Effects of Adding Linagliptin to Basal Insulin Regimen for Inadequately Controlled Type 2 Diabetes

A ≥52-week randomized, double-blind study

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OBJECTIVE—To evaluate the efficacy and long-term safety of linagliptin added to basal insulins in type 2 diabetes inadequately controlled on basal insulin with or without oral agents.

RESEARCH DESIGN AND METHODS—A total of 1,261 patients (HbA$_{1c}$ ≥7.0% [53 mmol/mol] to ≤10.0% [86 mmol/mol]) on basal insulin alone or combined with metformin and/ or pioglitazone were randomized (1:1) to double-blind treatment with linagliptin 5 mg once daily or placebo for ≥52 weeks. The basal insulin dose was kept unchanged for 24 weeks but could thereafter be titrated according to fasting plasma glucose levels at the investigators' discretion. The primary end point was the mean change in HbA$_{1c}$ from baseline to week 24. The safety analysis incorporated data up to a maximum of 110 weeks.

RESULTS—At week 24, HbA$_{1c}$ changed from a baseline of 8.3% (67 mmol/mol) by −0.6% (−6.6 mmol/mol) and by 0.1% (1.1 mmol/mol) with linagliptin and placebo, respectively (treatment difference −0.65% [95% CI −0.74 to −0.55] [−7.1 mmol/mol]; $P < 0.0001$). Despite the option to uptitrate basal insulin, it was adjusted only slightly upward (week 52, linagliptin 2.6 IU/ day, placebo 4.2 IU/day; $P < 0.003$), resulting in no further HbA$_{1c}$ improvements. Frequencies of hypoglycemia (week 24, linagliptin 22.0%, placebo 23.2%; treatment end, linagliptin 31.4%, placebo 32.9%) and adverse events (linagliptin 78.4%, placebo 81.4%) were similar between groups. Mean body weight remained unchanged (week 52, linagliptin −0.30 kg, placebo −0.04 kg).

CONCLUSIONS—Linagliptin added to basal insulin therapy significantly improved glycemic control relative to placebo without increasing hypoglycemia or body weight.

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Because of the progressive deterioration of pancreatic β-cell function in type 2 diabetes, many patients will eventually require the addition of a basal insulin regimen to their existing oral antihyperglycemic drugs (OADs) (1). Dosage of basal insulin is usually adjusted (titrated) to achieve a fasting plasma glucose (FPG) level of 5.5–6.1 mmol/L. Most treat-to-target studies showed successful improvement of HbA$_{1c}$ close to 7% (53 mmol/mol) when a structured insulin titration regimen was systematically implemented in a clinical research setting (2,3). Achieving the desired FPG level is difficult in clinical practice, however, mainly because of treatment inertia and failure to empower the patient to self-titrate (4). In

addition, patients and physicians are often reluctant to titrate insulin because of the fear of hypoglycemia. An alternative option to improve glycemic control in basal insulin–treated patients is to add another OAD to metformin, such as a dipeptidyl peptidase 4 (DPP-4) inhibitor. DPP-4 inhibitors are an attractive option, because they lower postprandial glucose concentrations more than FPG levels (5) and do not appear to increase the risk of hypoglycemia or weight gain.

Linagliptin is a DPP-4 inhibitor that is mainly excreted through the bile and gut, unlike other DPP-4 inhibitors, which primarily undergo renal excretion. Dose adjustment is not required with linagliptin, regardless of the degree of renal or hepatic impairment (6,7). This is beneficial in patients who require insulin treatment, because they frequently have more advanced disease, may be older, or may already have renal impairment. The potentially complementary effects of DPP-4 inhibitors and basal insulin on postprandial glucose and FPG, respectively, coupled with the low risk of weight gain or hypoglycemia associated with DPP-4 inhibitors, provide a clinical rationale for adding a DPP-4 inhibitor specifically to basal insulin therapy (with or without additional OADs). DPP-4 inhibitors were shown to be effective and safe when added to insulin therapy in type 2 diabetes; however, those studies were conducted in heterogeneous populations on multiple different insulin regimens without the option to uptitrate insulin doses (8–13).

