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

Melanie J. Davies,[1] Stephen C. Bain,[2] Stephen L. Atkin,[3] Peter Rossing,[4] David Scott,[5] Minara S. Shamkhalova,[6] Heidrun Bosch-Traberg,[7] Annika Syrén,[7] and Guillermo E. Umpierrez[8]

Diabetes Care 2016;39:222–230 | DOI: 10.2337/dc14-2883

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 an add-on to existing glucose-lowering medications in patients with inadequately controlled type 2 diabetes and moderate renal impairment.

RESEARCH DESIGN AND 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 (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^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]), *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 (GI) adverse effects (liraglutide, 35.7%; placebo, 17.5%). No difference in hypoglycemic episodes was observed between treatment groups (event rate/100 patient-years of exposure: liraglutide, 30.47; placebo, 40.08; *P* = 0.54). The estimated ratio to baseline for lipase was 1.33 for liraglutide and 0.97 for placebo (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.

[1]*Diabetes Research Centre, University of Leicester, Leicester, U.K.*
[2]*Institute of Life Science, Swansea University, Swansea, U.K.*
[3]*Qatar Foundation, Weill Cornell Medical College, Doha, Qatar*
[4]*Steno Diabetes Center, Gentofte, Denmark*
[5]*Clinical Research Development Associates, Rosedale, NY*
[6]*Department of Diabetic Nephropathy, Endocrinology Research Centre, Moscow, Russia*
[7]*Novo Nordisk A/S, Søborg, Denmark*
[8]*Division of Endocrinology, Metabolism and Lipids, Emory University, Atlanta, GA*

Corresponding author: Melanie J. Davies, melanie.davies@uhl-tr.nhs.uk.

Received 4 December 2014 and accepted 15 October 2015.

Clinical trial reg. no. NCT01620489, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-2883/-/DC1.

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, and end-stage. Stage 3 CKD (moderate renal impairment), defined as eGFR 30–59 mL/min/1.73 m^2, is further categorized as stage 3A (eGFR 45–59 mL/min/1.73 m^2) and stage 3B (30–44 mL/min/1.73 m^2) (1). In the U.S., CKD (eGFR $<$60 mL/min/1.73 m^2) occurs in $\sim$20% of patients with type 2 diabetes (2). In the UK Prospective Diabetes Study (UKPDS), 28% of patients with type 2 diabetes developed renal impairment after a median of 15 years after the 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 the safety risk in this population (9–12).

Liraglutide, a once-daily human glucagon-like peptide 1 (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 to $\leq$89 mL/min/1.73 m^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 an 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).

RESEARCH DESIGN AND METHODS

Trial Design

This trial was conducted 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 sites), Russian Federation (15 sites), Ukraine (6 sites), U.K. (9 sites), and U.S. (36 sites).

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 the sponsor remained blinded until trial completion. Stratification was based on the assessment of renal function (eGFR $<$45 or $\geq$45 mL/min/1.73 m^2 [MDRD formula]) using standardized creatinine measurements and insulin treatment (basal, premix, or no insulin). Liraglutide or placebo was 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 (Supplementary Fig. 1). At the discretion of the investigator, the dose escalation could have been extended up to 4 weeks in case of gastrointestinal (GI) adverse effects. Treatment was continued for 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 pretrial insulin dose was reduced by 20% at day 0 and kept fixed until the liraglutide dose escalation was complete. Titration to the pretrial insulin dose was allowed at the discretion of the investigator. Patients were to maintain their background diabetes medication throughout the trial. Patients using insulin or a sulfonylurea (SU) were allowed to reduce the dose of these agents if hypoglycemic episodes occurred.

Trial Population

Eligible trial patients were men and women, were aged 18–80 years (inclusive), were previously diagnosed with type 2 diabetes, had HbA_{1c} 7–10% (53–86 mmol/mol; inclusive), and were on stable diabetes treatment for $>$90 days before 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 patients were to have had moderate renal impairment $>$90 days before 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 (alanine transaminase $\geq$2.5$\times$ upper limit of normal [ULN]), history of chronic pancreatitis or idiopathic acute pancreatitis; New York Heart Association Functional Classification 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 Harmonisation 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 before the commencement of any trial-related activities.

