Diabetes, Obesity and Metabolism 13: 258–267, 2011.

ORIGINAL ARTICLE

Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial

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Aim: To assess the safety and efficacy of the potent and selective dipeptidyl peptidase-4 inhibitor linagliptin 5 mg when given for 24 weeks to patients with type 2 diabetes who were either treatment-naive or who had received one oral antidiabetes drug (OAD).
Methods: This multicentre, randomized, parallel group, phase III study compared linagliptin treatment (5 mg once daily, n = 336) with placebo (n = 167) for 24 weeks in type 2 diabetes patients. Before randomization, patients pretreated with one OAD underwent a washout period of 6 weeks, which included a placebo run-in period during the last 2 weeks. Patients previously untreated with an OAD underwent a 2-week placebo run-in period. The primary endpoint was the change in HbA1c from baseline after 24 weeks of treatment.
Results: Linagliptin treatment resulted in a placebo-corrected change in HbA1c from baseline of −0.69% ($p < 0.0001$) at 24 weeks. In patients with baseline HbA1c ≥ 9.0%, the adjusted reduction in HbA1c was 1.01% ($p < 0.0001$). Patients treated with linagliptin were more likely to achieve a reduction in HbA1c of ≥0.5% at 24 weeks than those in the placebo arm (47.1 and 19.0%, respectively; odds ratio, OR = 4.2, $p < 0.0001$). Fasting plasma glucose improved by −1.3 mmol/l ($p < 0.0001$) with linagliptin vs. placebo, and linagliptin produced an adjusted mean reduction from baseline after 24 weeks in 2-h postprandial glucose of −3.2 mmol/l ($p < 0.0001$). Statistically significant and relevant treatment differences were observed for proinsulin/insulin ratio ($p = 0.025$), Homeostasis Model Assessment-%B ($p = 0.049$) and disposition index ($p = 0.0005$). There was no excess of hypoglycaemic episodes with linagliptin vs. placebo and no patient required third-party intervention. Mild or moderate renal impairment did not influence the trough plasma levels of linagliptin.
Conclusions: Monotherapy with linagliptin produced a significant, clinically meaningful and sustained improvement in glycaemic control, accompanied by enhanced parameters of β-cell function. The safety profile of linagliptin was comparable with that of placebo.
Keywords: dipeptidyl peptidase-4, DPP-4 inhibitor, glycaemic control, linagliptin, monotherapy, type 2 diabetes

Date submitted 9 September 2010; date of first decision 22 September 2010; date of final acceptance 18 November 2010

Introduction

According to the World Health Organization (WHO), 220 million people worldwide have diabetes and 1.1 million people died from hyperglycaemic complications during 2005 [1]. Type 2 diabetes mellitus accounts for 90% of all cases. Intensive hyperglycaemia management remains crucial in reducing the incidence of diabetes complications. However, many patients with type 2 diabetes remain inadequately managed, partly because some current therapies can show poor tolerability or limited efficacy during chronic treatment [2], resulting in a progressive decline in glycaemic control [3]. With the prevalence of diabetes worldwide estimated to reach 366 million (4.4% of the global population) by 2030 [4], novel treatments with a better risk-to-benefit ratio are needed. Dipeptidyl peptidase-4 (DPP-4) inhibitors may offer such an opportunity.

DPP-4 inhibitors antagonize the serine peptidase DPP-4 (EC 3.4.14.5), responsible for the cleavage of several physiologically important incretin substrates, including gastric inhibitory polypeptide and glucagon-like peptide-1 (GLP-1) [5]. These incretins are key players in the physiological regulation of pancreatic α- and β-cells, and consequently contribute to the maintenance of glucose homeostasis [6–8]. Therefore, DPP-4 inhibition has become a target in the treatment of type 2 diabetes and a number of DPP-4 inhibitors have been licensed worldwide for this disease [9].

Linagliptin is a novel, selective, competitive DPP-4 inhibitor. *In vitro* data from Thomas et al. [10] showed that linagliptin inhibits DPP-4 with a half-maximal inhibitory concentration (IC_{50}) of approximately 1 nM, compared with sitagliptin (19 nM), alogliptin (24 nM), saxagliptin (50 nM) and vildagliptin (62 nM). In rodent models, linagliptin administration was associated with longer lasting improvements in

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glucose tolerance than seen with sitagliptin, saxagliptin and vildagliptin [10], and in healthy volunteers, single doses of 5 mg linagliptin reduced DPP-4 activity by 86.1% [11]. Owing to a long-terminal half-life (up to 184 h) because of strong binding to DPP-4, once-daily dosing of linagliptin is indicated [11]. However, because the fraction not bound to DPP-4 is rapidly eliminated, linagliptin exhibits nonlinear pharmacokinetics in animal models [12].

In male type 2 diabetes patients, 5 mg linagliptin once daily for 12 days inhibited plasma DPP-4 by >80% at steady-state plasma concentrations and increased levels of intact GLP-1 approximately threefold compared with placebo [13]. Between 2.5 and 10 mg, linagliptin produced dose-dependent reductions in glucose excursion following an oral glucose tolerance test, with the effect more marked 24 h after the last dose on day 12 than on day 1. In obese patients with type 2 diabetes, linagliptin (2.5, 5 or 10 mg) for 4 weeks increased the levels of intact GLP-1 up to fourfold during a meal tolerance test (MTT) and suppressed glucagon concentrations by up to 24% [14]. Linagliptin 5 mg produced a greater effect on glucose excursion than the other two doses with significant (one-sided at $p < 0.025$) placebo-subtracted changes in HbA1c [14]. A study in Japanese patients produced similar results [15].

We report the results of a phase III, placebo-controlled study assessing the safety and efficacy of linagliptin 5 mg when given for 24 weeks to patients with type 2 diabetes who were either treatment-naive or who had received one oral antidiabetes drug (OAD).

