



# 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial

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## Summary

**Background** Addition of a sulphonylurea to metformin improves glycaemic control in type 2 diabetes, but is associated with hypoglycaemia and weight gain. We aimed to compare a dipeptidyl peptidase-4 inhibitor (linagliptin) against a commonly used sulphonylurea (glimepiride).

**Methods** In this 2-year, parallel-group, non-inferiority double-blind trial, outpatients with type 2 diabetes and glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) 6·5–10·0% on stable metformin alone or with one additional oral antidiabetic drug (washed out during screening) were randomly assigned (1:1) by computer-generated random sequence via a voice or web response system to linagliptin (5 mg) or glimepiride (1–4 mg) orally once daily. Study investigators and participants were masked to treatment assignment. The primary endpoint was change in HbA<sub>1c</sub> from baseline to week 104. Analyses included all patients randomly assigned to treatment groups who received at least one dose of treatment, had a baseline HbA<sub>1c</sub> measurement, and had at least one on-treatment HbA<sub>1c</sub> measurement. This trial is registered at ClinicalTrials.gov, number NCT00622284.

**Findings** 777 patients were randomly assigned to linagliptin and 775 to glimepiride; 764 and 755 were included in analysis of the primary endpoint. Reductions in adjusted mean HbA<sub>1c</sub> (baseline 7·69% [SE 0·03] in both groups) were similar in the linagliptin (–0·16% [SE 0·03]) and glimepiride groups (–0·36% [0·03]; difference 0·20%, 97·5% CI 0·09–0·30), meeting the predefined non-inferiority criterion of 0·35%. Fewer participants had hypoglycaemia (58 [7%] of 776 vs 280 [36%] of 775 patients,  $p < 0·0001$ ) or severe hypoglycaemia (1 [ $< 1\%$ ] vs 12 [2%]) with linagliptin compared with glimepiride. Linagliptin was associated with significantly fewer cardiovascular events (12 vs 26 patients; relative risk 0·46, 95% CI 0·23–0·91,  $p = 0·0213$ ).

**Interpretation** The results of this long-term randomised active-controlled trial advance the clinical evidence and comparative effectiveness bases for treatment options available to patients with type 2 diabetes mellitus. The findings could improve decision making for clinical treatment when metformin alone is insufficient.

**Funding** Boehringer Ingelheim.

## Introduction

Diabetes mellitus, mainly the type 2 form, is a major public health issue globally and affected about 347 million individuals worldwide in 2008 (almost 10% of adults).<sup>1</sup> Afflicting 138 million people in China and India alone, diabetes exerts a substantial morbidity burden in developing countries as well as industrialised nations, and ageing and population growth is likely to intensify this burden.<sup>1</sup> Metformin is widely accepted as the first-line oral agent in the treatment of type 2 diabetes.<sup>2</sup> However, many patients on metformin monotherapy are unable to achieve or maintain long-term glycaemic control, mostly because of a progressive loss of insulin secretory function.<sup>3</sup> When metformin alone is insufficient, the choice of second-line treatment is challenging and there is no clear consensus on the optimum approach, although algorithms provide some guidance.<sup>2,4</sup> Efforts are ongoing to address this comparative-evidence

gap—notably, the planned GRADE trial, although this study will not produce results for about 8 years.

At present, the most common next step in treatment when a patient is not reaching their glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) target is to add a sulphonylurea.<sup>2</sup> This combination treatment offers improvements in glycaemic control, but is associated with hypoglycaemia and weight gain, both of which can have a potentially negative effect on cardiovascular risk, quality of life, and treatment adherence.<sup>5–7</sup> Until evidence emerges from long-term studies, short-term head-to-head trials of sulphonylureas versus other individual antihyperglycaemic agents could provide data to inform treatment decisions. Linagliptin is an oral, once-daily dipeptidyl peptidase-4 (DPP-4) inhibitor licensed in 2011 that improves glycaemic control by preventing the rapid degradation of incretin hormones, with a resulting glucose-dependent increase in stimulation of insulin secretion and inhibition of

Published Online  
June 28, 2012  
[http://dx.doi.org/10.1016/S0140-6736\(12\)60691-6](http://dx.doi.org/10.1016/S0140-6736(12)60691-6)

See Online/Comment  
[http://dx.doi.org/10.1016/S0140-6736\(12\)60859-9](http://dx.doi.org/10.1016/S0140-6736(12)60859-9)

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For more on the GRADE trial see <http://www2.bsc.gwu.edu/bsc/oneproj.php?pkey=60>

glucagon secretion. HbA<sub>1c</sub> reductions, ranging from 0·6% to 0·9%, with a low risk of hypoglycaemia and no weight gain, were reported when linagliptin was given either alone<sup>8</sup> or in combination with metformin<sup>9</sup> in patients with type 2 diabetes.

The aim of this hypothesis-driven study was to assess the long-term efficacy and safety of linagliptin compared with a commonly used sulphonylurea (glimepiride) as second-line treatment in participants with type 2 diabetes inadequately controlled on metformin. Additionally, as part of a large phase 3 programme, this study prospectively assessed cardiovascular safety.

## Methods

### Study design and patients

This randomised, double-blind, parallel-group, active-controlled, non-inferiority trial was undertaken at 209 sites that included primary and secondary care centres in 16 countries (Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, the UK, and the USA). The study consisted of a 2-week run-in with or without a previous 6-week washout period, followed by 104-week double-blind treatment, and 1-week follow-up.

Study investigators, at their discretion, approached individuals from their centres deemed appropriate to enrol for screening. Eligible study participants were aged 18–80 years, had type 2 diabetes, were receiving metformin at a stable dose of 1500 mg/day or more (or a maximum tolerated dose less than 1500 mg/day) alone or with one other oral antidiabetic drug, and had HbA<sub>1c</sub> 6·5–10·0% (on metformin alone) or 6·0–9·0% (on metformin and one additional oral antidiabetic drug) and a body-mass index (BMI) of 40 kg/m<sup>2</sup> or less irrespective of ethnicity. The main exclusion criteria were diagnoses of myocardial infarction, stroke, or transient ischaemic attack in the 6 months before screening, impaired hepatic function at screening, and treatment with rosiglitazone, pioglitazone, a glucagon-like peptide 1 (GLP-1) analogue or agonist, insulin, or an antiobesity drug in the 3 months before screening. Drug histories were recorded by investigators on case report forms as free text or against tick boxes for specific co-treatments of interest.

