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Article: Treatment

Efficacy and safety of linagliptin in persons with Type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study[1]

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Abstract

Aims To examine the efficacy and safety of the dipeptidyl peptidase-4 inhibitor linagliptin in persons with Type 2 diabetes mellitus inadequately controlled [HbA_{1c} 53–86 mmol/mol (7.0–10.0%)] by metformin and sulphonylurea combination treatment.

Methods A multi-centre, 24-week, randomized, double-blind, parallel-group study in 1058 patients comparing linagliptin (5 mg once daily) and placebo when added to metformin plus sulphonylurea. The primary endpoint was the change in HbA_{1c} after 24 weeks.

Results At week 24, the linagliptin placebo-corrected HbA_{1c} adjusted mean change from baseline was −7 mmol/mol (−0.62%) [95% CI −8 to −6 mmol/mol (−0.73 to −0.50%); $P < 0.0001$]. More participants with baseline HbA_{1c} ≥ 53 mmol/mol (≥ 7.0%) achieved an HbA_{1c} < 53 mmol/mol (< 7.0%) with linagliptin compared with placebo (29.2% vs. 8.1%, $P < 0.0001$). Fasting plasma glucose was reduced with linagliptin relative to placebo (−0.7 mmol/l, 95% CI −1.0 to −0.4; $P < 0.0001$). Improvements in homeostasis model assessment of β-cell function were seen with linagliptin ($P < 0.001$). The proportion of patients who reported a severe adverse event was low in both groups (linagliptin 2.4%; placebo 1.5%). Symptomatic hypoglycaemia occurred in 16.7 and 10.3% of the linagliptin and placebo groups, respectively. Hypoglycaemia was generally mild or moderate; severe hypoglycaemia was reported in 2.7 and 4.8% of the participants experiencing hypoglycaemic episodes in the linagliptin and placebo groups, respectively. No significant weight changes were noted.

Conclusions In patients with Type 2 diabetes, adding linagliptin to metformin given in combination with a sulphonylurea significantly improved glycaemic control and this was well tolerated. Linagliptin could provide a valuable treatment option for individuals with inadequate glycaemic control despite ongoing combination therapy with metformin and a sulphonylurea.

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Keywords dipeptidyl peptidase-4 inhibitor, linagliptin, metformin, sulphonylurea, Type 2 diabetes

Introduction

Patients with Type 2 diabetes mellitus who cannot achieve adequate glycaemic control with a single oral hypoglycaemic agent, usually first-line metformin therapy, normally progress to combination treatment where agents with complementary mechanisms are employed to achieve additive or synergistic improvements in glycaemic control [1–4]. Inadequate disease management on metformin alone usually results initially in the addition of a sulphonylurea drug [5]. However, when conventional oral hypoglycaemic agent combinations such as

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(Clinical Trials Registry No; NCT 00602472)

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these fail to maintain adequate control of blood glucose levels, the addition of new and mechanistically distinct oral hypoglycaemic agents may have a role in diabetes management.

Oral hypoglycaemic agents that act to increase the availability of endogenous incretins such as glucagon-like peptide-1 (GLP-1) may delay or avoid the need for exogenous insulin. Dipeptidyl peptidase-4 (DPP-4) rapidly degrades GLP-1, and DPP-4 inhibitors can offer new therapeutic options for patients with Type 2 diabetes. The inhibition of DPP-4 increases available GLP-1 levels, promoting increased insulin release and also the suppression of glucagon hypersecretion. Pharmacological inhibition of DPP-4 does not tend to lead to weight gain, which can be associated with insulin, sulphonylurea or thiazolidinedione treatments [6,7], and clinical studies have demonstrated that DPP-4 inhibitors can improve β-cell function and maintain glycaemic control for extended periods [8–10].

Linagliptin is a selective and potent DPP-4 inhibitor with a unique xanthine-based structure [11]. *In vitro* studies of DPP-4 inhibition resulted in IC_{50} values of 1 nM for linagliptin; 19 nM for sitagliptin; 24 nM for alogliptin; 50 nM for saxagliptin; and 62 nM for vildagliptin. In healthy volunteers, a single dose of linagliptin 5 mg inhibited DPP-4 by 86.1% [12], and the prolonged half-life of over 100 h and sustained inhibition of DPP-4 (> 80% at 24 h at steady state) for linagliptin allows once-daily dosing [13].

The pharmacokinetics of linagliptin has previously been shown to be different from that seen with other DPP-4 inhibitors, being non-linear owing to concentration-dependent tight binding to DPP-4 and rapid elimination of the unbound fraction [14]. Linagliptin excretion occurs by a predominantly non-renal mechanism, primarily via the faeces, with < 7% undergoing renal excretion [15]. This is in contrast to many DPP-4 inhibitors that are eliminated primarily via the kidney [16]. As a consequence of its predominantly non-renal route of excretion, linagliptin is not expected to require dose adjustment in patients with or at risk of declining renal function. Moreover, linagliptin is not a clinically relevant substrate for, or inhibitor of, cytochrome P450 isoenzymes or P-glycoprotein and it therefore has a low risk for drug–drug interactions [13,15].

