

Clinical utility and tolerability of linagliptin in diabetic patients

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Background: The purpose of this paper is to review the efficacy, safety, and tolerability of linagliptin in the management of hyperglycemia in adults with type 2 diabetes mellitus.

Methods: A Medline search was performed using the keywords “linagliptin” and “type 2 diabetes” for articles published September 2010 through July 2012. The literature search was limited by the following criteria: articles’ publication in the English language, clinical trials, randomized controlled trials, and research conducted in humans.

Results: A review of the data for linagliptin in the treatment of type 2 diabetes as monotherapy or in combination with other antidiabetic therapies suggests clinical efficacy in terms of reductions in glycosylated hemoglobin, fasting plasma glucose, and postprandial glucose. Most adverse events with linagliptin are considered to be mild to moderate in nature. Although linagliptin therapy may offer a low risk of hypoglycemia, the risk increases when it is used in combination with insulin secretagogues. Linagliptin can generally be considered weight neutral, but a weight increase was observed when linagliptin was used in combination with a thiazolidinedione.

Conclusion: Linagliptin is a once-daily oral medication used for the treatment of type 2 diabetes. The use of linagliptin as monotherapy or in combination with metformin, sulfonylureas, or pioglitazone led to improvement in glycemic control and was well tolerated by most patients.

Keywords: type 2 diabetes, linagliptin, dipeptidyl peptidase-4 inhibitor

Introduction

Linagliptin (Tradjenta®, Boehringer Ingelheim, Ridgefield, CT, USA) is a newly approved medication for the treatment of type 2 diabetes mellitus.¹ This agent is a potent inhibitor of the serine protease enzyme, dipeptidyl peptidase-4 (DPP-4), which is responsible for rapid degradation of two incretin hormones, glucagon-like-peptide 1 (GLP-1) and glucose insulinotropic polypeptide (GIP). GLP-1 and GIP have distinct physiologic actions in the regulation of glucose that would make their augmentation attractive in the patient with type 2 diabetes due to a propensity to achieve decreased levels of both hormones.²

GLP-1 is secreted from intestine endocrine L-cells in response to glucose and is responsible for stimulation of insulin release from the pancreas in a glucose-dependent manner. GLP-1 inhibits the release of glucagon, thereby decreasing hepatic gluconeogenesis and insulin inhibition. GLP-1 decreases gastric emptying, delaying arrival of glucose into the vasculature, and works centrally in the brain by increasing satiety with a decrease in food intake. Lastly, GLP-1 can increase β -cell mass by decreasing apoptosis and by increasing proliferation and neogenesis of β -cells.³ However, this has only been shown in animal models, with no evidence of this noted in humans

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as yet.⁴ GIP is secreted from the K-cells of the intestine wall, stimulates insulin secretion from the pancreas, and has been shown to decrease cellular death and increase regeneration of β -cells.³

Linagliptin has been shown to be a potent long-acting DPP-4 inhibitor. An in vitro study showed that linagliptin inhibited DPP-4 with a 50% inhibition concentration (IC_{50}) of about 1 nM, compared with sitagliptin (19 nM), alogliptin (24 nM), saxagliptin (50 nM), and vidagliptin (62 nM).⁵ Linagliptin has an elimination half-life of 131 hours,⁶ and achieves steady-state concentrations after three doses of 5 mg daily.¹ Linagliptin has also been shown to inhibit DPP-4 activity by more than 80% over 24 hours.^{6–8} The presence of these characteristics allows for once-daily oral dosing.⁷ Linagliptin undergoes primarily hepatic elimination, with approximately 85% of the drug excreted unchanged in the feces.⁹ Despite having a predominately hepatic route of elimination, the main metabolite is pharmacologically inactive.¹ The overall pharmacokinetic profile of linagliptin may avoid the need to adjust the dose in patients with renal or hepatic impairment. The recommendations provided by the package insert indicate no dose adjustments are required for renal or hepatic impairment.¹

Multiple therapies have now been introduced to the market that target the incretin hormone system. Current guidelines recommend that these treatments be considered as part of a “patient-centered approach” and be used as a component

of a two-drug or three-drug regimen in conjunction with metformin if a patient does not meet their individualized glycosylated hemoglobin (HbA1c) goal.¹⁰

Materials and methods

A Medline search was performed using the keywords “linagliptin”, “DPP-4 inhibitor”, and “type 2 diabetes” for articles published through July 2012. The literature search was limited by the following criteria: publication in the English language, clinical trials, randomized controlled trials, and research conducted in humans (Figure 1). Here we summarize the available data with a focus on the clinical utility and tolerability of linagliptin.

