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

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OBJECTIVE—This placebo-controlled study assessed long-term efficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin in patients with type 2 diabetes and severe renal impairment (RI).

RESEARCH DESIGN AND METHODS—In this 1-year, double-blind study, 133 patients with type 2 diabetes (HbA_{1c} 7.0–10.0%) and severe RI (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) at screening were randomized to linagliptin 5 mg (n = 68) or placebo (n = 65) once daily, added to existing background therapy. The primary efficacy end point was HbA_{1c} change from baseline to week 12. Efficacy and safety end points were assessed after 1 year.

RESULTS—At week 12, adjusted mean HbA_{1c} decreased by −0.76% with linagliptin and −0.15% with placebo (treatment difference, −0.60%; 95% CI −0.89 to −0.31; $P < 0.0001$). HbA_{1c} improvements were sustained with linagliptin (−0.71%) over placebo (0.01%) at 1 year (treatment difference −0.72%, −1.03 to −0.41; $P < 0.0001$). Mean insulin doses decreased by −6.2 units with linagliptin and −0.3 units with placebo. Overall adverse event incidence was similar over 1 year (94.1 vs. 92.3%). Incidence of severe hypoglycemia with linagliptin and placebo was comparably low (three patients per group). Linagliptin and placebo had little effect on renal function (median change in eGFR, −0.8 vs. −2.2 mL/min/1.73 m^2), and no drug-related renal failure occurred.

CONCLUSIONS—In patients with type 2 diabetes and severe RI, linagliptin provided clinically meaningful improvements in glycemic control with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure. The potential for linagliptin to spare insulin and provide long-term renal safety warrants further investigations.

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Diabetes, predominantly type 2, is reaching epidemic proportions, with global prevalence estimated to increase from 8.3%, affecting 366 million adults in 2011, to 9.9% or 552 million adults, by 2030 (1). Concurrent with this increase, the prevalence of chronic kidney disease (CKD) is rising worldwide (2,3). Diabetes has been identified as the leading cause of CKD, which may progress to end-stage renal disease (ESRD) or increase the risk of death (3,4). This association represents an increasing burden for patients and health care systems, particularly in developing countries (5,6).

Standards of diabetes care recommend reducing the risk, or slowing the progression, of CKD by optimizing glycemic control (7). However, most drugs available to treat hyperglycemia are affected by kidney function and should therefore be either avoided or used at reduced doses in patients with CKD (8,9). Consequently, there is a great need to focus on optimal diabetes management in patients with type 2 diabetes and CKD.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are one of the latest therapeutic classes of glucose-lowering medications. Within this class, linagliptin uniquely has a primarily nonrenal route of elimination, with only ~5% of the dose being excreted via the kidneys (10,11). This contrasts with other DPP-4 inhibitors, such as sitagliptin, vildagliptin, saxagliptin, and alogliptin that are predominantly cleared by renal excretion (12). Thus, linagliptin needs no dose adjustment in patients with impaired renal function (13,14). Dose adjustment is recommended for sitagliptin, saxagliptin, and vildagliptin in patients with creatinine clearance <50 mL/min, including those with ESRD requiring dialysis (12).

Previous clinical studies have shown that linagliptin achieves clinically meaningful improvements in glycemic control in patients with type 2 diabetes either as monotherapy (15–17) or in combination with metformin (18), metformin/sulfonylurea (19), or a thiazolidinedione (20). Those studies demonstrated the overall safety and tolerability of linagliptin (21). The objective of this study was to investigate the long-term efficacy, safety, and tolerability of linagliptin compared with placebo when administered in combination with existing glucose-lowering background therapy in patients with type 2 diabetes and severe renal impairment (RI) over 52 weeks.

RESEARCH DESIGN AND METHODS

Study population

Eligible study participants were women (nonfertile or using a medically approved

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A complete list of the study investigators can be found in the Supplementary Data online.

birth control method) and men aged 18–80 years, previously diagnosed with type 2 diabetes, who were treated with glucose-lowering agents, including insulin, sulfonylurea, glinides, pioglitazone, and α-glucosidase inhibitors. Existing glucose-lowering therapy must have remained unchanged for ≥8 weeks before study entry. Participants fulfilled the criteria for severe RI (CKD stage 4/5) at screening, having an estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease study equation of <30 mL/min/1.73 m^2 (while not receiving chronic dialysis). In addition, participants had an HbA_{1c} >7 and ≤10% (>53 and ≤86 mmol/mol) and a BMI ≤45 kg/m^2. Exclusion criteria at screening included the following: myocardial infarction (MI), stroke, or transient ischemic attack within the previous 6 months; any requirement for acute dialysis within the previous 3 months; renal transplantation; impaired hepatic function; and use of any other DPP-4 inhibitor or antiobesity drug within the previous 3 months.

