

Initial combination of linagliptin and metformin in patients with type 2 diabetes: efficacy and safety in a randomised, double-blind 1-year extension study

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SUMMARY

Objective: To determine the efficacy and safety of linagliptin in initial combination with metformin in patients with type 2 diabetes. **Methods:** This 1-year randomised, double-blind study was an extension of a 6-month randomised controlled trial, in which adults with type 2 diabetes received one of six treatment regimens (linagliptin 2.5 mg plus metformin 500 mg bid, linagliptin 2.5 mg plus metformin mg 1000 bid, metformin 1000 mg bid, metformin 500 mg bid, linagliptin 5 mg qd or placebo). In the extension, patients in the first three treatment groups continued their regimen (non-switched group, $n = 333$) while the metformin 500 mg bid, linagliptin 5 mg qd and placebo groups were re-randomised to one of the three continuing regimens (switched group, $n = 233$). **Results:** All three non-switched groups maintained reductions in glycosylated haemoglobin (HbA1c; mean \pm standard deviation reductions across the 1.5-year period: linagliptin 2.5 plus metformin 1000 bid, $-1.63 \pm 1.05\%$; linagliptin 2.5 plus metformin 500 bid, $-1.32 \pm 1.06\%$; metformin 1000 bid, $-1.25 \pm 0.91\%$) while the switched groups showed additional HbA1c reductions. During the extension, there were no clinically meaningful changes in body weight in any group. Adverse event rates were similar between groups, with most events being mild or moderate, and the incidence of investigator-defined hypoglycaemia was low, with no severe events. **Discussion:** Initial combination of linagliptin and metformin was well tolerated over the 1-year extension period, with low risk of hypoglycaemia, and improved glycaemic control vs. metformin alone. **Conclusion:** The initial combination of linagliptin and metformin appears to provide a useful treatment option in patients whose blood glucose levels are increased to an extent that metformin monotherapy may not achieve treatment targets.

Introduction

For patients with type 2 diabetes, control of hyperglycaemia is central to reducing the risk of long-term complications of the disease (1). The consensus of the American Diabetes Association and the European Association for the Study of Diabetes is that a glycosylated haemoglobin (HbA1c) target of $< 7.0\%$ is reasonable for most patients (1). To achieve this target, all except the most motivated patients will need pharmacotherapy in addition to lifestyle changes (1). However, clinical studies have shown that treatment with monotherapy does not achieve stable glucose control over time (2,3), suggesting patients could benefit from early treatment with combination therapy.

The combination of metformin with a dipeptidyl peptidase (DPP)-4 inhibitor appears to provide a rational candidate for combination therapy, as the two agents have complementary mechanisms of action. Metformin reduces hepatic glucose production and increases insulin sensitivity, while DPP-4 inhibitors stimulate insulin secretion by inhibiting the rapid breakdown of the incretin hormones glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (4). Metformin also stimulates GLP-1 secretion from the gut, providing further synergistic effects with DPP-4 inhibitors (5). In addition, metformin and DPP-4 inhibitors both have the advantages of being weight-neutral and associated with a low risk of hypoglycaemia, as well as the convenience of oral administration (6).

What's known

Many patients with type 2 diabetes need combination therapy to achieve target levels of glycaemic control, as measured by glycosylated haemoglobin (HbA1c). Metformin and linagliptin used in combination have been shown to successfully reduce HbA1c levels, with greater reductions compared with monotherapy than with either drug alone. As predicted from the safety profiles of the individual drugs, the combination was also well tolerated, and not associated with weight gain.

What's new

In this 1-year extension study, the combination of linagliptin and metformin continued to be well tolerated, with low rates of hypoglycaemia, and reductions in HbA1c were maintained. This suggests that the initial combination of linagliptin and metformin will provide a useful treatment option, which could be considered in patients for whom metformin monotherapy alone is unlikely to achieve treatment targets.

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Data from this study have previously been presented, in part, at the American Association of Clinical Endocrinologists (AAE) 21st Annual Scientific & Clinical Congress 23–27 May 2012; Philadelphia, PA, USA (Abstract #1326).

Clinical trials – registration and data posting.

NCT00915772, ClinicalTrials.gov

Disclosures

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The DPP-4 inhibitor linagliptin has been available since 2011 for use in patients with type 2 diabetes either as monotherapy or in combination with other commonly used antidiabetes agents. Its use as initial combination with metformin has been assessed in a 6-month randomised, placebo-controlled trial, in which the combination provided improved glycaemic control compared with metformin monotherapy (7). Here, we report a randomised, double-blind extension study assessing the 1-year safety and efficacy of linagliptin plus metformin in patients completing the 6-month trial.

Research design and methods

Study design

In this multicentre, randomised, double-blind, parallel-group extension study, patients with type 2 diabetes were assigned to linagliptin 2.5 mg plus metformin 500 mg (both twice daily [bid]), linagliptin 2.5 mg plus metformin 1000 mg (both bid) or metformin 1000 mg bid monotherapy for 54 weeks (Figure 1). This study was an extension of a randomised, double-blind, placebo-controlled 6-month trial (NCT00798161), the design of which has been described in detail elsewhere (7). Briefly, the 6-month trial included 791 men and women with type 2 diabetes who were either treatment naïve or had been treated with one oral antidiabetes drug (OAD), and who had HbA1c $\geq 7.5\%$ to $< 11.0\%$ at screening or after OAD washout. Patients were randomised to one of six groups: linagliptin 2.5 mg plus metformin 500 mg (both bid), linagliptin 2.5 mg plus metformin 1000 mg (both bid), linagliptin 5 mg once daily (qd),

metformin 500 mg bid, metformin 1000 mg bid or placebo. Screened patients with HbA1c $\geq 11.0\%$ after washout were not eligible for randomisation and instead received open-label linagliptin plus high-dose metformin for 6 months (8); however, these patients were not eligible for the extension.

