USA,

CKD (eGFR <60mL/min/1.73m^2) occurs in approximately 20% of patients with type 2

diabetes. (2). In the UKPDS, 28% of patients with type 2 diabetes developed renal

impairment after a median of 15 years after diagnosis of diabetes (3). Impaired renal

function is associated with increased cardiovascular risk which is further increased by

poor glycemic control (1,4).

Effective treatment of patients with type 2 diabetes and moderate renal impairment is

challenging. Pharmacokinetic aspects of drugs cleared by the kidney can be influenced

by renal impairment leading to the cessation or dosage reduction in many glucose-

lowering therapies (5-8) that may have reduced tolerability or increased safety risk in

this population (9-12).

Liraglutide, a once-daily human GLP-1 analog (13), is completely metabolized through a

proteolytic mechanism and is not predominantly eliminated by a single organ (14). A

single-dose (0.75 mg subcutaneously) pharmacokinetic trial with liraglutide provided

initial evidence that the exposure to liraglutide was not increased in patients with all

stages of renal impairment relative to patients with normal renal function (15). A meta-analysis from the six Liraglutide Effect and Action in Diabetes (LEAD) trials has shown that the glycemic efficacy and safety of liraglutide (1.2 mg or 1.8 mg) in patients with mild renal impairment (eGFR 60-≤89 mL/min/1.73m^2) was similar to those with normal renal function (16).

The primary objective of this trial was to demonstrate the superiority of liraglutide 1.8 mg versus placebo as add-on to existing oral glucose-lowering agents and/or insulin therapy on glycemic control after 26 weeks' treatment in patients with type 2 diabetes and moderate renal impairment (Stage 3 CKD) (Clinicaltrials.gov registry number: NCT01620489).

Methods

Trial Design

This trial was conducted in order to provide efficacy and safety data in a population with moderate renal impairment and to update the label with this information. This 26-week randomized, double-blind, placebo-controlled, parallel-group trial was conducted between June 2012 and August 2013 and included patients from 78 sites: France (4 sites), Poland (8), Russian Federation (15), Ukraine (6), UK (9), USA (36).

Trial patients who met the eligibility criteria at screening were randomized (1:1), using a sponsor-provided telephone- or web-based randomization system, to receive once-daily subcutaneously-administered liraglutide or placebo. Trial site personnel, patients and sponsor remained blinded until trial completion. Stratification was based on the

assessment of renal function (eGFR <45 or $\geq$45 mL/min/1.73m^2 [Modification of diet in renal disease formula; MDRD]) using standardized creatinine measurements and insulin treatment (basal, premix or no insulin). Liraglutide or placebo were initiated with a starting dose of 0.6 mg/day, with subsequent weekly dose-escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached (Supplemental Figure S1). At the discretion of the investigator, the dose escalation could have been extended up to 4 weeks in case of gastrointestinal side-effects. Treatment was continued for a total of 26 weeks with a 1-week follow-up period. For patients using insulin with an HbA$_{1c}$ $\leq$8% (64 mmol/mol) at screening, the pre-trial insulin dose was reduced by 20% at Day 0 and kept fixed until the liraglutide dose escalation was complete. Titration to the pre-trial insulin dose was allowed at the discretion of the investigator. Patients were to maintain their background diabetes medication throughout the trial. Patients using either insulin or a sulfonylurea (SU) were allowed to reduce the dose of these agents if hypoglycemic episodes occurred.

Trial Population

Eligible trial patients were male/female, aged 18-80 years (inclusive) previously diagnosed with type 2 diabetes, had HbA$_{1c}$ 7-10% (53-86 mmol/mol; inclusive) and on stable diabetes treatment for >90 days prior to screening. The following background diabetes treatments were allowed: monotherapy or dual therapy combinations of metformin and/or SU and/or pioglitazone; monotherapy with basal or premix insulin or any combination of basal or premix insulin with metformin and/or pioglitazone. The

patient was to have moderate renal impairment >90 days prior to screening (confirmed at screening) and have a BMI of 25-45 kg/m^2 (inclusive).

Key exclusion criteria at screening included: hypoglycemic unawareness and/or recurrent severe hypoglycemia as judged by the investigator; impaired liver function (ALAT $\geq$2.5× upper limit of normal; ULN), history of chronic pancreatitis or idiopathic acute pancreatitis; New York Heart Association class IV heart failure; episode of unstable angina, acute coronary event, cerebral stroke/transient ischemic attack or other significant cardiovascular event within the past 180 days; a systolic blood pressure (SBP) $\geq$180 mmHg or a diastolic blood pressure (DBP) $\geq$100 mmHg; a screening calcitonin value $\geq$50 ng/L; and personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

The trial was conducted according to the Declaration of Helsinki (17) and the International Conference on Harmonization of Good Clinical Practice (18) principles. The protocol was reviewed and approved by the appropriate independent ethics committees or institutional review boards. All patients provided written informed consent prior to the commencement of any trial related activities.

Assessments

The primary efficacy endpoint was the change in HbA$_{1c}$ from baseline to Week 26. Responder endpoints, at Week 26, for HbA$_{1c}$ <7.0% (53 mmol/mol) and HbA$_{1c}$ <7.0% (53 mmol/mol) with no hypoglycemic episodes were determined. Change from baseline

to Week 26 in fasting plasma glucose (FPG), body weight, BMI, SBP and DBP, fasting lipids and selected cardiovascular biomarkers were determined.

The total prescribed daily insulin dose was recorded, summarized by visit and the ratio to baseline at week 26 was determined.

Safety assessments included adverse events (AEs), change from baseline to Week 26 in renal function (eGFR [MDRD] (19), urinary albumin:creatinine ratio [UACR]), amylase, lipase and pulse rate. UACR was calculated as the mean of the morning urine samples from the day before the visit and the day of the visit.

Hypoglycemic episodes were categorized according to the ADA definition ($\leq$3.9 mmol/L; [70 mg/dL]) (20). Furthermore, a category of confirmed hypoglycemic events (subject unable to treat themselves (severe) and/or has a PG <3.1 mmol/L [56 mg/dL] or blood glucose <2.8 mmol/L [50 mg/dL] (minor)) was used in parallel with the ADA definition.

Statistical Analyses

Sample size was determined in order to demonstrate superiority of liraglutide versus placebo with regard to mean change in HbA_{1c} using a significance level of 5% and a two-sided test. Assuming a mean difference of 0.4%, a standard deviation of 1.1%, 137 evaluable patients per treatment arm were needed to achieve a power of 85%. All patients who received at least one dose of trial medication were included in the analyses. Descriptive statistics were used to summarize the data. The changes from

baseline to Week 26 for primary and secondary continuous endpoints were analyzed using a mixed-model repeated measurement (MMRM) analysis. A model with treatment, country, stratification groups as factors and baseline HbA_{1c} as a covariate, all nested within week, was used using an unstructured covariance matrix. Depending on distribution of data, a log transformation was used for some parameters before entering into the statistical model. For those, resulting estimated means were back-transformed to the original scale, giving estimates of treatment ratios instead of treatment differences. Dichotomous efficacy endpoints were analyzed using a logistic regression model. Frequencies were to be estimated for each treatment from the estimated odds for the corresponding treatment. The frequency for a treatment group was to be calculated as 100 x (estimate of treatment odds / (1+estimate of treatment odds). AEs were summarized descriptively. Confirmed hypoglycemic events were analyzed using a negative binomial regression model.

Results

Patient Disposition

In total, 279 patients were randomized to receive either liraglutide 1.8 mg or placebo (140 and 139 patients, respectively) (Supplemental Figure S2). Two patients in the placebo group were not exposed to trial medication. . All remaining patients exposed to either liraglutide (140) or placebo (137) were included in the analysis sets. Approximately 25% of patients in each group withdrew from the trial. More patients in the liraglutide group withdrew due to AEs (19; 13.6%) than in the placebo group (4; 2.9%).