The study was carried out according to the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice principles. The protocol was approved by the independent ethics committee or institutional review board at each participating site. All participants provided written informed consent.

Study design

This randomized, double-blind, placebo-controlled, parallel group study was carried out at 53 sites in six countries (Australia, Hong Kong, Israel, New Zealand, Ukraine, and U.S.). It comprised a 2-week, open-label, placebo run-in period, followed by a 52-week double-blind treatment period, and a 1-week follow-up period.

Study participants who met the eligibility criteria at screening and at the end of the 2-week placebo run-in period were randomized (1:1) to receive double-blind treatment with either linagliptin (5 mg/day) or placebo in addition to their glucose-lowering background therapy for 52 weeks. This allocation was stratified by HbA_{1c} (≤8 vs. >8% [≤64 vs. >64 mmol/mol]) and glucose-lowering background therapy. Study investigators and participants were blinded to treatment assignment for the duration of the study and to results of interim analyses.

To assess the glucose-lowering effect of adding linagliptin, stable doses of existing background therapy were maintained during the first 12 weeks of treatment (unless dose adjustment was required for safety reasons). During the following 40-week treatment period, background therapy could be adjusted according to glucose parameters.

Rescue therapy (any changes in treatment or doses of glucose-lowering background therapy during weeks 1–12 and/or addition of insulin during weeks 1–52) could be initiated based on failure to meet prespecified glycemic response criteria: a confirmed fasting plasma glucose (FPG) level >240 mg/mL (>13.3 mmol/L) during weeks 1–12, a confirmed FPG level >200 mg/dL (>11.1 mmol/L) during weeks 12–52, or a randomly determined glucose level >400 mg/dL (>22.2 mmol/L) at any time. Patients who failed to meet these criteria despite rescue therapy were discontinued from the study.

Routine laboratory analyses and determinations of HbA_{1c} and plasma glucose were performed by a central laboratory (Clearstone Facilities; Canada, U.S., Singapore, and/or France).

Study end points

The primary efficacy end point was the change from baseline to week 12 in HbA_{1c} to determine the superiority of linagliptin over placebo. Secondary efficacy end points included changes from baseline to week 52 in HbA_{1c}, FPG, glucose-lowering background therapy, and body weight.

Safety and tolerability end points included the frequency and intensity of adverse events (AEs), withdrawals because of AEs, physical examinations, 12-lead electrocardiograms, vital signs, and clinical laboratory assessments throughout the 52 weeks. Hypoglycemic events and severe hypoglycemic episodes were recorded (22). Additionally, an independent clinical event committee (CEC) prospectively reviewed, in a blinded fashion, all reports of treatment-emergent fatal events and suspected cardiovascular (CV) events and evaluated whether prespecified criteria for adjudication end points (CV death, stroke, MI, and hospitalization for unstable angina) were met.

Statistical analyses

Assuming that the SD of change from baseline in HbA_{1c} was 1.0% in both treatment groups, a total of 50 patients in each group were required to achieve a power of 93% to detect a 0.7% difference in HbA_{1c} change from baseline to week 12. An additional 15 patients per group were added to account for patients with potentially missing baseline HbA_{1c} values or without any on-treatment HbA_{1c} value, resulting in 65 patients per treatment group (25% planned dropout rate).

The primary efficacy end point, change from baseline to week 12 in HbA_{1c}, was tested using a superiority hypothesis of linagliptin to placebo at the two-sided 5% level of significance. A protocol-defined interim analysis was performed after all study participants completed the first 12 weeks. Type I error rate was controlled for the primary end point analyzed at 12 weeks.

The change from baseline to weeks 12 and 52 in HbA_{1c} was assessed using ANCOVA with treatment and glucose-lowering background drugs as fixed-classification effects and continuous HbA_{1c} and renal function at baseline as linear covariates. This analysis was performed on the full analysis set (FAS) using last observation carried forward (LOCF) to impute missing data. The FAS included randomized participants who received ≥1 dose of treatment and who had both a baseline and ≥1 on-treatment HbA_{1c} measurement. ANCOVAs were also used to assess changes in FPG at weeks 12 and 52 in the FAS (LOCF) and the change in body weight at week 52 in the FAS observed cases.

Logistic regression with baseline HbA_{1c}, treatment (linagliptin or placebo), glucose-lowering background therapy, baseline renal function, and treatment–baseline renal function interaction as covariates was used to assess the percentage of patients who attained the HbA_{1c} target (<7.0% [<53 mmol/mol]) in the FAS. Logistic regression with treatment, glucose-lowering background therapy, and baseline renal function as covariates was also used to analyze the percentage of patients who used rescue therapy on the FAS (observed cases). All values measured after intake of rescue medication were set to missing.