The aim of this study was to investigate the efficacy and safety of linagliptin 5 mg once daily for 24 weeks as add-on therapy in a homogenous population of basal insulin–treated patients with type 2 diabetes and inadequate glycemic control. As part of the unique study design, after the 24-week period, free insulin titration was allowed up to at least week 52 at the investigators' discretion. This determined longer term safety of linagliptin and tested whether changes in glycemic control were sustained or necessitated an increase in basal insulin dose.

RESEARCH DESIGN AND METHODS

Study design and patients

This randomized, double-blind, placebo-controlled, phase III study was conducted in 167 centers in 19 countries (Argentina, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Italy, Korea, Mexico, the Netherlands, Norway, Peru, Russia, Slovakia, Spain, Taiwan, and the U.S.).

Patients were eligible if they were ≥18 years of age with a diagnosis of type 2 diabetes, had inadequate glycemic control (HbA$_{1c}$ ≥7.0% [53 mmol/mol] to ≤10.0% [86 mmol/mol]), had a BMI of ≤45 kg/m^2, and were receiving treatment with basal insulin, alone or in combination with metformin and/or pioglitazone, for ≥12 weeks. Acceptable basal insulins were insulin glargine, insulin detemir, and neutral protamine Hagedorn insulin. The total prescribed insulin dose must not have changed by >10% of the baseline value during the 12 weeks before randomization.

Patients were ineligible if they had uncontrolled fasting hyperglycemia (glucose >13.3 mmol/L during placebo run-in); a myocardial infarction, stroke, or transient ischemic attack within 6 months before informed consent; impaired hepatic function (either alanine transaminase, aspartate transaminase, or alkaline phosphate >3 times the upper limit of normal); previous gastric bypass surgery; or any medical history of cancer (except basal cell carcinoma) in the 5 years before screening. Further exclusion criteria included hypersensitivity or allergy to the investigational products; contraindications to metformin or pioglitazone; treatment with rosiglitazone, sulfonylureas, glucagon-like peptide 1 analogs, DPP-4 inhibitors, or antiobesity drugs within the 3 months before informed consent; a history of alcohol or drug abuse in the previous 3 months; and current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks before informed consent. Premenopausal women who were nursing, pregnant, or not practicing an acceptable method of birth control were also ineligible.

The trial protocol was approved by the independent ethics committees or institutional review boards of all participating centers. The study was carried out according to the principles of the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice. All patients gave written, informed consent before participation.

Patients underwent a 2-week, open-label placebo run-in period to confirm their eligibility after the initial screening and to exclude those who were nonadherent. After this placebo run-in period, eligible patients were randomly assigned (1:1 ratio) to receive double-blind linagliptin 5 mg once-daily or placebo in addition to continued basal insulin for at least 52 weeks. Treatment assignment was determined by computer-generated random sequence with an interactive voice response system. Randomization was stratified by HbA$_{1c}$ (<8.5% [69 mmol/mol] vs. ≥8.5% [69 mmol/mol]), renal function (estimated glomerular filtration rate [eGFR]), and concomitant use of OADs (metformin only, pioglitazone only, metformin and pioglitazone, or none). Because the patients who were randomized early in the trial were treated until the study's end, the maximal possible treatment duration was 110 weeks. During the first 24 weeks of treatment, the doses of basal insulin (within 10% of baseline dose) and OADs were kept unchanged. After week 24, adjustments to the dose of basal insulin (but not OADs) were allowed according to the medical judgment of the investigator, with a treatment target for FPG of 6.1 mmol/L.

Rescue therapy could be initiated during randomized treatment if a patient met the following criteria: confirmed FPG (after overnight fast) >13.3 mmol/L during the first 12 weeks, FPG >11.1 mmol/L from weeks 12 to 24, or FPG >10.0 mmol/L or HbA$_{1c}$ >8.0% (64 mmol/mol) after week 24. For initiation of rescue medication, these criteria had to be confirmed by two measurements on separate days. Patients were withdrawn from the trial if the FPG remained above this threshold despite rescue therapy.