Demographics and Baseline Characteristics

Patient demographics and baseline characteristics were generally well-balanced

between the two treatment groups (Table 1). The mean age of the liraglutide group

appeared to be slightly higher than in the placebo group. Overall, 16.6% of patients

were elderly ($\geq$75 years) and almost half (49.8%) were 65-74 years. The mean duration

of diabetes was 15.9 years in the liraglutide group and 14.2 years in the placebo group.

Approximately 55% of patients were taking background insulin medication at screening

(basal insulin, 19.1%; premix insulin 36.1%). The mean BMI for all patients was 33.9

kg/m^2. The proportion of patients with Stage 3b CKD (eGFR [MDRD] 30-

<45mL/min/1.73m^2) was approximately 43% in both treatment groups.

Efficacy

After 26 weeks of treatment, HbA$_{1c}$ was reduced more with liraglutide (-1.05% [-11.4

mmol/mol] than with placebo (-0.38% [-4.18 mmol/mol]) (Figure 1A) with an estimated

treatment difference (ETD) of -0.66% [-7.25 mmol/mol] (95%CI -0.90% to -0.43%; -9.82

to -4.69 mmol/mol, *P*<0.0001). Sensitivity analyses, conducted *post-hoc* due to

concerns on missing data, corroborated the results from the MMRM analysis

(Supplemental Table S1). A *post-hoc* subgroup analysis for the mean change in HbA$_{1c}$

from baseline to week 26 between Stage 3A and Stage 3B CKD indicated that

liraglutide was as effective in reducing HbA$_{1c}$ in both groups (subgroup by treatment

interaction p=0.4897). The ETD for Stage 3A CKD was -0.72% [-7.86 mmol/mol]

(95%CI -1.03 to -0.41; -11.2 to -4.47 mmol/mol, *P*<0.0001). The ETD for Stage 3B CKD

was -0.57% [-6.26 mmol/mol] (95%CI -0.94 to -0.21; -10.2 to -2.29 mmol/mol P=0.0022 (Supplementary Table 5).(21)

More patients achieved the ADA target of HbA$_{1c}$ <7.0% [<53 mmol/mol] with liraglutide (52.8%) than with placebo (19.5%) (Figure 1B). The estimated odds ratio (EOR) of achieving this target (liraglutide/placebo) was 4.64 (95%CI 2.54-8.46, P<0.0001). More patients achieved the composite target of HbA$_{1c}$ <7.0% [<53 mmol/mol] and no minor or severe hypoglycemic episodes with liraglutide (33.2%) than with placebo (11.2%). The EOR of achieving this target was 3.94 (95%CI 2.12-7.30, P<0.0001). Although not pre-specified, the target analyses were performed with an HbA$_{1c}$ target of <7.5% since this may be more clinically relevant. The EOR of achieving HbA$_{1c}$ <7.5% [<58 mmol/mol] was 4.60 (95%CI 2.49-8.47, P<0.0001) and the EOR for the composite target was 3.72 (95%CI 2.07-6.69, P<0.0001).

Reductions in FPG were observed for both treatment groups (Figure 1C). The estimated mean change in FPG from baseline to Week 26 was -1.22 mmol/L (-22.0 mg/dL) with liraglutide and -0.57 mmol/L (-10.3 mg/dL) with placebo. The ETD was -0.65 mmol/L (-11.6 mg/dL) (95%CI -1.25 to -0.04 mmol/L; -22.5 to -0.76 mg/dL, P=0.036).

Both treatment groups exhibited a gradual weight reduction during the trial (Figure 1D). The patients in the liraglutide group had a greater reduction in body weight than the placebo group (-2.41 kg and -1.09 kg, respectively) with an ETD of -1.32 kg (95%CI -2.24 to -0.40 kg, P=0.0052). In addition, BMI was reduced more with liraglutide (-0.88

kg/m^2) than with placebo (-0.38 kg/m^2) with an ETD of -0.51 kg/m^2 (95%CI -0.83 to -0.18 kg/m^2, P=0.0022).

The total daily insulin dose at week 26 decreased by 8% in the liraglutide group and by 3% in the placebo group. The changes in the dose of sulfonylureas were not determined.

From baseline to Week 26, there was no treatment difference observed for change in the fasting lipid profile (P-value range 0.21 to 0.81) (Supplementary Table S2).

Several biomarkers were evaluated in order to assess the cardiovascular effects of liraglutide (Supplementary Table S3).

SBP reduction occurred in both treatment groups (-2.45 mmHg with liraglutide; -0.33 mmHg with placebo) but there was no difference between treatments (P=0.25). There was no difference between treatments in DBP (P=0.89).

Safety

Over the 26-week trial period, the overall incidence of AEs and serious AEs (SAE) was comparable between the two treatment groups (Table 2). The patients recovered from the AE/SAE with equal frequency between both treatment groups. A *post-hoc* analysis based on eGFR subgroup indicated that there was no difference in the percentage of subjects treated with liragutide who reported AEs (75.9% and 77.0% for Stage 3A and Stage 3B CKD, respectively; Supplementary Table 5).(21) The most common AEs

reported with liraglutide were gastrointestinal (35.7%), which tended to resolve quickly, and the majority were considered mild in severity. However, for subjects in the liraglutide group who withdrew due to a GIAE (9 subjects; 11 events), the majority of AEs were either moderate (6 events) or severe (4 events). The most frequently reported gastrointestinal AEs were nausea (21.4%) and vomiting (12%). AEs within the gastrointestinal disorder and metabolism and nutrition disorders system organ classes are known side-effects of liraglutide and the GLP-1 receptor agonist class. The higher rates of these events reported in the liraglutide group were expected and were in line with previous results observed in the liraglutide clinical program. A *post-hoc* analysis based on eGFR subgroup indicated that there was a slight difference in the percentage of subjects treated liraglutide who reported GIAEs where more subjects with Stage 3A CKD (38.0%) reported these types of AEs than those with Stage 3B CKD (32.8%).(21) In the liraglutide group there was one SAE of renal impairment, and in the placebo group there was one SAE each for renal impairment and urethral stenosis. The number of SAE by eGFR subgroup were low (*post-hoc*); however, there was a trend of approximately twice as many SAEs in subjects with Stage 3B CKD (liraglutide 9 subjects, [14.8%]; placebo 9 subjects [15.3%]) than in those with Stage 3A CKD (liraglutide 5 subjects [6.3%]; placebo 6 subjects [7.7%]).(21) There were five deaths in the trial; four in the liragutide group (diabetic ketoacidosis; cerebral hemorrhage; biliary sepsis; and cerebrovascular accident, pulmonary fibrosis, pulmonary edema, left ventricular failure and pneumonia [the last five terms for one patient]) and one in the placebo group (atherosclerosis) (Supplemental Table S4). The deaths were not clustered within a specific system organ class or eGFR stratum (liraglutide: 2 subjects

Stage 3A stratum; 2 subjects Stage 3B stratum; placebo: Stage 3B stratum). The

relationship to trial product was assessed by the investigator as unlikely for the four

liraglutide cases and as possible for the placebo case.

In the liraglutide group 20.7% of patients (97 episodes) and in the placebo group 26.3%

(160 episodes) experienced documented symptomatic hypoglycemic episodes (20)

(Figure 2A). One severe hypoglycemic episode was reported in a 46-year-old female

treated with liraglutide who had a baseline HbA_{1c} of 7.1% but did not reduce the insulin

dose at randomization as advised by the protocol. The patient did not lose

consciousness, but carbohydrates were administered by another person. In the

liraglutide group, 5.7% of patients experienced a confirmed hypoglycemic event

whereas 10.9% of patients in the placebo group experienced one, as estimated from a

logistic regression model (P=0.076). No difference in event rates of confirmed

hypoglycemic episodes were observed between the treatment groups (event-rate/100

patient-years exposure: liraglutide 30.47, placebo 40.08; estimated treatment ratio

(ETR)=0.76, 95%CI 0.31-1.84, P=0.54).