Methods

Study design

This randomized, double blind, parallel-group study (figure 1) compared treatment with either linagliptin 5 mg or placebo for 24 weeks in male and female patients with type 2 diabetes. Patients were aged 18–80 years with a body mass index (BMI) ≤40 kg/m^2 and were either treatment-naive or had previously received one OAD (although this did not include thiazolidinediones, owing to their prolonged treatment effect profile). In the placebo group, 93 patients were treatment-naive and 70 had received one previous OAD. For the linagliptin group, the numbers were 187 and 146, respectively. The regimen of any OAD had not changed for at least 10 weeks before enrolment. Pretreated patients stopped OAD therapy and went without medication for 6 weeks prior to randomization. The last 2 weeks of this period were an open-label placebo run-in. Treatment-naive patients directly entered the 2-week placebo run-in. Eligible patients then received treatment with 5 mg linagliptin or placebo for 24 weeks. An MTT was taken in a subset of patients (67 in the linagliptin arm and 24 in the placebo arm) 30 min after dosing at Week 24. During the MTT, each patient ingested two nutrition bars and 1 unit (200 ml) of a formula diet (Ensure Plus®, Abbott Nutrition, Columbus, OH, USA) within a 15-min time period. Blood samples were collected at 1 and 2 h after ingestion.

All patients were provided with home blood glucose monitoring (HBGM) equipment and supplies for use at home during the whole study period. Training on the correct use

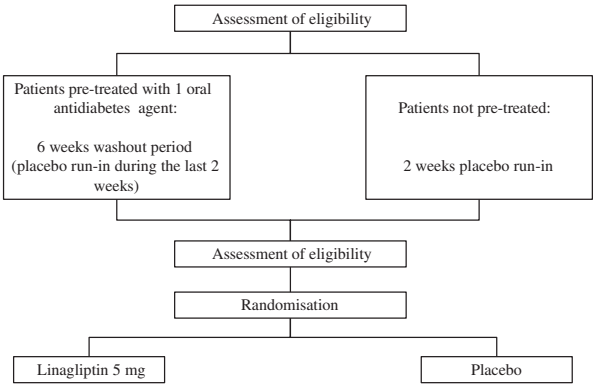

Figure 1. Schematic diagram of trial design and dosing schedule.

of the HBGM equipment during each phase of the trial was provided by the investigator or designated site personnel during the run-in and washout periods.

Rescue medication (metformin) could be initiated, during the randomized period only, if a patient had a confirmed glucose level >13.3 mmol/l after an overnight fast. 'Confirmed' was defined as a minimum of two plasma glucose measurements made on different days, with at least one measurement having been taken at the investigational site. If a patient's fasting glucose levels remained >13.3 mmol/l despite the initiation of rescue therapy, the patient was discontinued from the study.

The trial complied with principles in the Declaration of Helsinki (1996 version) and the International Conference of Harmonization (ICH) harmonized tripartite guideline for Good Clinical Practice (GCP). The Independent Ethics Committee or Institutional Review Board of participating centres reviewed the protocol, patient information sheet, informed consent form and insurance policy. Written informed consent was obtained from each patient before entering the study.

Participants

Participants were enrolled from 66 trial sites in 11 countries (Croatia, India, Italy, Israel, Malaysia, Poland, Romania, Slovakia, Ukraine, Thailand and The Netherlands). To be considered eligible at screening, HbA1c levels had to be between 6.5 and 9.0% in pretreated patients or between 7.0 and 10% in treatment-naive patients. At the start of the run-in period, an HbA1c level of 7.0–10.0% in both groups was required. The main exclusion criteria were myocardial infarction, stroke or transient ischaemic attack within 6 months of study enrolment; impaired hepatic function at screening or receiving rosiglitazone, pioglitazone, GLP-1 analogues, insulin or antiobesity drugs (e.g. sibutramine, rimonabant or orlistat) within 3 months of enrolment. Investigators also excluded patients receiving systemic steroids at enrolment or those who had received dose changes in any thyroid hormone treatment within 6 weeks of screening.

Study medication and randomization

Eligible patients were randomized to linagliptin 5 mg or placebo (2 : 1 ratio) using a computer-generated sequence supplied

by interactive voice or web response systems (Perceptive Informatics, Berlin, Germany). Randomization was stratified by HbA1c (<8.5% vs. ≥8.5%) and by whether or not patients had previously received an OAD. The study was fully un-blinded after database lock.

Patients were instructed to take study medication with about 150 ml of water at approximately the same time every day. Patients received linagliptin or placebo at the investigational site on the days of clinic visits.

Criteria for evaluation

The primary endpoint was change from baseline in HbA1c after 24 weeks of treatment, adjusted for baseline HbA1c and previous OAD. There were five secondary endpoints after 24 weeks of treatment: (i) absolute response—percentage of patients that attained target HbA1c (<7.0% or <6.5%), (ii) relative response—HbA1c lowered by at least 0.5%, (iii) reduction from baseline in HbA1c by visit over time, (iv) change from baseline in fasting plasma glucose (FPG) and (v) MTT—change in 2-h postprandial glucose (2hPPG) from baseline.

Several other endpoints were assessed: use of rescue therapy, Homeostasis Model Assessment (HOMA) indices for insulin resistance and β-cell function, and the disposition index (DI), derived from the indices for insulin sensitivity and insulin secretion. HOMA and DI were determined at baseline and after 24 weeks of treatment. Changes from baseline in body weight, waist circumference and lipid parameters were assessed after 24 weeks. Several MTT parameters were derived after 24 weeks, including the area under the curve (AUC) for glucose, insulin, C-peptide and the insulin AUC to glucose AUC ratio. Changes in plasma proinsulin/insulin ratio, plasma linagliptin concentrations immediately before the next dose and plasma DPP-4 inhibition were determined.