Changes in glucose-lowering background therapy and safety were analyzed in the treated set (TS) using descriptive statistics. The TS included randomized participants who received ≥1 dose of treatment.

RESULTS

Patient disposition

A total of 133 patients were randomized to receive either linagliptin or placebo in addition to their glucose-lowering background therapy (68 vs. 65 patients, respectively). The primary efficacy analysis

was performed for 128 patients (FAS). Of those, 106 patients (linagliptin, 56; placebo, 50) had data available from baseline to week 12, and data for the remaining patients were imputed using LOCF either because they were missing or their data were recorded after intake of rescue medication. The 1-year study was completed by 97 (72.9%) patients (linagliptin, 72.1; placebo, 73.8%) (Fig. 1). The primary reasons for discontinuation were AEs (linagliptin, 11.8; placebo, 16.9%) and refusal to continue medication (linagliptin, 10.3; placebo, 1.5%). One patient in the linagliptin group refused to continue due to perceived lack of efficacy. The others who refused to continue gave no cause. Other reasons for discontinuation were lack of therapeutic effect (linagliptin, 1.5; placebo, 1.5%) and loss to follow-up (linagliptin, 1.5; placebo, 4.6%). Mean exposure to study treatment was 313 and 299 days in the linagliptin and placebo groups, respectively. Median exposure was 364 days in both groups.

Demographics and baseline characteristics

Patient demographics and baseline clinical characteristics were generally well-balanced between groups (Table 1). Mean ± SD age, BMI, and baseline HbA_{1c} were 64.4 ± 10.3 years, 32.0 ± 5.8 kg/m^2, and 8.2 ± 1.0% (66 ± 11 mmol/mol), respectively. Overall, most patients were white (73.7%). There were more men (60.2%) than women (39.8%), with a higher proportion of men in the linagliptin group than in the placebo group (66.2 vs. 53.8%, respectively). More than half of patients were aged ≥65 years (55.6%), classified as obese (BMI ≥30 kg/m^2, 66.2%), and had an HbA_{1c} ≥8% (≥64 mmol/mol; 54.7%). Most patients (96.1%) had type 2 diabetes for >5 years and were receiving glucose-lowering background monotherapy (76.7%), with 63.9% treated with insulin alone and 18.0% with insulin combination therapy. The most common concomitant medications (linagliptin vs. placebo) were antihypertensive agents (94.1 vs. 100.0%), lipid-lowering agents (77.9 vs. 80.0%), and acetylsalicylic acid (67.6 vs. 69.2%). The most frequent concomitant diagnoses were hypertension (94.1 vs. 100.0%), diabetic nephropathy (88.2 vs. 95.4%), diabetic retinopathy (63.2 vs. 53.8%), and metabolic syndrome (54.4 vs. 61.5%). All patients had protocol-defined severe RI at screening. However, due to common fluctuations in renal function seen in advanced stages of kidney disease, 14.3% of patients had eGFR in the range of 30–60 mL/min/1.73 m^2 at baseline (assessed ≥2 weeks after screening). The classification of 92.7% of patients in the linagliptin group remained severe RI at baseline (Table 1). In addition, slightly different formulae were used to calculate eGFR at the initial screening by the central laboratory and at baseline evaluations by the linagliptin study program. Patients were randomized based on the central laboratory calculation of eGFR, which did not take race into account, whereas baseline eGFR values were classified on the linagliptin program formula, which included race as a factor.