Assessments

The primary efficacy end point was the change in HbA_{1c} from baseline to week 26. Responder end points 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-to-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 American Diabetes Association (ADA) definition (≤3.9 mmol/L [≤70 mg/dL]) (20). Furthermore, a category of confirmed hypoglycemic events (subject unable to treat him- or herself [severe] and/or has a plasma glucose <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 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% and an SD 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 end points were analyzed using a mixed-model repeated-measurement analysis. A model with treatment, country, and 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 they were entered 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 end points were analyzed using a logistic regression model. Frequencies were estimated for each treatment from the estimated odds for the corresponding treatment. The frequency for a treatment group was calculated as 100 × [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 liraglutide 1.8 mg (n = 140) or placebo (n = 139) (Supplementary Fig. 2). Two patients in the placebo group were not exposed to the trial medication. All remaining patients exposed to liraglutide (n = 140) or placebo (n = 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 older than in the placebo group. Overall, 16.6% of patients were elderly (≥75 years), and 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 to <45 mL/min/1.73 m^2) was ∼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]) (Fig. 1*A*), 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], P < 0.0001). Sensitivity analyses, conducted post hoc due to concerns about missing data, corroborated the results from the mixed-model repeated-measurement analysis (Supplementary Table 1). 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 (P = 0.4897 for subgroup by treatment interaction). 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], 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], 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%) (Fig. 1*B*). 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 prespecified, the target analyses were performed with an HbA_{1c} target of <7.5% because 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 (Fig. 1*C*). 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 [−22.5 to −0.76], P = 0.036).

Both treatment groups exhibited a gradual weight reduction during the trial (Fig. 1*D*). The patients in the liraglutide group had a greater reduction in body weight than the placebo group (−2.41 and −1.09 kg, respectively) with an ETD of −1.32 kg (95% CI −2.24 to −0.40, 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, 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 SUs were not determined.

From baseline to week 26, there was no treatment difference observed for change in the fasting lipid profile (P = 0.21–0.81) (Supplementary Table 2).

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, mean (SD), years	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, mean (SD), years	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, geometric mean (CV), IU	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)
HbA_{1c}, mean (SD), mmol/mol	64.8 (8.66)	63.9 (9.33)
FPG, mean (SD), mmol/L	9.48 (3.270)	9.27 (2.842)
FPG, mean (SD), mg/dL	170.83 (58.92)	167.03 (51.21)
Body weight, mean (SD), kg	93.63 (17.41)	95.63 (17.65)
BMI, mean (SD), kg/m^2	33.4 (5.4)	34.5 (5.4)
eGFR, geometric mean (CV), mL/min/1.73 m^2	45.4 (0.23)	45.5 (0.25)
eGFR, mL/min/1.73 m^2, *n* (%)		
30 to <45	61 (43.6)	59 (43.1)
45–59	78 (55.7)	78 (56.9)
>59	1 (0.7)	0 (0.0)
UACR, geometric mean (CV), mg/g	55.5 (7.58)	69.8 (5.75)
Blood pressure, mean (SD), mmHg		
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

CV, coefficient of variance. *Combination of background medication not allowed according to the protocol.

Several biomarkers were evaluated to assess the cardiovascular effects of liraglutide (Supplementary Table 3).

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

During 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% for stage 3A and 77.0% for stage 3B CKD; Supplementary Table 5) (21). The most common AEs reported with liraglutide were GI (35.7%), which tended to resolve quickly, and most were considered mild in severity. However, for subjects in the liraglutide group who withdrew due to a GI AE (9 subjects; 11 events), the majority of AEs were moderate (6 events) or severe (4 events). The most frequently reported GI AEs were nausea (21.4%) and vomiting (12%). AEs within the GI disorder and metabolism and nutrition disorders system organ classes are known adverse 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 the eGFR subgroup indicated that there was a slight difference in the percentage of subjects treated liraglutide who reported GI AEs, where more subjects with stage 3A CKD (38.0%) reported 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 SAEs 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 liraglutide group (diabetic ketoacidosis, cerebral hemorrhage, biliary sepsis, 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) (Supplementary Table 4). 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