The safety criteria were incidence and intensity of adverse events, withdrawals because of adverse events, physical examination, 12-lead electrocardiogram, vital signs and clinical laboratory parameters. A central laboratory (MDS Pharma Services Central Laboratories, Baillet en France, France, and Singapore) performed routine laboratory investigations and determined levels of HbA1c, plasma glucose, insulin, proinsulin and C-peptide. HbA1c was analysed using the automated National Glycohemoglobin Standardization Program (NGSP) certified ion exchange high-performance liquid chromatography method. FPG was analysed by the photometric glucose oxidase method. Insulin, proinsulin and C-peptide concentrations were measured using chemiluminescent immunoassays. Linagliptin plasma levels were determined (Covance Laboratories Limited, Harrogate, UK) and DPP-4 activity assessed using a semi-quantitative enzyme activity assay with fluorescence detection (Institut für Klinische Forschung und Entwicklung GmbH, Mainz, Germany).

Statistical analysis

The primary endpoint—change in HbA1c between baseline and 24 weeks—was assessed using analysis of covariance (ANCOVA) at the level of $\alpha = 0.05$ (two-sided) based on the full analysis set (FAS). The FAS consisted of randomized patients treated with at least one dose of study medication and who had HbA1c measured at baseline and at least once during treatment. The model included 'treatment' and 'prior OAD' as fixed classification effects and 'HbA1c baseline' as the linear covariate. Last observation carried forward (LOCF) replaced missing data.

The per-protocol set (PPS) excluded patients in FAS who had important protocol violations. FAS-completers comprised FAS patients who completed the study and had HbA1c measured after 24 weeks' treatment. The treated set included patients treated with at least one dose of study medication. The MTT set consisted of patients in the FAS who had a valid MTT performed at baseline and once on-treatment. Sensitivity analyses repeated the primary analysis using the PPS and the FAS-completers as well as a mixed model for repeated measurements that included 'treatment', 'visit', 'visit by treatment interaction' and 'prior use of OAD' as fixed classification effects and 'HbA1c baseline' as linear covariate. ANCOVA models assessed the homogeneity of the treatment effect on the primary endpoint across baseline HbA1c values, previous OADs and by centre. All analyses were repeated for change in FPG using the FAS.

Change in 2hPPG was analysed for the MTT set using ANCOVA with 'treatment', 'prior OAD', 'HbA1c baseline' and '2hPPG at baseline' as covariates. Subgroup analyses of the change in HbA1c from baseline were performed for age, sex (with weight subgroup), race, ethnicity, geographical region, BMI, baseline HbA1c, number of previous OADs (0 or 1), time since diagnosis, presence of metabolic syndrome at baseline, baseline HOMA-IR, baseline HOMA-%B and baseline proinsulin/insulin ratio.

The responder analysis determined the percentage of patients who attained the target HbA1c (<7.0% or <6.5%) or a lowering of HbA1c of ≥0.5% after 24 weeks of treatment. Missing values because of premature discontinuation were considered failures. The observed cases (OC) approach analysed changes in HbA1c, FPG, body weight, HOMA-%B and HOMA-IR, MTT parameters, percentage of patients who received rescue therapy and time to start rescue therapy. Data were censored at the start of rescue therapy or discontinuation. Missing data were not replaced. Descriptive statistics were used for other efficacy endpoints.

Assuming a standard deviation of 1% for HbA1c change from baseline at 24 weeks, the planned sample size of 150 patients in the placebo group and 300 patients in the linagliptin group was sufficient to detect a 0.7% difference between the treatment groups with a power of more than 95%. The planned sample size was chosen to fulfil the overall sample size requirements of the study with regard to the safety database.

The trial is registered with ClinicalTrials.gov as NCT00621140.

Results

Table 1 summarizes the demographics and baseline characteristics for the 167 patients that received placebo and the

Table 1. Demographics and baseline characteristics.

	Placebo	Linagliptin	Total
Number of patients, N	167	336	503
Gender, N (%)			
Male	79 (47.3)	164 (48.8)	243 (48.3)
Female	88 (52.7)	172 (51.2)	260 (51.7)
Race, N (%)			
American Indian/Alaska Native	1 (0.6)	0 (0.0)	1 (0.2)
Asian	76 (45.5)	156 (46.4)	232 (46.1)
White	90 (53.9)	180 (53.6)	270 (53.7)
Ethnicity, N (%)			
Not Hispanic/Latino	163 (97.6)	330 (98.2)	493 (98.0)
Hispanic/Latino	4 (2.4)	6 (1.8)	10 (2.0)
Age (years)			
Mean (s.d.)	54.4 (10.3)	56.4 (10.1)	55.7 (10.2)
Age groups (years), N (%)			
<65	140 (83.8)	258 (76.8)	398 (79.1)
65–74	26 (15.6)	71 (21.1)	97 (19.3)
≥75	1 (0.6)	7 (2.1)	8 (1.6)
Baseline weight (kg)			
Mean (s.d.)	79.21 (15.95)	78.53 (16.73)	78.76 (16.46)
Baseline BMI [kg/m^2]			
Mean (s.d.)	29.08 (4.84)	29.04 (4.80)	29.05 (4.81)
Baseline BMI, categorical (kg/m^2), N (%)			
<25	41 (24.6)	71 (21.1)	112 (22.3)
25 to <30	60 (35.9)	130 (38.7)	190 (37.8)
≥30	66 (39.5)	135 (40.2)	201 (40.0)
Baseline eGFR (MDRD staging) (ml/min/1.73 m^2), N (%)			
≥90	76 (45.5)	141 (42.0)	217 (43.1)
60 to <90	83 (49.7)	165 (49.1)	248 (49.3)
30 to <60	4 (2.4)	14 (4.2)	18 (3.6)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

336 patients that received linagliptin (the treated set). Figure 2 shows the patient disposition.