End points and assessments

The primary efficacy end point was the change from baseline in HbA$_{1c}$ after 24 weeks of treatment. Secondary end points included changes from baseline in HbA$_{1c}$ and FPG with time, change from baseline in FPG after 52 weeks of treatment, the proportion of patients achieving HbA$_{1c}$ <7% (53 mmol/mol), the proportion of patients achieving ≥0.5% (5.5 mmol/mol) reduction in HbA$_{1c}$, and the change from baseline in mean basal insulin dose after 52 weeks of treatment. Other end points included the use of rescue medication and mean change in body weight to the end of treatment.

Safety end points included the frequency and intensity of adverse events (AEs), including hypoglycemia and clinically relevant new or worsening findings in physical examination, 12-lead electrocardiogram, vital signs, lipid parameters, and clinical laboratory assessments. An independent external adjudication committee reviewed treatment-emergent fatal events and suspected events of stroke or cardiac ischemia (including myocardial infarction), hospitalization for heart failure, stent thrombosis, and revascularization procedures. Follow-up for all AEs, including those persisting after a patient had completed (or withdrawn prematurely from) the trial, continued until the event had resolved or been sufficiently characterized.

Statistical analyses

Allowing for SD of change in HbA$_{1c}$ from baseline of 1.2% (13.1 mmol/mol), 284 patients per treatment group were sufficient to achieve 93% power to detect a 0.35% (3.8 mmol/mol) difference between groups in change in HbA$_{1c}$ from baseline to week 24. The larger sample size of 600 patients in each group allowed adequate exposure data to be collected for the regulatory requirement to detect rare cardiovascular events across the entire linagliptin program.

The primary end point was evaluated with ANCOVA at the level of α = 0.025 (one-sided). The statistical model included "treatment," "concomitant OADs," and "baseline renal function impairment category" as fixed classification effects and "baseline HbA$_{1c}$" as linear covariate. This analysis was performed on the full analysis set (FAS), comprising all randomized patients treated with at least one dose of study medication, with a baseline HbA$_{1c}$ measurement and at least one on-treatment HbA$_{1c}$ measurement within the first 24 weeks of double-blind treatment. An approach of last observation carried forward (LOCF) was used to replace missing data.

Secondary end points were evaluated in the FAS with an ANCOVA model with LOCF. Changes in FPG with time were analyzed for the FAS (observed case set [OC]; i.e., patients with available data) by means of descriptive statistics. The impact of treatment on the use of rescue medication was assessed by means of logistic regression, and the time to first use of rescue therapy was evaluated by Kaplan-Meier

analysis. The impact of treatment on the occurrence of hypoglycemia was investigated by means of logistic regression and Kaplan-Meier analysis. Safety end points were evaluated for the treated set (all patients who were treated with at least one dose of study medication) by means of descriptive statistics. AEs were described according to the *Medical Dictionary for Drug Regulatory Affairs* (version 14.0). Hypoglycemia was analyzed by three levels of intensity: plasma glucose ≤4 mmol/L accompanied by typical symptoms of hypoglycemia, plasma glucose <3 mmol/L accompanied by typical symptoms of hypoglycemia but without need for external assistance, and severe hypoglycemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

RESULTS

Patient disposition, demographics, and baseline clinical characteristics

This study was conducted between August 2009 and September 2011. A total of 1,261 patients were randomized to receive linagliptin (n = 631) or placebo (n = 630) once daily (Fig. 1). Of these, 1,063 patients (84.3%) completed the trial (543 [86.1%] receiving linagliptin vs. 520 [82.5%] receiving placebo). The main reasons for discontinuation were AEs

(linagliptin 4.0%, placebo 5.2%) and refusal to continue study medication (linagliptin 3.3%, placebo 4.1%). Mean exposures to study medication were 435.5 days in the linagliptin group and 422.4 days in the placebo group (medians 444 and 448 days, respectively).

Demographic and clinical characteristics were similar between treatment groups at baseline and are presented in Table 1.