The study was undertaken according to the Declaration of Helsinki and Good Clinical Practice principles. The protocol was approved by the independent ethics committee or institutional review board for each participating site. A data safety monitoring board reviewed safety data after a 52-week interim analysis and recommended that the study continue to 104 weeks. All participants provided written informed consent before participation.

### Procedures

Participants receiving metformin monotherapy entered a 2-week open-label placebo run-in period. Those receiving metformin and one additional oral antidiabetic drug

entered a 6-week washout period followed by the 2-week open-label placebo run-in. By the start of the placebo run-in, the HbA<sub>1c</sub> inclusion criterion was 6·5–10·0% for all participants. Participants meeting the eligibility criteria at the end of the placebo run-in were randomly assigned in a 1:1 ratio to double-blind, double-dummy treatment with linagliptin (5 mg once daily) or glimepiride (initially 1 mg once daily) added to ongoing metformin (dose unchanged throughout the study). After the starting dose of 1 mg once daily, glimepiride was uptitrated stepwise in 1 mg increments up to a maximum of 4 mg once daily, at 4-week intervals during the first 12 weeks of treatment. Glimepiride was uptitrated by investigators if the patients' self-monitored fasting plasma glucose (FPG) values were greater than 6·1 mmol/L. At any time, glimepiride could be downtitrated to prevent recurrent hypoglycaemic events.

During double-blind treatment, all participants outside the USA received one tablet and one capsule daily: either one 5 mg tablet of linagliptin plus one placebo capsule, or one glimepiride capsule plus one placebo tablet. Participants in the USA (where the 3 mg glimepiride capsule was unavailable) received one tablet and two capsules daily: either one 5 mg linagliptin tablet plus two placebo capsules, or one 1 mg, 2 mg, or 4 mg glimepiride capsule plus one placebo capsule plus one placebo tablet, or one 1 mg glimepiride capsule plus one 2 mg glimepiride capsule plus one placebo tablet. Participants were instructed to take their study drug at the same time every day with water (150 mL).

Rescue treatment (pioglitazone) could be started during the trial if a participant had a confirmed FPG higher than 13·3 mmol/L at any visit or HbA<sub>1c</sub> higher than 8·5% from week 28 to week 104. If participants did not meet these prespecified glycaemic control criteria despite rescue treatment, they discontinued participation in the trial. Treatment adherence was defined as the number of tablets or capsules taken since the last count, as a percentage of the number that should have been taken, and was assessed by study personnel who counted remaining tablets or capsules brought by patients at each visit. Non-adherence (<80% or >120%) was treated as a protocol violation.

The primary efficacy endpoint was change in HbA<sub>1c</sub> from baseline to week 104. The two key secondary endpoints were occurrence of hypoglycaemic episodes up to 104 weeks and change in bodyweight from baseline to week 104. Other secondary endpoints were change in HbA<sub>1c</sub> from baseline to week 52, HbA<sub>1c</sub> reduction over time, occurrence of HbA<sub>1c</sub> on treatment of less than 7·0% or less than 6·5% at week 104, occurrence of HbA<sub>1c</sub> reduction of 0·5% or greater at week 104, change in FPG from baseline to week 52 and 104, change in 2-h postprandial glucose from baseline to week 104 during a meal tolerance test in a subset of participants who received a standardised breakfast of two nutrition bars and a drink (Ensure Plus, Abbott Nutrition, Columbus, OH, USA), and changes from baseline in total cholesterol,

LDL cholesterol, HDL cholesterol, and triglycerides. The changes in plasma proinsulin/insulin ratio and in homeostasis model assessment of insulin resistance (HOMA-IR) from baseline to week 104 were used to indirectly assess pancreatic  $\beta$ -cell function and insulin resistance.

Safety and tolerability endpoints included the incidence and intensity of adverse events, withdrawals because of adverse events, physical examination, 12-lead electrocardiogram, vital signs, and clinical laboratory measures. Hypoglycaemic events and severe hypoglycaemic episodes were also recorded.<sup>10</sup> Additionally, a masked independent clinical event committee prospectively reviewed all reported treatment-emergent fatal events, suspected events of stroke, myocardial ischaemia (including myocardial infarction), admission to hospital for heart failure, stent thrombosis, and revascularisation procedures. The committee members evaluated whether prespecified criteria for adjudication endpoints (cardiovascular death, stroke, myocardial infarction, and admission to hospital for unstable angina) were met. All adverse events including those persisting after study completion were followed up by investigators until they had resolved or been sufficiently characterised. Any serious or significant adverse events were reported immediately to the sponsor.

### Randomisation and masking

Treatment assignment was done with a computer-generated random sequence, stratified by HbA<sub>1c</sub> (<8·5% vs  $\geq$ 8·5%) and previous use of an oral antidiabetic drug (metformin monotherapy vs metformin plus another drug). Assignment used a central interactive voice or web response system with randomisation codes generated by the study sponsor. Study investigators and participants were masked to treatment assignment for the duration of the trial. Placebo and active treatments were identical in appearance. Only dedicated personnel could access the randomisation codes for treatment assignment, and could provide access in an emergency only.