Linagliptin trough concentrations and DPP-4 inhibition

The geometric mean trough plasma concentrations of linagliptin remained constant over time: 6.4 and 6.5 nmol/l at Weeks 12 and 24, respectively. Median DPP-4 inhibition at these time points was 84.2 and 82.8%, respectively. DPP-4 inhibition rose with increasing linagliptin trough concentrations, being 72.1 and 91.0% in the lower and upper quartiles, respectively. DPP-4 inhibition was >80% at nadir in >80% of patients in the third and upper quartile of linagliptin trough concentrations.

At baseline, most patients had a normal renal function [estimated glomerular filtration rate (eGFR) ≥90 ml/min/1.73 m^2; 43.1%] or mild renal impairment (eGFR 60 to <90 ml/min/1.73 m^2; 49.3%). However, 3.6% of patients had moderate renal impairment (eGFR 30 to <60 ml/min/1.73 m^2) and no eGFR measurements were available for 20 patients. Nonetheless, there was no difference in the mean linagliptin trough levels over time between patients with normal renal function and those with mild or moderate renal impairment, 8.0 ± 7.3, 8.0 ± 7.6 and 6.6 ± 1.8 nmol/l, respectively.

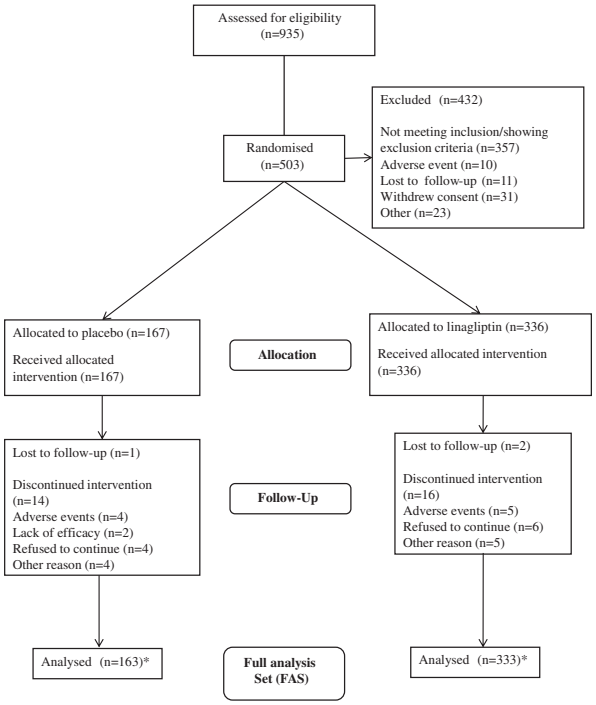

Figure 2. Flow diagram of patient disposition. *Seven patients were excluded from the full analysis set (FAS) as they had no on-treatment HbA1c measurement.

Efficacy and biomarkers

Adjusted mean differences of the changes in HbA1c, FPG and 2hPPG between baseline and Week 24 significantly favoured linagliptin over placebo (Table 2). The adjusted mean difference in the change in HbA1c comparing linagliptin and placebo was −0.69% ($p < 0.0001$). The difference between linagliptin and placebo in adjusted mean HbA1c increased over time (−0.46% at 6 weeks to −0.69% at 24 weeks, all $p < 0.0001$). Figure 3 shows the non-adjusted absolute HbA1c values over time of treatment. Figure 4a, b shows the change in HbA1c from baseline over time for the subsets of patients who underwent washout and those who did not. Linagliptin-treated patients undergoing washout showed smaller reductions from baseline than patients without washout. However, the placebo-corrected change from baseline in HbA1c at 24 weeks was comparable (−0.67 and −0.72%, respectively, not statistically significant). Linagliptin treatment resulted in a greater reduction of FPG (adjusted mean change −1.3 mmol/l; $p < 0.0001$) and 2hPPG (adjusted mean change −3.2 mmol/l; $p < 0.0001$) compared with placebo after 24 weeks. Figure 5 shows the adjusted mean change in 2hPPG from baseline after 24 weeks of treatment.

Several biomarkers and indices also showed statistically significant changes that favoured linagliptin compared with placebo. The improvement in glycaemic control achieved with linagliptin was associated with enhancement of markers of β-cell function, such as proinsulin/insulin ratio, HOMA-%B, and DI (Table 3). Following the MTT, the total glucose AUC at 24 weeks significantly favoured linagliptin (Table 4). Twice as many patients in the placebo arm required rescue therapy than

Table 2. Adjusted means for the change from baseline at week 24 in HbA1c [FAS (LOCF)], FPG [FAS (LOCF)] and 2hPPG [MTT set (OC)].

	Placebo	Linagliptin
HbA1c (%)		
Number of patients with baseline and on-treatment results	163	333
Baseline		
Mean (s.e.)	8.00 (0.07)	8.00 (0.05)
Change from baseline		
Adjusted* mean (s.e.)	0.25 (0.07)	−0.44 (0.05)
Comparison vs. placebo (diff. linagliptin−placebo)		
Adjusted* mean (s.e.)		−0.69 (0.08)
95% Confidence interval		−0.85, −0.53
p value		<0.0001
FPG (mmol/l)		
Number of patients with baseline and on-treatment results	149	318
Baseline		
Mean (s.e.)	9.2 (0.2)	9.1 (0.1)
Change from baseline		
Adjusted* mean (s.e.)	0.8 (0.2)	−0.5 (0.1)
Comparison vs. Placebo (diff. linagliptin−placebo)		
Adjusted* mean (s.e.)		−1.3 (0.2)
95% confidence interval		−1.7, −0.9
p value		<0.0001
2hPPG (mmol/l)		
Number of patients with baseline and on-treatment results	24	67
Baseline		
Mean (s.e.)	13.5 (0.9)	14.3 (0.5)
Change from baseline		
Adjusted* mean (s.e.)	1.4 (0.6)	−1.9 (0.3)
Comparison vs. placebo (diff. linagliptin−placebo)		
Adjusted* mean (s.e.)		−3.2 (0.7)
95% confidence interval		−4.6, −1.9
p value		<0.0001

s.e., standard error; FAS, full analysis set; FPG, fasting plasma glucose; LOCF, last observation carried forward; 2hPPG, 2-h postprandial glucose, MTT, meal tolerance test; OC, observed cases.
*Model includes continuous baseline HbA1c, continuous FPG, continuous 2hPPG (for each parameter), number of prior antidiabetes drugs and treatment.