Patients from the six double-blind treatment groups who completed the 6-month trial were eligible for the extension if they were not being treated with rescue medication at the last visit. Patients who had been randomised to linagliptin 2.5 mg plus metformin 500 mg (both bid, hereafter referred to as linagliptin 2.5 + metformin 500), linagliptin 2.5 mg plus metformin 1000 mg (both bid, hereafter referred to as linagliptin 2.5 + metformin 1000) or metformin 1000 mg (bid, hereafter referred to as metformin 1000) in the 6-month trial continued on this medication in the extension. Patients previously randomised to metformin 500 mg bid were randomised 1:1 to metformin 1000 or linagliptin 2.5 + metformin 500; patients previously randomised to linagliptin 5 mg qd were randomised 1:1 to linagliptin 2.5 + metformin 500 or linagliptin 2.5 + metformin 1000 and patients previously randomised to placebo were randomised 1:1:1 to linagliptin 2.5 + metformin 500, linagliptin 2.5 + metformin 1000 or metformin 1000. Randomisation was performed centrally without stratification, using a pseudo-random number generator. To maintain double-blind conditions, all patients received active trial medication plus a matching placebo.

The total treatment period was 54 weeks, with a 2-week titration period followed by 52 weeks of treatment. To reduce the risk of gastrointestinal adverse effects with metformin, patients assigned

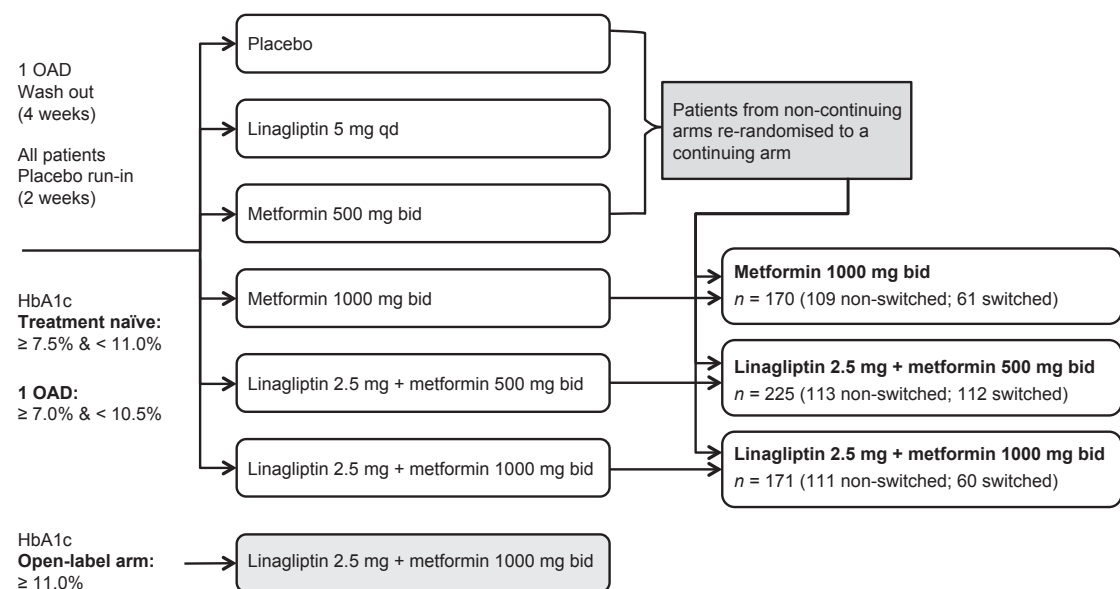


Figure 1 Study design. Bid, twice daily; HbA1c, glycosylated haemoglobin; OAD, oral antidiabetes drug; qd, once daily

metformin 1000 mg bid who had not received metformin in the 6-month trial received metformin 500 mg bid during the 2-week titration period; the metformin dose was then increased to 1000 mg bid. Other patients had a simulated titration period to maintain the treatment blind but had no change in their dose of trial medication.

After the first visit (week 0), patients returned to the study site at weeks 2, 6, 18, 30, 42 and 54 of the double-blind treatment period, as well as a follow-up visit 1 week after completing treatment. Patients had a complete physical exam at week 0, a 12-lead electrocardiogram (ECG) at weeks 0, 18 and 54, and vital signs (blood pressure and pulse rate) recorded at week 0, 6, 18, 30, 42 and 54. Adverse events (AEs) were recorded at every visit. Blood and urine samples were collected at the start of the extension and at weeks 2, 6, 18, 30, 42 and 54. Routine laboratory assessments and fasting plasma glucose (FPG) were determined for all timepoints; HbA1c was determined at all timepoints except week 2, with all determinations performed by a central laboratory.

Patients had been provided with home blood glucose monitoring (HBGM) equipment during the 6-month trial, and all patients were re-trained, if needed, during the extension. HBGM testing was to be performed once per week after an overnight fast during the treatment period and at least once daily during the 1-week follow-up period. It could also be performed any time the patient had symptoms of hyper- or hypoglycaemia.

During the first 6 weeks, the investigator could begin rescue medication if the patient had a fasting glucose level > 11.1 mmol/l or a randomly determined glucose level > 22.2 mmol/l, confirmed by a second determination of > 11.1 mmol/l after an overnight fast, done at the study site on a different day. After week 6, rescue therapy could be started if the patient had a fasting glucose level > 10.0 mmol/l or a randomly determined glucose level > 19.4 mmol/l, confirmed by a measurement > 10.0 mmol/l after an overnight fast, done at the study site on a different day. Rescue medication could be started at any time if a patient had HbA1c $> 8.5\%$. The choice (a sulphonylurea, thiazolidinedione or insulin) and dosage of rescue medication was at the investigator's discretion but only one additional antidiabetic therapy was to be used. If blood glucose levels remained above the defined limits despite rescue therapy (detected at study visits or in HBGM, and confirmed as above), the patient was to be discontinued from the trial for lack of efficacy.