Renal function was assessed as a safety parameter. There was no significant difference

in ratio to baseline for serum creatinine between the treatment groups after 26 weeks

(P=0.26). The mean observed change in eGFR (MDRD) from baseline to Week 26

including last observation carried forward (LOCF) was -0.35 mL/min/1.73m^2 in the

liraglutide group and +0.37 mL/min/1.73m^2 in the placebo group. The estimated ratio of

week 26 to baseline for eGFR (MDRD) for the liraglutide group was 0.99 (-1%) and for

the placebo group was 1.01 (+1%) (Figure 2B). The ETR of 0.98 (95%CI 0.94-1.02, P=0.36) indicated that liraglutide did not affect eGFR. The estimated ratio of Week 26 to baseline for UACR was 0.87 with liraglutide and 1.05 with placebo. The ETR of 0.83 (95%CI 0.62-1.10, P=0.19) was not statistically significant. Overall, there was no difference seen in renal function parameters between treatment groups.

At baseline, 12.9% and 16.8% of patients had an amylase ≥ULN in the liraglutide and placebo groups, respectively. At Week 26, 20.0% and 20.2% of patients had an amylase ≥ULN in the liraglutide and placebo groups, respectively. No amylase values ≥3× ULN were observed in the trial. The mean observed change in amylase levels from baseline to Week 26 including LOCF was 9.10 U/L for the liraglutide group and -0.31 U/L for the placebo group. The estimated ratio to baseline for amylase for the liraglutide group was 1.15 and for the placebo group was 1.01 (ETR 1.14, P<0.0001).

In the liraglutide group, 31.4% of patients had a baseline lipase value ≥ULN and at Week 26, 48.6% of patients had a lipase ≥ULN (Figure 2C). Twenty-nine patients (27.6%) shifted from a normal lipase value at baseline to a high value at Week 26. Twenty-two patients (21.0%) had elevated lipase levels at baseline which remained elevated at Week 26. In the placebo group, 24.1% of patients had a baseline lipase value ≥ULN and at Week 26, 20.4% of patients had a lipase ≥ULN. Seven patients (6.5%) shifted from normal lipase to a high value at Week 26. Fifteen patients (13.9%) had elevated lipase levels at baseline which remained elevated at Week 26. The mean observed change from baseline to Week 26 including LOCF was 18.97 U/L for the

liraglutide group and -1.70 U/L for the placebo group. The estimated ratio to baseline for lipase in the liraglutide group was 1.33 and for the placebo group was 0.97 (ETR 1.37, *P*<0.0001). At Week 26, no patient treated with liraglutide, but one patient treated with placebo, had a lipase $\geq$3× ULN. None of the patients with either elevated amylase or lipase had clinical evidence of acute pancreatitis (Supplemental material for workup details).

One non-serious AE of chronic pancreatitis was observed in the trial. A 72-year-old male with a duration of diabetes of 6.7 years (liraglutide group) had a history of elevated amylase and lipase levels for several years prior to trial entry but no clinical symptoms of pancreatitis. An ultrasound, performed due to elevated baseline lipase (>3× ULN) and amylase (>2× ULN) , showed diffuse changes in pancreatic parenchyma. The asymptomatic patient was diagnosed with chronic pancreatitis on Day 11 of treatment and was withdrawn.

Mean pulse increased more with liraglutide (3.20 beats/min) than with placebo (0.23 beats/min) (Figure 2D). This increase occurred by Week 2 and remained stable throughout the remainder of the trial. The ETD was 2.98 beats/min (95%CI 0.71-5.24, *P*=0.010). At Week 26, 30.2% of liraglutide patients and 23.6% of placebo patients had a >10 beats/min pulse increase from baseline. 13.2% and 9.1% of liraglutide and placebo patients, respectively, exhibited a >15 beats/min pulse increase from baseline whereas a small percentage (1.9% and 2.7%, respectively) had a >20 beats/min pulse

increase from baseline. The percentage of patients with unchanged or decreased pulse at Week 26 was 23.6% (liraglutide) and 44.5% (placebo).

Conclusions

In patients with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2) and uncontrolled type 2 diabetes, addition of liraglutide to background glucose-lowering therapy produced clinically meaningful reductions in HbA$_{1c}$ and FPG compared to placebo after 26 weeks of treatment. There was a greater percentage of responders in the liraglutide group compared to the placebo group for the dichotomous endpoints of: HbA$_{1c}$ below 7.0% (<53 mmol/mol) and HbA$_{1c}$ below 7.0% (<53 mmol/mol) and no hypoglycemic episodes. These results demonstrate that better glycemic control is achieved with liraglutide than with placebo in patients with type 2 diabetes and moderate renal impairment.

Few clinical trials have reported results with a GLP-1 receptor agonist in patients with type 2 diabetes and moderate renal impairment (22). Results from an albiglutide active comparator-controlled (sitagliptin) trial in patients with mild (51.7%), moderate (41.0%) and severe (7.3%) renal impairment (eGFR $\geq$15 to <90 mL/min/1.73m^2) (23) demonstrated that once-weekly albiglutide was more efficacious than sitagliptin. Like liraglutide, albiglutide is degraded by enzymatic catabolism (23) whereas exenatide (24) and lixisenatide (25) are eliminated by renal clearance.

Patients with type 2 diabetes and renal impairment have an increased risk of cardiovascular events (4). Patients in this trial were obese thus increasing cardiovascular risk further. Liraglutide improved various cardiovascular markers compared to placebo. Patients treated with liraglutide lost more body weight than those treated with placebo and exhibited a greater reduction in BMI. There was a greater increase in pulse with liraglutide than with placebo. Approximately twice as many patients in the placebo group exhibited unchanged or decreased pulse compared to the liraglutide group. The long-term clinical effect of an increase in pulse has not yet been established.

While the reductions in weight and SBP were similar to the LEAD trials, the ETD for the change in HbA_{1c} from baseline was considerably lower. However, this trial population was older (68.0 and 66.3 years for the liraglutide and placebo groups, respectively) and had a longer duration of diabetes (15.9 and 14.2 years for the liraglutide and placebo groups, respectively) than those in the LEAD trials (age: 53.0-57.5 years; duration of diabetes 5.4-9.2 years.(26-32)

It is of clinical relevance that there was no worsening of renal function in patients treated with liraglutide while on diverse background glucose-lowering therapy. Treatment differences were not observed in the Week-26 ratio to baseline for eGFR. The observed UACR as an indication of a patient's albuminuria was 17% lower with liraglutide

although not statistically significant. Albuminuria is not only a marker for kidney damage but it is also a cardiovascular risk factor (33,34).

Patients with chronic kidney disease and diabetes are at increased risk of hypoglycemia, particularly when using insulin (35). A smaller percentage of patients treated with liraglutide experienced a hypoglycemic episode than those treated with placebo. There was a comparable risk in the event rate of hypoglycemia between both groups. Considering that more than half of the patients were treated with insulin, this supports that liraglutide does not increase the hypoglycemia risk in this population.