patients randomized to linagliptin (20.9 vs. 10.2%, respectively; OR = 0.3, p = 0.0002).

The percentage of patients with a baseline HbA1c ≥7.0% who achieved HbA1c <7.0% after 24 weeks' treatment with linagliptin was 25.2% (77/306) compared with 11.6% (17/147) in the placebo group (OR = 2.9, p = 0.0006). Furthermore, 47.1 and 19.0% of patients receiving linagliptin and placebo, respectively, achieved an HbA1c reduction ≥0.5% at 24 weeks (OR = 4.2, p < 0.0001). Subgroup analyses of adjusted mean changes in HbA1c from baseline showed a consistent treatment effect across the different subgroups. For example, figure 6 shows the adjusted mean change from baseline HbA1c stratified by baseline HbA1c. Linagliptin patients with a baseline HbA1c level of ≥9.0% showed a greater reduction in HbA1c (−0.86%) than seen in the group overall; the placebo-corrected

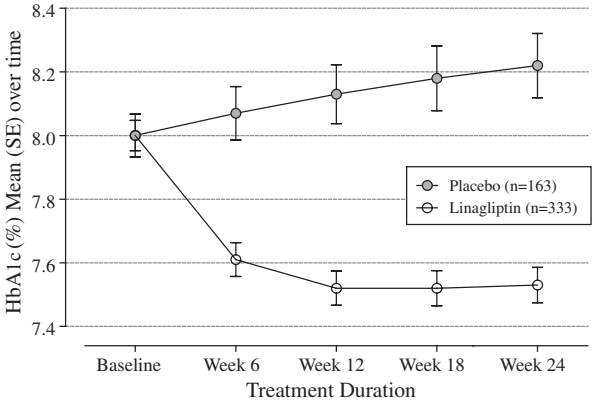

Figure 3. HbA1c over time (mean ± s.e.) following treatment with linagliptin 5 mg or placebo for 24 weeks—FAS (LOCF). Differences in change from baseline in HbA1c between placebo and linagliptin were significant at each time point after baseline (p < 0.0001). FAS, full analysis set; LOCF, last observation carried forward.

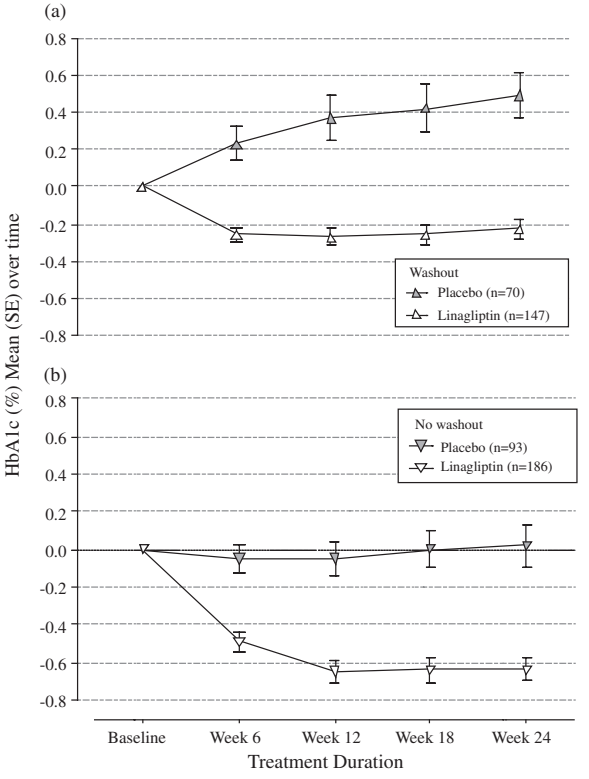

Figure 4. (a) Mean change from baseline in HbA1c following treatment with linagliptin 5 mg or placebo for 24 weeks for patients who had been treated with one oral antidiabetes drug (OAD) and underwent washout—FAS (LOCF). (b) Mean change from baseline in HbA1c following treatment with linagliptin 5 mg or placebo for 24 weeks for patients who were treatment-naive and did not require washout—FAS (LOCF). FAS, full analysis set; LOCF, last observation carried forward (LOCF).

adjusted mean change in this subgroup was −1.01% (95% CI −1.42 to −0.60; p < 0.0001). The placebo-corrected adjusted mean changes in the other subgroups were −0.57% (95% CI −0.85 to −0.30; p < 0.0001), −0.55% (95% CI −0.94 to

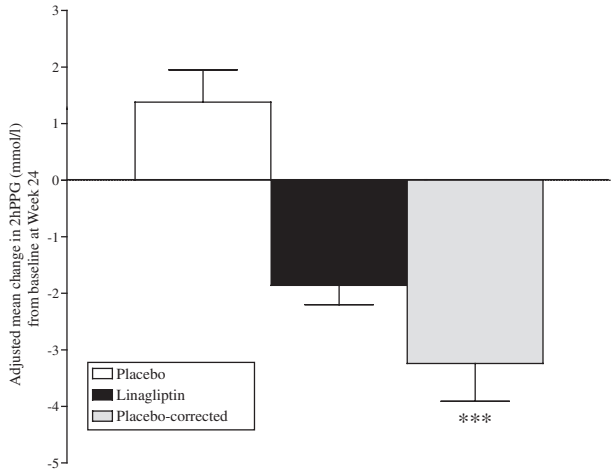

Figure 5. Adjusted mean change (±s.e.) from baseline of 2hPPG at week 24. ***$p < 0.0001$ vs. placebo.