The trial was carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Har-

monised Tripartite Guideline for Good Clinical Practice, and the protocol was approved by the Independent Ethics Committees/Institutional Review Boards of the participating centres. All patients provided written informed consent before initiation of any study-related procedure.

Patients

Patients who had completed the double-blind treatment phase of the previous 6-month trial, were not on rescue medication and provided informed consent were eligible to continue into this extension. Patients were excluded if they had any clinical condition that, in the opinion of the investigator, would not allow safe conduct of the trial; alcohol abuse within the 3 months before informed consent; or drug abuse that, in the opinion of the investigator, would have interfered with trial participation. Women who were pregnant or nursing, or who were of child-bearing potential and not using an acceptable birth-control method, were also excluded.

Outcome measures and statistical analyses

The primary end-point was safety, assessed by the incidence and intensity of AEs, withdrawal because of AEs, clinically relevant new or worsening findings in physical examination or ECG reported as AEs, changes from baseline in vital signs and changes from baseline in clinical laboratory assessments. Patients were required to report any AEs spontaneously and specific questions were asked when needed to more precisely describe an AE. AEs were coded centrally using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 (International Federation of Pharmaceutical Manufacturers and Associations).

Based on analyses of other compounds in the DPP-4 inhibitor class, hypersensitivity reactions (e.g., angio-oedema and anaphylaxis), renal events (e.g., renal failure) and increased liver enzymes were pre-defined as events of special interest. In addition, pancreatitis and severe cutaneous adverse reactions were defined as AEs of special interest in accordance with regulatory recommendations. Significant events were identified using a combination of standardised MedDRA queries and investigator-reported AEs.

Hypoglycaemic episodes were regarded as AEs and were recorded by investigators as either asymptomatic hypoglycaemia (an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration of ≤ 3.9 mmol/l), documented symptomatic hypoglycaemia (an event with typical symptoms of hypoglycaemia; this category was further divided by plasma glucose concentration of ≥ 3.9 , ≥ 3.0 to ≤ 3.9 , < 3.0 mmol/l or not measured), or severe hypoglycaemic episode (an

event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions).

All reported AEs suspected of being stroke, cardiac ischaemia (including myocardial infarction [MI]) or cardiovascular death were reviewed in a blinded fashion by an independent clinical event committee.

Analysis of AEs was based on treatment-emergent AEs. To avoid double-counting of AEs in the 6-month trial, all AEs occurring before or on the day of first drug intake in the extension were assigned to the previous study, while all AEs occurring from the day after first drug intake in the extension were assigned to this study. Worsening of AEs or new occurrences of AEs reported in the preceding 6-month trial were reported as AEs in the extension study. Any new occurrence of AEs within 7 days after the patient's last intake of trial medication was assigned to the treatment period, while any AE occurring > 7 days after stopping study drug was assigned to the posttreatment period.

Safety analyses were performed on the treated set, defined as all patients who received ≥ 1 dose of trial medication in this extension trial. Descriptive analyses were presented for all patients, as well as separately for the switched set, defined as all patients from the treated set who changed treatment between the 6-month trial and this extension.

Secondary end-points were change from baseline in HbA1c and FPG, the percentages of patients who achieved target HbA1c levels of < 7.0% or < 6.5%, the percentages of patients with a reduction in HbA1c levels of $\geq 0.5\%$ after 54 weeks of treatment and use of rescue therapy. Other end-points were change in body weight and waist circumference from baseline to week 54.

Efficacy analyses were exploratory, employing descriptive statistics. To provide meaningful analyses, measures of glucose control within the three randomised groups were analysed according to treatment in the previous 6-month trial. Changes in HbA1c and FPG were performed separately for the switched set and the non-switched set (all patients who continued the same treatment between the 6-month trial and this extension study) using observed cases. Values obtained after rescue therapy were excluded and considered missing values. For the non-switched set, changes in HbA1c and FPG from the baseline of the 6-month trial were analysed in addition to changes from the start of the extension study.

Results

This study was conducted in 101 centres in 14 countries (Canada, Croatia, Estonia, France, Germany,

India, Lithuania, Mexico, the Netherlands, Romania, Russia, Sweden, Tunisia and Ukraine) between 30 June 2009 and 16 June 2011. In total, 687 patients completed the 6-month trial and 567 patients were randomised to the extension study, of whom 566 were treated with ≥ 1 dose of study drug (Figure 2). Of the 566 treated patients, 333 (59%) continued the treatment they had been randomly assigned in the 6-month trial, while 233 patients (41%) switched treatments. Across the three treatment groups, 455 patients (80.4%) completed the 54-week period and 111 patients (19.6%) prematurely discontinued the study. Reasons for discontinuation were comparable across the groups, with the most common reason for discontinuation in all groups being an AE (36 patients, 6.4%). The mean (\pm standard deviation [SD]) duration of exposure to study drug was comparable across the three groups (metformin 1000: 342 ± 89 days; linagliptin 2.5 + metformin 500: 344 ± 86 days; linagliptin 2.5 + metformin 1000: 341 ± 99 days).

Across all patients who received study drug in the extension, the mean age was 55.8 years, and most patients (78.3%) were younger than 65 years. Approximately half the patients were men (54.8%), and more than half were white (65.2%). For the switched sets and the non-switched sets, demographic characteristics and diabetes history at the extension study baseline (i.e., end of the 6-month trial) were comparable for the three randomised treatments (Table 1). Mean HbA1c and FPG values were similar between study arms, and as expected, baseline values for mean HbA1c and FPG were lower in the non-switched patients (Table 1), as the switched groups included patients who had previously received placebo.