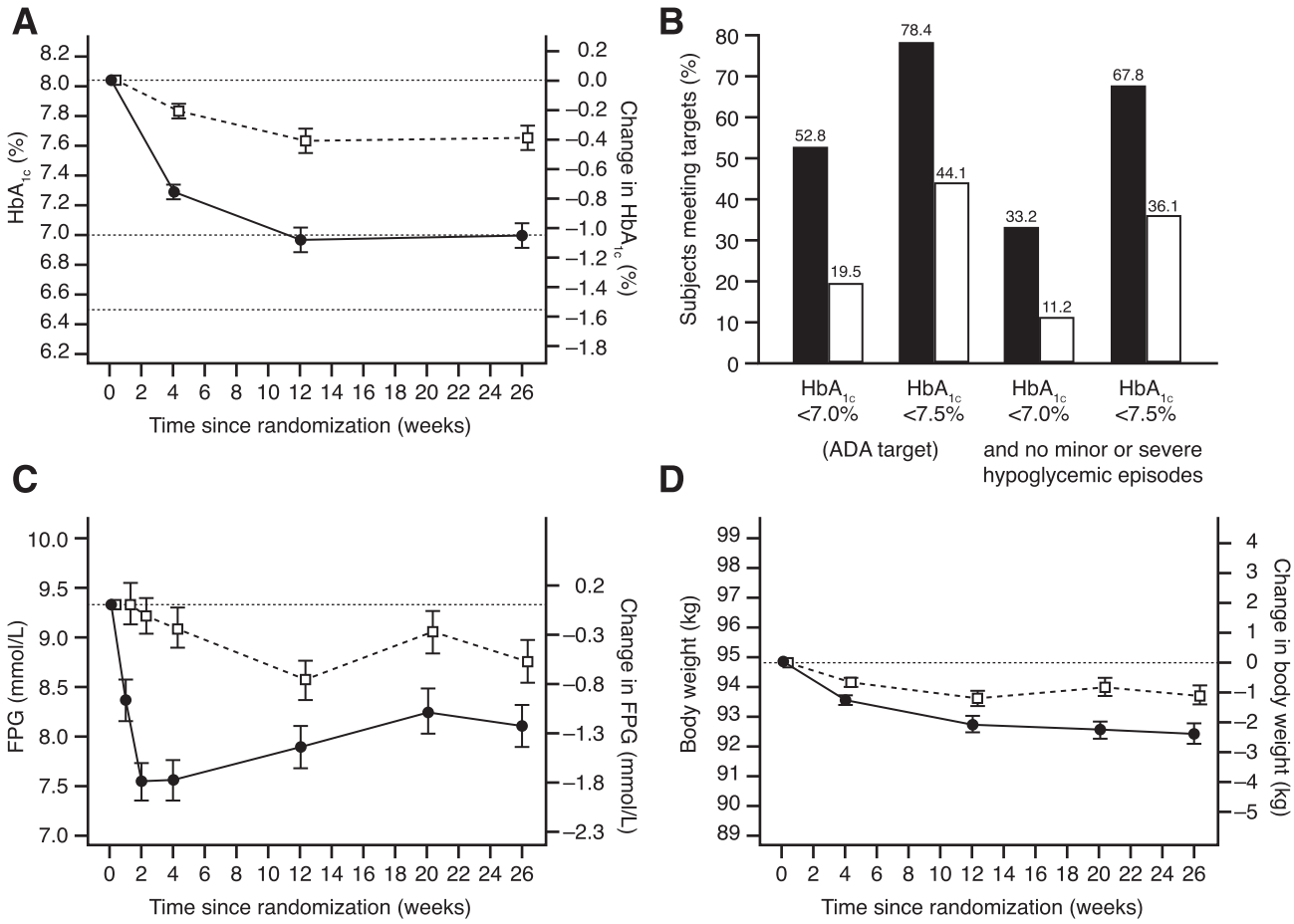

Figure 1—*A*: Estimated means plot (±SE) of HbA_{1c} (%) by treatment week and change from baseline to week 26. *B*: Responder end points for HbA_{1c} <7.0%, HbA_{1c} <7.5%, HbA_{1c} <7.0% and no minor or severe hypoglycemic episodes, and HbA_{1c} <7.5% and no minor or severe hypoglycemic episodes at week 26. *C*: Estimated means plot (±SE) of FPG (mmol/L) by treatment week and change from baseline to week 26. *D*: Estimated means plot (±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.

the four liraglutide deaths and as possible for the placebo death.