Efficacy outcomes

Changes in HbA$_{1c}$ and FPG. Linagliptin was superior to placebo in reducing HbA$_{1c}$ after 24 weeks (Supplementary Table 1). The adjusted mean (SE) change in HbA$_{1c}$ from baseline at week 24 for linagliptin was −0.58% (0.08) (−6.3 [0.9] mmol/mol), compared with 0.07% (0.08) (0.8 [0.9] mmol/mol) for placebo, resulting in a placebo-adjusted mean change in HbA$_{1c}$ from baseline of −0.65% (95% CI −0.74 to −0.55) (−7.1 mmol/mol; P < 0.0001). After 52 weeks, the adjusted mean changes in HbA$_{1c}$ from baseline were −0.48% (0.08) (−5.2 [0.9] mmol/mol) for linagliptin and 0.05% (0.08) (0.5 [0.9] mmol/mol) for placebo (placebo-adjusted difference −0.53% [95% CI −0.64 to −0.43], −5.8 mmol/mol; P < 0.0001). The treatment difference between linagliptin and placebo was maintained for 76 weeks (Fig. 2A).

At week 24, the placebo-adjusted decrease in FPG was −0.6 mmol/L

(95% CI −0.9 to −0.4; P < 0.001). During the period when insulin titration was allowed and recommended, improvement in FPG was sustained in the linagliptin group, whereas FPG decreased in the placebo group in parallel with a small increase in basal insulin dose (Fig. 2B). By week 52, the mean changes in FPG from baseline were similar between the groups (linagliptin baseline 7.8 mmol/L, 52-week 7.6 mmol/L, change from baseline −0.2 [0.2] mmol/L; placebo baseline 7.8 mmol/L, 52-week 7.6 mmol/L, change from baseline −0.3 [0.2] mmol/L). The FPG target of <6.1 mmol/L was achieved by 24.6% of patients in the linagliptin group and 19.1% of the placebo group. Of these patients, 29.6% and 38.1% experienced hypoglycemia in the linagliptin and placebo groups, respectively.

Among patients with baseline HbA$_{1c}$ ≥7.0% (53 mmol/mol), after 52 weeks an HbA$_{1c}$ <7.0% (53 mmol/mol) was achieved by 16% and 7% of the linagliptin and placebo groups, respectively (P < 0.001). Compared with the placebo group, patients in the linagliptin group were more likely to have a decrease in HbA$_{1c}$ of ≥0.5% (5.5 mmol/mol) after 52 weeks of treatment (37% linagliptin vs. 17% placebo; P < 0.0001).

Subgroup analyses of HbA$_{1c}$ changes from baseline. Analysis of change in HbA$_{1c}$ by prespecified subgroups demonstrated no significant interaction with
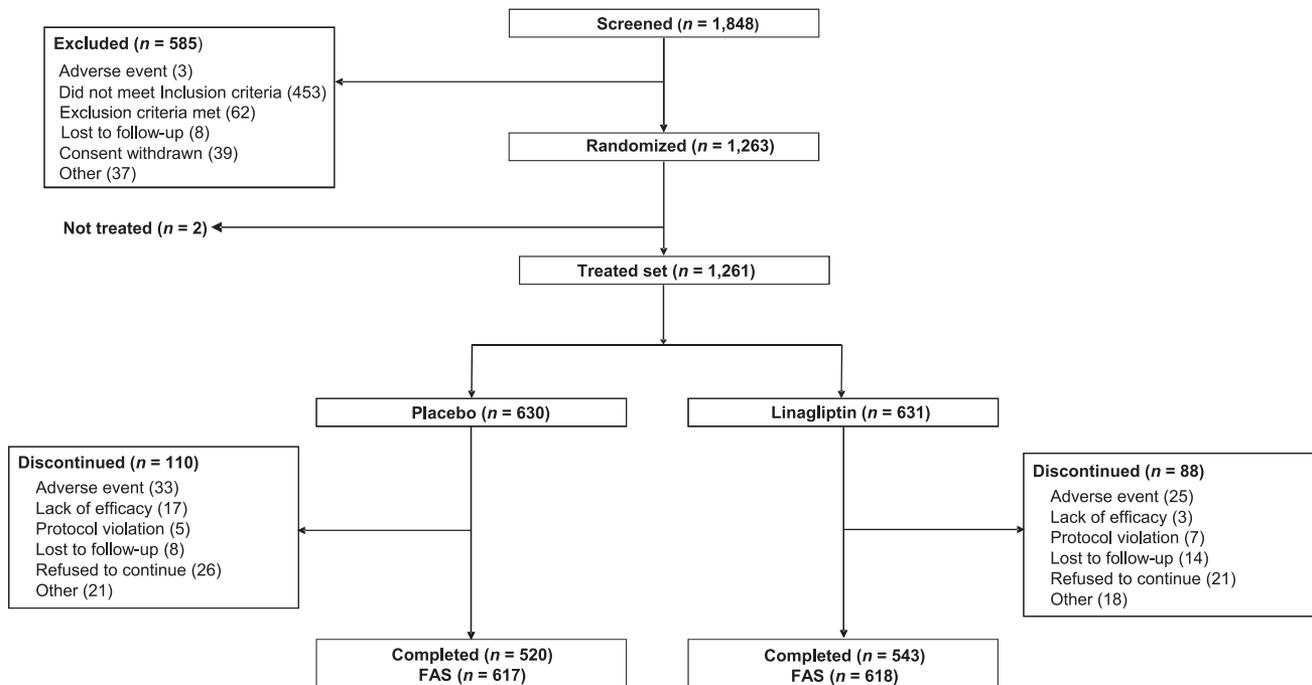