It has been shown that linagliptin, owing to its wide safety margin in dosing, is well tolerated at doses > 100-fold in excess of the proposed therapeutic dose of 5 mg [13]. In Phase II clinical trials in patients with Type 2 diabetes, linagliptin produced significant improvements in glycaemic control, with significant reductions in both fasting plasma glucose and HbA_{1c} levels [17,18].

With a mechanism of action complementary to that of both metformin and the sulphonylureas, the co-administration of an incretin agent such as linagliptin may be a rational step to achieve control of blood glucose levels. The indication that linagliptin has a low potential to interact adversely with metformin and/or sulphonylureas supports this combination [13].

This study is a Phase III clinical trial investigating the efficacy, safety and tolerability of linagliptin (5 mg once daily) compared with placebo, when administered for a 24-week period as add-on to metformin plus a sulphonylurea, in persons with Type 2 diabetes having inadequate glycaemic control.

Patients and methods

Study design

This randomized, placebo-controlled, double-blind, parallel-group study was performed at 100 trial centres in 11 countries: Argentina, Belgium, Canada, China, Germany, Korea, the Philippines, Russia, Taiwan, Turkey and the UK. Following a 2-week placebo run-in period, patients were randomized (3:1), stratified by HbA_{1c} value [< 69 vs. ≥ 69 mmol/mol (< 8.5 vs. ≥ 8.5%)], to 24 weeks of treatment with linagliptin (5 mg once daily) or placebo, in addition to their established background therapy of metformin in combination with a sulphonylurea. Patients who changed their dose of background therapy remained in the trial to provide safety data.

All patients were provided with self blood glucose-monitoring equipment for use during the whole study period, with training provided on the correct use of the equipment during each phase of the trial by either the investigator or designated site personnel. In addition, all patients received dietary counselling.

During the first 12 weeks of treatment, rescue medication (pioglitazone and, in Canada only, insulin) was initiated if a patient had a confirmed fasting glucose level of > 13.3 mmol/l. During the last 12 weeks of randomized treatment, rescue medication was initiated if a patient had a confirmed fasting glucose level of > 11.1 mmol/l or a random glucose level of > 22.2 mmol/l. Patients discontinued if the fasting glucose levels remained > 13.3 mmol/l during the first 12 weeks or > 11.1 mmol/l during the last 12 weeks despite rescue medication, and if the investigator anticipated no further glucose-lowering effect.

This study was conducted in accordance with the Declaration of Helsinki (1996 version), the International Conference of Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and applicable regulatory requirements. Local and central ethical review boards approved the study. The Independent Ethics Committee or Institutional Review Board of participating centres reviewed the protocol, patient information sheet, informed consent form and insurance policy, and written informed consent was obtained from each participant before entering the study.

Study participants

The study enrolled men and women with Type 2 diabetes aged ≥ 18 and ≤ 80 years, with a BMI ≤ 40 kg/m^2 and HbA_{1c} ≥ 53 mmol/mol (≥ 7.0%) and ≤ 86 mmol/mol (≤ 10.0%) despite receiving a total daily dose of ≥ 1500 mg metformin (or the maximum tolerated dose, if lower) and the maximum tolerated dose of sulphonylurea. The dose and regimen of metformin and the sulphonylurea were unchanged for ≥ 10 weeks before enrolment.

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Patients were excluded from the trial if their clinical conditions would, in the investigator's opinion, interfere with participation and safety. Myocardial infarction, stroke or transient ischaemic attack within 6 months before enrolment; impaired hepatic function; renal failure or renal impairment; current acute or chronic metabolic acidosis; hereditary galactose intolerance; or being unable or unwilling to avoid nursing or pregnancy were all exclusion criteria. Patients treated with rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months of enrolment were also excluded.

Study determinations

Central laboratories [MDS Pharma Services Central Laboratories, Baillet en France (France), North Brunswick (USA), Singapore and Beijing (China) and Laboratory Hidalgo (Argentina)] performed haematology, urinalysis, clinical chemistry [including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides] and HbA_{1c} determinations. The percentage of HbA_{1c} from total haemoglobin was analyzed by a validated high-performance liquid chromatography Variant II™ method in a National Glycohemoglobin Standardization Program (NGSP) Level I certified assay. Corresponding International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized values for HbA_{1c} were calculated using the relationship: IFCC value (in mmol/mol) = 10.93 × NGSP value (in %) −23.5 [19,20]. Conversion of standard deviation (SD) from % to mmol/mol was by the following equation: IFCC value (in mmol/mol) = 10.93 × NGSP value (in %). These conversions were undertaken after statistical analyses had been conducted. MDS Pharma Services (Baillet en France) determined fasting plasma glucose and insulin levels. All analyses used validated assays.

Statistical analysis

A sample size of 800 patients (600 linagliptin and 200 placebo) was required to ensure > 99% power to detect a 0.7% treatment difference in this study, assuming a SD of 1.2% for the difference in HbA_{1c} from baseline.