Documented symptomatic hypoglycemic episodes occurred in 20.7% of patients (97 episodes) in the liraglutide group and in 26.3% of patients (160 episodes) in the placebo group (20) (Fig. 2*A*). One severe hypoglycemic episode was reported in a 46-year-old woman 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. A confirmed hypoglycemic event occurred in 5.7% of patients in the liraglutide group and in 10.9% of patients in the placebo group, 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 of 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 the 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 the last observation carried forward (LOCF) was −0.35 mL/min/1.73 m^2 in the liraglutide group and +0.37 mL/min/1.73 m^2 in the placebo group. The estimated ratio of week 26 to baseline for eGFR (MDRD) was 0.99 (−1%) for the liraglutide group and was 1.01 (+1%) for the placebo group (Fig. 2*B*). The ETR of 0.98 (95% CI 0.94–1.02, P = 0.36) indicated that liraglutide did not affect the 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, no difference was seen in renal function parameters between treatment groups.

At baseline, 12.9% in the liraglutide group and 16.8% in the placebo group had an amylase at the ULN or higher. At week 26, 20.0% in the liraglutide group and 20.2% in the placebo group had an amylase at the ULN or higher. No amylase values three or more times the ULN were observed in the trial. The mean observed change in amylase levels from baseline to week 26, including LOCF, was 9.10 units/L for the liraglutide group and −0.31 units/L for the placebo group. The estimated ratio to baseline for amylase was 1.15 for the liraglutide group and 1.01 for the placebo group (ETR 1.14, $P < 0.0001$).

In the liraglutide group, 31.4% of patients had a baseline lipase value at

Table 2—Summary of treatment emergent AEs

	Liraglutide 1.8 mg			Placebo		
Event	Patients (*n*)	%	Events (*n*)	Patients (*n*)	%	Events (*n*)
AEs	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
SAEs	14	10.0	21	15	10.9	20
Possibly or probably related	65	46.4	157	37	27.0	88
GI	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
GI	9	6.4	11	1	0.7	1
Frequently reported AE						
GI 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
GFR 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 five SAEs listed as fatal.

ULN or higher, and at week 26, 48.6% of patients had a lipase at the ULN or higher (Fig. 2*C*). 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 at the ULN or higher, and at week 26, 20.4% of patients had a lipase at the ULN or higher. 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 that remained elevated at week 26. The mean observed change from baseline to week 26, including LOCF, was 18.97 units/L for the liraglutide group and −1.70 units/L for the placebo group. The estimated ratio to baseline for lipase was 1.33 in the liraglutide group and was 0.97 for the placebo group (ETR 1.37, $P < 0.0001$). At week 26, no patient treated with liraglutide, but one patient treated with placebo, had a lipase of three times the ULN or higher. None of the patients with elevated amylase or lipase had clinical evidence of acute pancreatitis (see Supplementary Data for workup details).

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

The mean pulse increased more with liraglutide (3.20 bpm) than with placebo (0.23 bpm) (Fig. 2*D*). This increase occurred by week 2 and remained stable throughout the remainder of the trial. The ETD was 2.98 bpm (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 bpm pulse increase from baseline, and 13.2% and 9.1% of liraglutide and placebo patients, respectively, exhibited a >15 bpm pulse increase from baseline, whereas 1.9% and 2.7%, respectively, had a >20 bpm 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/1.73 m^2) and uncontrolled type 2 diabetes, the addition of liraglutide to background glucose-lowering therapy produced clinically meaningful reductions in HbA_{1c} and FPG compared with placebo after 26 weeks of treatment. The percentage of responders was greater in the liraglutide group than in the placebo group for the dichotomous end points of HbA_{1c} <7.0% (<53 mmol/mol) and HbA_{1c} <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 ≥15 to <90 mL/min/1.73 m^2) (23) demonstrated that once-weekly albiglutide was more efficacious than sitagliptin. Like liraglutide, albiglutide is degraded by enzymatic catabolism (23), whereas exenatide (24)

