Treatment With the Dipeptidyl Peptidase-4 Inhibitor Linagliptin or Placebo Followed by Glimepiride in Patients With Type 2 Diabetes With Moderate to Severe Renal Impairment: A 52-Week, Randomized, Double-Blind Clinical Trial

Markku Laakso,[1] Julio Rosenstock,[2] Per-Henrik Groop,[3] Anthony H. Barnett,[4] Baptist Gallwitz,[5] Uwe Hehnke,[6] Ilkka Tamminen,[7] Sanjay Patel,[8] Maximilian von Eynatten,[6] and Hans-Juergen Woerle[6]

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Chronic kidney disease (CKD) is frequently comorbid with type 2 diabetes, and glucose-lowering treatment options are limited for such patients (1). We investigated the efficacy and safety of linagliptin, a dipeptidyl peptidase-4 inhibitor, in type 2 diabetic patients with moderate to severe renal impairment and insufficient glycemic control.

This randomized, double-blind, parallel-group clinical trial comprised a 12-week, placebo-controlled phase followed by a 40-week, active-controlled extension. The study was conducted between 17 March 2010 and 18 June 2012 at 52 outpatient clinics in nine countries (ClinicalTrials.gov, NCT01087502). Patients with type 2 diabetes, HbA_{1c} 7.0–10.0% (53–86 mmol/mol), and estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m^2 were randomized 1:1 to double-blind treatment with linagliptin 5 mg/day or placebo for 12 weeks; placebo patients were then switched to glimepiride 1–4 mg/day, with double blinding maintained using a double-dummy design, and treatments continued until week 52. Glimepiride could be uptitrated in 1-mg increments from a 1-mg starting dose to a maximum of 4 mg at 4-week intervals during the first 12 weeks of the extension if patients' self-monitored fasting blood glucose values were $>$110 mg/dL. The primary end point was change in HbA_{1c} from baseline to week 12 in the full-analysis set (FAS; all randomized patients who received $\geq$1 dose of study drug and had a baseline and $\geq$1 postbaseline measurement of HbA_{1c}); missing data were imputed using last observation carried forward. Secondary end points included change in HbA_{1c} from baseline over time. The incidence of adverse events (AEs) was evaluated for the treated set (TS; all randomized patients who received $\geq$1 dose of study drug).

A total of 235 patients were randomized to linagliptin (n = 113) or placebo (n = 122), constituting the TS. The FAS comprised 113 and 120 linagliptin and placebo patients, respectively. Baseline demographic and clinical characteristics were similar between treatment groups. Overall, participants had a mean ± SD age of 66.6 ± 9.3 years and HbA_{1c} of 8.1 ± 0.9% (65 ± 10 mmol/mol); 63.4% were male, 70.2% were white, 86% were receiving insulin, and the mean eGFR was 37.2 mL/min/1.73 m^2. After 12 weeks, the adjusted mean ± SE change from baseline in HbA_{1c} was –0.53 ± 0.11% (–5.8 ± 1.2 mmol/mol) with linagliptin and –0.11 ± 0.11% (–1.3 ± 1.2 mmol/mol) with placebo, a placebo-corrected change with linagliptin of –0.42% (95% CI –0.60 to –0.24 [–4.6 mmol/mol, 95% CI –6.5 to –2.6]; $P < 0.0001$). After 52 weeks, adjusted mean change from baseline in HbA_{1c} was –0.64% (–7.0 mmol/mol) and –0.50% (–5.5 mmol/mol) in the linagliptin and placebo/glimepiride groups, respectively (Fig. 1*A*).

During the placebo-controlled 12 weeks, AEs occurred in approximately three-quarters of both treatment groups (linagliptin, 76.1%; placebo, 73.8%) but were drug-related in fewer than one-quarter (linagliptin, 23.9%; placebo, 24.6%). Fewer than 10% of linagliptin and placebo patients reported serious AEs (7.1% and 8.2%, respectively) or AEs leading to discontinuation of study drug (3.5 vs. 4.9%). During the extension, fewer linagliptin than glimepiride patients reported any AE (90.7 vs.

[1]*Department of Medicine, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland*
[2]*Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX*
[3]*Department of Medicine, Division of Nephrology, Helsinki University Central Hospital, Helsinki, Finland; Folkhälsan Institute of Genetics, Folkhälsan Research Center, Biomedicum Helsinki, Helsinki, Finland; and Baker IDI Heart and Diabetes Institute, Melbourne, Australia*
[4]*Diabetes and Endocrinology Centre, Heart of England National Health Service Foundation Trust, and University of Birmingham, Birmingham, U.K.*
[5]*Department of Medicine IV, Universitäts-Klinikum Tübingen, Tübingen, Germany*
[6]*Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany*
[7]*Boehringer Ingelheim Ky, Helsinki, Finland*
[8]*Boehringer Ingelheim Ltd., Bracknell, U.K.*

Corresponding author: Markku Laakso, markku.laakso@kuh.fi.