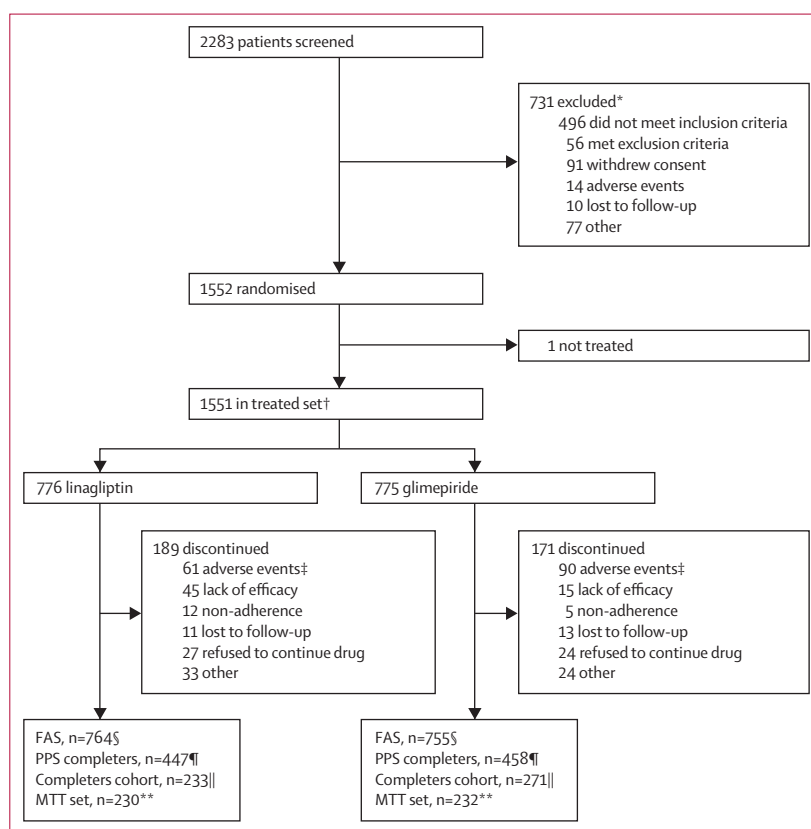
### Statistical analysis

SAS version 9.2 was used for all analyses. On the assumption of an SD of change in HbA<sub>1c</sub> from baseline of 1·3%, a sample size of 707 participants per treatment group was needed for 90% power to show non-inferiority through a 97·5% CI for treatment difference in the adjusted mean change from baseline to endpoint of less than 0·35% HbA<sub>1c</sub> at the level of  $\alpha=0\cdot0125$  (one-sided).

The primary efficacy analysis of change in HbA<sub>1c</sub> was assessed with ANCOVA with treatment and previous use of oral antidiabetic drugs as fixed factors and baseline HbA<sub>1c</sub> as a linear covariate. This analysis was done on the full analysis set using last observation carried forward to impute missing data; the full analysis set included all patients randomly assigned to study groups who received at least one dose of treatment, had a baseline HbA<sub>1c</sub>

measurement, and had at least one on-treatment HbA<sub>1c</sub> measurement. The study included an interim analysis at 52 weeks and a full analysis at 104 weeks. Consequently, to protect the total  $\alpha$  at 0·05 (two-sided) despite multiple testing of the primary endpoint, the total  $\alpha$  level was divided to give  $\alpha$  of 0·025 (two-sided) for the interim and full analysis. Thus, non-inferiority for HbA<sub>1c</sub> was tested with a 97·5% confidence interval rather than the standard 95% CI. Additionally, the  $\alpha$  of 0·0125 (one-sided) was chosen to test for non-inferiority, which is one-sided by definition.

Sensitivity analyses repeated the primary efficacy analysis using the per-protocol set (PPS) completers (observed cases; included patients in the full analysis set who did not have important protocol violations, completed at least 684 days of treatment, and had HbA<sub>1c</sub> measured at week 104). Additionally, to identify which patients benefited most from treatment, a post-hoc responder analysis of change in HbA<sub>1c</sub> from baseline to



**Figure 1: Trial profile**

\*One patient might have had more than one inclusion or exclusion criterion. †Treated set included randomised patients who received at least one dose of treatment. ‡Recorded by the investigators on the discontinuation page.

§Full analysis set (FAS) included randomised patients who received at least one dose of treatment, had a baseline glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) measurement, and had at least one on-treatment HbA<sub>1c</sub> measurement.

¶Per-protocol set (PPS) completers included patients in FAS who did not have important protocol violations, completed at least 684 days of treatment, and had HbA<sub>1c</sub> measured at week 104. ||Completers cohort included PPS completers who met specific glycaemic targets (from week 4 to week 12, fasting plasma glucose [FPG]  $\leq$ 13·3 mmol/L; after week 12 through week 16, FPG  $\leq$ 12·2 mmol/L; after week 16 to week 28, FPG  $\leq$ 11·1 mmol/L; after week 28 to week 52, HbA<sub>1c</sub>  $\leq$ 8%; and after week 52 to week 104, HbA<sub>1c</sub>  $\leq$ 7·5%). \*\*Meal tolerance test (MTT) set included patients in the FAS who had a valid MTT done at baseline and once on treatment.

	Linagliptin (n=776)	Glimepiride (n=775)
Age (years)	59.8 (9.4)	59.8 (9.4)
<65 years	525 (68%)	520 (67%)
≥65 years	251 (32%)	255 (33%)
Sex		
Male	462 (60%)	471 (61%)
Female	314 (40%)	304 (39%)
Ethnic origin		
White	660 (85%)	659 (85%)
Asian	94 (12%)	96 (12%)
Black or African American	20 (3%)	18 (2%)
Other	2 (<1%)	2 (<1%)
Bodyweight (kg)	86.1 (17.6)	86.8 (16.7)
Body-mass index (kg/m <sup>2</sup> )	30.2 (4.8)	30.3 (4.6)
Type 2 diabetes duration*		
≤1 year	50 (7%)	58 (8%)
>1 year and ≤5 years	316 (41%)	291 (39%)
>5 years	398 (52%)	406 (54%)
HbA <sub>1c</sub> * (%)	7.7% (0.9)	7.7% (0.9)
HbA <sub>1c</sub> <7%	173 (23%)	162 (21%)
HbA <sub>1c</sub> ≥7% and <8%	318 (42%)	346 (46%)
HbA <sub>1c</sub> ≥8% and <9%	203 (27%)	175 (23%)
HbA <sub>1c</sub> ≥9%	70 (9%)	72 (10%)
FPG* (mmol/L)	9.1 (2.4)	9.2 (2.3)
Use of OAD at screening*		
Monotherapy	535 (70%)	534 (71%)
Dual therapy	228 (30%)	220 (29%)
Triple therapy	1 (<1%)	1 (<1%)
Metformin dose*		
<1500 mg	58 (8%)	44 (6%)
≥1500 mg	706 (92%)	711 (94%)

Data are n (%) or mean (SD). HbA<sub>1c</sub>=glycated haemoglobin A<sub>1c</sub>. FPG=fasting plasma glucose. OAD=oral antidiabetic drug. \*Full analysis set (linagliptin, n=764; glimepiride, n=755).