Volume depletion events, such as nausea, vomiting and diarrhea, in patients with CKD, could, potentially, adversely affect kidney function (1). Even though more patients treated with liraglutide reported these types of events in this trial, most were mild in intensity and resolved quickly. There was one severe case of nausea and two of vomiting reported in the liraglutide group. In the LEAD 1-5 trials, the incidence of nausea, diarrhea and vomiting ranged from 6.8-40%, 7.9-18.7%, and 5-17%, respectively(26-32). Even though the number of patients with moderate or severe renal impairment was small in the meta-analysis of the LEAD trials, the patients taking liraglutide experienced nausea more frequently (21%) than those with normal renal function (12%) indicating that patients with renal impairment may experience more gastrointestinal effects when treated with liraglutide.(16)

Compared to results from the albiglutide trial, the overall incidence of GIAE between daily liraglutide (35.7%) and once-weekly albiglutide (31.7%) was similar. However, the incidence of nausea and vomiting was higher with daily liraglutide (nausea 21.4%; vomiting 12.1%) than with once-weekly albiglutide (nausea 4.8%; vomiting 1.6%). These trials had different designs (active comparator- vs placebo-controlled) and different inclusion criteria (albiglutide included patients with eGFR ≥15-<90 mL/min/1.73m2 [Stages 2-4 CKD]). (23) . Hydration status should be monitored if vomiting occurs in patients with impaired renal function who are receiving renin-angiotensin system blocking agents and/or diuretics.

Increases in serum amylase and lipase values, of unknown mechanism, have been seen previously with liraglutide and therefore routine monitoring of pancreatic enzymes was performed. Even though amylase was shown to be elevated more in the liraglutide group compared to the placebo group at Week 26, the median amylase value was below the ULN. Increases in lipase in the liraglutide group were seen as early as Week 2. More patients shifted from a normal baseline lipase value to an elevated value at Week 26 with liraglutide than with placebo. The median lipase value in the liraglutide group at Week 26 was close to the ULN. However, the median baseline level of lipase seemed to be higher in this patient population with moderate renal impairment than observed in previous studies (36). Approximately 20% of patients with type 2 diabetes have elevated lipase levels (36). An association between eGFR reductions and elevated baseline lipase and amylase has been observed in patients with type 2 diabetes (37). Within Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome

Results (LEADER) trial, 24% of patients (n=1840) with moderate renal impairment and 12% of the patients (n=3417) with normal eGFR demonstrated elevated lipase levels at baseline (37). In this trial, approximately 20-30% of patients had elevated baseline lipase levels. However, since more patients treated with liraglutide had lipase elevations at the end of treatment than those with placebo, it is apparent that these elevations are not caused just by type 2 diabetes and renal impairment. Lipase and amylase increases have also been seen with other GLP-1 receptor agonists and DPP-4 inhibitors (38).

The high withdrawal rate (~25%) in both treatment groups is a limitation of this trial. This trial investigated an older and frailer population, which might lead to more AEs, specifically gastrointestinal effects, being experienced by the patients. Several post-hoc sensitivity analyses, conducted due to concerns on missing data, supported the conclusions of the primary statistical method. Even though the withdrawal rate in both groups was similar, the reasons and timing were different. Patients treated with liraglutide tended to withdraw due to AEs, about half of which were gastrointestinal; whereas, those treated with placebo discontinued due to meeting withdrawal criteria, predominantly unacceptable hyperglycemia or changes in diabetes medication. Patients treated with liraglutide tended to withdraw earlier in the trial and due to GI side-effects, which corresponds to the AE patterns observed in other liraglutide trials. Subjects treated with placebo tended to withdraw later in the trial. Caution should be exercised if nausea or vomiting occurs in patients with moderate renal impairment to ensure proper evaluation if mild pancreatitis is suspected. The rather short duration of the trial does not allow predicting long-term glycemic responses.

The placebo-controlled design of this trial is another limitation. However, liraglutide was investigated as an add-on to a wide array of glucose-lowering medications including insulin. As such, we believe that placebo was the most appropriate comparator.

An additional limitation for this trial is that stratification by eGFR was based on results at the screening visit even though eGFR was also assessed at the randomization visit. It is acknowledged that serum creatinine levels may have varied between the visits. Nonetheless, this would be as likely in both the liraglutide and the placebo groups and therefore, should not bias the results of the trial.

Liraglutide did not affect renal function, demonstrated better glycemic control and weight reduction with no increase in hypoglycemia risk but with higher withdrawals due to GI adverse events than placebo in patients with type 2 diabetes and moderate renal impairment.

Author contributions

MJD, SCB, SLA, PR, DS, MSS, AS, HB-T and GEU contributed to the writing, revisions, critical review and approval of the final manuscript. AS and HB-T contributed to trial conduct or data collection and performed data analysis or interpretation. MJD is the guarantor of this work, and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1 Demographic and baseline characteristics

	Liraglutide 1.8 mg (N=140)	Placebo (N=137)
Sex, n, (%)		
Female	65 (46.4)	72 (52.6)
Male	75 (53.6)	65 (47.4)
Age, years, mean (SD)	68.0 (8.3)	66.3 (8.0)
Age group, n (%)		
18-64 years	38 (27.1)	55 (40.1)
65-74 years	72 (51.4)	66 (48.2)
>75 years	30 (21.4)	16 (11.7)
Duration of diabetes, years, mean (SD)	15.9 (8.9)	14.2 (7.5)
Race, n (%)		
White	123 (87.9)	129 (94.2)
Black or African American	14 (10.0)	4 (2.9)
Asian non-Indian	2 (1.4)	1 (0.7)
Asian Indian	1 (0.7)	0
Native Hawaiian or other Pacific Islander	0	1 (0.7)
Other	0	2 (1.5)
Insulin treatment, n (%)		
Basal	29 (20.7)	24 (17.5)
Premix	48 (34.3)	52 (38.0)
No insulin	63 (45.0)	61 (44.5)
Total daily insulin dose, Geo mean (CV)	47.1 (0.70)	50.8 (0.85)
Oral glucose-lowering therapies, n (%)		
Metformin	14 (10.0)	12 (8.8)
SU	15 (10.7)	19 (13.9)

Pioglitazone	1 (0.7)	1 (0.7)
Metformin + SU	26 (18.6)	25 (18.2)
Repaglinide*	1 (0.7)	0 (0.0)
Metformin + pioglitazone	1 (0.7)	1 (0.7)
SU + pioglitazone	1 (0.7)	1 (0.7)
MET+SU fixed combination*	1 (0.7)	1 (0.7)
Metformin + SU + pioglitazone	1 (0.7)	0 (0.0)
Metformin + SU + acarbose*	1 (0.7)	0 (0.0)
HbA$_{1c}$ %, mean (SD)	8.08 (0.792)	8.00 (0.853)
mmol/mol, mean (SD)	64.8 (8.66)	63.9 (9.33)
FPG mmol/L, mean (SD)	9.48 (3.270)	9.27 (2.842)
mg/dL, mean (SD)	170.83 (58.92)	167.03 (51.21)
Body Weight, kg, mean (SD)	93.63 (17.41)	95.63 (17.65)
BMI, kg/m^2, mean (SD)	33.4 (5.4)	34.5 (5.4)
eGFR (mL/min/1.73m^2), geo mean (CV)	45.4 (0.23)	45.5 (0.25)
eGFR (mL/min/1.73m^2), N (%)		
30- <45	61 (43.6)	59 (43.1)
45-59	78 (55.7)	78 (56.9)
>59	1 (0.7)	0 (0.0)
Urinary albumin:creatinine ratio (mg/g), geo mean (CV)	55.5 (7.58)	69.8 (5.75)
Blood pressure, mm Hg, mean (SD)		
Systolic	135.2 (14.8)	136.8 (14.4)
Diastolic	77.2 (9.8)	78.1 (9.3)
Hypertension, % patients at screening	90.0	88.3