Excluded (n = 585)
Adverse event (3)
Did not meet Inclusion criteria (453)
Exclusion criteria met (62)
Lost to follow-up (8)
Consent withdrawn (39)
Other (37)

Screened (n = 1,848)

Randomized (n = 1,263)

Not treated (n = 2)

Treated set (n = 1,261)

Placebo (n = 630)

Linagliptin (n = 631)

Discontinued (n = 110)
Adverse event (33)
Lack of efficacy (17)
Protocol violation (5)
Lost to follow-up (8)
Refused to continue (26)
Other (21)

Discontinued (n = 88)
Adverse event (25)
Lack of efficacy (3)
Protocol violation (7)
Lost to follow-up (14)
Refused to continue (21)
Other (18)

Completed (n = 520)
FAS (n = 617)

Completed (n = 543)
FAS (n = 618)

Figure 1—*Patient disposition.*

Table 1—*Baseline demographics and clinical characteristics*

	Linagliptin	Placebo
Demographics		
Patients (treated set[a])	631	630
Males	329 (52.1)	329 (52.2)
Age (years)	59.7 ± 9.9	60.4 ± 10.0
Age group		
<65 years	431 (68.4)	408 (64.8)
65–74 years	165 (26.1)	181 (28.7)
≥75 years	35 (5.5)	41 (6.5)
Race		
American Indian/Alaskan Native	4 (0.6)	6 (1.0)
Asian	80 (12.7)	74 (11.7)
Black/African American	41 (6.5)	39 (6.2)
Hawaiian/Pacific Islander	2 (0.3)	3 (0.5)
Caucasian	504 (79.9)	508 (80.6)
BMI (kg/m^2)	30.8 ± 5.4	31.2 ± 4.9
Renal function (eGFR) according to MDRD		
Normal renal function (≥90 mL/min)	277 (43.9)	275 (43.7)
Mild impairment (60 to <90 mL/min)	292 (46.3)	283 (44.9)
Moderate impairment (30 to <60 mL/min)	59 (9.4)	68 (10.8)
Severe to end-stage impairment (<30 mL/min)	3 (0.5)	4 (0.6)
Clinical characteristics		
Patients (FAS[b])	618	617
HbA$_{1c}$ (%)	8.31 ± 0.85	8.29 ± 0.85
HbA$_{1c}$ (mmol/mol)	67 ± 9.3	67 ± 9.3
FPG (mmol/L)	8.2 ± 2.6	8.4 ± 2.6
Time since diagnosis of diabetes		
≤1 year	14 (2.3)	12 (1.9)
>1 to ≤5 years	86 (13.9)	66 (10.7)
>5 years	518 (83.8)	539 (87.4)
Basal insulin dose (IU/day)	41.5 ± 31.9	40.1 ± 27.3
Concomitant OADs		
None	96 (15.5)	102 (16.5)
Metformin only	470 (76.1)	464 (75.2)
Pioglitazone only	6 (1.0)	6 (1.0)
Metformin plus pioglitazone	46 (7.4)	45 (7.3)