**Table 1: Demographic and baseline clinical characteristics in the treated set of patients**

week 104 was done on the completers cohort, which was defined in an identical way to the per-protocol cohort used in a comparative study of sitagliptin and glipizide.<sup>11</sup> The completers cohort consisted of PPS completers who met specific glycaemic targets to remain in the study without the use of rescue treatment (FPG ≤13.3 mmol/L, week 4–12; FPG ≤12.2 mmol/L, week 12–16; FPG ≤11.1 mmol/L, week 16–28; HbA<sub>1c</sub> ≤8.0%, week 28–52; and HbA<sub>1c</sub> ≤7.5%, week 52–104).

The analyses we have described for change in HbA<sub>1c</sub> were also done for change in FPG. Changes in 2-h postprandial glucose, plasma proinsulin:insulin ratio, and HOMA-IR were assessed with ANCOVA. Change in postprandial glucose was done on the meal tolerance test set (last observation carried forward). Changes in plasma proinsulin:insulin ratio and in HOMA-IR included the full analysis set (last observation carried forward).

The key secondary analysis of the occurrence of hypoglycaemic events was assessed with the Cochran-Mantel-Haenszel test on the treated set (all patients randomly assigned to study groups who received at least one dose of study drug) and the key secondary analysis of the change from baseline in bodyweight was assessed with an ANCOVA model done on the full analysis set (last observation carried forward). Safety analyses were done on the treated set with descriptive statistics. The relative risk (RR) of cardiovascular events after treatment was compared with a  $\chi^2$  test.

The trial is registered at ClinicalTrials.gov, number NCT00622284.

### Role of the funding source

The sponsor was involved in study design, data collection, data review, and data analysis. All authors had full access to the data and had final responsibility for the content of the manuscript. BG had the final decision to submit for publication.

### Results

The trial took place between Feb 12, 2008, and Dec 21, 2010. 1552 participants were randomly assigned to receive either linagliptin (n=777) or glimepiride (n=775) in addition to metformin (figure 1). Of 1551 patients who received study drug, 1191 (77%) completed the 2-year study (587 [76%] of 777 on linagliptin vs 604 [78%] of 775 on glimepiride). The primary reasons for discontinuation were adverse events and lack of therapeutic effect. Loss to follow-up was similarly low in both treatment groups. The proportion of participants who started rescue treatment during the study was similar between groups (189 [25%] of 764 patients on linagliptin vs 162 [21%] of 755 on glimepiride;  $p=0.117$ ). At least 93% of patients (1377 of 1463) were adherent with study drug dosing throughout the trial. Mean exposure to study treatment was 627.2 (SD 212.8) days in the linagliptin group and 624.8 (227.2) days in the glimepiride group. Median exposure was 729 days in both the linagliptin (IQR 713–735) and glimepiride (721–735) groups.

Demographic and clinical characteristics were well balanced between treatment groups (table 1). During the study, mean glimepiride daily dose was 2.7 (SD 1.1) mg at week 12 and reached a plateau at 3.0 (SD 1.2) mg from week 28 to week 104. Cardiovascular risk factors at baseline were well balanced between treatment groups (appendix p 1). Most participants (1419 [91%] of 1551) received other treatments in addition to study drugs, most commonly antihypertensive agents, lipid-lowering agents, and aspirin, and the prescription pattern was similar in both treatment groups. The proportion of participants starting these drugs during the treatment period was slightly lower in the linagliptin group than in the glimepiride group: antihypertensive agents (174 [22%] of 776 patients on linagliptin vs 212 [27%] of 775 on

See Online for appendix

glimepiride), lipid-lowering agents (77 [10%] vs 102 [13%]), and acetylsalicylic acid (70 [9%] vs 73 [9%]).

After 2 years of treatment, linagliptin was non-inferior to glimepiride in reducing HbA<sub>1c</sub> (table 2). At week 104, adjusted mean changes in HbA<sub>1c</sub> from a baseline of 7.7% were -0.16% with linagliptin and -0.36% with glimepiride in the full analysis set; the difference between treatment groups met the non-inferiority criterion and was 0.20% (97.5% CI 0.09–0.30;  $p=0.0004$ ,  $<0.0125$  [one-sided]). HbA<sub>1c</sub> changes with linagliptin and glimepiride across subgroups of BMI and ethnic origin were consistent with the overall changes (data not shown). At week 52, adjusted mean changes in HbA<sub>1c</sub> were -0.38% (SE 0.03) with linagliptin versus -0.60% (0.03) with glimepiride in the full analysis set (difference 0.22%, 97.5% CI 0.13–0.31;  $p=0.0007$ ,  $<0.0125$  [one-sided]).

At week 104 in the PPS completers, adjusted mean changes in HbA<sub>1c</sub> from a baseline of 7.4% and 7.5% were -0.35% with linagliptin versus -0.53% with glimepiride (table 2); the difference between treatment groups was 0.17% (97.5% CI 0.07–0.28;  $p=0.0001$ ,  $<0.0125$  [one-sided]). In the completers cohort, adjusted mean changes in HbA<sub>1c</sub> (figure 2) from a baseline of 7.2% and 7.3% to week 104 were -0.56% with linagliptin versus -0.63% with glimepiride; the treatment difference was 0.08% (95% CI 0.00–0.15;  $p=0.0468$ ,  $<0.05$  [two-sided]). With the exception of better glycaemic control at baseline in the completers cohort than in the full analysis set (HbA<sub>1c</sub> 7.3% vs 7.7%, 87% vs 66% of patients with HbA<sub>1c</sub> <8%, FPG 8.3 mmol/L vs 9.2 mmol/L; appendix p 1), there were no differences in other clinical and anthropometric measures.