*combination of background medication not allowed according to the protocol

SD=standard deviation; geo mean= geometrical mean; CV=coefficient of variance

Table 2 Summary of Treatment Emergent Adverse Events

Event	Liraglutide 1.8 mg			Placebo		
	N	%	E	N	%	E
Adverse events	107	76.4	365	94	68.6	341
Mild	89	63.6	242	77	56.2	218
Moderate	47	33.6	98	50	36.5	109
Severe	17	12.1	25	8	5.8	14
Serious adverse events	14	10.0	21	15	10.9	20
Possibly or probably related	65	46.4	157	37	27.0	88
Gastrointestinal	40	28.6	86	12	8.8	23
Fatal	4	2.9	8*	1	0.7	1
Leading to withdrawal	19	13.6	26	4	2.9	6
Gastrointestinal	9	6.4	11	1	0.7	1
Frequently reported AE						
Gastrointestinal disorders	50	35.7	115	24	17.5	47
Nausea	30	21.4	39	6	4.4	10
Mild	22	15.7	26	6	4.4	9
Moderate	10	7.1	12	1	0.7	1
Severe	1	0.7	1	0	0	0
Vomiting	17	12.1	18	3	2.2	4
Mild	8	5.7	9	1	0.7	2
Moderate	7	5.0	7	2	1.5	2
Severe	2	1.4	2	0	0	0
Diarrhea	10	7.1	13	4	2.9	6
Mild	8	5.7	9	2	1.5	2
Moderate	3	2.1	4	2	1.5	4
Constipation	8	5.7	9	2	1.5	2

Mild	7	5.0	8	2	1.5	2
Moderate	1	0.7	1	0	0	0
Investigations	38	27.1	61	33	24.1	55
Increased amylase	3	2.1	3	4	2.9	4
Increased lipase	21	15.0	23	12	8.8	13
Glomerular filtration rate decreased	9	6.4	10	7	5.1	14
Infections and infestations	29	20.7	34	35	25.5	46
Nasopharyngitis	7	5.0	7	16	11.7	17
Upper respiratory tract infection	4	2.9	4	7	5.1	8
Nervous system disorders	20	14.3	25	11	8.0	36
Headache	7	5.0	8	4	2.9	8
Renal and urinary disorders	13	9.3	13	16	11.7	19
Renal impairment	7	5.0	7	8	5.8	8
Cardiac Disorders	5	3.6	8	4	2.9	6

*One patient had 5 SAEs listed as fatal

N=number of patients; E=number of events
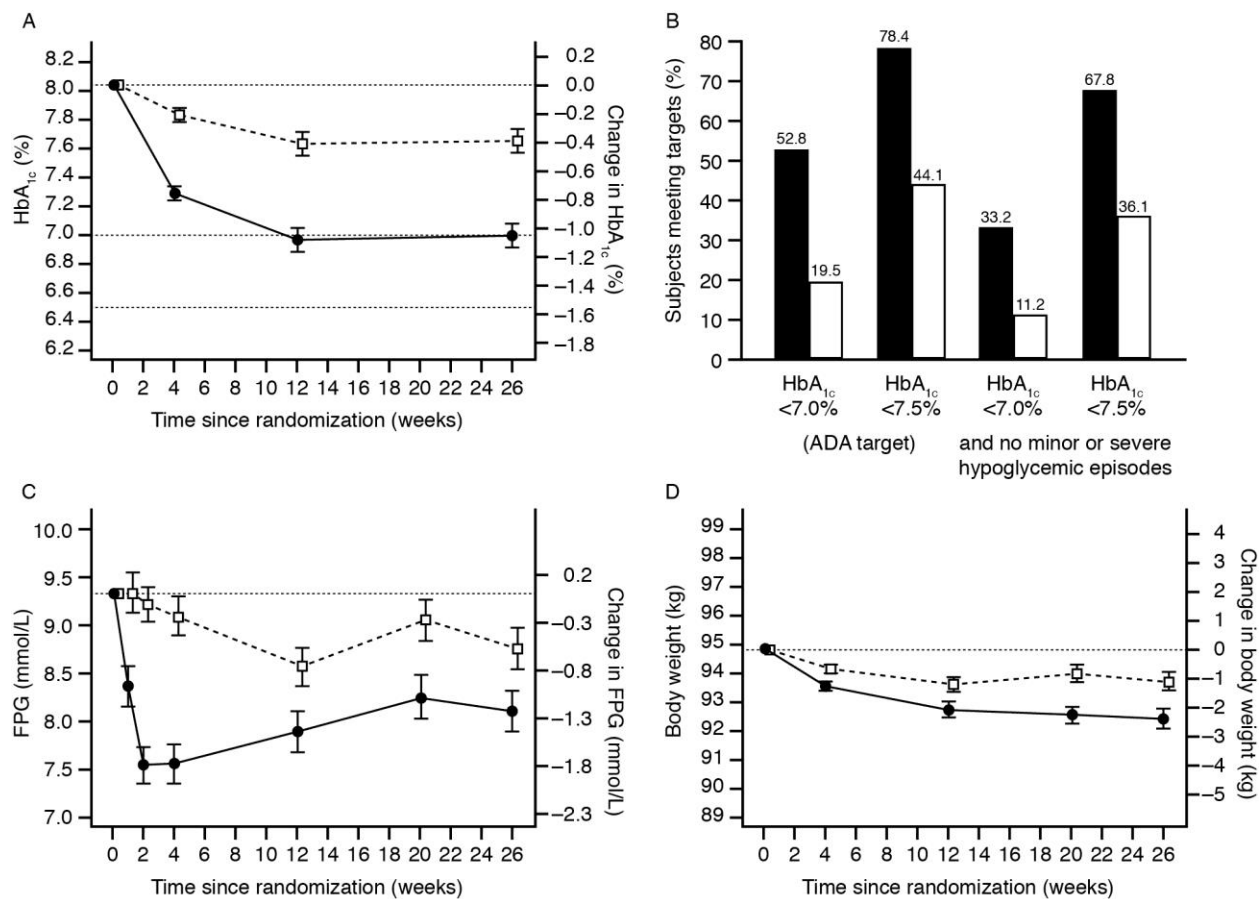
Figure 1 A: Estimated means plot ($\pm$ SE) of HbA$_{1c}$ (%) by treatment week and change from baseline to week 26. B: Responder endpoints for HbA$_{1c}$ <7.0%, HbA$_{1c}$ <7.5%, HbA$_{1c}$ <7.0% and no minor or severe hypoglycemic episodes and HbA$_{1c}$ <7.5% and no minor or severe hypoglycemic episodes at week 26. C: Estimated means plot ($\pm$ SE) of fasting plasma glucose (mmol/L) by treatment week and change from baseline to week 26. D: Estimated means plot ($\pm$ SE) of body weight (kg) by treatment week and change from baseline to week 26. Black circle/black bar liraglutide 1.8 mg; white square/white bar placebo
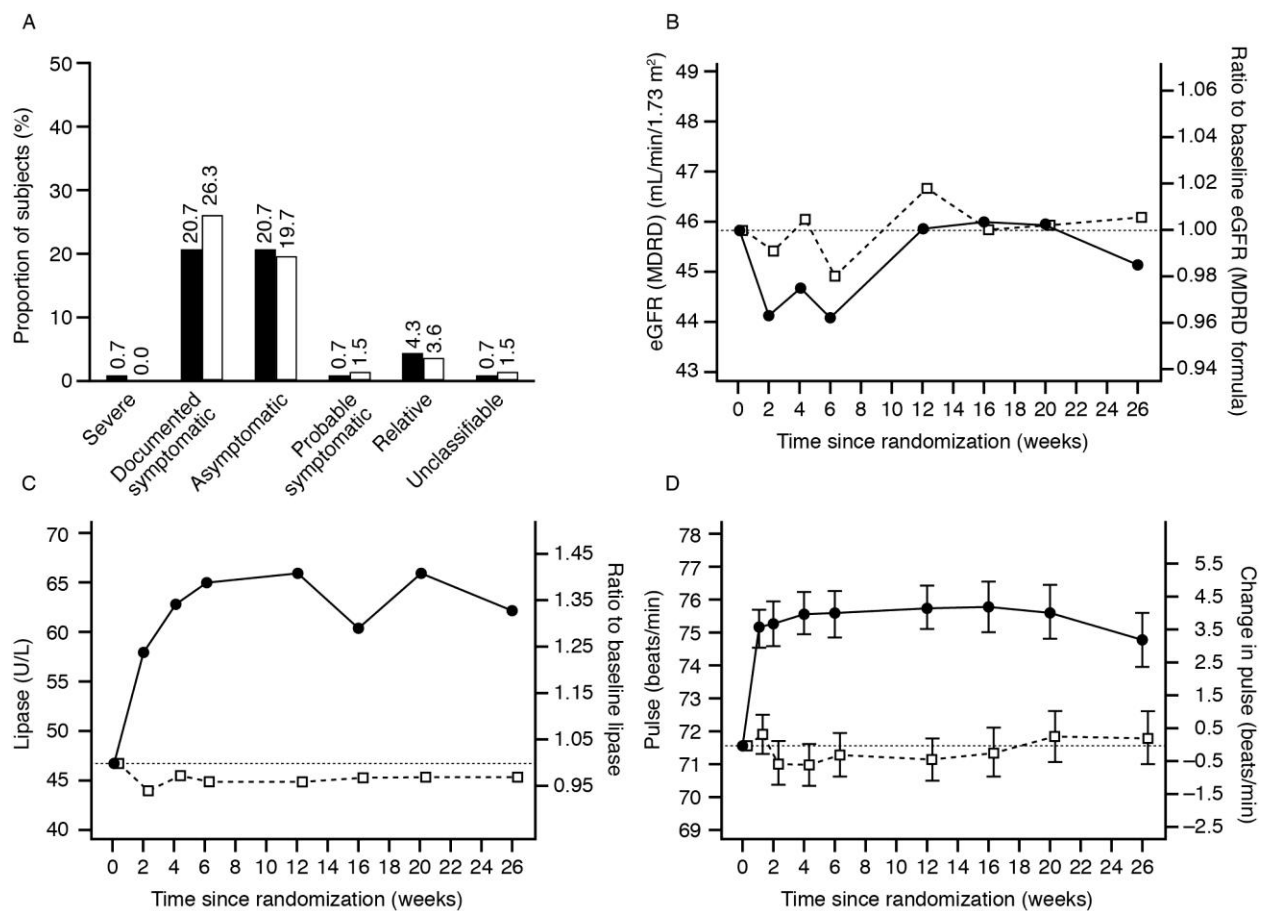
Figure 2-A: Summary of ADA defined hypoglycemia (severe: patient unable to treat themselves; documented symptomatic: PG ≤3.9 mmol/L [70 mg/dL]; asymptomatic: PG≤ 3.9 mmol/L [70 mg/dL]; relative: symptomatic and PG >3.9 mmol/L [70 mg/dL[). B: Estimated means plot of eGFR (MDRD formula) by treatment week and ratio to baseline at week 26. C: Estimated means plot of lipase (U/L) by treatment week and ratio to baseline at week 26. D: Estimated means plot (± SE) of pulse (beats/min) by treatment week and estimated means change from baseline to week 26. Black circle/black bar liraglutide 1.8 mg; white square/white bar placebo