As the non-switched set had continued taking the same trial medication from the previous trial, changes in HbA1c were analysed from the baseline visit of the 6-month trial (Figure 3). Here, the mean \pm SD HbA1c was comparable across treatment groups at baseline (metformin 1000: $8.47 \pm 0.85\%$; linagliptin 2.5 + metformin 500: $8.61 \pm 0.87\%$; linagliptin 2.5 + metformin 1000: $8.61 \pm 0.96\%$), and had decreased in all groups by the end of the 6-month trial/start of the extension study (metformin 1000: $7.31 \pm 0.88\%$; linagliptin 2.5 + metformin 500: $7.34 \pm 0.96\%$; and linagliptin 2.5 + metformin 1000: $6.93 \pm 0.85\%$). During the extension, all three groups maintained the reduction in HbA1c achieved at the end of the 6-month trial, with changes of $0.12 \pm 0.72\%$, $0.08 \pm 0.74\%$ and $0.13 \pm 0.54\%$, for the metformin 1000 group, linagliptin 2.5 + metformin 500 and linagliptin 2.5 + metformin 1000 groups, respectively (Figure 3). Subgroup analyses of

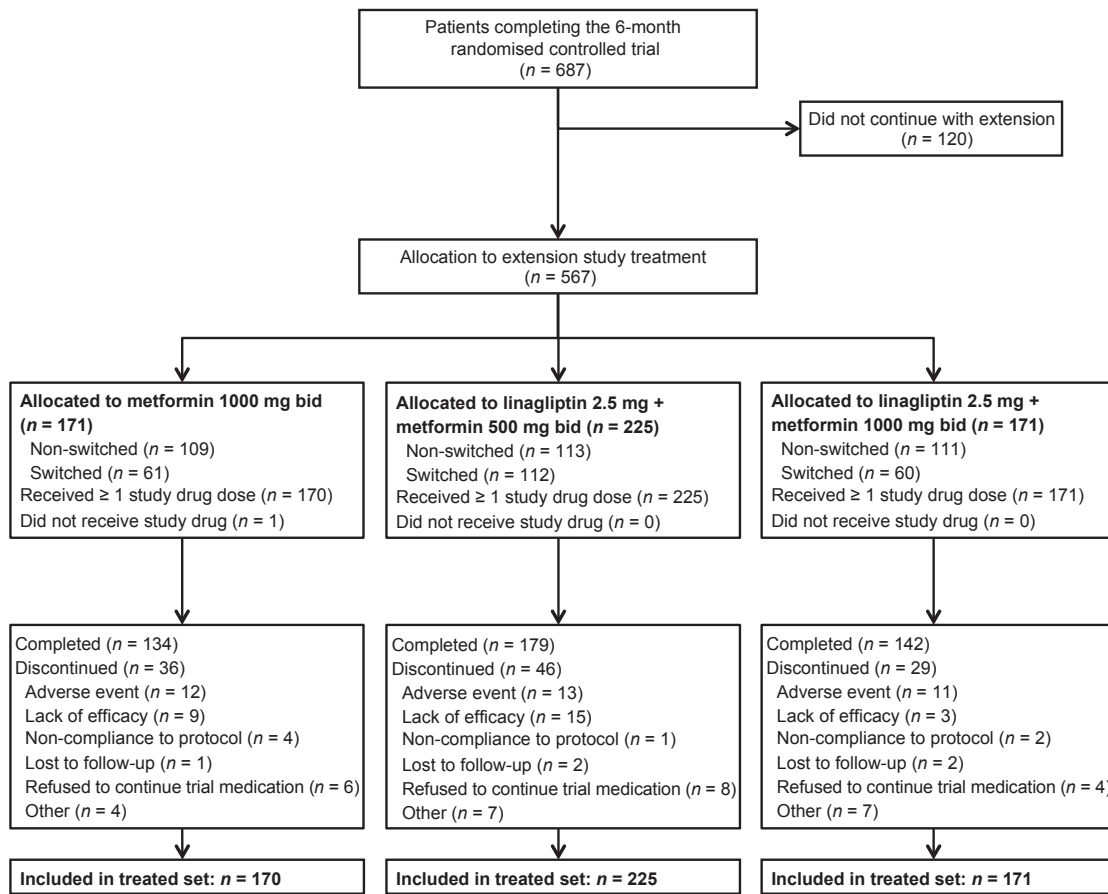


Figure 2 Patient flow. Bid, twice daily. Lack of efficacy includes patients who discontinued because of hyperglycaemia. The disposition of patients who switched or did not switch treatments from trial 1218.46 to this extension trial was not analysed

unadjusted HbA1c change by baseline for non-switched patients who would typically warrant treatment with initial combination therapy indicated that the efficacy response was greatest in patients with higher baseline HbA1c levels ($\geq 9\%$) than in those with moderate levels (HbA1c 8.0 to $< 9.0\%$; Figure 4). Notably, only 14 of 31 patients with baseline HbA1c levels $\geq 9\%$ remained in the metformin monotherapy group at the end of the extension trial.

Because patients had already completed the 6-month study, it was expected that some would already have achieved target HbA1c levels at the beginning of the extension. For the non-switched patients (treated set, observed cases), 37/105 (35.2%), 41/113 (36.3%) and 67/111 (60.4%) of the metformin 1000, linagliptin 2.5 + metformin 500 and linagliptin 2.5 + metformin 1000 groups, respectively, had HbA1c $< 7\%$ at the end of the 6-month study. At week 54, the proportions of patients in these groups with HbA1c $< 7\%$ were 33/69 (47.8%), 24/66 (36.4%) and 46/78 (59.0%), showing an apparent percentage increase in the metformin group,

because patients who did not achieve control discontinued the study.