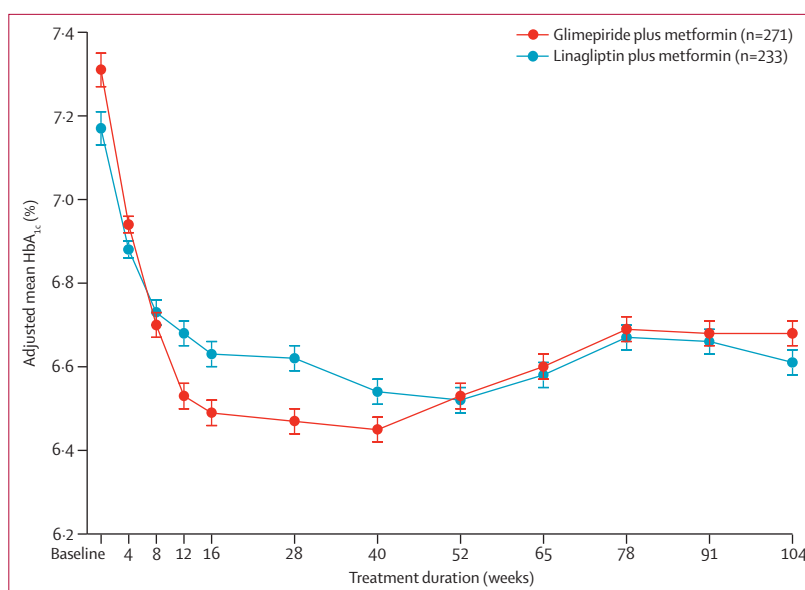
HbA<sub>1c</sub> less than 7% at week 104 was achieved by 232 (30%) of 764 patients on linagliptin and 263 (35%) of 755 on glimepiride in the full analysis set. Similar results were seen in the completers cohort, but in a greater proportion (176 [76%] of 233 patients on linagliptin vs 207 [76%] of 271 on glimepiride). HbA<sub>1c</sub> less than 6.5% was achieved by 92 (12%) of 764 patients in the linagliptin group and 120 (16%) of 755 in the glimepiride group in the full analysis set. 200 (26%) of 764 patients on linagliptin and 253 (34%) of 755 on glimepiride in the full analysis set achieved an HbA<sub>1c</sub> reduction of 0.5% or greater.

Both treatment groups had adjusted mean decreases in FPG at week 104 (-0.13 [SE 0.08] mmol/L with linagliptin vs -0.48 [0.08] mmol/L with glimepiride); the treatment difference was 0.35 mmol/L (95% CI 0.14–0.57;  $p=0.0012$ ,  $<0.05$  [two-sided]). At week 52, adjusted mean decreases in FPG were -0.48 (SE 0.07) mmol/L with linagliptin and -0.90 (0.07) mmol/L with glimepiride (difference 0.42 mmol/L, 95% CI 0.24–0.61;  $p<0.0001$ ). In the meal tolerance test set, both treatment groups showed adjusted mean decreases in 2-h postprandial glucose (-1.58 [SE 0.24] mmol/L with linagliptin vs -1.04 [0.24] mmol/L with glimepiride); the treatment difference was -0.54 mmol/L (95% CI -1.17 to 0.09;  $p=0.0918$ ). The adjusted mean changes in total glucose

	Linagliptin	Glimepiride	Difference (linagliptin–glimepiride)		
			Adjusted* mean (SE, %)	CI	p value
<b>HbA<sub>1c</sub> in full analysis set (LOCF)</b>					
n	764	755	..	..	..
Mean at baseline (SE, %)	7.69% (0.03)	7.69% (0.03)	..	..	..
Change from baseline					
Mean (SE, %)	-0.21% (0.03)	-0.41% (0.03)	..	..	..
Adjusted* mean (SE, %)	-0.16% (0.03)	-0.36% (0.03)	0.20% (0.05)	0.09–0.30†	0.0004‡
<b>HbA<sub>1c</sub> in PPS completers (OC)</b>					
n	477	458	..	..	..
Mean at baseline (SE, %)	7.43% (0.04)	7.53% (0.04)	..	..	..
Change from baseline					
Mean (SE, %)	-0.37% (0.04)	-0.61% (0.04)	..	..	..
Adjusted* mean (SE, %)	-0.35% (0.04)	-0.53% (0.04)	0.17% (0.05)	0.07–0.28†	0.0001‡
<b>HbA<sub>1c</sub> in the completers cohort</b>					
n	233	271	..	..	..
Mean at baseline (SE, %)	7.17% (0.04)	7.31% (0.04)	..	..	..
Change from baseline					
Adjusted* mean (SE, %)	-0.56% (0.03)	-0.63% (0.03)	0.08% (0.04)	0.00–0.15§	0.0468¶

HbA<sub>1c</sub>=glycated haemoglobin A<sub>1c</sub>. LOCF=last observation carried forward. PPS=per-protocol set. OC=observed cases.  
 \*Model includes treatment, baseline HbA<sub>1c</sub>, and number of previous oral antidiabetic drugs. †97.5% CI. ‡ $p<0.0125$ , one-sided. §95% CI. ¶ $p<0.05$ , two-sided.

**Table 2: Change in HbA<sub>1c</sub> from baseline to week 104**



**Figure 2: Timecourse of adjusted\* mean HbA<sub>1c</sub> values over 2 years in the completers cohort†**  
 Error bars show SE. HbA<sub>1c</sub>=glycated haemoglobin A<sub>1c</sub>. \*Model includes treatment, baseline HbA<sub>1c</sub>, and number of previous oral antidiabetic drugs. †Completers cohort equivalent to per-protocol set completers cohort used in previous comparative study of a dipeptidyl peptidase-4 inhibitor versus a sulphonylurea.<sup>11</sup>

area under the curve during 2 h after the test meal were -2.90 (SE 0.43) mmol\*h/L with linagliptin versus -1.70 (0.43) mmol\*h/L with glimepiride (treatment difference -1.21 mmol\*h/L, 95% CI -2.33 to -0.09;  $p=0.0347$ ,  $<0.05$  [two-sided]).