Efficacy and Safety of Liraglutide versus Placebo as Add-on to Glucose Lowering Therapy in Patients with Type 2 Diabetes and Moderate Renal Impairment
(LIRA-RENAL): A Randomized Clinical Trial

<u>Supplemental Material:</u>

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Workup to Assess Possible Cases of Pancreatitis

The investigator was to ensure that subjects were informed of the characteristic symptoms of acute pancreatitis as part of the informed consent process. Confirmed cases of pancreatitis were to be followed-up with investigations of other potential causes (tests such as gallbladder ultrasound, triglycerides, liver enzymes, detailed history of concomitant medications or alcohol were suggested for follow up as part of the Investigators considerations relative to local standards of practice). If the investigator suspected acute pancreatitis, all suspected drugs were to be discontinued until confirmatory tests were conducted and appropriate treatment initiated. Subjects diagnoses with acute pancreatitis (as a minimum 2 of 3: characteristic abdominal pain, amylase and/or lipase >3×UNR or characteristic findings on CT scan /MRI) were to be withdrawn from the study.

Table 1 Change in HbA$_{1c}$ (%) from Baseline to Week 26 from Post-hoc Sensitivity Analyses

	N		Change at week 26 (%)		ETD	95% CI	CI width	p-value
	Lira	Placebo	Lira	Placebo				
Primary analysis (MMRM)	127	136	-1.05	-.038	-0.66	-0.90; -0.43	0.47	<0.0001
ANCOVA LOCF	135	136	-1.07	-.038	-0.69	-0.89; -0.50	0.39	<0.0001
Simple imputation post-hoc sensitivity analysis								
Unmodified BOCF	140	137	-0.86	-0.28	-0.58	-0.76; -0.39	0.37	<0.0001
BOCF and LOCF	140	137	-1.04	-0.37	-0.66	-0.86; -0.47	0.39	<0.0001
Multiple imputation post-hoc sensitivity analyses								
Placebo MI	140	137	-0.92	-0.39	-0.53	-0.75; -0.32	0.43	<0.0001
Differentiated MI	140	137	-1.01	-0.39	-0.62	-0.84; -0.40	0.44	<0.0001

Data are estimates from MMRM (primary analysis) and ANCOVA (sensitivity analyses) models with treatment, country and stratification group as fixed factors and the baseline value as covariate. N: number of subjects contributing to the analysis. ANCOVA: analysis of covariance. BOCF: baseline observation carried forward. CI: confidence interval. CI width: upper minus lower CI limit. ETD: estimated treatment difference. Lira: liraglutide. LOCF: last observation carried forward. MI, multiple imputation. MMRM: mixed model for repeated measurement.

Table 2 Observed Fasting Lipids at Baseline and at Week 26 (LOCF) and Estimated Treatment Ratio

	Total cholesterol (mmol/L), mean (SD)	LDL cholesterol (mmol/L), mean (SD)	VLDL cholesterol (mmol/L), mean (SD)	HDL cholesterol (mmol/L), mean (SD)	Trigylcerides (mmol/L), mean (SD)	Free fatty acids (mmol/L), mean (SD)
Liraglutide, Week 0	4.67 (1.24)	2.48 (1.05)	1.01 (0.52)	1.15 (0.30)	2.32 (1.50)	0.86 (0.41)
Liraglutide Week 26 (LOCF)	4.62 (1.34)	2.49 (1.08)	0.91 (0.53)	1.19 (0.35)	2.09 (1.39)	0.80 (0.34)
Placebo Week 0	4.74 (1.27)	2.52 (1.06)	1.00 (0.74)	1.20 (0.31)	2.33 (2.46)	0.89 (0.42)
Placebo Week 26 (LOCF)	4.59 (1.31)	2.43 (1.12)	0.87 (0.43)	1.25 (0.32)	1.99 (1.12)	0.82 (0.35)
Estimated treatment ratio* (95%CI) p	1.02 (0.97; 1.08) 0.4611	1.06 (0.97; 1.15) 0.2082	0.97 (0.88; 1.06) 0.4658	0.99 (0.94; 1.05) 0.8101	0.97 (0.88; 1.07) 0.5683	1.02 (0.90; 1.16) 0.7132

LOCF, last observation carried forward; SD, standard deviation; LDL, low density lipoprotein; VLDL, very low density lipoprotein; HDL, high density lipoprotein; *estimated treatment ratio=estimated ratio to baseline for liraglutide/estimated ratio to baseline for placebo (statistical analysis performed on log scale).