Data are *n* (%) or mean ± SD. MDRD, Modification of Diet in Renal Disease Study equation. [a]All patients who were treated with at least one dose of study medication. [b]All patients who had a baseline and at least one on-treatment HbA$_{1c}$ measurement.

treatment according to renal function category ($P = 0.5784$), type of basal insulin ($P = 0.9511$), age group ($P = 0.1000$), concomitant use of OADs ($P = 0.64$), sex ($P = 0.98$), or BMI ($P = 0.99$), indicating that none of these factors altered the efficacy of linagliptin. Subgroup variables with significant ($P < 0.10$) interactions with treatment were baseline HbA$_{1c}$ ($P = 0.0725$), geographical region ($P = 0.0548$), race ($P = 0.0603$), and time since diabetes diagnosis ($P = 0.0017$). Placebo-adjusted mean (SD) changes in HbA$_{1c}$ were greatest for patients with a baseline HbA$_{1c}$ of ≥9.0% (75 mmol/mol) (−0.83% [0.10]), patients who were from Asia (−1.00 [0.15]) or of Asian race (−0.93 [0.14]), and patients who had been diagnosed with diabetes for >5 years (−0.72% [0.05]). The placebo-adjusted mean change from baseline in HbA$_{1c}$ after 24 weeks was −0.52% (−5.7 mmol/mol) for patients taking no OADs at baseline (*n* = 96 [15.50%]; $P < 0.0001$), −0.67% (−7.3 mmol/mol) for those taking metformin only (*n* = 470 [76.1%]; $P < 0.0001$), −0.76% (−8.3 mmol/mol) for those taking pioglitazone only (*n* = 12 [1.0%]; $P = 0.129$), and −0.71% (−7.8 mmol/mol) for patients taking both metformin and pioglitazone (*n* = 91 [7.4%]; $P < 0.0001$).