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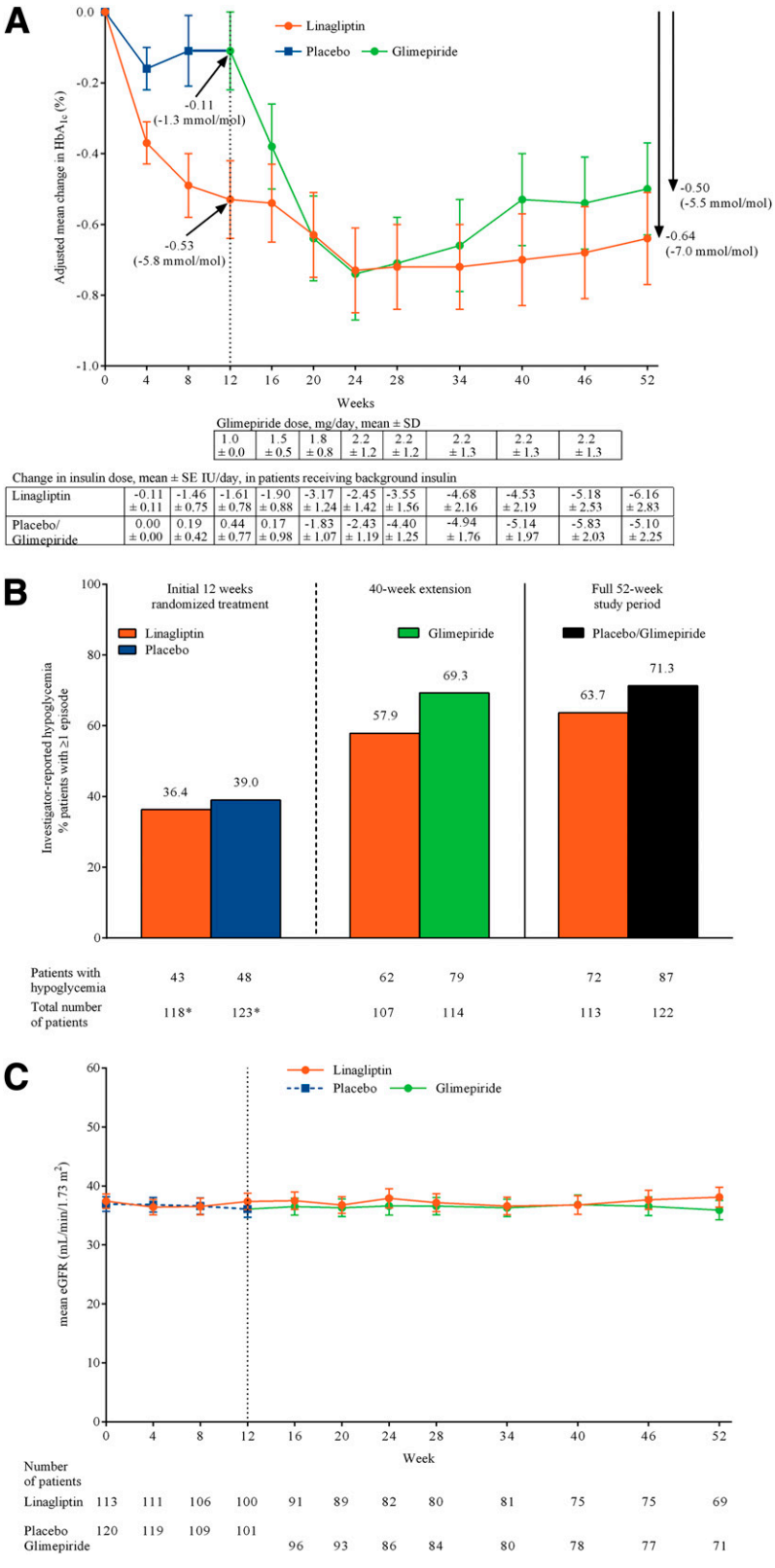

Figure 1—*A*: Change from baseline in HbA_{1c} in the FAS (last observation carried forward). *B*: Investigator-reported hypoglycemia in the TS (confirmed plasma glucose concentration ≤70 mg/dL and/or symptoms attributed to hypoglycemia). *C*: Change in eGFR over time in the FAS (observed cases). *Data are for the TS including the six patients from the noncompliant study site: linagliptin, $n = 118$; placebo, $n = 123$.

96.5%), a serious AE (22.4 vs. 26.3%), or an AE leading to discontinuation (4.7 vs. 9.6%). Adjudicated cardiovascular events occurred in fewer linagliptin patients ($n = 3$) than glimepiride patients ($n = 8$); adjudicated hospitalization for heart failure occurred in seven and six linagliptin and placebo/glimepiride patients, respectively. Investigator-reported hypoglycemia occurred in fewer linagliptin patients than in placebo or glimepiride patients during the first 12 weeks and extension (Fig. 1*B*). Severe hypoglycemia (requiring third-party assistance) occurred in six linagliptin and six placebo/glimepiride patients. eGFR remained stable throughout the 52 weeks in both groups (Fig. 1*C*). Further details on baseline characteristics, secondary end points, and AEs are available from http://trials.boehringer-ingelheim.com/content/dam/internet/opu/clinicaltrial/com_EN/results/1218/1218.64_U13-1283-01-DS.pdf.

The prevalence of patients with type 2 diabetes and CKD has increased substantially in recent decades (1). In this 52-week study, linagliptin was well tolerated and efficacious in type 2 diabetic patients with moderate or severe renal impairment. Importantly, renal function remained stable during the study. Hypoglycemia in type 2 diabetic patients is increasingly recognized as an important issue; for some patients with CKD, preventing hypoglycemia may be more important than achieving tight glycemic control (1). Not unexpectedly, given the high rate of insulin use, the incidence of hypoglycemia was relatively high in both groups; however, fewer linagliptin-treated patients experienced hypoglycemia compared with glimepiride-treated patients. Previous studies utilizing a comparative design versus sulfonylureas have found dipeptidyl peptidase-4 inhibitors to exert similar glucose-lowering efficacy but with fewer AEs in patients with renal impairment (2–4). Among the limitations of our study, observations during the extension are hypothesis-generating only, due to the design. In conclusion, this study suggests that linagliptin can elicit beneficial changes in glycemic control with an acceptable side-effect profile in type 2 diabetic patients with moderate or severe renal impairment, a population that is considered vulnerable with few treatment options.

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