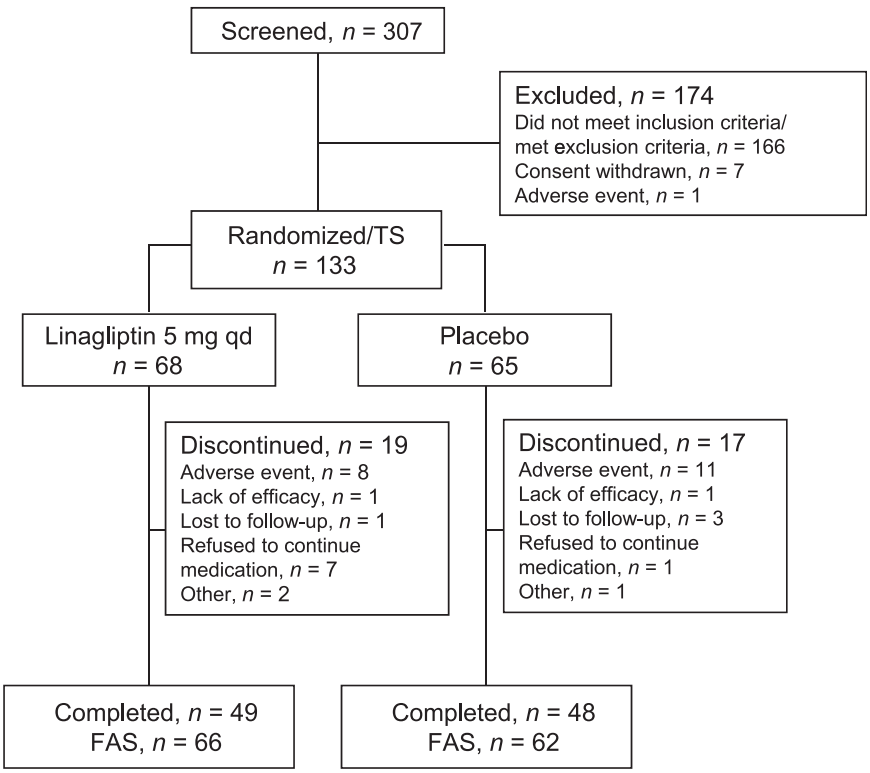

Figure 1—*Flow chart of participants. The first participant was enrolled on 11 December 2008, and the last participant completed assessments on 5 January 2011. qd, once daily.*

Efficacy

Adjusted mean HbA_{1c} change from baseline over time is shown in Fig. 2*A*. At weeks 12 (primary end point) and 52 (secondary end point), linagliptin was superior to placebo in lowering HbA_{1c} (Fig. 2*B*). Treatment differences for linagliptin versus placebo were −0.60% (95% CI −0.89 to −0.31; $P < 0.0001$) at week 12 and −0.72% (95% CI −1.03 to −0.41; $P < 0.0001$) at week 52. Similar results were seen in subgroups with baseline HbA_{1c} ≤8 and >8% (≤64 and >64 mmol/mol) (Fig. 2*C*). The proportion of patients with baseline HbA_{1c} ≥7% who reached the target of HbA_{1c} <7% (<53 mmol/mol) at week 52 tended to be higher with linagliptin than with placebo (18.0 vs. 9.8%, respectively; odds ratio 2.886, 95% CI 0.769–10.836; $P = 0.2225$).

Both the linagliptin and placebo groups demonstrated similar decreases from baseline to week 12 in FPG (adjusted mean change, −0.49 vs. −0.39 mmol/L; treatment difference, −0.10; 95% CI −1.35 to 1.16; $P = 0.8802$). A similar result was seen at week 52 (adjusted mean change, −0.30 vs. −0.38 mmol/L; treatment difference, 0.07; 95% CI, −0.82 to 0.97; $P = 0.8698$).

The proportion of patients with ≥1 change in daily glucose-lowering background therapy from baseline to week 52 was similar between groups (47.1 vs. 50.8%). In the linagliptin group, 81.3% of patients with changes in background therapy had ≥1 dose decrease, and 34.4% had ≥1 dose increase. In the placebo group, 42.4% of patients with changes had ≥1 dose decrease, and 60.6% had ≥1 dose increase. Background insulin therapy was adjusted in 28 patients in the linagliptin and placebo groups (51.9 vs. 50.9% of insulin-treated

Table 1—*Demographic and baseline clinical characteristics in the TS*

	Linagliptin (*n* = 68)	Placebo (*n* = 65)
Age (years)	64.0 ± 10.9	64.9 ± 9.6
<65 years [*n* (%)]	29 (42.6)	30 (46.2)
≥65 years [*n* (%)]	39 (57.4)	35 (53.9)
Sex [*n* (%)]		
Men	45 (66.2)	35 (53.8)
Women	23 (33.8)	30 (46.2)
Race [*n* (%)]		
White	53 (77.9)	45 (69.2)
Asian	8 (11.8)	11 (16.9)
Black/African American	6 (8.8)	7 (10.8)
Other	2 (3.1)	1 (1.5)
Body weight (kg)	89.9 ± 19.0	85.7 ± 17.6
BMI (kg/m^2)	32.3 ± 5.8	31.7 ± 5.9
BMI <30 kg/m^2 [*n* (%)]	18 (26.5)	27 (41.5)
BMI ≥30 kg/m^2 [*n* (%)]	50 (73.5)	38 (58.5)
eGFR (mL/min/1.73 m^2)	22.1 ± 6.3	25.1 ± 6.9
eGFR [*n* (%) in each category][a]		
30–60 mL/min/1.73 m^2	5 (7.4)	14 (21.5)
15–30 mL/min/1.73 m^2	55 (80.9)	45 (69.2)
<15 mL/min/1.73 m^2	8 (11.8)	6 (9.2)
Duration of type 2 diabetes, >5 years [*n* (%)]	64 (97.0)	59 (95.2)
HbA_{1c} (%)[b]	8.2 ± 1.1	8.2 ± 0.9
HbA_{1c} [*n* (%) in each category][b]		
<7% (<53 mmol/mol)	5 (7.6)	1 (1.6)
≥7 and <8% (53–64 mmol/mol)	29 (43.9)	23 (37.1)
≥8 and <9% (64–75 mmol/mol)	21 (31.8)	25 (40.3)
≥9% (≥75 mmol/mol)	11 (16.7)	13 (21.0)
FPG[b] (mmol/L)	8.3 ± 4.4	8.9 ± 3.6
Glucose-lowering background therapy [*n* (%)]		
Insulin		
Monotherapy	39 (57.4)	46 (70.8)
Combination therapy	15 (22.1)	9 (13.8)
Mean baseline dose [units (SD)]	67.7 (50.7)	62.9 (57.7)
Sulfonylurea		
Monotherapy	9 (13.2)	7 (10.8)
Combination therapy with any other OAD(s)	4 (5.9)	2 (3.0)
Glitazone	—	1 (1.5)
α-Glucosidase inhibitor + glinide	1 (1.5)	—