Table 3 Cardiovascular Biomarkers at Week 26

Biomarker	Liraglutide 1.8 mg	Placebo
hs-CRP		
ratio to baseline, estimated means	0.82	1.08
estimated treatment ratio (lira/placebo) (95% CI), p	0.76 (0.61; 0.96), 0.0220	
BNP		
ratio to baseline, estimated means	0.83	1.07
estimated treatment ratio (lira/placebo) (95% CI), p	0.78 (0.63; 0.97), 0.0273	
PAI-1		
ratio to baseline, estimated means	1.10	0.98
estimated treatment ration (lira/placebo) (95% CI), p	1.13 (0.96; 1.32) 0.1413	

Table 4 Details of Fatal Events

Treatment group	Sex	Age (yrs)	Duration of diabetes (yrs)	Pertinent Medical History	Strata (eGFR [mL/min/1.73 m^2]; insulin)	Days of Exposure	Preferre term(s) of f event
Liraglutide	Male	65	5.6	Significant CV disease; cerebral ischemia; hepatic steatosis; prostatic adenoma	$\geq$45; premix	125	Diabetic ketoacido
Liraglutide	Male	73	21.6	CV disease; hyperlipidemia	$\geq$45; basal	139	Cerebra hemorrha
Liraglutide	Male	70	32.5	CV disease; chronic pulmonary disease; sleep apnea; depression	<45; premix	131	Biliary sep
Liraglutide	Female	79	17.3	CV disease; pacemaker; conductive heart disease; hypertension; musculoskeletal disorder; osteoarthritis	<45; basal	33	Cerebrovas accident pulmona fibrosis; pulmona edema; le ventricula failure; pneumor
Placebo	Male	74	26.9	CV disease; myocardial infarctions; congestive heart failure; hyperlipidemia; transient ischemia attacks; cerebrovascular accident	<45; premix	116	Arterioscler

*Causality was assessed by the investigator; eGFR estimated glomerular filtration rate.

Table 5 Efficacy and Safety by eGFR strata and for the overall trial

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, estimated; 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

BL, baseline; AE, adverse events; SAE, serious adverse events; GI AE, gastrointestinal adverse events

Randomization

Treatment phase: 26 weeks

Background insulin therapy and/or OAD + liraglutide 1.8 mg (N=140)

n=279

Background medication was to remain stable throughout the trial except the dose for insulin or SU may be reduced in the case of hypoglycemia

Background insulin therapy and/or OAD + placebo (N=137; 139 randomized)

| 0 | 3 | 12 | 16 | 20 | 26 | 27 |

Time (weeks)

Liraglutide dose escalation

Follow-up

For patients on insulin with HbA$_{1c}$ ≤8% at screening

Day 0 to 21/28:
During the liraglutide dose escalation, the pre-trial insulin dose should be reduced by 20% at day 0 and kept fixed until liraglutide dose escalation is complete (further insulin dose reduction allowed for safety reasons)

Day 22/29 to Week 26:
Titration to ≤pre-trial insulin dose allowed if needed at the discretion of the investigator