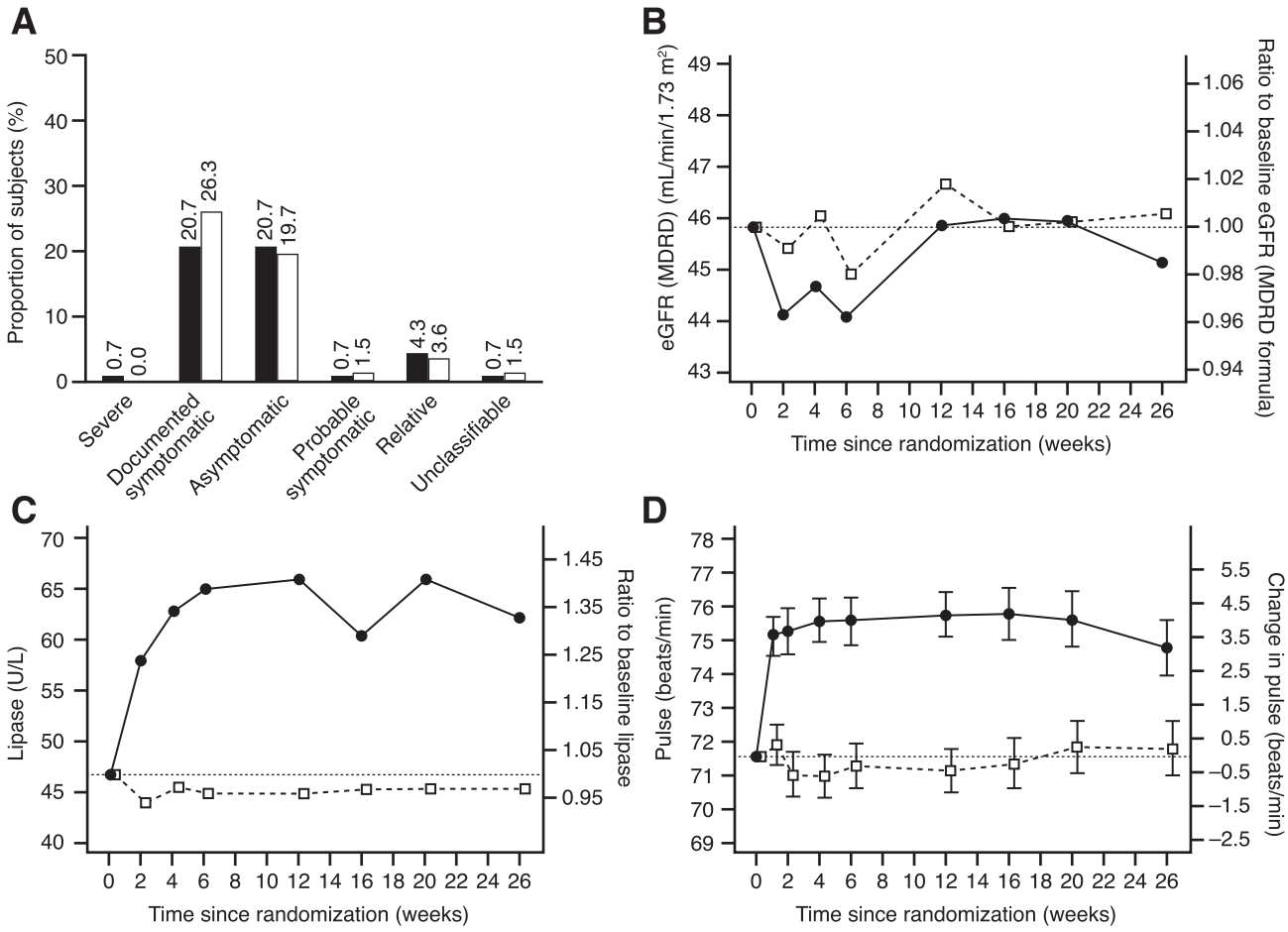

Figure 2—*A*: Summary of ADA-defined hypoglycemia (severe: patients unable to treat themselves; documented symptomatic: plasma glucose [PG] ≤3.9 mmol/L [70 mg/dL]; asymptomatic: PG ≤3.9 mmol/L [70 mg/dL]; relative: symptomatic and PG >3.9 mmol/L [70 mg/dL]). *B*: Estimated means plot of eGFR (MDRD formula) by treatment week and ratio to baseline at week 26. *C*: Estimated means plot of lipase (units/L) by treatment week and ratio to baseline at week 26. *D*: Estimated means plot (±SE) of pulse (bpm) 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.

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 with 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 with the liraglutide group. The long-term clinical effect of an increase in pulse has not yet been established.

Although 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 is also a cardiovascular risk factor (33,34).

Patients with CKD 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 the 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. One severe case of nausea and two of vomiting were reported in the liraglutide group.

In the LEAD 1–5 trials, the incidence of nausea, diarrhea, and vomiting ranged from 6.8 to 40%, 7.9 to 18.7%, and 5 to 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 GI effects when treated with liraglutide (16).