Data are expressed as mean ± SD unless stated otherwise. OAD, oral antidiabetes drug. [a]At screening, all 133 patients included in the study had confirmed severe RI. [b]FAS.

patients). The mean percentage change in daily insulin dose was −9.4% in the linagliptin group and −0.5% in the placebo group. This represented a mean (± SE) absolute change in dose of −6.2 (4.7) units with linagliptin and −0.3 (2.1) units with placebo. Details of mean change over time in background insulin therapy are provided in Supplementary Fig. 1. In addition, changes in background sulfonylurea therapy occurred in five patients in each treatment group (38.5 vs. 55.5% of sulfonylurea-treated patients, respectively). By study end, no patients were receiving sulfonylurea therapy in the linagliptin group, but mean daily dose increased 5.0% in the placebo group.

The proportion of patients requiring rescue therapy was lower with linagliptin than placebo (24.2 vs. 48.4%, respectively). The odds for use of rescue therapy were significantly lower with linagliptin than placebo (odds ratio, 0.345; 95% CI 0.160–0.747; $P = 0.0069$).

Over the 1-year treatment period, body weight decreased in both groups. At week 52, adjusted mean changes from baseline in body weight were −1.83 kg with linagliptin versus −0.29 kg with placebo (treatment difference, −1.53 kg; 95% CI −4.11 to 1.04; $P = 0.2370$).

Safety and tolerability

Over the 1-year treatment period, the overall incidence of AEs was similar between the linagliptin and placebo groups (94.1 vs. 92.3%, respectively; Table 2). The proportion of patients experiencing drug-related AEs was also similar between the linagliptin and placebo groups (45.6 vs. 44.6%). Hypoglycemia (42.6 vs. 40.0%) and hyperglycemia (4.4 vs. 3.1%) were the most common drug-related AEs in the linagliptin and placebo groups, respectively. The most commonly reported AEs (>5% in any group) are summarized in Table 2. The majority of AEs were of mild or moderate intensity in both groups.

Over the 1-year treatment period, small numbers of patients experienced severe hypoglycemia in either group (linagliptin, 3 [4.4%]; placebo, 3 [4.6%]) (Table 2). Symptomatic hypoglycemia was experienced by a similar proportion of patients in both groups (linagliptin, 24 [33.5%]; placebo, 22 [33.8%]). Asymptomatic hypoglycemia occurred in more patients in the linagliptin group (38 [55.9%] vs. 23 [35.4%]). This resulted in a higher overall incidence of hypoglycemia in patients treated with linagliptin than with placebo (43 [63.2%] vs. 32 [49.2%], respectively). Overall, the majority of patients with hypoglycemia were receiving insulin as monotherapy or in combination with another glucose-lowering agent(s) (linagliptin, 36 [83.7%]; placebo, 27 [84.4%]). The difference in overall incidence of hypoglycemia between patients treated with linagliptin and those treated with placebo was only notably different during the first 12 weeks of treatment when background therapy was fixed (first 12 weeks, 33 [48.5%] vs. 17 [26.2%]; last 40 weeks, 34 [50.0%] vs. 29 [44.6%]).