Analysis of the primary endpoint, change in HbA_{1c} mmol/mol (%) levels between baseline and 24 weeks, involved testing a superiority hypothesis vs. placebo using analysis of covariance (ANCOVA) at the level of $\alpha = 0.05$ (two-sided) with treatment as factor and baseline HbA_{1c} mmol/mol (%) as covariate. The primary analysis was performed on the full analysis set, consisting of all randomized participants who were treated with at least one dose of study medication, had a baseline HbA_{1c} measurement and at least one on-treatment HbA_{1c} measurement. A last observation carried forward approach was used to replace missing data. Sensitivity analyses were performed to assess the impact of important protocol violations and premature discontinuation, and to assess missing data assumptions, i.e. mixed-model repeated measures.

Secondary endpoints included: proportion of participants achieving HbA_{1c} of < 48 or < 53 mmol/mol (< 6.5 or < 7.0%, respectively) after 24 weeks; proportion of participants showing HbA_{1c} reduction of ≥ 6 mmol/mol (≥ 0.5%) after 24 weeks of therapy; and change from baseline in fasting plasma glucose. Other endpoints included: use of rescue medication; fasting plasma insulin; homeostasis model assessment (HOMA-β and HOMA-IR) and disposition index; and changes in body weight, waist circumference and plasma lipids. Secondary and other endpoints were analyzed by exploratory ANCOVA; hypoglycaemic events and the use of rescue medication were analyzed by logistic regression and Kaplan–Meier analysis. ANCOVA for fasting biomarkers (HOMA-IR and HOMA-β) and derived indices used baseline HbA_{1c} and the baseline value of the respective biomarker or derived index as continuous covariates. In the analysis of HOMA data, patients receiving rescue medication were not included and a last observation carried forward approach was used to impute missing data.

Tolerability and safety assessments included the incidence and intensity of adverse events, withdrawals because of adverse events, physical examination, vital signs (blood pressure and pulse), 12-lead electrocardiogram and clinical laboratory measurements, and were summarized using descriptive statistics without tests for significance.

Results

Patient disposition and demographics

Of the 1598 participants enrolled, 1136 entered the 2-week placebo run-in, and 793 and 265 participants were randomized to linagliptin and placebo, respectively (Fig. 1). Overall, the percentages of patients with HbA_{1c} < 69 mmol/mol or ≥ 69 mmol/mol (< 8.5 or ≥ 8.5%) were comparable between the two treatment groups. A total of 600 patients (56.7%) had HbA_{1c} < 69 mmol/mol (< 8.5%) (56.6% placebo; 56.7% linagliptin), while 458 patients (43.3%) had HbA_{1c} ≥ 69 mmol/mol (≥ 8.5%) (43.4% placebo; 43.3% linagliptin). Three participants, one in the linagliptin arm and two in the placebo arm, did not receive treatment and were excluded from all analyses. Seventy-nine participants prematurely discontinued [linagliptin: $n = 58$ (7.3%); placebo: $n = 21$ (8.0%)] because of adverse events, non-compliance or refusal to continue study medication.

Baseline and demographic data were similar between the two groups (Table 1). Overall mean (SD) age was 58.1 (9.8) years, mean (SD) baseline HbA_{1c} was 65.5 (6.5) mmol/mol [8.14% (0.81%)], with 77% of individuals having a baseline HbA_{1c} between 53 mmol/mol and < 75 mmol/mol (7.0 and < 9.0%, respectively), and 57.0% of patients had normal renal function. Mean (SD) baseline fasting plasma glucose was 8.9 (2.0) mmol/l, and a total of 762 patients (73.3%) were diagnosed as having had Type 2 diabetes for > 5 years at the time of screening.

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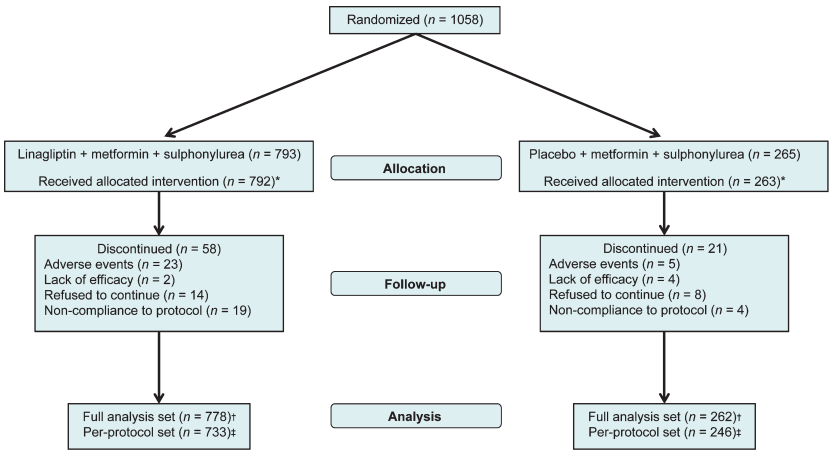

FIGURE 1 Trial profile. *The treated set comprised all patients randomized to therapy, excluding the three patients (one in the linagliptin arm; two in the placebo arm) who, following randomization, did not receive their allocated intervention. †The full analysis set (1040 patients) comprised all patients from the treated set who had both a baseline HbA_{1c} measurement and at least one on-treatment HbA_{1c} measurement available. ‡The per-protocol set (979 patients) was a subset of the full analysis set that included all patients who did not have an important protocol violation that impacted on efficacy.