Compared with results from the albiglutide trial, the overall incidence of GI AEs 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 $\geq$15 to $<$90 mL/min/1.73 m^2 [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 elevated more in the liraglutide group than in 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). Lipase levels are elevated in ~20% of patients with type 2 diabetes (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 = 1,840) with moderate renal impairment and 12% of the patients (n = 3,417) with normal eGFR demonstrated elevated lipase levels at baseline (37). In this trial, ~20–30% of patients had elevated baseline lipase levels. However, because 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 dipeptidyl peptidase 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 GI effects, being experienced by the patients. Several post hoc sensitivity analyses, conducted due to concerns about 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 GI, 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 adverse 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. We acknowledge 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 and demonstrated better glycemic control and weight reduction, with no increase in hypoglycemia risk but with higher withdrawals due to GI AEs than placebo in patients with type 2 diabetes, and moderate renal impairment.

Acknowledgments. The authors thank all the investigators, study teams, and patients for participating in this study. Editorial support was provided by Michele Wells, PhD, of Novo Nordisk, Inc.

Funding. This study was sponsored by Novo Nordisk A/S.

Duality of Interest. M.J.D. has attended advisory panels for Novo Nordisk, Novartis, Sanofi, Eli Lilly & Co., AstraZeneca, Boehringer Ingelheim, Omnia-Med, Janssen, and Merck Sharp & Dohme; has attended speakers' bureaus for Novo Nordisk, Sanofi, Eli Lilly & Co., Merck Sharp & Dohme, AstraZeneca, Mitsubishi Tanabe Pharma Corp., and Boehringer Ingelheim; has acted as consultant for Novo Nordisk, Sanofi, Eli Lilly & Co., and Merck Sharp & Dohme; and has received research support from Novo Nordisk, Novartis, Eli Lilly & Co., and Merck Sharp & Dohme. S.C.B. has attended advisory panels for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Eli Lilly & Co., Merck Sharp & Dohme, Novo Nordisk, Omnia-Med, and Sanofi and is a board member for Glycosmedia. S.L.A. has attended advisory panels and speakers bureaux for Novo Nordisk. D.S. has attended advisory panels for Boehringer Ingelheim, consulted for Novo Nordisk, and has received unrestricted educational grants funded by Novo Nordisk and jointly by Eli Lilly & Co. and Boehringer Ingelheim. P.R. is an employee of the Steno Diabetes Center; has attended advisory panels for Novo Nordisk, Janssen, Eli Lilly & Co., Bristol-Myers Squibb, AstraZeneca, and Boehringer Ingelheim (fees to institution); has received research support from Novo Nordisk and AbbVie; and holds shares in Novo Nordisk. M.S.S. has received research support from Novo Nordisk, Boehringer Ingelheim, Merck Sharp & Dohme, and Sanofi. H.B.-T. and A.S. are full-time employees of Novo Nordisk. G.E.U. has attended advisory panels for Boehringer Ingelheim, Merck, Novo Nordisk, and Regeneron and has received research support to Emory University from Boehringer Ingelheim, Merck, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.J.D., S.C.B., S.L.A., P.R., D.S., M.S.S., H.B.-T., A.S., and G.E.U. contributed to the writing, revisions, critical review, and approval of the final manuscript. H.B.-T. and A.S. contributed to trial conduct or data collection and performed data analysis or interpretation. M.J.D. 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.

Prior Presentation. Parts of this study were presented in abstract form at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014, and at the 50th Annual Meeting of the European Association for the Study of Diabetes, Vienna, Austria, 15–19 September 2014.