Renal function over time was assessed as a safety parameter. Average eGFR values did not decrease by a clinically meaningful degree with either linagliptin or placebo (median difference from baseline to the last value on treatment −0.8 vs. −2.2 mL/min/1.73 m^2). Time course of mean ± SE eGFR over 1 year is presented in Fig. 2*D*. The incidences of AEs related to renal and urinary disorders were similar between the linagliptin and placebo groups (25.0 vs. 21.5%, respectively). No renal failure related to linagliptin was reported. Mean trough concentrations of linagliptin were similar across visits (ranging from ~7 to 10 nmol/L). The incidence of CEC-adjudicated CV

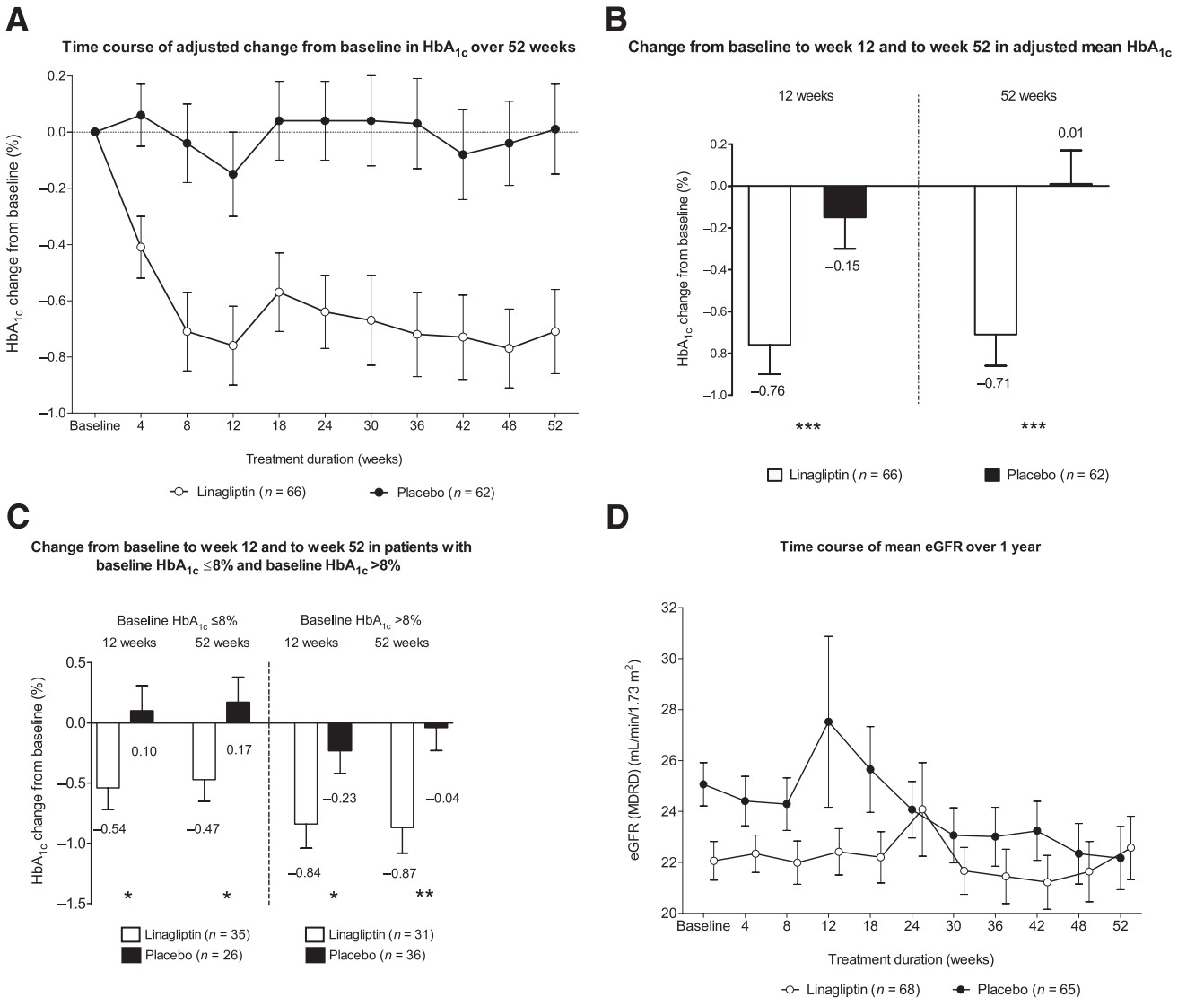

Figure 2—*Time course of adjusted mean ± SE change from baseline in HbA_{1c} over 52 weeks* (A) *in the FAS (LOCF). Change from baseline to week 12 and to week 52 in adjusted mean ± SE HbA_{1c} in all patients* (B) *and in patients with baseline HbA_{1c} ≤8% and baseline HbA_{1c} >8%* (C) *in the FAS (LOCF). Time course of mean ± SE eGFR over 1 year in the TS* (D). **P < 0.01, **P < 0.001, ***P < 0.0001 vs. placebo. White bars/circles, linagliptin; black bars/circles, placebo. MDRD, modification of diet in renal disease.*

events was similar in both groups (Table 2). Three deaths in each group were reported during the study. None were suspected to be treatment related.