The overall incidence of hypoglycaemic events was, significantly, 4·8-times lower with linagliptin than with glimepiride (58 [7%] of 776 vs 280 [36%] of 775 patients;  $p<0\cdot0001$ ; appendix p 2). Notably, severe hypoglycaemia occurred in one patient receiving linagliptin compared

with 12 patients receiving glimepiride (appendix p 2; no event was fatal). The frequency of events in patients who had hypoglycaemia was also lower in the linagliptin group (appendix p 2). The proportion of patients achieving HbA<sub>1c</sub> less than 7% and having at least one hypoglycaemic event was four-times lower with linagliptin than with glimepiride (31 [4%] of 776 vs 152 [20%] of 775 patients). Bodyweight decreased with linagliptin ( $-1\cdot4$  [SE 0·2] kg) but increased with glimepiride ( $1\cdot3$  [0·2] kg) from similar mean baseline values ( $86\cdot0$  [SE 0·7] vs  $87\cdot0$  [0·6] kg); the treatment difference was  $-2\cdot7$  kg (97·5% CI  $-3\cdot2$  to  $-2\cdot2$ ,  $p<0\cdot0001$ ; appendix p 2).

Plasma proinsulin:insulin ratio and HOMA-IR decreased with linagliptin, but increased with glimepiride ( $-0\cdot01$  [SE 0·01] vs  $0\cdot03$  [0·01] pmol/mU and  $-0\cdot82$  [0·19] vs  $0\cdot03$  [0·19] [mU/L]×[mmol/L], respectively) from similar mean baseline values ( $0\cdot20$  [SE 0·01] vs  $0\cdot19$  [0·01] pmol/mU and  $5\cdot07$  [0·18] vs  $5\cdot53$  [0·23] [mU/L]×[mmol/L], respectively). Treatment differences were  $-0\cdot04$  pmol/mU (95% CI  $-0\cdot06$  to  $-0\cdot03$ ,  $p<0\cdot0001$ ) for proinsulin:insulin ratio and  $-0\cdot85$  (95% CI  $-1\cdot37$  to  $-0\cdot33$ ,  $p=0\cdot0014$ ) for HOMA-IR.

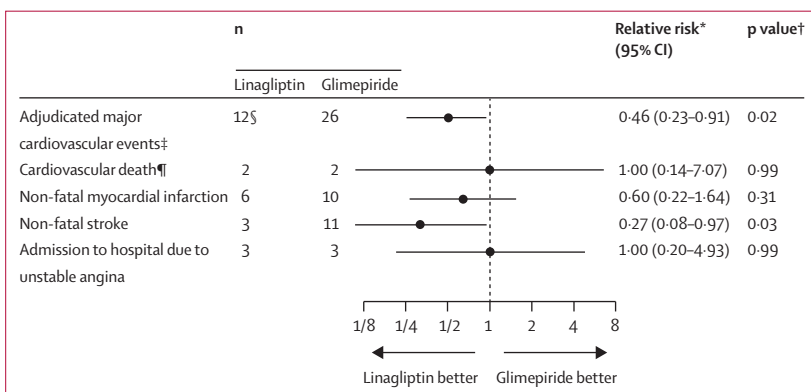
Lipid concentrations did not change substantially. Mean change in total cholesterol was  $0\cdot00$  (SD 0·8) mmol/L with linagliptin (baseline  $4\cdot7$  [SD 1·0] mmol/L) and  $0\cdot0$  (0·9) mmol/L with glimepiride (baseline  $4\cdot7$  [1·1] mmol/L). LDL cholesterol slightly increased with both linagliptin ( $0\cdot03$  [SD 0·69] mmol/L, baseline  $2\cdot64$  [0·90] mmol/L) and glimepiride ( $0\cdot09$  [0·72] mmol/L, baseline  $2\cdot56$  [0·87] mmol/L). From baseline  $1\cdot22$  (SD 0·32 and  $0\cdot33$ , respectively) mmol/L, HDL cholesterol increased slightly with linagliptin ( $0\cdot02$  [0·38] mmol/L) and was virtually unchanged ( $-0\cdot01$  [0·18]) with glimepiride. Triglycerides decreased slightly in both the linagliptin group ( $0\cdot11$  [SD 1·52] mmol/L, baseline  $2\cdot04$  [1·54] mmol/L) and the glimepiride group ( $0\cdot07$  [1·48] mmol/L, baseline  $2\cdot12$  [1·41] mmol/L).

During the 2-year treatment period, the overall incidence of adverse events was lower with linagliptin than with glimepiride (table 3). The proportion of patients with drug-related adverse events was also lower with linagliptin than with glimepiride. This difference was related mainly to the raised incidence of hypoglycaemia in the glimepiride group. Most adverse events in both treatment groups were mild or moderate in intensity. Table 3 summarises the most commonly reported events (>5% in any group). The proportion of patients with neoplasms or gastrointestinal or skin disorders was similar between treatment groups (table 3). Eight deaths (four in each group) occurred during treatment and none were judged by the investigator to be related to study drug. Causes of deaths in the linagliptin group were cardiorespiratory arrest, sudden cardiac death, bronchial carcinoma, and aortic aneurysm; causes of death in the glimepiride group were abdominal infection, sudden cardiac death, myocardial infarction, and metastatic bronchial carcinoma or acute renal failure (serious adverse events are described in the appendix pp 3–5).