Diabetes-related complications were common, with macrovascular diseases present in 80.2 and 81.2% in the placebo and linagliptin groups, respectively; metabolic syndrome was present in 65.4 and 69.1%, respectively, and microvascular complications in 47.1 and 45.6%, respectively.

Efficacy

Baseline HbA_{1c} was similar at 66 mmol/mol (8.14%) and 66 mmol/mol (8.15%) in the placebo and linagliptin groups, respectively (Table 2; Fig. 2). Linagliptin was superior to placebo for the adjusted mean change seen in HbA_{1c} between baseline and week 24 [placebo-corrected adjusted mean change from baseline at week 24: −7 mmol/mol; 95% confidence interval (CI) −8.0 to −5.5 (−0.62%; 95% CI −0.73 to −0.50); $P < 0.0001$]. Sensitivity analyses of the per-protocol set (participants without important protocol violations) were consistent with the primary analysis of the full analysis set. For the per-protocol set, the placebo-corrected adjusted mean change in HbA_{1c} from baseline at week 24 was −6.7 mmol/mol; 95% CI −8.0 to −5.4 (−0.61%; 95% CI −0.73 to −0.49); $P < 0.0001$.

Baseline fasting plasma glucose was 9.0 and 8.8 mmol/l for the placebo and linagliptin groups, respectively (Table 2). Linagliptin produced a greater adjusted mean change in fasting plasma glucose than placebo between baseline and week 24 (placebo-corrected adjusted mean change from baseline at week 24: −0.7 mmol/l; 95% CI −1.0 to −0.4; $P < 0.0001$).

Among participants with a baseline $HbA_{1c} \geq 53$ mmol/mol (≥ 7.0%), 29.2 and 8.1% of the linagliptin and placebo groups, respectively, achieved $HbA_{1c} < 53$ mmol/mol (< 7.0%) (odds ratio 5.5; $P < 0.0001$). Of those with an initial HbA_{1c} of 53 to < 64 mmol/mol (7.0 to < 8.0%), 46.3% on linagliptin and 14.4% on placebo achieved HbA_{1c} of < 53 mmol/mol (< 7%). This target was similarly achieved by a greater proportion of patients on linagliptin vs. placebo with a baseline HbA_{1c} of 64 to < 75 mmol/mol (8.0 to < 9.0%), 22.2 vs. 4.2%, respectively, and those with baseline $HbA_{1c} > 75$ mmol/mol (> 9.0%), 5.9 vs. 2.1%, respectively. The proportion of participants achieving a reduction in HbA_{1c} of ≥ 6 mmol/mol (≥ 0.5%) was 58.2% with linagliptin and 30.2% with placebo. Finally, 32.5% of participants in the linagliptin group showed reductions in $HbA_{1c} \geq 11$ mmol/mol (≥ 1%) compared with 11.5% with placebo. Figure 3 illustrates the adjusted mean change in HbA_{1c} from baseline to 24 weeks, stratified by baseline HbA_{1c}. Patients treated with linagliptin with a baseline HbA_{1c} level of ≥ 75 mmol/mol (≥ 9.0%) showed a greater reduction in HbA_{1c} than the overall cohort [−13 mmol/mol; 95% CI −14.2 to −11.1; (−1.16%; 95% CI −1.30 to −1.02)] compared with placebo [−5 mmol/mol; 95% CI −7.2 to −1.9; (−0.41%; 95% CI −0.65 to −0.17); $P < 0.0001$]. Additionally, in elderly patients, another vulnerable patient group, linagliptin showed a reduction in HbA_{1c} mmol/mol (%) compared with placebo: the adjusted mean (SE) change from baseline was −7 mmol/mol (0.3) [−0.68% (0.03)] in the linagliptin group ($n = 565$) vs. −1 mmol/mol (0.7) [−0.08% (0.06)] in the placebo group ($n = 192$) in the < 65 years subgroup ($P < 0.0001$), −9 mmol/mol (0.7) [−0.79% (0.06)] in the linagliptin group ($n = 175$) vs. −2 mmol/mol (1.1) [−0.15% (0.10)] in the placebo group ($n = 622$) in the 65–74 years subgroup ($P < 0.0001$) and −10 mmol/mol (1.4) [−0.92% (0.13)] in the linagliptin group ($n = 38$) vs. −3 mmol/mol (3.2) [−0.31% (0.29)] in the placebo group ($n = 8$) in the ≥ 75 years subgroup ($P = 0.0533$).