Results

Linagliptin monotherapy

This Phase IIa study conducted by Forst et al followed a randomized, double-blind, within-dose level, parallel, placebo-controlled design and examined the pharmacokinetic and pharmacodynamic properties of linagliptin in patients with type 2 diabetes after 4 weeks of treatment.¹¹ Participants enrolled in this study were either treatment-naïve or had received up to two oral antidiabetic therapies other than a thiazolidinedione. Participants were 21–70 (median 62) years of age, had a body mass index of 18.5–35 kg/m², and had an HbA1c $\leq$ 8.5% for treatment-naïve and/or one oral antidiabetic therapy, and $\leq$ 8.0% for patients treated with two

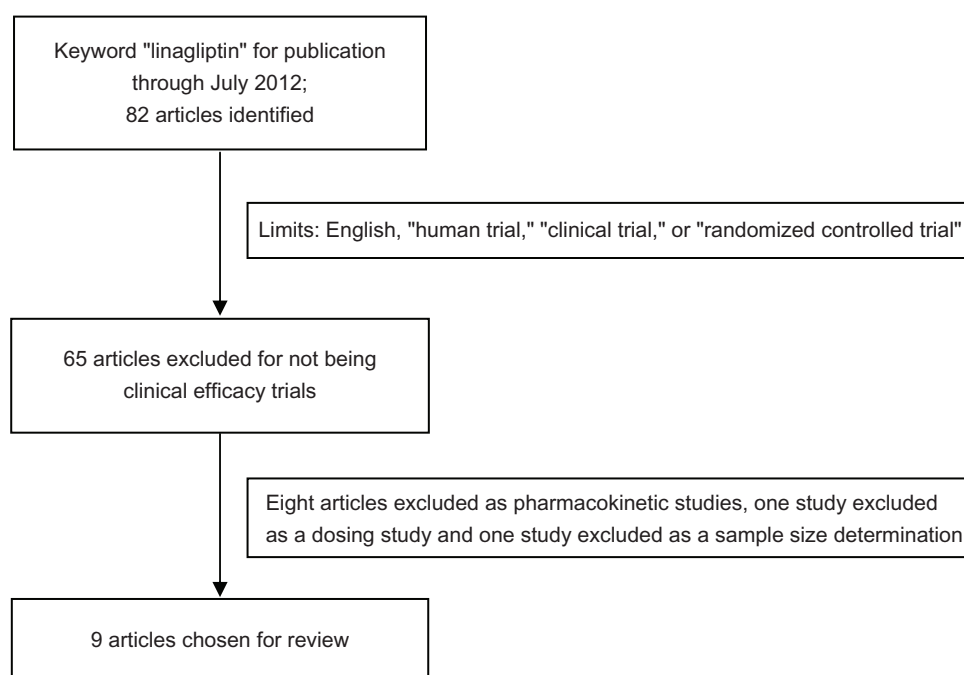


Figure 1 Flowchart of literature selection.

oral antidiabetic therapies. The HbA1c for the total cohort of 77 patients was 7.0%. In participants receiving an oral antidiabetic therapy, a washout period of 14 days was required. Eligible patients were randomly assigned to receive linagliptin 2.5 mg ($n = 26$), 5 mg ($n = 16$), 10 mg ($n = 19$), or placebo ($n = 16$). Statistically significant decreases in mean HbA1c from baseline were observed at the end of the 4-week period for all the linagliptin groups compared with placebo. The placebo-corrected mean change in HbA1c was -0.31% for linagliptin 2.5 mg, -0.37% for linagliptin 5 mg, and -0.28% for linagliptin 10 mg ($P = <0.025$). Statistically significant decreases in fasting plasma glucose and postprandial plasma glucose were also observed from baseline to the end of the study period for all linagliptin doses (see Table 1).