	Linagliptin (n=776)	Glimepiride (n=775)
<b>Overall</b>		
Any adverse event	663 (85%)	706 (91%)
Serious adverse events	135 (17%)	162 (21%)
Drug-related adverse events	118 (15%)	300 (39%)
Adverse events leading to discontinuation*	60 (8%)	85 (11%)
Deaths	4 (1%)	4 (1%)
<b>Most common adverse event (&gt;5% in any treatment group), by preferred term</b>		
Hypoglycaemia	58 (7%)	280 (36%)
Nasopharyngitis	124 (16%)	125 (16%)
Back pain	71 (9%)	65 (8%)
Upper respiratory tract infection	62 (8%)	59 (8%)
Diarrhoea	53 (7%)	61 (8%)
Bronchitis	52 (7%)	61 (8%)
Arthralgia	63 (8%)	47 (6%)
Pain in extremity	41 (5%)	30 (4%)
Hypertension	48 (6%)	60 (8%)
Urinary tract infection	50 (6%)	52 (7%)
Headache	50 (6%)	40 (5%)
Dizziness	26 (3%)	48 (6%)
Cough	47 (6%)	38 (5%)
Hyperglycaemia	40 (5%)	41 (5%)
<b>Adverse event of special interest, by system organ class</b>		
Neoplasms	42 (5%)	43 (6%)
Gastrointestinal disorders	215 (28%)	220 (28%)
Pancreatitis	1 (<1%)	0
Skin or subcutaneous tissue disorders	119 (15%)	95 (12%)

Data are n (%). \*Recorded on case report forms.

**Table 3: Summary of clinical adverse events during 2 years in the treated set of patients**



**Figure 3: Relative risk of cardiovascular events, independently adjudicated by a clinical event committee in the treated set of patients**

\*With continuity correction of 0.5. †From  $\chi^2$  test. ‡Patients who had at least one of the following events: cardiovascular death, myocardial infarction, stroke, and admission to hospital due to unstable angina. §Includes two patients who each had two different cardiovascular events, and therefore the total (12) is less than the sum of patients who had individual cardiovascular events (14). ¶Including fatal stroke and fatal myocardial infarction.

Prospectively captured and adjudicated major cardiovascular events occurred in 12 (2%) of 776 patients treated with linagliptin and 26 (3%) of 775 patients treated with glimepiride, resulting in an RR of 0.46 (95% CI 0.23–0.91;  $p=0.0213$ ) compared with glimepiride (figure 3). This finding was mainly attributable to a significantly lower number of non-fatal strokes in patients on linagliptin compared with glimepiride (RR 0.27, 95% CI 0.08–0.97;  $p=0.0315$ ) without any relation to a hypoglycaemic event. Laboratory variables and vital signs did not reveal any clinically significant findings. No notable differences in renal function were recorded between treatment groups.

## Discussion

This long-term study showed that in patients with type 2 diabetes inadequately controlled on metformin, linagliptin was non-inferior to glimepiride in lowering HbA<sub>1c</sub> (treatment difference within the prespecified non-inferiority margin of 0.35%), but was associated with significantly less hypoglycaemia and weight loss. Linagliptin was also associated with significantly fewer cardiovascular events compared with glimepiride (panel).

Much evidence strongly suggests a beneficial effect of good glycaemic control on the progression of microvascular complications in diabetes,<sup>12</sup> but the association between HbA<sub>1c</sub> and macrovascular complications remains controversial.<sup>13–16</sup> Nevertheless, HbA<sub>1c</sub> remains a strong predictor of patient outcomes and diabetes-associated morbidity and mortality. Present guidelines recommend that HbA<sub>1c</sub> goals of less than 7% should be individually tailored for most adults with diabetes,<sup>2,4</sup> because concerns remain that aggressive glucose-lowering treatment might increase cardiovascular risk.

As an add-on to metformin, both linagliptin and glimepiride caused significant and sustained reductions in HbA<sub>1c</sub> as well as in fasting and postprandial glucose concentrations. This trial had fairly good retention and adherence rates. The percentage of patients receiving rescue treatment (roughly 22–25%) did not differ significantly between study groups. Previous studies of the same length comparing a DPP-4 inhibitor with a sulphonylurea reported failure to attain glycaemic control in about 52% of patients<sup>11</sup> and use of rescue treatment in 13–14%,<sup>17</sup> although the criteria for failure and rescue were defined slightly differently between studies.

Of note, despite similar glucose-lowering efficacy, linagliptin was associated with fewer side-effects than was glimepiride with respect to hypoglycaemia risk, weight gain, and cardiovascular events. Since hypoglycaemia can have substantial negative clinical consequences in terms of cognitive function, mortality, morbidity, adherence to treatment, and quality of life,<sup>18</sup> its prevention is a crucial component of any diabetes management programme.<sup>4</sup> However, hypoglycaemia continues to be the principal adverse effect and safety concern associated with the use of sulphonylureas.<sup>18</sup>

## Panel: Research in context

### Systematic review

We searched PubMed and ISI Web of Science for randomised double-blind clinical trials of 52 weeks or longer in duration that compared a dipeptidyl peptidase-4 (DPP-4) inhibitor with a sulphonylurea in patients with type 2 diabetes receiving metformin (English language original research articles published before January, 2012; search terms were “dipeptidyl peptidase-4 inhibitor”, “sulphonylurea”, “type 2 diabetes”, and synonyms). Three studies were identified,<sup>11,17,24</sup> two comparing different DPP-4 inhibitors with glipizide over 1 year (saxagliptin)<sup>24</sup> and 2 years (sitagliptin)<sup>11</sup> and one that, like ours, compared a DPP-4 inhibitor (vildagliptin) with glimepiride during a 2-year period (although that study's length and primary endpoint were changed after it began).<sup>17</sup> These studies showed non-inferior reductions in glycated haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) with the DPP-4 inhibitor compared with the sulphonylurea, with lower risk of hypoglycaemia and no weight gain.