−0.16; $p = 0.0049$), and −0.71% (95% CI −1.00 to −0.42; $p < 0.0001$) for baseline HbA1c <7.5%, 7.5 to <8.0%, and 8.0 to <9.0%, respectively. There was a notable diversity in race (Table 1); however, the adjusted mean change in HbA1c from baseline at Week 24 in the linagliptin group was similar in the two main populations, Asian and White. Sensitivity analyses confirmed the results observed for the primary endpoint.

Safety

Linagliptin monotherapy was well tolerated during the 24 weeks of treatment. In the total patient group, 6.6% discontinued treatment prematurely, most frequently following adverse events (1.8%) or a refusal to continue medication (2.0%). In general, a greater proportion of patients receiving placebo compared with the patients treated with linagliptin reported at least one adverse event (58.7 and 52.4%, respectively; Table 5) or serious adverse events (4.2 and 3.0%, respectively). None of the serious adverse events was considered drug-related. Four patients in each group (2.4 and 1.2%, respectively, for placebo and linagliptin) discontinued following adverse events. One patient in each group (placebo 0.6%, linagliptin 0.3%) developed hypoglycaemia, although neither required third-party assistance. The patient receiving placebo suffered one hypoglycaemic episode on rescue medication. The patient receiving linagliptin experienced asthenia and two to three hypoglycaemic episodes and was not on rescue medication.

Hyperglycaemia was the most frequently reported adverse event (22.8% with placebo and 8.6% with linagliptin). The most frequently reported adverse events (frequency >2%) that were more common with linagliptin than placebo were headache (2.7 vs. 1.2%, respectively), hypertension (3.6 vs. 1.2%, respectively) and back pain (2.7 vs. 1.8%, respectively). Furthermore, 5.1 and 3.6% of the linagliptin and placebo groups, respectively, experienced drug-related adverse events. No clinically significant findings emerged regarding laboratory analyses or vital signs. No notable differences in renal function were observed between treatment groups and eGFR did not appear to influence tolerability. Neither body weight nor waist circumference differed significantly from baseline in either group, confirming that linagliptin is weight neutral.

Table 3. Adjusted mean change from baseline in fasting biomarkers and derived indices at Week 24—FAS (OC).

	Placebo	Linagliptin
Proinsulin/insulin ratio		
Number of patients with baseline and on-treatment results	47	142
Baseline, mean (s.e.)	0.18 (0.01)	0.20 (0.01)
Adjusted mean change from baseline (s.e.)	0.02 (0.02)	−0.02 (0.01)
Comparison vs. placebo		
Adjusted mean (s.e.)		−0.04 (0.02)
95% confidence interval		−0.074, −0.005
p value		0.025
HOMA-IR [(mU/l) × (mmol/l)]		
Number of patients with baseline and on-treatment results	57	157
Baseline, mean (s.e.)	5.6 (0.5)	7.1 (0.6)
Adjusted mean change from baseline (s.e.)	−1.3 (0.5)	−1.1 (0.3)
Comparison vs. placebo		
Adjusted mean (s.e.)		0.2 (0.6)
95% confidence interval		−0.9, 1.3
p value		0.73
HOMA-%B [(mU/l)/(mmol/l)]		
Number of patients with baseline and on-treatment results	57	157
Baseline, mean (s.e.)	62.3 (5.2)	66.9 (4.5)
Adjusted mean change from baseline (s.e.)	−17.2 (9.7)	5.0 (5.9)
Comparison vs. placebo		
Adjusted mean (s.e.)		22.2 (11.2)
95% confidence interval		0.09, 44.3
p value		0.049
Disposition index [1/((mmol/l) × (mmol/l))]		
Number of patients with baseline and on-treatment results	107	257
Baseline, mean (s.e.)	12.1 (0.6)	12.8 (0.7)
Adjusted mean change from baseline (s.e.)	−0.7 (0.9)	3.1 (0.6)
Comparison vs. placebo		
Adjusted mean (s.e.)		3.7 (1.1)
95% confidence interval		1.6, 5.8
p value		0.0005

s.e., standard error; HOMA-IR, Homeostasis Model Assessment of insulin resistance; HOMA-%B, Homeostasis Model Assessment of β-cell function.

Discussion

In this phase III study, monotherapy with linagliptin 5 mg once daily for 24 weeks produced significant, clinically meaningful and sustained improvements in glycaemic control compared with placebo. Changes in HbA1c, FPG and 2hPPG reflected the improved pre- and postprandial glycaemic control induced by linagliptin treatment. Enhancement of parameters of β-cell function may help to sustain glycaemic control. Linagliptin monotherapy resulted in a safety profile comparable to that of placebo, with a very low risk of hypoglycaemia and no clinically

Table 4. Adjusted mean change from baseline in MTT parameters at week 24—MTT set (OC).