References

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013;3:1–163
2. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2013 Annual Data Report*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2013
3. Reutens AT. Epidemiology of diabetic kidney disease. Med Clin North Am 2013;97:1–18
4. Avogaro A, Schernthaner G. Achieving glycemic control in patients with type 2 diabetes and renal impairment. Acta Diabetol 2013;50:283–291
5. Herrington WG, Nye HJ, Aung T. Metformin use in chronic kidney disease: new evidence to guide dosing. QJM 2013;106:1059–1061
6. Chan JC, Scott R, Arjona Ferreira JC, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes Obes Metab 2008;10:545–555
7. Schweizer A, Dejager S. Experience with vildagliptin in patients ≥75 years with type 2 diabetes and moderate or severe renal impairment. Diabetes Ther 2013;4:257–267
8. McGill JB, Sloan L, Newman J, et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study. Diabetes Care 2013;36:237–244
9. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Int 2014;85:962–971
10. Krepinsky J, Ingram AJ, Clase CM. Prolonged sulfonylurea-induced hypoglycemia in diabetic patients with end-stage renal disease. Am J Kidney Dis 2000;35:500–505
11. Rabkin R, Ryan MP, Duckworth WC. The renal metabolism of insulin. Diabetologia 1984;27:351–357
12. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med 2001;161:1653–1659
13. Knudsen LB, Nielsen PF, Huusfeldt PO, et al. Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. J Med Chem 2000;43:1664–1669
14. Malm-Erjefalt M, Bjornsdottir I, Vanggaard J, et al. Metabolism and excretion of the once-daily human glucagon-like peptide-1 analog liraglutide in healthy male subjects and its in vitro degradation by dipeptidyl peptidase IV and neutral endopeptidase. Drug Metab Dispos 2010;38:1944–1953
15. Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. Br J Clin Pharmacol 2009;68:898–905
16. Davidson JA, Brett J, Falahati A, Scott D. Mild renal impairment and the efficacy and safety of liraglutide. Endocr Pract 2011;17:345–355
17. World Medical Association. *Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects*. 59th WMA General Assembly, Seoul. 1 October 2008.
18. International Conference on Harmonisation. *ICH Harmonised Tripartite Guideline*. Good Clinical Practice, 01 May 1996
19. Levey AS, Coresh J, Greene T, et al.; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–254
20. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–1249
21. Scott D, Umpierrez G, Atkin S, et al. Efficacy and safety of liraglutide versus placebo by eGFR subgroup in subjects with type 2 diabetes and moderate renal impairment (LIRA-RENAL): a randomized trial (Abstract). J Am Soc Nephrol 2014;25:75A
22. Giorda CB, Nada E, Tartaglino B. Pharmacokinetics, safety, and efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in patients with type 2 diabetes mellitus and renal or hepatic impairment. A systematic review of the literature. Endocrine 2014;46:406–419
23. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. Diabetes Care 2014;37:2723–2730
24. Copley K, McCowen K, Hiles R, Nielsen LL, Young A, Parkes DG. Investigation of exenatide elimination and its in vivo and in vitro degradation. Curr Drug Metab 2006;7:367–374
25. Dicembrini I, Bigiarini M, Mannucci E. Lixisenatide: clinical profile and available evidence. Diabetes Manage 2014;4:71–84
26. Davies MJ, Kela R, Khunti K. Liraglutide - overview of the preclinical and clinical data and its role in the treatment of type 2 diabetes. Diabetes Obes Metab 2011;13:207–220
27. Marre M, Shaw J, Brändle M, et al.; LEAD-1 SU study group. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med 2009;26:268–278
28. Nauck M, Frid A, Hermansen K, et al.; LEAD-2 Study Group. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 study. Diabetes Care 2009;32:84–90
29. Garber A, Henry R, Ratner R, et al.; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473–481
30. Zinman B, Gerich J, Buse JB, et al.; LEAD-4 Study Investigators. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care 2009;32:1224–1230
31. Russell-Jones D, Vaag A, Schmitz O, et al.; Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SU Study Group. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia 2009;52:2046–2055
32. Buse JB, Rosenstock J, Sesti G, et al.; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39–47
33. Gerstein HC, Mann JF, Yi Q, et al.; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421–426
34. Schmieder RE, Mann JF, Schumacher H, et al.; ONTARGET Investigators. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. J Am Soc Nephrol 2011;22:1353–1364
35. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 2009;4:1121–1127
36. Steinberg W, DeVries JH, Wadden TA, Jensen CB, Svendsen CB, Rosenstock. Tu1502 longitudinal monitoring of lipase and amylase in adults with type 2 diabetes and obesity: evidence from two phase 3 randomized clinical trials with the once-daily GLP-1 analog liraglutide. Gastroenterology 2012;142:S850–S851
37. Steinberg WM, Nauck MA, Zinman B, et al.; LEADER Trial investigators. LEADER 3–lipase and amylase activity in subjects with type 2 diabetes: baseline data from over 9000 subjects in the LEADER Trial. Pancreas 2014;43:1223–1231
38. Lando HM, Alattar M, Dua AP. Elevated amylase and lipase levels in patients using glucagonlike peptide-1 receptor agonists or dipeptidyl-peptidase-4 inhibitors in the outpatient setting. Endocr Pract 2012;18:472–477