As the switched set had received various treatments in the previous 6-month trial, changes in HbA1c were analysed from the start of the extension study. At this timepoint, the mean \pm SD HbA1c was $7.76 \pm 1.10\%$ in the metformin 1000 group ($n = 60$), $7.95 \pm 1.04\%$ in the linagliptin 2.5 + metformin 500 group ($n = 111$) and $8.15 \pm 1.15\%$ in the linagliptin 2.5 + metformin 1000 group ($n = 59$). The mean change in HbA1c from baseline to week 54 was more marked in the linagliptin 2.5 + metformin 1000 group ($-0.96 \pm 1.05\%$, $n = 39$) than in the linagliptin 2.5 + metformin 500 group ($-0.63 \pm 0.83\%$, $n = 66$) and the metformin 1000 group ($-0.42 \pm 0.76\%$, $n = 32$).

To compare initial combination therapy vs. add-on therapy, changes in HbA1c were analysed from the baseline visit of the 6-month trial for the 50 patients switched from metformin 500 to linagliptin 2.5 + metformin 500 therapy and the 66 patients maintained on initial combination therapy. The

Table 1 Baseline patient and clinical characteristics (treated set)

	Metformin 1000 (<i>n</i> = 170)		Linagliptin 2.5 + metformin 500 (<i>n</i> = 225)		Linagliptin 2.5 + metformin 1000 (<i>n</i> = 171)	
	Switched (<i>n</i> = 61)	Non-switched (<i>n</i> = 109)	Switched (<i>n</i> = 112)	Non-switched (<i>n</i> = 113)	Switched (<i>n</i> = 60)	Non-switched (<i>n</i> = 111)
Age (years)	55.7 ± 10.5	55.6 ± 10.9	55.1 ± 10.3	56.8 ± 11.1	56.1 ± 11.5	55.6 ± 10.5
Men (%)	34 (55.7)	59 (54.1)	62 (55.4)	58 (51.3)	37 (61.7)	60 (54.1)
Race (%)						
White	63.9	62.4	65.2	71.7	68.3	60.4
Asian	36.1	36.7	34.8	26.5	31.7	38.7
Black	0.0	0.9	0.0	1.8	0.0	0.9
BMI (kg/m ²)	29.5 ± 5.5	29.2 ± 5.1	28.3 ± 4.5	29.8 ± 5.3	28.8 ± 4.9	28.5 ± 4.8
eGFR (%)						
≥ 90 ml/min	49.2	60.6	60.7	51.3	43.3	53.2
60 to < 90 ml/min	42.6	34.9	36.6	46.9	50.0	39.6
30 to < 60 ml/min	3.3	1.8	1.8	1.8	5.0	5.4
Missing	4.9	2.8	0.9	0.0	1.7	1.8
Duration of type 2 diabetes (%)						
≤ 1 year	39.3	37.6	42.9	40.7	46.7	38.7
> 1–5 years	31.1	45.9	35.7	32.7	41.7	37.8
> 5 years	29.5	16.5	21.4	26.5	11.7	23.4
HbA1c (%)*	7.76 ± 1.10	7.31 ± 0.88	7.95 ± 1.04	7.34 ± 0.96	8.15 ± 1.15	6.93 ± 0.85
FPG (mg/dl)†	164.8 ± 39.4	152.0 ± 38.5	174.5 ± 44.4	159.6 ± 43.8	173.8 ± 43.1	142.8 ± 28.1

Values are mean ± standard deviation or % of patients.

eGFR was calculated according to the Modification of Diet in Renal Disease equation.

BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin.

*Includes all treated patients with a baseline HbA1c value, for the switched/non-switched groups: metformin 1000 mg, *n* = 60/*n* = 105; linagliptin 2.5 mg + metformin 500 mg, *n* = 111/*n* = 113; linagliptin 2.5 mg + metformin 1000 mg, *n* = 59/*n* = 111.

†Includes all treated patients with a baseline FPG value, for the switched/non-switched groups: metformin 1000 mg, *n* = 59/*n* = 105; linagliptin 2.5 mg + metformin 500 mg, *n* = 108/*n* = 107; linagliptin 2.5 mg + metformin 1000 mg, *n* = 58/*n* = 107.

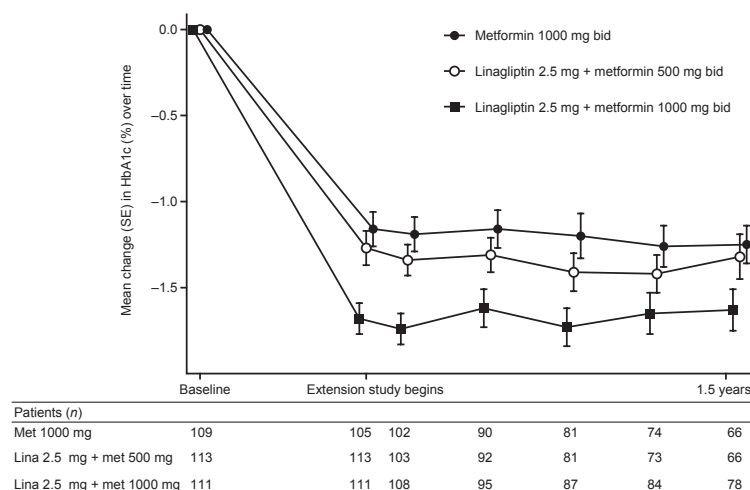


Figure 3 Mean change in glycosylated haemoglobin (HbA1c) in the non-switched set. Bid, twice daily; lina, linagliptin; met, metformin; SE, standard error. Treated set, observed cases. HbA1c values were recorded throughout the 6-month study, but for clarity, only baseline and end-of-study data points for the 6-month study are shown here, see ref. (7) for details of 6-month study. Data points have been offset for clarity