	Placebo	Linagliptin
Total glucose AUC [mmol*h/l]		
Number of patients with baseline and on-treatment results	23	65
Baseline, mean (s.e.)	25.6 (1.1)	25.8 (0.7)
Adjusted mean change from baseline (s.e.)	1.3 (0.9)	−1.9 (0.5)
Comparison vs. placebo		
Adjusted mean (s.e.)		−3.3 (1.1)
95% confidence interval		−5.4, −1.2
p value		0.0026
Total insulin AUC [pmol*h/l]		
Number of patients with baseline and on-treatment results	11	44
Baseline, mean (s.e.)	760.1 (87.5)	756.6 (42.0)
Adjusted mean change from baseline (s.e.)	−75.0 (80.2)	0.3 (39.9)
Comparison vs. placebo		
Adjusted mean (s.e.)		75.4 (89.8)
95% confidence interval		−105.0, 255.7
p value		0.41
Total C-peptide AUC [pmol*h/l]		
Number of patients with baseline and on-treatment results	12	51
Baseline, mean (s.e.)	4397.7 (324.9)	3644.7 (164.5)
Adjusted mean change from baseline (s.e.)	−197.1 (391.6)	568.8 (185.3)
Comparison vs. placebo		
Adjusted mean (s.e.)		765.9 (438.6)
95% confidence interval		−112.1, 1643.8
p value		0.086
Total insulin AUC/total glucose AUC ratio [pmol/mmol]		
Number of patients with baseline and on-treatment results	10	44
Baseline, mean (s.e.)	28.8 (5.3)	30.2 (2.0)
Adjusted mean change from baseline (s.e.)	−5.0 (3.9)	2.2 (1.9)
Comparison vs. placebo		
Adjusted mean (s.e.)		7.1 (4.3)
95% confidence interval		−1.6, 15.9
P value		0.11
Total insulin AUC/total C-peptide AUC ratio		
Number of patients with baseline and on-treatment results	8	30
Baseline, mean (s.e.)	0.16 (0.01)	0.22 (0.02)
Adjusted mean change from baseline (s.e.)	−0.01 (0.02)	−0.05 (0.01)
Comparison vs. placebo		
Adjusted mean (s.e.)		−0.04 (0.03)
95% confidence interval		−0.09, 0.02
p value		0.16
Total glucose AUC/(total insulin AUC/total C-peptide AUC ratio) [mmol*h/l]		
Number of patients with baseline and on-treatment results	8	30
Baseline, mean (s.e.)	173.5 (15.7)	145.2 (11.5)
Adjusted mean change from baseline (s.e.)	18.8 (18.1)	18.9 (9.3)
Comparison vs. placebo		
Adjusted mean (s.e.)		0.03 (20.7)
95% confidence interval		−42.2, 42.2
p value		1.00

AUC, area under the curve; s.e., standard error; MTT, meal tolerance test; OC, observed cases.

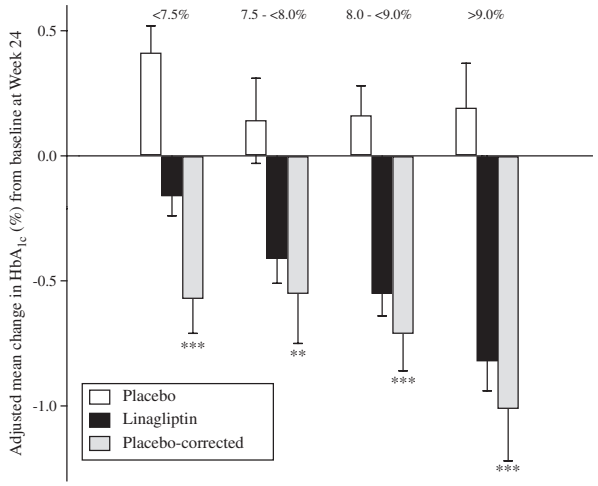

Figure 6. Adjusted mean (s.e.) change from baseline in HbA1c (%) by subgroups—FAS (LOCF). Asterisks denote statistically significant changes ($^{**}p = 0.0049$, $^{***}p < 0.0001$).

significant changes in body weight or waist circumference. Median DPP-4 inhibition exceeded 80%, in agreement with the results of *in vitro* studies showing that linagliptin potently and selectively inhibits the target enzyme [10,16].

The extent of glycaemic improvement associated with DPP-4 inhibition has been summarized in a Cochrane review evaluating 25 clinical studies of between 12 and 52 weeks' duration. Sitagliptin (11 studies involving 6743 patients) and vildagliptin (14 studies with 6121 patients) both produced similar reductions in HbA1c levels of approximately 0.7 and 0.6%, respectively, compared with placebo [17]. The improvements in glycaemic control reported for linagliptin in this study are consistent with those previously described for the DPP-4 class. These data add to a growing body of evidence that linagliptin 5 mg once daily is an effective and well-tolerated treatment for type 2 diabetes [13–15]. Linagliptin improved HOMA and 2hPPG concentration—indicative of enhanced β-cell function—consistent with increased availability of endogenous GLP-1 and similar to what is observed with other DPP-4 inhibitors [18–20].

Dose-ranging studies indicate that the therapeutic window of linagliptin is likely to be >100-fold higher than the therapeutic dose of 5 mg [13]. This study confirms that linagliptin is associated with a very favourable safety and tolerability profile and does not increase the risk of hypoglycaemia and weight

Table 5. Frequency of patients with adverse events occurring at an incidence of more than 2% in either treatment group on the preferred term level, by overall frequency and system organ class—treated set.

	Placebo, N (%)	Linagliptin, N (%)
Number of patients	167	336
Number of patients with any AE	98 (58.7)	176 (52.4)
Infections and infestations	38 (22.8)	55 (16.4)
Nasopharyngitis	7 (4.2)	13 (3.9)
Upper respiratory tract infection	5 (3.0)	9 (2.7)
Respiratory tract infection	4 (2.4)	1 (0.3)
Viral infection	4 (2.4)	1 (0.3)
Metabolism and nutrition disorders	45 (26.9)	44 (13.1)
Hyperglycaemia	38 (22.8)	29 (8.6)
Dyslipidaemia	4 (2.4)	4 (1.2)
Nervous system disorders	4 (2.4)	15 (4.5)
Headache	2 (1.2)	9 (2.7)
Vascular disorders	2 (1.2)	17 (5.1)
Hypertension	2 (1.2)	12 (3.6)
Musculoskeletal and connective tissue disorders	10 (6.0)	32 (9.5)
Back pain	3 (1.8)	9 (2.7)
Investigations	11 (6.6)	21 (6.3)
Blood glucose increased	3 (1.8)	7 (2.1)

gain compared with placebo. No new safety concerns were raised and these results are consistent with previous studies of linagliptin [11,13–15].