Use of rescue therapy and changes in background therapy. More patients required rescue medication in the placebo group (50.4%) than in the linagl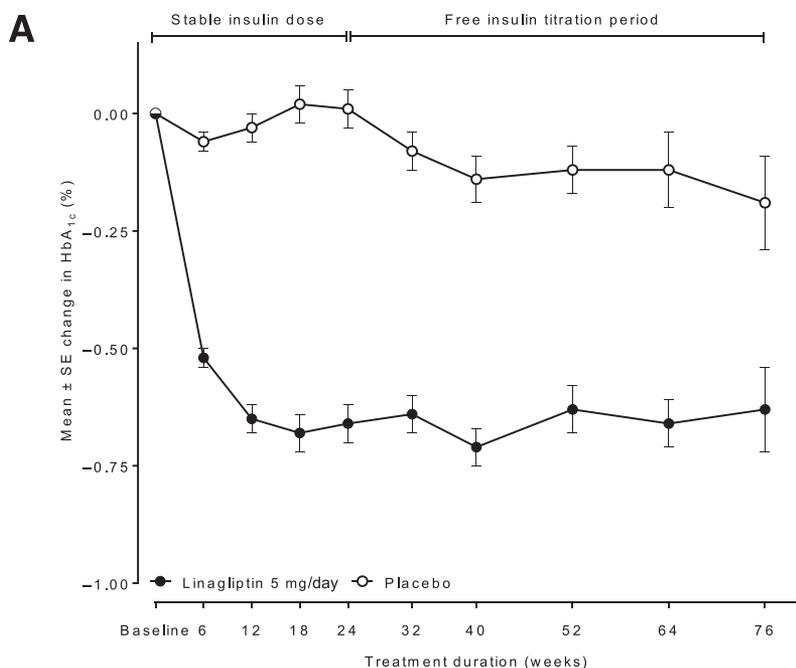iptin group (38.2%); the odds ratio (linagliptin vs. placebo) for rescue medication was 0.575 (95% CI 0.454–0.728; $P < 0.0001$). The mean (SD) change in basal insulin dose to week 24 (when dose was to have remained within 10% of baseline) was 0.1 (0.2) IU for patients treated with linagliptin and 0.4 (0.2) IU for those treated with placebo. From week 24, mean basal insulin dose increased in the linagliptin group to a lesser extent than in the placebo group (Fig. 2*B*). The adjusted mean (SD) changes from baseline in insulin dose at week 52 were 2.6 (0.8) IU for linagliptin and 4.2 (0.8) IU for placebo ($P < 0.003$).
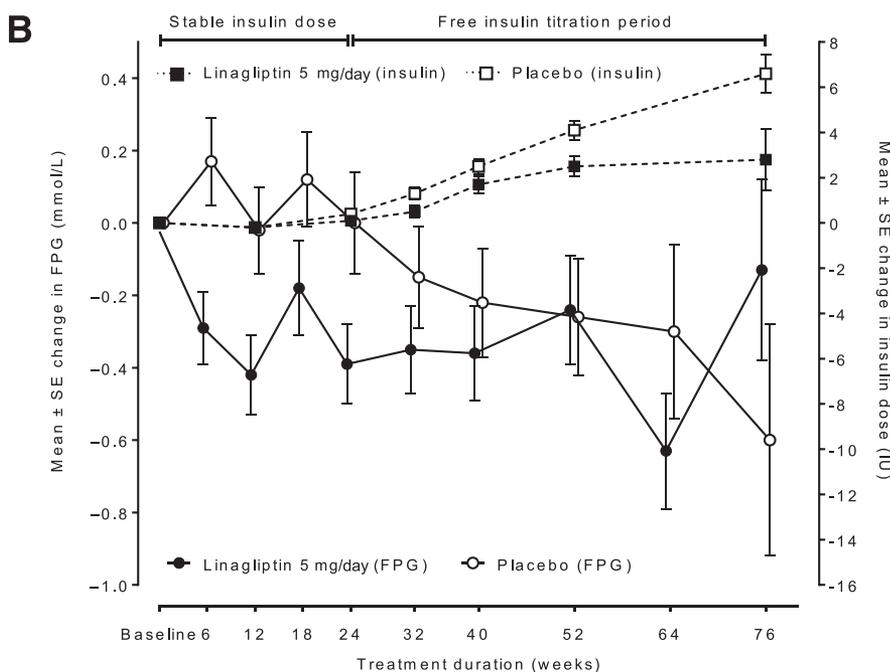
Safety and tolerability

The overall incidence of patients with ≥1 reported AE was comparable between treatment groups (linagliptin 78.4%, placebo 81.4%) (Supplementary Table 2). AEs were primarily of mild or moderate intensity; AEs of severe intensity occurred in 8.2% and 8.3% of patients in the linagliptin and placebo groups, respectively. The most commonly reported severe AEs in both treatment groups were hypoglycemia, coronary artery disease, osteoarthritis, cardiac failure, pneumonia, diarrhea, arthralgia, gastroenteritis, acute renal failure, and subdural hematoma. AEs considered to be drug-related occurred in 18.7% and 22.2% of linagliptin and placebo patients, respectively. Drug-related hypoglycemia occurred in 83 (15.1%) and 95 (13.2%) patients in the linagliptin and placebo groups, respectively, and was the only drug-related AE with an incidence greater than 2%. There were no imbalances between treatment groups for other drug-related AEs. AEs leading to discontinuation of trial medication occurred in 21 patients (3.3%) in the linagliptin group and 28 patients (4.4%) in the placebo group. There were no clinically relevant changes in vital signs or laboratory parameters in either group, including no between-group imbalance in shifts in stage of renal impairment.

The percentage of patients with investigator-defined hypoglycemia was not different between groups either at week 24 (linagliptin 22.0%, placebo 23.2%) or at the end of treatment (linagliptin 31.4%, placebo 32.9%). Incidence of severe hypoglycemia was also similar between groups (week 24 linagliptin 0.3%, placebo 0.6%; end of treatment linagliptin 1.7%, placebo 1.1%) (Supplementary Table 2).