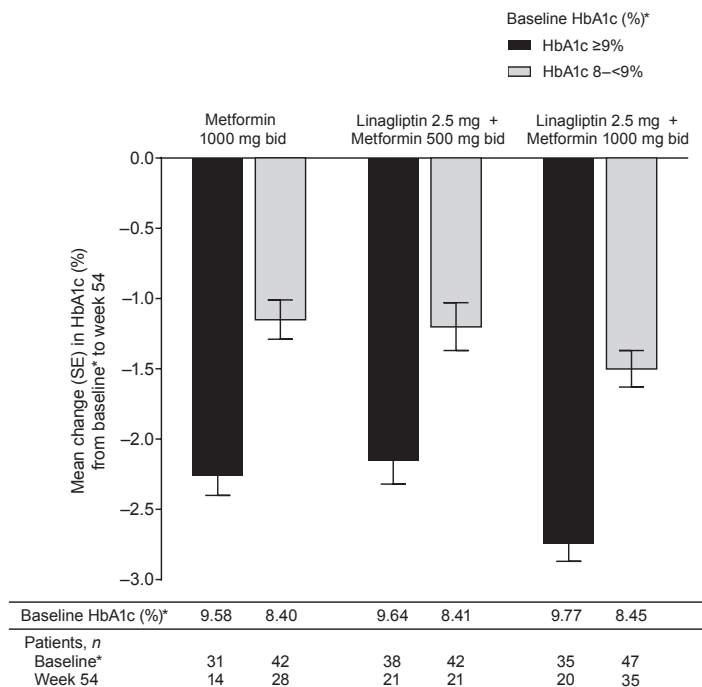


Figure 4 Mean change in glycosylated haemoglobin (HbA1c) at week 54 by baseline HbA1c in the non-switched set. Bid, twice daily; SE, standard error. Treated set, observed cases. HbA1c values were recorded throughout the 6-month study, but for clarity, only baseline and end-of-study data points for the 6-month study are shown here, see ref. (7) for details of 6-month study. *At start of 6-month trial

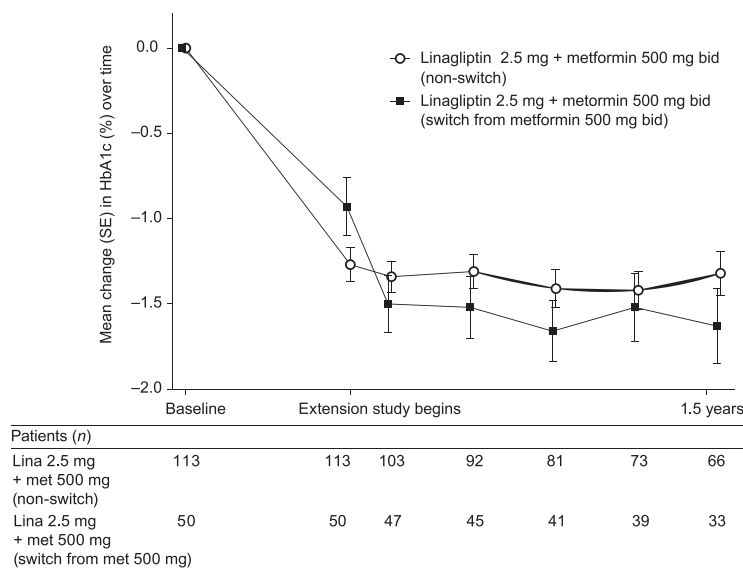


Figure 5 Mean change in glycosylated haemoglobin (HbA1c) in those switched from metformin 500 mg to the linagliptin 2.5 + metformin 500 group vs. maintained on initial combination therapy. Bid, twice daily; lina, linagliptin; met, metformin; SE, standard error. Treated set, observed cases. HbA1c values were recorded throughout the 6-month study, but for clarity, only baseline and end-of-study data points for the 6-month study are shown here, see ref. (7) for details of 6-month study. Data points have been offset for clarity

mean ± SD change in HbA1c from baseline to week 54 was $-1.63 \pm 1.25\%$ for those patients switched from therapy with metformin 500 to linagliptin 2.5 + metformin 500 compared with $-1.32 \pm 1.06\%$ for those patients maintained on therapy with linagliptin 2.5 + metformin 500 (Figure 5).

For FPG, mean \pm SD values for the non-switched set were comparable for the three groups at the baseline of the 6-month study (metformin 1000: 185.5 ± 46.3 mg/dl; linagliptin 2.5 + metformin 500: 193.49 ± 55.2 mg/dl; linagliptin 2.5 + metformin 1000: 191.08 ± 44.4 mg/dl). By the start of the extension study, mean FPG had decreased by -32.83 ± 38.54 mg/dl in the metformin 1000 group, -32.03 ± 45.50 mg/dl in the linagliptin 2.5 + metformin 500 group and -47.43 ± 44.85 mg/dl in the linagliptin 2.5 + metformin 1000 group. These reductions seen at the end of the preceding trial were maintained in each of the three treatment groups at week 54 of the extension trial, with changes of -1.92 ± 30.2 mg/dl in the metformin 1000 group, -0.35 ± 32.1 mg/dl in the linagliptin 2.5 + metformin 500 group and 1.83 ± 25.0 mg/dl in the linagliptin 2.5 + metformin 1000 group (Figure 3).

At the start of the extension study, switched patients had higher FPG levels, with mean \pm SD values of 164.8 ± 39.4 in the metformin 1000 group ($n = 59$), 174.5 ± 44.4 in the linagliptin 2.5 + metformin 500 group ($n = 108$) and 173.8 ± 43.1 in the linagliptin 2.5 + metformin 1000 group ($n = 58$). The mean change from baseline to week 54 was -14.63 ± 25.45 mg/dl in the metformin 1000 group ($n = 30$), -13.74 ± 38.95 mg/dl in the linagliptin 2.5 + metformin 500 group ($n = 68$) and -34.38 ± 30.94 mg/dl in the linagliptin 2.5 + metformin 1000 group ($n = 37$).