Figure S1 Trial design

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                    ┌─────────────────────────┐
                    │   Screened (n=764)      │
                    └─────────────────────────┘
                                │
                                │         ┌──────────────────────────────────────────┐
                                │────────▶│ Excluded  (n=485)                        │
                                │         │ • Not meeting inclusion criteria (n=453) │
                                │         │ • Met exclusion criteria (n=23)          │
                                │         │ • Declined to participate (n=0)          │
                                ▼         │ • Other reasons (n=21)                   │
                    ┌─────────────────────┴────┐                                      │
                    │   Randomized (n=279)     │                                      │
                    └──────────────────────────┘
```

Screened (n=764)

Excluded (n=485)
• Not meeting inclusion criteria (n=453)
• Met exclusion criteria (n=23)
• Declined to participate (n=0)
• Other reasons (n=21)

Randomized (n=279)

Liraglutide 1.8 mg (n=140)
• Received allocated intervention (n=140)

Placebo (n=139)
• Received allocated intervention (n=137)
• Did not receive allocated intervention
  (one randomized in error; one due to
  meeting withdrawal criteria) (n=2)

Discontinued (n=35)*
• Adverse event (n=19)
• Non compliance (n=0)
• Withdrawal criteria (n=17)
  - Subject may withdraw at will any time (n=7)
  - Safety concern or judged non-compliant (n=6)
  - Acute pancreatitis (n=1)**
  - Unacceptable hyperglycemia (n=1)
  - Change in background diabetes treatment
    not in accordance with protocol (n=2)
• Other (n=1)

*2 subjects withdrew due to an AE and
meeting withdrawal criteria

**Subject (liraglutide) had an adverse event
(chronic pancreatitis) leading to withdrawal.
The primary reason given for withdrawal was
withdrawal criteria #4 (acute pancreatitis).

Discontinued (n=34)
• Adverse event (n=4)
• Non compliance (n=3)
• Withdrawal criteria (n=25)
  - Subject may withdraw at will any time (n=7)
  - Safety concern or judged non-compliant (n=5)
  - Acute pancreatitis (n=0)
  - Unacceptable hyperglycemia (n=4)
  - Change in background diabetes treatment
    not in accordance with protocol (n=9)
• Other (n=2)

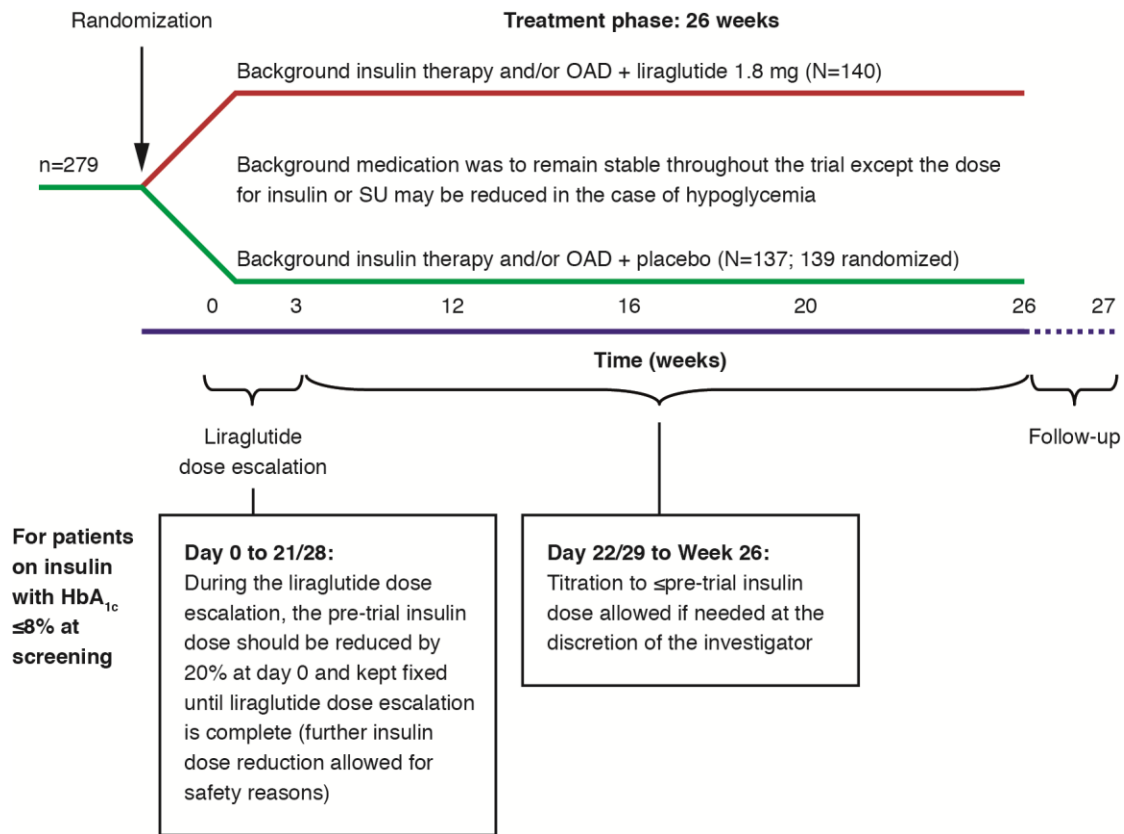Completed (n=105)
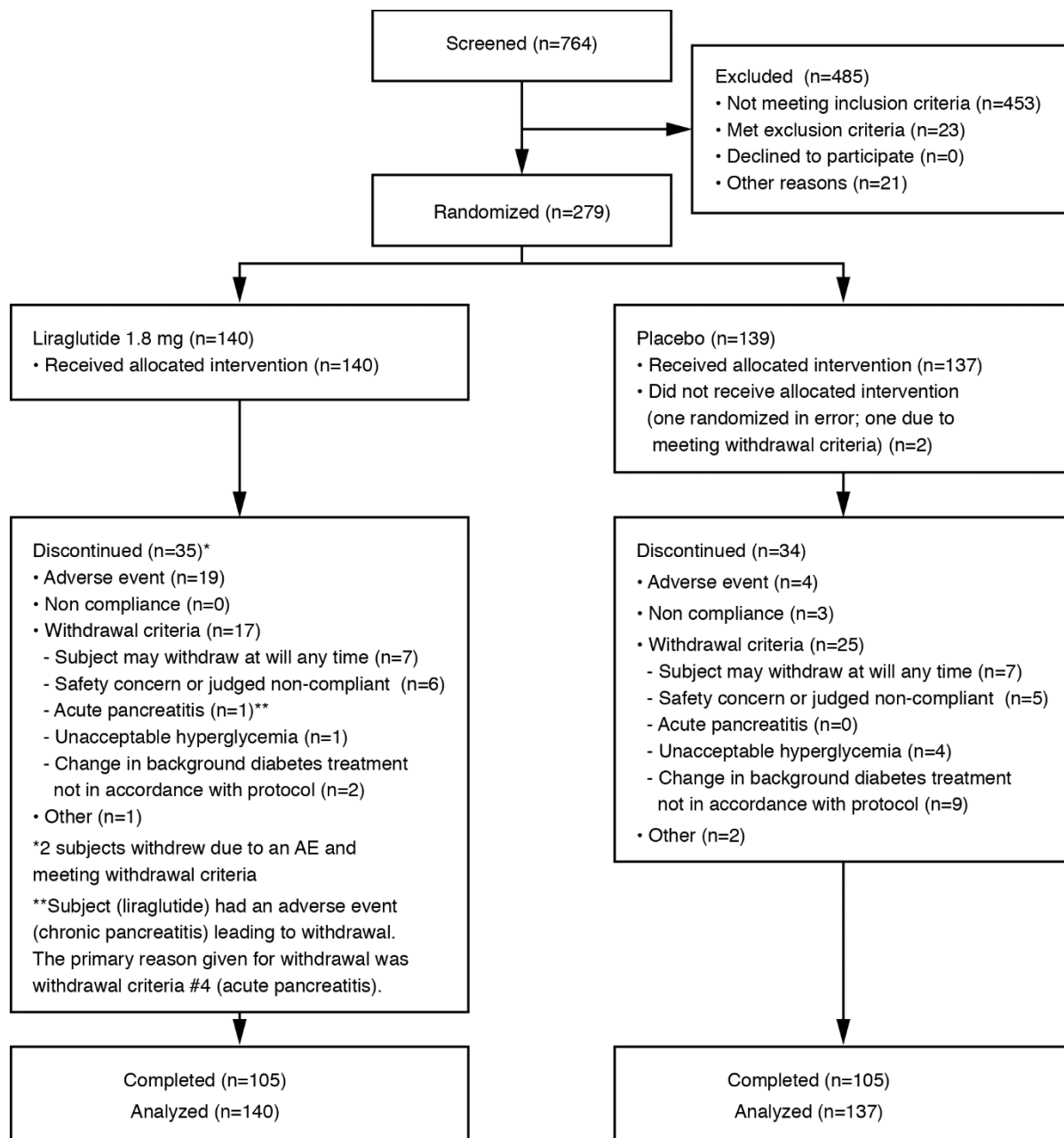Analyzed (n=140)

Completed (n=105)
Analyzed (n=137)

Figure S2 Consort Flow diagram

Protocol Amendments

There were 1 global and 7 local substantial protocol amendments to the final protocol (dated 09-April-2013). Protocol amendments were approved according to local requirements prior to implementation.

Table 3 List of Substantial Protocol Amendments

Amendment number	Issue date	Timing of change (before/after FSFV)	Countries affected	Key changes
1	27 FEB 2012	Before	United States	Pregnancies in partners of trial subjects to be reported
2	06 SEP 2012	After	France	Opening of new sites
3	18 SEP 2012	After	Poland	Opening of new sites
4	04 OCT 2012	After	France	Opening of new sites
5	14 NOV 2012	After	France	Opening of new sites
6	02 JAN 2013	After	United States	Change of text in Section 21 regarding FDA 1572 form
7	27 NOV 2012	After	Poland	Opening of new sites
8	09 APR 2013	After	Global	Changes to Table of contents, List of abbreviations, Section 6.4 Withdrawal criteria, Section 8.1 Visit procedures, Section 8.7 Assessments for safety, Section 9.1 Trial products, Section 12.3 Follow-up of adverse events, Section 14 Monitoring procedures, Section 17.3 Statistical Analysis of Primary endpoint, Appendix B, Master SI/IC Version 2.0 Section 1.5, SI/IC Version 1.0 Additional assessment for subjects with confirmed abnormality of the C-cells introduced.

FSFV=first subject first visit

The primary change in the US substantial amendment 1 (27 Feb 2012) was per an FDA request on Dec 9, 2011. Language was added in protocol section 12.4, Pregnancy to include if subjects or their partners become pregnant during the trial. Additionally, a pregnant partner consent form was written.

Changes in US substantial amendment 6 (02 Jan 2013) included one change made in protocol section 21, Critical documents, to clarify who should fill out the FDA 1572 form. In addition, errors were found in previously approved US local substantial amendment no. 1 dated 27 Feb 2012. The section numbers were incorrectly identified in amendment no. 1 as sections 12.4 and 12.4.1. This was corrected to sections 12.5 and 12.5.1 in the current amendment.

Global substantial protocol amendment number 8 (09 Apr 2013) included the following updates:

- Inclusion of *RET* gene testing upon granted informed consent and according to local law. The main reason for this global substantial protocol amendment was to allow for genetic testing of subjects with C-cell abnormality confirmed by pathology reports (medullary thyroid carcinoma [MTC] or C-cell hyperplasia). The subjects were to be asked to consent to have an additional blood sample taken to identify germline *RET* gene mutations associated with multiple endocrine neoplasia 2 (MEN2) syndrome. The genetic testing was only performed if consent had given by the subject and if allowed according to local law.

- Update to Protocol Section 12.3 Follow-up of adverse events. A minor mistake in the protocol template was corrected.

- Update to Protocol Section 17 Statistical Considerations. Based on consistent FDA feedback on use of LOCF in clinical trials in general, the statistical analyses section had been revised so that the primary statistical analysis will be performed using a mixed model for repeated measurements (MMRM), whereas ANCOVA using LOCF will be performed as described as a sensitivity analysis.

- General administrative and editorial updates. In addition, a few minor inconsistencies were discovered which were corrected to ensure correct interpretation of the trial protocol. This included an update of Appendix B.

- Update of master subject information/informed consent (SI/IC) and introduction of an additional SI/IC for subjects with confirmed C-cell abnormality. The master SI/IC was updated to reflect the possibility of genetic testing in case of thyroid surgery during the trial and an additional SI/IC was introduced to be obtained only from subjects with confirmed C-cell abnormality.

The remaining 5 local substantial amendments allowed for opening of new sites.