CONCLUSIONS—This 1-year randomized, double-blind, placebo-controlled study was designed and powered to investigate the long-term safety, tolerability, and efficacy of an oral glucose-lowering agent exclusively in patients with type 2 diabetes and severe RI. The results show that the addition of the oral DPP-4 inhibitor linagliptin (5 mg once daily) to background glucose-lowering therapy provided a clinically meaningful HbA_{1c} reduction after 12 weeks that was sustained over 52 weeks. Throughout the study, linagliptin was well tolerated, with a safety and tolerability profile similar to placebo in this vulnerable patient population. In particular, linagliptin was associated with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure.

Glycemic control is fundamental to diabetes management (7). Several large clinical trials have demonstrated an association between hyperglycemia and the progression of microvascular complications, such as CKD, in patients with type 2 diabetes (23–25). However, antihyperglycemic treatment options are limited in patients with type 2 diabetes and CKD because many oral glucose-lowering agents are cleared by the kidney. Therefore, in patients with severe RI, most of these therapies are either not recommended or contraindicated (e.g., α-glucosidase inhibitors, metformin, glucagon-like peptide-1 receptor agonists, and some first-generation sulfonylureas) or may require significant dose reduction (e.g., second-generation sulfonylureas, repaglinide, and DPP-4 inhibitors) (8,9). Although advanced CKD does not affect the metabolism of thiazolidinediones, these agents must also be used with caution because of the increased risk of fluid retention and heart failure (26).

In this study, adding linagliptin to glucose-lowering background therapy

Table 2—*Safety results over 1 year in the TS*

	Linagliptin (*n* = 68)	Placebo (*n* = 65)
Overall incidence of AEs [*n* (%)]		
Any AE	64 (94.1)	60 (92.3)
Serious AEs	25 (36.8)	27 (41.5)
Drug-related AEs	31 (45.6)	29 (44.6)
AEs leading to discontinuation	9 (13.2)	11 (16.9)
Deaths	3 (4.4)	3 (4.6)
Most common AE (occurring in >5% in either group by preferred term) [*n* (%)]		
Hypoglycemia	43 (63.2)	32 (49.2)
Hyperglycemia	19 (27.9)	23 (35.4)
Hyperkalemia[a]	21 (30.9)	16 (24.6)
RI[b]	11 (16.2)	4 (6.2)
Diarrhea	10 (14.7)	6 (9.2)
Urinary tract infection	6 (8.8)	8 (12.3)
Constipation	8 (11.8)	4 (6.2)
Blood creatinine phosphokinase increased	7 (10.3)	7 (10.8)
Edema peripheral	7 (10.3)	7 (10.8)
Upper respiratory tract infection	5 (7.4)	7 (10.8)
Pruritus	3 (4.4)	6 (9.2)
Nasopharyngitis	6 (8.8)	3 (4.6)
Anemia	3 (4.4)	5 (7.7)
Back pain	4 (5.9)	5 (7.7)
Cough	3 (4.4)	5 (7.7)
Muscle spasms	5 (7.4)	2 (3.1)
Nausea	5 (7.4)	1 (1.5)
Acute renal failure[a]	5 (7.4)	4 (6.2)
Arthralgia	4 (5.9)	4 (6.2)
Fall	3 (4.4)	4 (6.2)
Headache	2 (2.9)	4 (6.2)
Angina pectoris	4 (5.9)	3 (4.6)
Bronchitis	4 (5.9)	2 (3.1)
Influenza	4 (5.9)	1 (1.5)
Pain in extremity	4 (5.9)	3 (4.6)
Incidence of hypoglycemia by intensity [*n* (%)][c]		
Asymptomatic hypoglycemia[d]	38 (55.9)	23 (35.4)
Mild hypoglycemia[e]	14 (20.6)	11 (16.9)
Moderate hypoglycemia[f]	10 (14.7)	11 (16.9)
Severe hypoglycemia[g]	3 (4.4)	3 (4.6)
Frequency of CV events confirmed by a CEC [*n* (%)]		
Nonfatal stroke	1 (1.5)	1 (1.5)
Nonfatal MI	4 (5.9)	2 (3.1)
CV death, MI, stroke, and hospitalization for unstable angina	7 (10.3)	9 (13.8)

[a]No events in either group were deemed as drug-related. [b]One event in the linagliptin group and none in the placebo group was deemed drug-related. [c]≥2 hypoglycemic events were experienced by 48.5 and 33.8% of linagliptin- and placebo-treated patients, respectively. [d]Event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤3.9 mmol/L. [e]Measured plasma glucose concentration ≥3.0 and ≤3.9 mmol/L. [f]Measured plasma glucose concentration <3.0 mmol/L. [g]Event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

provided a clinically significant placebo-corrected reduction of 0.7% in HbA_{1c} after 52 weeks in patients with type 2 diabetes and severe RI. This finding is in line with previous 24-week studies that reported that linagliptin (5 mg once daily) used either alone or in combination with oral diabetes medications was associated with placebo-corrected HbA_{1c} reductions ranging from 0.5–0.9% in patients with uncontrolled type 2 diabetes and normal renal function or mild to moderate RI (15,17,18,20). These studies have shown linagliptin to improve HbA_{1c} in patients with renal function ranging from normal to severe RI.