Use of rescue therapy and changes in weight and waist circumference were analysed for switched and non-switched patients together, for the period of the extension study only. The overall incidence of rescue medication use was lower in the linagliptin 2.5 + metformin 1000 treatment group (14.0%) than in the linagliptin 2.5 + metformin 500 (27.6%) and metformin 1000 (24.7%) treatment groups. During the extension study, there were no clinically meaningful changes in weight, with mean \pm SD changes of -0.4 ± 2.7 kg, 0.2 ± 3.0 kg and -0.7 ± 3.2 kg in the metformin 1000, linagliptin 2.5 + metformin 500 and linagliptin 2.5 + metformin 1000 groups, respectively. Similarly, there were no clinically meaningful differences in the change in waist circumference, with mean \pm SD changes of 0.2 ± 4.1 cm, -0.2 ± 3.8 cm and -1.0 ± 3.3 cm for the three groups.

Safety

In the treated set, the incidences of treatment-emergent AEs during the extension period were comparable across the groups, ranging between 66% and 77% (Table 2). Most AEs were of mild or moderate intensity, with the majority considered unrelated to study drug. The most frequent AEs by preferred term were hyperglycaemia and worsening diabetes mellitus

(Table 2). Overall, the proportion of patients discontinuing because of AEs was similar among the groups. The most frequent AE leading to discontinuation of treatment was a decreased glomerular filtration rate (Table 2). One patient discontinued treatment because of hypoglycaemia (linagliptin 2.5 + metformin 500 group).

Serious AEs (SAEs) were reported in 33 patients (Table 2). Four patients died during the trial (two in the linagliptin 2.5 + metformin 500 group and one patient each in the metformin 1000 and linagliptin 2.5 + metformin 1000 groups); none of the deaths were considered related to study drug. There were no predefined cutaneous adverse reactions or patients with pancreatitis. Hepatic AEs were uncommon and the incidences were comparable across groups (Table 2). Three patients were reported with hypersensitivity reactions (bronchospasm for one patient in the metformin 1000 group and urticaria for two patients in the linagliptin 2.5 + metformin 1000 group), while renal failure was reported for one patient in the metformin 1000 group and for one patient in the linagliptin 2.5 + metformin 1000 group. None of these events were considered to be drug-related.

During the extension study, there were nine pre-specified cardiovascular events confirmed by the independent clinical event committee: in the metformin 1000 group, one non-fatal stroke and one non-fatal MI; in the linagliptin 2.5 + metformin 500 group, one non-fatal stroke, three non-fatal MIs and two unstable anginas; and in the linagliptin 2.5 + metformin 1000 group, two unstable anginas. None of these events was considered to be drug-related.

There were no clinically meaningful changes in vital signs in any treatment group, nor were there any clinically meaningful or unexpected changes in any haematology, biochemistry or urinalysis laboratory variables. In the posttreatment period, 14 patients across the three groups had an AE; none were SAEs.

For the switched set, the AE profile did not differ markedly from that of the overall treated set, and the number of SAEs and of AEs leading to discontinuation were low and comparable across the three groups (Table 2). As with the overall group, the most frequent AEs by preferred term were hyperglycaemia and worsening diabetes mellitus.

In the treated set, the numbers of patients across groups who received rescue medication were small. The incidence of reported AEs while patients were on rescue medication (metformin 1000 group: 69.0% [$n = 29/42$], linagliptin 2.5 + metformin 500 group: 62.9% [$n = 39/62$], linagliptin 2.5 + metformin 1000 group: 70.8% [$n = 17/24$]) was similar to the incidence while not on rescue medication (metformin

Table 2 Safety summary: AEs during the 54-week extension period (treated set)

Percent of patients	Metformin 1000 (<i>n</i> = 170)		Linagliptin 2.5 + metformin 500 (<i>n</i> = 225)		Linagliptin 2.5 + metformin 1000 (<i>n</i> = 171)	
	Switched (<i>n</i> = 61)	All (<i>n</i> = 170)	Switched (<i>n</i> = 112)	All (<i>n</i> = 225)	Switched (<i>n</i> = 60)	All (<i>n</i> = 171)
Any AE	75.4	72.9	64.3	66.2	75.0	77.2
Any drug-related AE	16.4	15.9	7.1	8.4	18.3	14.0
SAE*	3.3	4.1	5.4	5.3	8.3	8.2
AE leading to discontinuation†	4.9	5.9	4.5	4.9	8.3	5.3
Decreased eGFR	1.6	0.6	2.7	3.1	5.0	2.9
Hypoglycaemia	0	0	0.9	0.4	0	0
Prespecified significant AEs‡						
Hepatic AEs	4.9	7.6	2.7	4.9	5.0	6.4
Renal AEs	0.0	0.6	0.0	0.0	1.7	0.6
Hypersensitivity reactions	0.0	0.6	0.0	0.0	1.7	1.2
Hypoglycaemic event§	4.9	2.9	7.1	4.9	5.0	6.4
Of which severe	0.0	0.0	0.0	0.0	0.0	0.0

AE, adverse event; eGFR, estimated glomerular filtration rate; SAE, serious adverse event.

*SAE defined as any AE that resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalisation or was a congenital anomaly/birth defect. Any other serious important medical event (based upon appropriate medical judgment) that may have jeopardised the patient and may have required medical or surgical intervention to prevent one of the other above-mentioned outcomes was also regarded as an SAE. Two SAEs were deemed drug-related (cardiogenic shock and supraventricular tachycardia, both occurring in the same patient in the linagliptin 2.5 + metformin 1000 group on day 295 and assessed by the investigator as being drug-related because they occurred within 1 h of administration of medication. The patient required hospitalisation and study medication was discontinued; the patient recovered).