The sitagliptin product label recommends a dose adjustment in type 2 diabetes patients with moderate or severe renal insufficiency or end-stage renal disease in the US [21]. In Europe, vildagliptin and sitagliptin are not recommended for type 2 diabetes patients with moderate or severe renal impairment or for those undergoing haemodialysis for end-stage renal disease [22,23]. In the present phase III study, linagliptin trough concentrations in patients with mild or moderate renal impairment were similar to those in patients with normal renal function, which supports the concept that there may be no requirement for linagliptin dose adjustment in renally impaired patients. This finding may be explained by the fact that linagliptin clearance occurs primarily through non-renal pathways [24]. As only a minor proportion of a linagliptin dose is renally excreted [13], linagliptin may be less likely to accumulate in renally impaired type 2 diabetes patients. Furthermore, the potency of linagliptin means that the binding capacity of the target DPP-4 enzyme is saturated at low doses.

This study has certain limitations. The washout period was only 6 weeks, for ethical reasons, so that there was not a stable baseline in the patients who had received a prior OAD. As a consequence, there was a continuous rise in HbA1c over time in the placebo group and a smaller drop from baseline in the linagliptin group. This may be caused by incomplete washout of the effect of prior treatment on HbA1c, because it is known that the effect of treatment on HbA1c may last up to 12 weeks. However, the difference between placebo and linagliptin HbA1c levels with and without washout was comparable, supporting the concept of sustained efficacy (figure 4).

This study was of short duration and thus the results of chronic treatment with linagliptin cannot be determined. Chronic treatment with some diabetes therapies is associated with the progressive loss of glycaemic control [3]. In contrast, DPP-4 inhibitors act in a glucose-dependent manner and may augment β-cell function [18–20]. Studies of longer duration are needed to test whether DPP-4 inhibitors, through their actions on β-cells, may attenuate the loss of glycaemic control over time that has been seen in diabetes patients treated with established medications. As the difference in adjusted mean HbA1c values between linagliptin and placebo increased over time and did not plateau by the end of this study, it is possible that the benefits offered by linagliptin would increase over a longer period of treatment and longer-duration extension studies are ongoing to determine whether linagliptin efficacy is sustained over time.

The clinically relevant reductions in HbA1c seen with linagliptin in this trial were largely comparable with those of other antihyperglycaemic agents [17–20,25] and were not associated with an increased risk of hypoglycaemia. This can be a side effect of treatment with drugs that stimulate insulin secretion independent of glucose concentration, for example, the sulfonylureas [26]. Treatment with linagliptin and resultant inhibition of the DPP-4 enzyme led to a glucose-dependent increase in insulin secretion without any increased incidence of hypoglycaemic episodes compared with placebo. In contrast to some other OADs [27], linagliptin was also found to be weight-neutral—an advantageous characteristic given that many patients with type 2 diabetes are overweight or obese. In addition, linagliptin was well tolerated with a placebo-like incidence of gastrointestinal side effects, which can be elevated in patients treated with metformin or GLP-1 agonists [28].

In conclusion, monotherapy with linagliptin 5 mg for 24 weeks produced a statistically significant, clinically meaningful and sustained improvement of glycaemic control in patients with poorly controlled type 2 diabetes. Changes in FPG, HbA1c and several other outcome parameters reflect the improved glycaemic control produced by linagliptin. Compared with placebo, linagliptin had a beneficial effect on markers of β-cell function in the present trial. In animal models, DPP-4 inhibitors have been shown to have a disease-modifying effect [29]. Long-term clinical trials are needed to explore whether linagliptin may have an effect on the durability of glycaemic control compared with other OADs. Finally, linagliptin has an excellent safety and tolerability profile and an incidence of adverse events similar to that of placebo. As there was no difference in the mean linagliptin trough levels over time between patients with normal renal function and those with mild or moderate renal impairment, this suggests that no dose adjustment may be required in patients with renal insufficiency. Taken together, these data suggest that linagliptin could help meet the need for an innovative OAD to improve the management of the increasing number of patients with type 2 diabetes.

Acknowledgements

Boehringer Ingelheim would like to thank the subjects and staff who participated in this study. This work was supported

by Boehringer Ingelheim. Writing and editorial assistance was provided by Mark Greener, of PHASE II International which was contracted by Boehringer Ingelheim for these services. Data from this study have previously been presented as poster 695-P at the 70th Scientific Sessions of the American Diabetes Association (ADA) 2010 in Orlando, Florida.

Conflict of Interest

S. D. P. and A. H. B. have received honoraria for attending meetings, consultancy fees, speaker fees and/or travel grants from Boehringer Ingelheim.

H. H., D. N., H.-J. W. and K. A. D. are employees of Boehringer Ingelheim and have declared that they have no other conflict of interest.

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). S. D. P., A. H. B., H. H, D. N., H.-J. W. and K. A. D. contributed to the design of the study. S. D. P., A. H. B., H. H., H.-J. W. and K. A. D. participated in data collection. S. D. P., A. H. B., H. H., D. N., H.-J. W. and K. A. D. participated in data analysis. All authors contributed to the writing or revision of the manuscript. All authors saw and approved the final version of the manuscript.

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Appendix

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