Comparisons of the efficacy of other DPP-4 inhibitors are limited due to differences in study design and patient populations; however, the HbA_{1c} improvements in patients with type 2 diabetes and moderate or severe RI with linagliptin were similar, or greater, than those seen with other DPP-4 inhibitors. Placebo-corrected HbA_{1c} reductions were −0.4 to −0.7% for vildagliptin after 52 weeks (27) and 0.4 and 0.7% for saxagliptin after 12 and 52 weeks, respectively (28,29). Mean HbA_{1c} change from baseline with sitagliptin was 0.7% after 54 weeks in an active-comparator extension study (30). This is noteworthy given that linagliptin, in contrast to other DPP-4 inhibitors, does not require dose adjustment in patients with severe RI, whereas a recent study reported that sitagliptin was frequently used at inappropriate doses in patients with type 2 diabetes and RI, and only 15% of patients with moderate to end-stage RI received recommended doses (31).

HbA_{1c} is a function of both fasting and postprandial glucose levels (32). The FPG reductions observed with linagliptin over placebo do not seem to fully account for the HbA_{1c} change, suggesting that postprandial glucose reductions, which can occur with incretin-based therapies, must have made more substantial contributions than FPG reductions. This contention is supported by previous observations of linagliptin's positive effects on postprandial glucose (15,18).

Long-term improvements in glycemic control with linagliptin were associated with a trend toward decreases in background insulin therapy in the current study. This could help optimize diabetes management but warrants further studies to determine the extent of this effect. Linagliptin use was also associated with a numerically smaller decline in eGFR than placebo despite slightly worse kidney function at baseline. However, many factors can impact progressive renal disease in this population, and longer-term clinical studies are needed to explore the potential effects of linagliptin on renal function. Along with a previous finding that linagliptin exposure did not vary in patients with normal, mild, or moderate RI (33), the pharmacokinetic data from this study confirm that linagliptin is not expected to accumulate at any degree of impaired renal function.

Glycemic control becomes problematic in advanced CKD because of the risk of hypoglycemia secondary to reduced renal gluconeogenesis and clearance of insulin as well as of some antihyperglycemic agents and/or their metabolites (34). This study showed that symptomatic hypoglycemic events and severe hypoglycemic episodes occurred at similar rates in the linagliptin and placebo groups. The higher rate of asymptomatic hypoglycemic events is most likely explained by the protocol-fixed background treatment in the first 12 weeks of this study.

Patients with type 2 diabetes and CKD have high risk for CV disease. The U.S. Food and Drug Administration requires evidence that therapies for diabetes do not cause unacceptable increases in CV risk (35). Retrospective analyses of data from DPP-4 inhibitors have not suggested any increased CV risk (36). In a prespecified and prospective meta-analysis, linagliptin was associated with a reduced CV event rate (37). In the current study, mortality and risk of CV events were similar between the linagliptin and placebo groups, but the sample size was small. A large prospective ongoing trial (CAROLINA; ClinicalTrials.gov: NCT01243424) will evaluate the effect of linagliptin on CV outcomes.

Our study is limited by the exclusion of patients with ESRD requiring chronic dialysis, which could affect the extrapolation of data to this population. However, as linagliptin undergoes high-affinity binding to DPP-4, no impact of hemodialysis on drug exposure is expected. Additionally, it has been shown that linagliptin concentrations were not significantly increased in patients with ESRD compared with other degrees of RI (14). Therefore, it is unlikely that differences in linagliptin exposure between CKD stages 1–4 patients and ESRD patients (CKD stage 5) could affect the efficacy or safety of linagliptin.

In conclusion, this placebo-controlled, double-blind trial evaluated the safety and efficacy of a DPP-4 inhibitor exclusively in patients with type 2 diabetes and severe RI. These results confirm that linagliptin provides clinically meaningful improvements in glycemic control without unacceptable side effects in this vulnerable patient population. This supports the use of linagliptin as an effective once-daily treatment option in patients with type 2 diabetes and severe RI, without the inconvenience of dose adjustments or more frequent assessments of renal function specifically for dose calculation. In addition, renal function with linagliptin remained stable over time, and overall insulin doses were reduced. Investigations to evaluate these observations further are currently underway.

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