†Additional AEs leading to discontinuation of study treatment (all patients): one patient with anaemia (linagliptin 2.5 + metformin 500 group), two patients with acute myocardial infarction (one patient in the metformin 1000 group and one patient in the linagliptin 2.5 + metformin 500 group), one patient with cardiogenic shock and supraventricular tachycardia (in the same patient in the linagliptin 2.5 + metformin 1000 group*), one patient with fatigue (metformin 1000 group), one traffic accident (linagliptin 2.5 + metformin 500 group), one of each of the following altered lab values (in the metformin 1000 group: alanine aminotransferase increased, blood amylase increased, glycosylated haemoglobin increased, and transaminases increased), four patients with worsened diabetes mellitus (one patient each in the metformin 1000 and the linagliptin 2.5 + metformin 500 groups; two patients in the linagliptin 2.5 + metformin 1000 group), and two patients with hyperglycaemia (one patient in the metformin 1000 group and one patient in the linagliptin 2.5 + metformin 500 group), and one patient with cerebrovascular accident (metformin 1000 group).

‡Prespecified significant AEs and AEs of special interest (hepatic AEs, renal AEs, hypersensitivity reactions, severe cutaneous adverse reactions and pancreatitis) were identified using Medical Dictionary for Regulatory Activities version 14.0 standard queries. Five significant events were considered drug-related by the investigator: three patients for whom glomerular filtration rate decreased (two in the metformin 1000 group and one in the linagliptin 2.5 + metformin 1000 group), one patient for whom alanine aminotransferase increased (in the metformin 1000 group), and one patient with alcoholic hepatitis (in the linagliptin 2.5 + metformin 1000 group).

§Hypoglycaemic episodes were based on investigator reporting; they were to be classified as severe by investigators if the event required the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

1000 group: 65.9% [*n* = 112/170], linagliptin 2.5 + metformin 500 group: 62.3% [*n* = 139/223], linagliptin 2.5 + metformin 1000: 75.9% [*n* = 129/170]). Reported incidences of metabolism and nutrition disorders were slightly higher on rescue than not on rescue, ranging from 29.2% to 35.7% and 18.8% to 24.1%. For the switched set, the overall incidence and pattern of reported AEs for patients receiving vs. not receiving rescue medication was comparable with the findings for the treated set.

Conclusions

Surveys of prescription patterns in primary care show that the majority of newly diagnosed patients with type 2 diabetes are treated with metformin monotherapy (9). Higher HbA1c levels are associated with increased likelihood of being prescribed combination therapy, perhaps reflecting recommendations from expert groups that initial combination therapy (rather than stepwise addition of agents) should be considered for patients unlikely to achieve control with monotherapy (1,10). In

clinical practice, using combination therapies offers the advantages of achieving target HbA1c control early and maintaining targets without the need for additional therapies, and the combination of metformin with a DPP-4 inhibitor provides greater HbA1c control than either monotherapy (11). Further advantages of the combination of metformin with a DPP-4 inhibitor are that there are no major safety concerns, and no increased risks of hypoglycaemia or weight gain.

This study provides additional data on safety and efficacy for patients with type 2 diabetes who were initially treated with either the combination of linagliptin and metformin or metformin alone. Initial combination therapy with linagliptin and metformin in patients with type 2 diabetes has previously been shown to be superior to metformin monotherapy, with significantly improved reductions in HbA1c and FPG levels over 6 months (7). In this extension study, the HbA1c and FPG reductions were maintained over a subsequent blinded follow-up period of 1 year, with the linagliptin and metformin combination showing better glucose control than metformin alone. For patients with continuous treatment, mean reductions in HbA1c from the start of treatment were $-1.25 \pm 0.11\%$ for the metformin 1000 group, $-1.32 \pm 0.13\%$ for the linagliptin 2.5 + metformin 500 group and $-1.63 \pm 0.12\%$ for the linagliptin 2.5 + metformin 1000 groups, with the decrease in the first 6-month trial maintained over the 1-year extension. Furthermore, the majority of patients who were at target HbA1c after 6 months of treatment maintained these goals after 18 months, although a number of patients discontinued treatment, thus explaining the apparent increase in the proportion of patients achieving goal in the metformin monotherapy group.

Initial combination therapy may be preferred over a stepwise approach to therapy for some patients. Comparison of initial combination therapy with low-dose metformin plus linagliptin to initial monotherapy with metformin followed by add-on linagliptin showed that both strategies are similarly effective in lowering HbA1c. However, there were ~50% fewer patients in the metformin 500-mg monotherapy group at the start of the extension study, suggesting lack of durability with this approach. Consistent with results from the initial trial (7), patients with high vs. moderate baseline HbA1c values achieved the greatest HbA1c reductions with combination therapy.

In the extension study, the incidence of all treatment-emergent AEs and treatment-related AEs was comparable across study arms, and the incidence of AEs leading to discontinuation was low. This confirms the results of previous observations that linagliptin in combination with metformin is associated with a low risk of hypoglycaemia and is weight neutral in the long term (12–14).

In summary, this 52-week, randomised, blinded extension study provides further evidence that linagliptin in combination with metformin can be used over an extended time period without additional safety burden, as indicated by comparable safety profiles of metformin monotherapy and combination therapy. In addition, the clinically meaningful improvements in glycaemic control previously seen with the combination of linagliptin and metformin over 6 months were sustained. Because of the chronic nature of the disease, patients with type 2 diabetes will require glucose-lowering combination therapies, such as linagliptin and metformin, for many years, and the results of this 1-year comparative effectiveness study support the use of combination therapy for the early treatment of type 2 diabetes.

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Author contributions

All authors were involved in the collection and analysis/interpretation of data, and revised the article critically and provided approval of the final version. TH, SW, H-JW and TM were involved in the study concept and design. RJ provided statistical analysis.

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