Another randomized, double-blind, parallel-group study comparing treatment with either linagliptin 5 mg or placebo for 24 weeks in patients with type 2 diabetes was conducted by Del Prato et al.¹² Patients were aged 18–80 (mean 55.7) years with a body mass index ≤ 40 kg/m², and were either treatment-naïve or previously treated with one oral antidiabetic therapy other than a thiazolidinedione. Pretreated patients underwent a 6-week washout period, with the last 2 weeks being an open-label placebo run-in. Treatment-naïve patients entered directly into the 2-week placebo run-in period. HbA1c levels had to be between 6.5% and 9.0% in non-treatment-naïve patients or between 7.0% and 10% in treatment-naïve patients. Eligible patients were then randomized to receive treatment with linagliptin 5 mg or placebo for 24 weeks. The adjusted mean difference in the change of HbA1c comparing linagliptin and placebo was -0.69% ($P < 0.0001$). The primary endpoint was adjusted for baseline HbA1c and previous oral antidiabetic therapy. Treatment with linagliptin also resulted in significant decreases in fasting plasma glucose and postprandial plasma glucose compared with placebo (see Table 1).

Combination therapy

Linagliptin versus placebo as add-on therapy to metformin

Taskinen et al performed a randomized, double-blind, placebo-controlled, multicenter, parallel-group study in 701 patients with type 2 diabetes aged 18–80 years.¹³ Subjects included had a mean age of 56.5 years, a body mass index ≤ 40 kg/m², and a mean baseline HbA1c of 8.1%. Subjects eligible for inclusion needed to have received metformin at a dose ≥ 1500 mg/day (or the maximum tolerated dose) and not more than one other oral antidiabetic therapy. In patients who had previously been treated with metformin

monotherapy, HbA1c had to be 7.0%–10.0% at screening; for patients treated with an additional medication, A1c had to be 6.5%–9.0%. Patients taking antidiabetic therapy in addition to metformin were instructed to stop the medication and then underwent a 6-week washout period that included an open-label placebo run-in phase in the last 2 weeks. For patients taking metformin monotherapy at enrolment, only the 2-week run-in phase was required. All eligible patients continued their usual dose of metformin and were then randomized to treatment with either linagliptin 5 mg once daily or placebo for 24 weeks. The primary endpoint was the change from baseline HbA1c, adjusted for baseline HbA1c and the use of monotherapy versus combination therapy at enrolment, after 24 weeks of treatment. At the end of the study, linagliptin reduced the mean HbA1c level by 0.49%, whereas HbA1c in the placebo group rose by 0.15% ($P < 0.0001$). The placebo-corrected reduction in HbA1c was 0.64%. Linagliptin also led to significant reductions versus placebo in both fasting plasma glucose and postprandial plasma glucose ($P < 0.0001$, see Table 2).

Linagliptin + metformin versus linagliptin alone, metformin alone, and placebo

Haak et al conducted a 24-week, randomized, double-blind, placebo-controlled Phase III trial in 791 patients who were either treatment-naïve or had been treated with one other antidiabetic therapy.¹⁵ Eligible patients were 18–80 years of age, had a diagnosis of type 2 diabetes, and had a body mass index of ≤ 40 kg/m². In treatment-naïve participants, HbA1c had to be $\geq 7.5\%$ and $< 11\%$, and for patients pretreated with one antidiabetic therapy had to be $\geq 7.0\%$ to $\leq 10.5\%$. Patients pretreated with one antidiabetic therapy entered a 4-week washout period followed by a 2-week placebo run-in period that all patients participated in. Subjects were then treated for 24 weeks with one of two free combinations of linagliptin (linagliptin 2.5 mg twice daily + metformin 500 mg twice daily or 1000 mg twice daily) or placebo, linagliptin 5 mg once daily, metformin 500 mg twice daily, or metformin 1000 mg twice daily monotherapy. The primary endpoint was change in HbA1c from baseline to 24 weeks of treatment, adjusted for baseline HbA1c and previous oral antidiabetic therapy. Mean baseline HbA1c values were similar for all treatment groups, with an overall mean of 8.7%. The adjusted placebo-corrected mean (95% confidence interval) changes in HbA1c were -1.7% (-2.0% , -1.4%) for linagliptin + metformin 1000 mg; -1.3% (-1.6 , -1.1) for linagliptin + metformin 500 mg; -1.2% (-1.5% , -0.9%) for metformin 1000 mg; -0.8% (-1.0 , -0.5) for

Table 1 Efficacy and safety of linagliptin monotherapy for the treatment of type 2 diabetes