A total of 715 patients (linagliptin, $n = 540$; placebo, $n = 175$) had data available for the HOMA analysis. At baseline, most clinically relevant characteristics (for example, age, BMI and duration of diabetes) were essentially similar between those patients who were included vs. those not included in the analysis (see also Supporting Information, Table S1). Baseline HbA_{1c} levels were slightly higher in patients that were not included in the analysis [67 mmol/mol (8.32%)] compared with those

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Table 1 Demographics and baseline characteristics of the treated set of patients

	Placebo	Linagliptin	Total
Number of patients	263	792	1055
Gender, *n* (%)			
Male	127 (48.3)	371 (46.8)	498 (47.2)
Female	136 (51.7)	421 (53.2)	557 (52.8)
Race, *n* (%)			
American Indian/Alaska Native	4 (1.5)	6 (0.8)	10 (0.9)
Asian	141 (53.6)	404 (51.0)	545 (51.7)
Black or African American	2 (0.8)	6 (0.8)	8 (0.8)
White	116 (44.1)	376 (47.5)	492 (46.6)
Ethnicity, *n* (%)			
Not Hispanic/Latino	204 (77.6)	611 (77.1)	815 (77.3)
Hispanic/Latino	58 (22.1)	180 (22.7)	238 (22.6)
Missing	1 (0.4)	1 (0.1)	2 (0.2)
Age (years)			
Mean (SD)	57.6 (9.7)	58.3 (9.9)	58.1 (9.8)
Age groups (years), *n* (%)			
< 65	192 (73.0)	575 (72.6)	767 (72.7)
65–74	63 (24.0)	179 (22.6)	242 (22.9)
≥ 75	8 (3.0)	38 (4.8)	46 (4.4)
Baseline weight (kg)			
Mean (SD)	76.8 (16.8)	76.5 (16.8)	76.6 (16.8)
Baseline BMI (kg/m^2)			
Mean (SD)	28.2 (4.5)	28.4 (4.8)	28.3 (4.7)
Baseline BMI, categorical (kg/m^2), *n* (%)			
< 30	185 (70.4)	532 (67.2)	717 (67.9)
≥ 30	78 (29.7)	260 (32.8)	338 (32.0)
Baseline eGFR (MDRD staging) (ml/min/1.73 m^2)*, *n* (%)			
≥ 90	158 (60.1)	443 (55.9)	601 (57.0)
60 to < 90	83 (31.6)	282 (35.6)	365 (34.6)
30 to < 60	16 (6.1)	37 (4.7)	53 (5.0)
Missing	6 (2.3)	30 (3.8)	36 (3.4)
Baseline eCcr (ml/min)*, *n* (%)			
> 80	198 (75.3)	586 (74.0)	784 (74.3)
50–80	50 (19.0)	156 (19.7)	206 (19.5)
30 to < 50	9 (3.4)	19 (2.4)	28 (2.7)
Missing	6 (2.3)	31 (3.9)	37 (3.5)
Duration of diabetes, *n* (%)			
Up to 1 year	5 (1.9)	24 (3.1)	29 (2.8)
> 1–5 years	64 (24.4)	185 (23.8)	249 (23.9)
> 5 years	193 (73.3)	569 (73.1)	762 (73.3)

*No patients were reported for the eGFR and eCcr categories of < 30 ml/min.
eCcr, estimated creatinine clearance rate; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

included [65 mmol/mol (8.1%)]. Additionally, there was a greater proportion of placebo patients in the higher HbA_{1c} categories of 64–75 mmol/mol (8.0–9.0%) and > 75 mmol/mol (> 9.0%). β-cell function, as reflected by changes in HOMA-β (SD) values, significantly improved from baseline to week 24 with linagliptin. HOMA-β at baseline was 36.8 (2.1) vs. 45.0 (2.2) (mU/l)/(mmol/l) for the placebo and linagliptin groups, respectively. After 24 weeks, HOMA-β decreased in the placebo group by 9.1 (4.3) (mU/l)/(mmol/l) compared with an increase in the linagliptin group of 7.8 (2.5) (mU/l)/(mmol/l). The treatment difference between linagliptin and placebo was 16.9 (mU/l)/(mmol/l) (95% CI 7.1–26.7; P = 0.0008). Insulin resistance as depicted by HOMA-IR at baseline was 3.4 (0.2) vs. 4.1 (0.2) (mU/l) × (mmol/l) for the placebo and linagliptin groups, respectively. The adjusted mean change in insulin resistance (HOMA-IR) from baseline to week 24 was −0.06 (mU/l) × (mmol/l) with linagliptin and −0.74 (mU/l) × (mmol/l) with placebo. The treatment difference was 0.7 (mU/l) × (mmol/l) (95% CI 0.1–1.3; P = 0.018).

Safety and tolerability

Overall, 66.3 and 59.7% of the linagliptin and placebo groups, respectively, experienced adverse events (Table 3). Only 3.2 and 3.8% of the linagliptin and placebo groups, respectively, experienced serious adverse events; 2.4 and 1.5%, respectively, experienced adverse events of severe intensity, all others were mild or moderate. Regarding drug-related adverse events, 17.9

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Table 2 Adjusted means for the change from baseline at week 24 in HbA_{1c} [full analysis set (last observation carried forward)] and fasting plasma glucose [full analysis set (last observation carried forward)]