### Interpretation

When metformin and lifestyle interventions fail to achieve glycaemic control in a patient with type 2 diabetes, the optimum choice for an additional pharmacotherapy is unclear. Although sulphonylureas are the most commonly added oral antidiabetic drugs in this scenario, the DPP-4 inhibitors offer non-inferior glucose-lowering efficacy with a reduced risk of hypoglycaemia and weight gain, as shown by our study and the others we have described. Our study is the longest, to date, of linagliptin compared with a sulphonylurea and also used external prospective adjudication to rule on cases of possible cardiovascular events. A hypothesis-generating finding from this study was that patients receiving the DPP-4 inhibitor had significantly fewer cardiovascular events. These potential vascular effects will be further explored in ongoing cardiovascular outcomes studies of linagliptin and other DPP-4 inhibitors.

By improving insulin secretion independently of the ambient blood glucose concentration, sulphonylureas carry the risk of intermittent hyperinsulinaemic hypoglycaemia, a risk that increases substantially with age.<sup>19</sup> Data from the UK Hypoglycaemia Study group have shown that the risk of sulphonylurea-induced severe hypoglycaemia is nearly one in ten,<sup>20</sup> a rate which was confirmed in the present active-controlled study. Additionally, up to 10% of episodes of sulphonylurea-induced severe hypoglycaemia in type 2 diabetes can be fatal.<sup>21</sup> In the present study, linagliptin was associated with a substantial reduction of frequency and severity of hypoglycaemic events compared with glimepiride. Since the glucose-lowering effects of DPP-4 inhibitors are largely dependent on raised blood glucose and subside as glucose concentrations return to normal, the probability of hypoglycaemia during treatment with linagliptin is inherently low.

Most patients with type 2 diabetes are overweight or obese<sup>22</sup> and so weight management is also an integral part of treatment.<sup>23</sup> However, sulphonylureas often cause weight gain.<sup>2</sup> In our study, patients treated with glimepiride gained an average of 1.3 kg, whereas patients treated with linagliptin lost an average of 1.4 kg after 2 years. The present study is consistent with previous trials of other DPP-4 inhibitors, which reported similar HbA<sub>1c</sub> reductions compared with sulphonylureas and reduced hypoglycaemia and weight gain.<sup>11,17,24</sup>

Interestingly, linagliptin treatment was associated with fewer cardiovascular events than was glimepiride. On one hand, the likelihood that this finding was due to chance (type 1 error) cannot be discounted, because the study was neither planned nor powered for cardiovascular outcomes. On the other hand, however, potential vascular effects of so-called gliptins might directly relate to their mode of action of DPP-4 inhibition or be a result of increased endogenous GLP-1 concentrations.<sup>25</sup> Both mechanisms could account for the consistently described risk ratios of less than 1.0 as previously reported in pooled cardiovascular analyses of DPP-4 inhibitors.<sup>26–28</sup> Alternatively, an increase in cardiovascular risk associated with sulphonylureas is another possibility that remains controversial, as shown by contradictory reports from retrospective studies in different populations.<sup>29</sup> To conclusively establish whether linagliptin reduces cardiovascular risk compared with a sulphonylurea, a large trial (CAROLINA, NCT01243424) designed specifically to evaluate the effect of linagliptin versus glimepiride on cardiovascular outcomes is underway. Cardiovascular outcomes studies of other DPP-4 inhibitors are also ongoing that, by contrast with CAROLINA, are comparing with placebo in addition to standard-of-care (NCT00790205, NCT01107886, NCT00968708).

Further limitations of the present study include that the study period of 2 years was fairly short to assess cardiovascular safety and does not allow definitive long-term evaluation of treatment durability. Conversely, the robust design was a study strength that confers high internal validity for causal inference of the relative effects of linagliptin and glimepiride. The prespecified, independent adjudication of cardiovascular events was also a study strength that allowed improved characterisation of the cardiovascular safety profile.

Although glycaemic control remains the central feature of type 2 diabetes management for all oral antidiabetic drugs, their side-effect profiles (including cardiovascular safety) are increasingly important to consider. The present study supports that linagliptin provides non-inferior glucose-lowering efficacy with a reduced risk of hypoglycaemia and weight gain as compared with glimepiride. With respect to cardiovascular safety, presently we can only conclude that linagliptin treatment is not associated with increased cardiovascular risk, as was also noted in a pooled analysis of linagliptin phase 3 trials including the present study.<sup>30</sup> Our findings support

the use of linagliptin in combination with metformin as a therapeutic option for treatment of type 2 diabetes. This study adds to the evidence base for evaluation of recommendations for second-line treatment after metformin. Ongoing studies will further inform future guidelines.

#### Contributors

BG participated in the study concept and design, patient enrolment, endpoint adjudication, and the collection, analysis, and interpretation of data. JR participated in the analysis and interpretation of data and actively revised and edited the report. TR participated in the study conduct and the analysis and interpretation of data. SB planned and did the statistical analysis. SP participated in the study conduct and the collection, analysis, and interpretation of data. MvE participated in the analysis and interpretation of data. KAD contributed to the study concept and design and participated in the interpretation of data. HJW participated in the study design and conduct, and the interpretation of data. All authors revised the report for important intellectual content and have seen and approved the final version.

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# Conflicts of interest

BG is a member of advisory boards for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Merck, Roche, Sanofi, and Takeda and has also received honoraria from these companies for giving lectures. JR has served on scientific advisory boards and received honorarium or consulting fees from Pfizer, Roche, Sanofi, Novo Nordisk, Eli Lilly, MannKind, GlaxoSmithKline, Takeda, Daiichi Sankyo, Johnson & Johnson, Novartis, Boehringer Ingelheim, and Lexicon. He has also received grants or research support from Merck, Pfizer, Sanofi, Novo Nordisk, Roche, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Takeda, Novartis, AstraZeneca, Amylin, Johnson & Johnson, Daiichi Sankyo, MannKind, Lexicon, and Boehringer Ingelheim. TR, SB, SP, MvE, KAD, and HJW are employees of Boehringer Ingelheim.

# Acknowledgments

This study was sponsored by Boehringer Ingelheim. We thank the patients who participated in this study, Barbara Uhlig-Laske for her assistance with global coordination of this trial, and Audrey Koitka-Weber who was contracted by Boehringer Ingelheim to provide medical writing support.

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