Authors and study design	Dose (Patients, n)	Study parameters	Efficacy results				Tolerability results
Forst et al ¹¹ R, DB, PG, PC Patients with type 2 diabetes not controlled by up to two ADT (excluding TZD) or treatment-naïve	Linagliptin 2.5 mg (n = 26)	Primary: safety and tolerability	At week 4:				Most common: Nasopharyngitis (5 patients or 6%) Back pain (4 patients or 5%) The incidence was similar between placebo-treated and linagliptin-treated patients No subjects showed signs or symptoms of hypoglycemia Body weight decreased in all treatment groups Serious adverse events: one event not related to study drug Most common: Hyperglycemia (8.6% linagliptin versus 22.8% placebo) Nasopharyngitis (3.9% linagliptin versus 4.2% placebo) One patient in each group experienced hypoglycemia Body weight did not differ significantly from baseline in either group at the end of the study period
	Linagliptin 5 mg (n = 16)	Secondary: FPG	A1c change (%)	FPG change (mg/dL)	PPG change (mg/dL)		
	Linagliptin 10 mg (n = 19)	PPG	-0.31 ^{ab}	-19.2 ^{ab}	-32.4 ^{ab}		
	Placebo: n = 16	A1c	-0.37 ^{ab}	-21.4 ^{ab}	-52.5 ^{ab}		
	Total: 4 weeks		-0.28 ^{ab}	-16.6 ^{ab}	-27.2 ^{ab}		
	Notes: ^a P < 0.025 compared with placebo; ^b placebo-corrected.						
Del Prato et al ¹² R, DB, PC, PG Patients with type 2 diabetes not controlled by one ADT (excluding TZD) or were treatment-naïve	Linagliptin 5 mg (n = 336)	Primary: A1c	At week 24:				Most common: Hyperglycemia (8.6% linagliptin versus 22.8% placebo) Nasopharyngitis (3.9% linagliptin versus 4.2% placebo) One patient in each group experienced hypoglycemia Body weight did not differ significantly from baseline in either group at the end of the study period
	Placebo (n = 167)	Secondary: A1c < 7.0% and <6.5%	A1c change (%)	FPG change (mg/dL)	PPG change (mg/dL)		
	Total: 24 weeks	A1c lowered by >0.5%	-0.69 ^{ab}	-23.4 ^{ab}	-57.7 ^{ab}		
	Notes: ^a P < 0.0001; ^b placebo-corrected.						
	Among patients with a baseline A1c ≥ 7%, 25.2% of individuals treated with linagliptin versus 11.6% of those in the placebo group achieved A1c < 7% at 24 weeks (P = 0.0006). The percentage of patients achieving an A1c reduction ≥ 0.5% at 24 weeks was 47.1% with linagliptin and 19% with placebo (P < 0.0001).						

Abbreviations: A1c, glycosylated hemoglobin; ADT, antidiabetic therapy; DB, double-blind; FPG, fasting plasma glucose; MC, multicenter; PG, parallel-group; PC, placebo-controlled; PPG, postprandial plasma glucose; R, randomized; TZD, thiazolidinediones.

metformin 500 mg; and -0.6% (-0.9% , -0.3%) for linagliptin monotherapy (all $P < 0.0001$). Significant reductions in fasting plasma glucose from baseline to the end of the study period were seen with combination therapies relative to metformin monotherapy. The placebo-corrected changes in fasting plasma glucose from baseline were also statistically significant for each group. This study did not assess changes in postprandial plasma glucose (see Table 2).

Linagliptin versus placebo in combination with metformin and sulfonylurea

This randomized, placebo-controlled, double-blind, parallel-group study enrolled subjects with type 2 diabetes receiving metformin ≥ 1500 mg/day (or the maximum tolerated dose) and the maximum tolerated dose of sulfonylurea.¹⁶ Patients were 18–80 (mean 58.1) years of age, with a body mass index ≤ 40 kg/m² and HbA1c $\geq 7.0\%$ and $\leq 10.0\%$ (mean 8.14%). Following a 2-week placebo run-in, a total of 1055 participants were randomized to treatment with linagliptin 5 mg once daily or placebo, in addition to the established background therapy of metformin in combination with a sulfonylurea. The primary endpoint was the change in HbA1c levels between baseline and 24 weeks, stratified by baseline HbA1c value. After 24 weeks, linagliptin was superior to placebo for the adjusted mean change in HbA1c from baseline. The linagliptin placebo-corrected adjusted mean change from baseline was -0.62% ($P < 0.0001$). Linagliptin also produced greater reductions in fasting plasma glucose than placebo at week 24 ($P < 0.0001$, see Table 2).