	Placebo	Linagliptin
HbA_{1c} (%)		
Number of patients with baseline and on-treatment results	262	778
Baseline		
Mean (SE) (mmol/mol, IFCC)	65.5 (0.4)	65.6 (0.2)
Mean (SE) (%, NGSP)	8.14 (0.05)	8.15 (0.03)
Change from baseline		
Adjusted* mean (SE) (mmol/mol, IFCC)	−1.1 (0.5)	−7.9 (0.3)
Adjusted* mean (SE) (%, NGSP)	−0.10 (0.05)	−0.72 (0.03)
Comparison vs. placebo (difference linagliptin – placebo)		
Adjusted* mean (SE) (mmol/mol, IFCC)		−6.8 (0.7)
95% CI (mmol/mol, IFCC)		(−8.0, −5.5)
Adjusted* mean (SE) (%, NGSP)		−0.62 (0.06)
95% CI (%, NGSP)		(−0.73, −0.50)
P-value		< 0.0001
Fasting plasma glucose (mmol/l)		
Number of patients with baseline and on-treatment results	248	739
Baseline		
Mean (SE)	9.0 (0.1)	8.8 (0.1)
Change from baseline		
Adjusted† mean (SE)	0.4 (0.1)	−0.3 (0.1)
Comparison vs. placebo (difference linagliptin – placebo)		
Adjusted† mean (SE)		−0.7 (0.2)
95% CI		(−1.0, −0.4)
P-value		< 0.0001

*Model includes continuous baseline HbA_{1c} and treatment.
†Model includes continuous baseline HbA_{1c}, continuous fasting plasma glucose and treatment.
CI, confidence interval; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Programme.

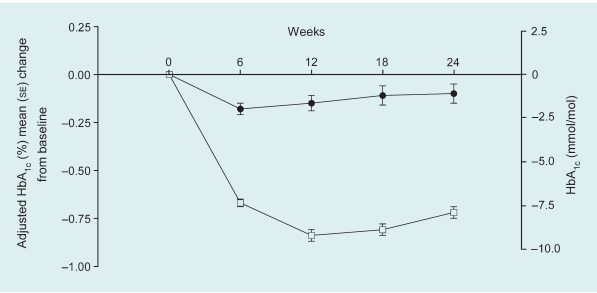

FIGURE 2 Adjusted mean change from baseline in HbA_{1c} over time following treatment with linagliptin 5 mg (□, n = 778) or placebo (●, n = 262) for 24 weeks as add-on therapy to metformin and a sulphonylurea [full analysis set (last observation carried forward)] (P < 0.0001 for all; statistical analyses were performed on HbA_{1c} % data only).

and 11.4% of cases were reported for the linagliptin and placebo groups, respectively. The most frequently reported adverse event was hypoglycaemia, which occurred in 22.7 and 14.8% of patients in the linagliptin and placebo groups, respectively. The odds ratio for the occurrence of any hypoglycaemic event with linagliptin was 1.64 (95% CI 1.14–2.38; P = 0.0083). Symptomatic hypoglycaemia occurred in 16.7 and 10.3% of the linagliptin and placebo groups, respectively. Severe hypoglycaemia (requiring the assistance of another person to administer carbohydrate, glucagon or other resuscitative actions) was less frequent in the linagliptin group than in the placebo group (2.7 vs. 4.8% of participants experiencing a hypoglycaemic episode, respectively). The overall rate of discontinuation from the trial because of adverse events was low (linagliptin: 2.9%; placebo: 1.9%). The mean changes in blood pressure (systolic/diastolic) from baseline at week 24 were 0.63 mmHg/0.59 mmHg for the placebo group and −0.31 mmHg/0.08 mmHg for the linagliptin group. Generally, treatment with linagliptin in combination with metformin and sulphonylurea was well tolerated and no new safety concerns arose in this trial.

Of patients receiving linagliptin, 5.4% required rescue medication, compared with 13.0% of patients receiving placebo. The median time to requiring rescue medication was shorter for patients receiving placebo (119 days) than with linagliptin (132 days); in addition, the likelihood of requiring rescue medication was approximately three times lower with linagliptin (odds ratio 0.361; P < 0.0001). No meaningful change in body weight or waist circumference occurred from baseline to week 24 (Table 4). Mean values of triglycerides were above the normal reference range at both baseline (236 mg/dl placebo; 234 mg/dl linagliptin) and at last value on treatment (224 mg/dl placebo; 236 mg/dl linagliptin), with a decrease

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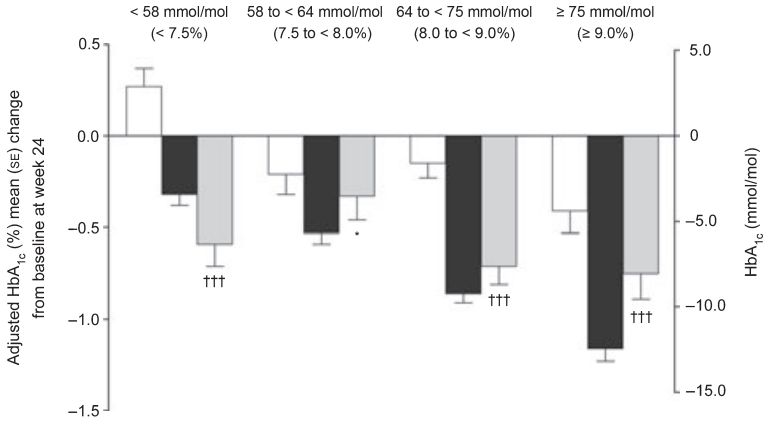

FIGURE 3 Adjusted mean change (± SE, plotted in one direction only, for clarity) in HbA_{1c} after 24 weeks by baseline HbA_{1c} following treatment with linagliptin 5 mg (black bars) or placebo (white bars) as add-on therapy to metformin and a sulphonylurea; linagliptin placebo-corrected HbA_{1c} also shown (grey bars) [full analysis set (last observation carried forward)] (*P = 0.011; †††P < 0.0001; statistical analyses were performed on HbA_{1c} % data only).