There was no significant change from baseline in mean body weight at either week 24 (linagliptin −0.16 [0.12] kg, placebo 0.12 [0.11] kg) or at week 52 (linagliptin −0.3 [0.19] kg, placebo

Figure 2—A: *Mean HbA$_{1c}$ change from baseline with time out to 76 weeks (FAS, OC).* B: *Mean FPG change (FAS, OC) and mean change in insulin dose (FAS, original results) from baseline with time out to 76 weeks.*

−0.04 [0.18] kg). Adjudicated cardiovascular events occurred in 18 linagliptin patients (2.9%) and 11 placebo patients (1.7%). Cardiovascular deaths occurred in 5 patients (0.8%) in the linagliptin group and 1 (0.2%) in the placebo group. Total mortality, however, was comparable between the arms, with 5 deaths in each group.

CONCLUSIONS—In patients with inadequate glycemic control despite treatment with OADs, basal insulin therapy is recommended with or without additional OADs (14). This phase III clinical trial demonstrated that, in basal-insulin treated patients with type 2 diabetes and inadequate glycemic control (15,16), the addition of linagliptin 5 mg once-daily improved glycemic control without increasing the risk of hypoglycemia or body weight gain. These improvements were not affected by concomitant use of OADs, type of basal insulin, age, or degree of renal impairment.

Previous studies have also shown that DPP-4 inhibitors can significantly decrease HbA$_{1c}$ concentration when added to various insulin regimens, with the exception of sitagliptin, without an additional risk of hypoglycemia (8–13). Our study differs from the previous trials in specifically testing a more homogenous population of basal insulin–treated patients and including both a period of stable insulin dosing, permitting robust assessment of the efficacy and safety of add-on linagliptin, and an extension period, during which patients were allowed to adjust the insulin according to the investigator criteria.

Addition of linagliptin to basal insulin was associated with a low frequency of hypoglycemia, implying that dose reduction of basal insulin to avoid hypoglycemia when coadministering linagliptin may not be necessary. Although the extension period was intended primarily to provide long-term safety data for linagliptin, it also provided additional information on utilization in clinical practice. In the previous trials of other DPP-4 inhibitors, the insulin dose was either kept stable (8,9,13) or titrated (10–12), but not both. During the extension period, the insulin dose was increased more in the placebo group than in the linagliptin group. The magnitude of the increase in insulin dose, however, was much less than recommended in the study protocol (i.e., to achieve an FPG target of 6.1 mmol/L). Because no forced titration was requested, this may have resulted in some "titration inertia." Of note, the proportion of elderly patients

and patients with renal impairment was high in the study, and it appears likely that investigators may have been more reluctant to uptitrate basal insulin because age and renal impairment both increase risk of hypoglycemia. The mean FPG change from baseline at week 52 was similar between groups, indicating that clinicians were targeting similar FPG goals. Nevertheless, significantly lower HbA$_{1c}$ values were obtained with linagliptin.

Patients themselves are also often reluctant to uptitrate insulin because of the potentially increased risk of hypoglycemia. This represents a significant consideration driving the need for additional treatments such as linagliptin to improve glycemic control. The low risk of hypoglycemia with linagliptin could potentially reduce indirect costs, such as hospitalization, and this may counterbalance the added direct expense (17,18).

In contrast to other DPP-4 inhibitors, linagliptin has a primarily nonrenal route of elimination and therefore does not require dose adjustment in patients with impaired renal function (6,19). Because many patients taking insulin have impaired renal function, this is a potential advantage of linagliptin relative to other DPP-4 inhibitors. A previous study found linagliptin to be well tolerated and efficacious in long-term use in patients with severe renal impairment (20).

In conclusion, this study shows that addition of linagliptin to basal insulin improves glycemic control without increasing hypoglycemia or inducing weight gain, with the additional advantage that the dose does not need to be altered in the elderly or in those with impaired renal function.

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