Table 3 Frequency of patients with adverse events occurring at an incidence of > 2% in either treatment group on the preferred term level, by overall frequency and system organ class – treated set

	n (%)	
	Placebo + metformin + sulphonylurea	Linagliptin + metformin + sulphonylurea
Number of patients	263	792
Any adverse event	157 (59.7)	525 (66.3)
Serious	10 (3.8)	25 (3.2)
Severe	4 (1.5)	19 (2.4)
Adverse events leading to discontinuation of trial drug	5 (1.9)	23 (2.9)
Drug-related adverse events	30 (11.4)	142 (17.9)
Metabolism and nutrition disorders	68 (25.9)	246 (31.1)
Hypoglycaemia	39 (14.8)	180 (22.7)
Hyperglycaemia	23 (8.7)	45 (5.7)
Infections and infestations	76 (28.9)	170 (21.5)
Upper respiratory tract infection	25 (9.5)	46 (5.8)
Urinary tract infection	14 (5.3)	26 (3.3)
Nasopharyngitis	12 (4.6)	41 (5.2)
Nervous system disorders	30 (11.4)	77 (9.7)
Headache	13 (4.9)	33 (4.2)
Dizziness	12 (4.6)	29 (3.7)
Gastrointestinal disorders	48 (18.3)	103 (13.0)
Diarrhoea	9 (3.4)	21 (2.7)
Abdominal pain upper	7 (2.7)	9 (1.1)
Nausea	6 (2.3)	10 (1.3)
Musculoskeletal and connective tissue disorders	24 (9.1)	97 (12.2)
Back pain	8 (3.0)	13 (1.6)
Arthralgia	4 (1.5)	21 (2.7)
General disorders and administration site conditions	19 (7.2)	61 (7.7)
Asthenia	5 (1.9)	19 (2.4)
Respiratory, thoracic and mediastinal disorders	7 (2.7)	33 (4.2)
Cough	3 (1.1)	19 (2.4)
Vascular disorders	6 (2.3)	34 (4.3)
Hypertension	5 (1.9)	19 (2.4)
Psychiatric disorders	9 (3.4)	18 (2.3)
Insomnia	6 (2.3)	5 (0.6)

with respect to baseline only in the placebo group (mean change from baseline −12 mg/dl) (Table 4). The mean changes from baseline to the last value on treatment for total cholesterol, HDL cholesterol and LDL cholesterol were similar in both treatment groups (Table 4). The mean changes from baseline to the last value on treatment for urea, creatinine, total bilirubin, uric acid, total protein and albumin were also similar in both treatment groups (data not shown).

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Table 4 Change from baseline in body weight, waist circumference and plasma lipids at week 24 – full analysis set (observed cases)

	Placebo	Linagliptin
Body weight (kg)		
Number of patients analyzed	222	714
Baseline, mean (SE)	77.4 (1.1)	76.6 (0.6)
Adjusted* mean change from baseline (SE)	−0.06 (0.16)	0.27 (0.09)
Comparison vs. placebo		
Adjusted mean (SE)		0.33 (0.19)
95% CI		(−0.04, 0.69)
P-value		0.0803
Waist circumference (cm)		
Number of patients analyzed	222	710
Baseline, mean (SD)	97.2 (13.3)	97.2 (12.8)
Change from baseline, mean (SD)	0.0 (4.0)	−0.2 (4.3)
Plasma lipids (mg/dl)†		
Total cholesterol		
Number of patients analyzed	260	771
Baseline, mean (SD)	176 (19)	176 (18)
Change from baseline‡, mean (SD)	2 (14)	2 (13)
HDL		
Number of patients analyzed	258	762
Baseline, mean (SD)	39 (16)	38 (15)
Change from baseline‡, mean (SD)	1 (9)	0 (8)
LDL		
Number of patients analyzed	258	768
Baseline, mean (SD)	138 (31)	139 (31)
Change from baseline‡, mean (SD)	5 (22)	5 (23)
Triglycerides		
Number of patients analyzed	260	769
Baseline, mean (SD)	236 (210)	234 (166)
Change from baseline‡, mean (SD)	−12 (185)	1 (142)

*Model includes baseline HbA_{1c}, baseline weight and treatment.
†To convert the values for cholesterol to mmol/l, multiply by 0.02586. To convert the values for triglycerides to mmol/l, multiply by 0.01129.
CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
‡Last value on treatment minus baseline value (normalized values).

Discussion

Within 3 years of diagnosis, 50% of people with Type 2 diabetes require combination therapy to attain HbA_{1c} targets and, by 9 years post-diagnosis, the proportion is 75% [21]. This study assessed the efficacy and safety of 24 weeks of treatment with the DPP-4 inhibitor linagliptin in patients with Type 2 diabetes having inadequate glycaemic control (HbA_{1c} ≥ 53.0 and ≤ 85.8 mmol/mol; ≥ 7.0% and ≤ 10.0%) despite treatment with metformin and sulphonylurea.

Linagliptin administered as a once-daily 5-mg dose resulted in a significant and clinically meaningful improvement in glycaemic control. The improvements observed are broadly consistent with three other placebo-controlled Phase III studies conducted in patients with different background therapies, which have also demonstrated that linagliptin produces clinically and statistically significant reductions in HbA_{1c} and fasting plasma glucose levels [22–24]. In the present study, significantly more participants with baseline HbA_{1c} ≥ 53.0 mmol/mol (≥ 7.0%) achieved HbA_{1c} < 53.0 mmol/mol (< 7.0%) with linagliptin than with placebo as add-on to metformin plus sulphonylurea therapy. Therefore, treatment with linagliptin may help to increase the proportion of patients that achieve the target HbA_{1c} values suggested in treatment guidelines [4,5]. Additionally, this study showed that linagliptin improved markers of β-cell function, producing a statistically significant and clinically relevant improvement in HOMA-β. The changes seen in this Phase III study are consistent with improved β-cell function in Type 2 diabetes, which probably reflects increased availability of endogenous GLP-1, and they are similar to results with other DPP-4 inhibitors [8–10]. The reason for the improvement in insulin sensitivity with placebo in this study is not clear but could be attributable to slight improvements in weight and HbA_{1c} levels that were observed following 24 weeks of placebo treatment. The decline in HOMA-β observed in the placebo group is likely to be the result of progressive deterioration in β-cell function.

Treatment-induced hypoglycaemia represents a major concern in patients with diabetes. In this study, hypoglycaemia was more common with linagliptin than with placebo. The increased frequency is consistent with previous observations with DPP-4 inhibitors when used in combination with sulphonylurea drugs, where hypoglycaemia occurred in > 10% of patients [1], despite the fact that monotherapy with DPP-4 inhibitors, including linagliptin, is not associated with a significantly increased risk of hypoglycaemia [25,26]. It is of interest to note that, in the present study, severe hypoglycaemic episodes were more frequent with placebo than with linagliptin in combination with metformin and sulphonylurea.

Despite the potential for hypoglycaemia when added to pre-existing sulphonylurea therapy, linagliptin exhibited a favourable tolerability profile, with no overall increase in other adverse events when compared with placebo, and no new safety concerns emerged. The adverse event profile of linagliptin was broadly comparable with previous studies and other Phase III results, supporting the good safety and tolerability profile of linagliptin [13,22]. The occurrence of skin disorders was low (< 5%) and comparable between the linagliptin and placebo groups in this and the other reported Phase III studies [22–24]. Rates of respiratory and urinary tract infections, as well as nasopharyngitis, were also low in the linagliptin group (< 6%).

Many patients who do not show adequate glycaemic control with metformin plus sulphonylurea treatment progress to insulin therapy. Exogenous insulin remains the most effective

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anti-hyperglycaemic agent, but many patients wish to avoid insulin therapy as it may increase the potential for hypoglycaemia and promote clinically significant weight gain [27], an undesirable side effect of many treatments for Type 2 diabetes. In the present study, neither group showed significant changes in weight from baseline. With the triple therapy including linagliptin, a significantly greater proportion of participants achieved target HbA_{1c} levels than with a combination of the other two oral hypoglycaemic agents, and thus the requirement for insulin initiation may be postponed in patients treated with linagliptin. The increase in hypoglycaemic episodes in the linagliptin-treated patients compared with those on placebo in combination with metformin and sulphonylurea is indicative of the enhanced glucose-lowering effect of the triple therapy [2,28]. The finding that the greatest reductions in HbA_{1c} were achieved in patients with the highest baseline HbA_{1c} levels is in agreement with previous studies and may suggest the need for dose adjustment of the sulphonylurea in order to prevent hypoglycaemia [29,30].

In conclusion, linagliptin when added to a combination of metformin and sulphonylurea was well tolerated and produced statistically significant and clinically meaningful improvements in glycaemic control in patients with Type 2 diabetes. The favourable tolerability profile demonstrated indicates that the same dose of linagliptin (5 mg) would be suitable for all patients without the need for dose titration, and changes in HOMA indices with linagliptin are consistent with an enhancement of β-cell function. Linagliptin as an add-on to background therapy may provide a valuable treatment option in many patients with Type 2 diabetes on combination treatment with metformin and sulphonylurea who show inadequate glycaemic control.

Competing interests

RS, KAD and HJW are employees of Boehringer Ingelheim, the sponsor of the study. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographics and baseline characteristics of the patients included and excluded from the HOMA analyses.

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Appendix

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