Linagliptin versus glimepiride in combination with metformin

This randomized, double-blind, parallel-group, active-controlled, noninferiority trial was conducted by Gallwitz et al in 1519 patients with type 2 diabetes, aged 18–80 years, and a body mass index of ≤ 40 kg/m².¹⁷ Eligible subjects were receiving metformin 1500 mg/day (or the maximum tolerated dose) alone with an HbA1c of 6.5%–10.0% or 6.0%–9.0% on metformin and one other oral antidiabetic therapy. Mean baseline HbA1c and age were 7.7% and 59.8 years in each group, respectively. Participants receiving metformin and one additional antidiabetic therapy entered a 6-week washout period followed by a 2-week open-label placebo run-in. Those receiving metformin monotherapy entered directly into a 2-week, open-label, placebo run-in period. Subjects who met the inclusion criteria were then randomly assigned to treatment with linagliptin 5 mg once daily or glimepiride at an initial dose of 1 mg daily added to the current dose

of metformin. The primary endpoint was the change in HbA1c from baseline to week 104, and was stratified by baseline HbA1c and previous antidiabetic therapy use. After 2 years of treatment, linagliptin was noninferior to glimepiride in reducing HbA1c. Adjusted mean changes were -0.16% with linagliptin and -0.36% with glimepiride. The difference between the treatment groups met the noninferiority criteria and was 0.20% ($P < 0.125$). As add-on to metformin, both linagliptin and glimepiride caused significant reductions in fasting plasma glucose and postprandial plasma glucose. The treatment differences for reductions in fasting and postprandial plasma glucose, respectively, were 6.31 mg/dL ($P = 0.012$) and 9.73 mg/dL ($P = 0.0918$, see Table 2).

The 12-week, multicenter, randomized, double-blind, placebo-controlled, five parallel-group study conducted by Forst et al included patients with type 2 diabetes aged 21–75 (mean 60) years with a body mass index of 25–40 kg/m².¹⁴ Patients were eligible if they were pretreated with metformin alone (baseline HbA1c levels had to be 7.5%–10%) or treated with metformin and one other oral antidiabetic therapy other than a thiazolidinedione (baseline HbA1c levels had to be 7.0%–9.0%). Eligible patients who had already received metformin monotherapy entered a 2-week open-label run-in phase. Patients who received metformin plus one other antidiabetic therapy entered a 6-week washout period, with the last 2 weeks being an open-label run-in phase. Three doses of linagliptin (1, 5, and 10 mg once daily) were explored when added to metformin. There was also an open-label treatment arm where patients were randomized to receive glimepiride (1, 2, or 3 mg once daily) as add-on therapy to metformin. The mean placebo-corrected lowering of HbA1c levels was 0.39% for linagliptin 1 mg ($P = 0.005$), 0.75% for 5 mg ($P < 0.001$), and 0.73% for 10 mg ($P < 0.001$). The change in mean placebo-corrected HbA1c from baseline was -0.90% for glimepiride. The reduction in HbA1c with open-label glimepiride was numerically greater versus linagliptin, but not statistically significant. Fasting plasma glucose reductions were also found to be significantly greater with all doses of linagliptin than with placebo at week 12. Postprandial plasma glucose changes were not addressed in this study (see Table 2).

Linagliptin versus placebo as add-on to pioglitazone therapy

This randomized, double-blind, placebo-controlled, multicenter, parallel-group study was conducted by Gomis et al in 389 patients with type 2 diabetes and aged 18–80 (mean 57.5) years.¹⁸ At baseline, the patients had HbA1c

Table 2 Efficacy and safety of linagliptin in combination with other ADTs for the treatment of type 2 diabetes

Authors and study design	Dose, patients (n)	Study parameters
Taskinen et al ¹³ R, DB, PC, PG Patients with uncontrolled type 2 diabetes receiving maximum tolerated dose metformin and not more than one other ADT	Linagliptin 5 mg (n = 524) + metformin Placebo (n = 177) + metformin Total: 24 weeks	Primary: A1c Secondary: Body weight FPG PPG A1c < 7.0% and <6.5% A1c lowered by >0.5%
Forst et al ¹⁴ R, DB, PC, PG Patients with type 2 diabetes not controlled on metformin alone or with metformin and one other ADT (except TZD)	Linagliptin 1 mg (n = 65) + metformin Linagliptin 5 mg (n = 66) + metformin Linagliptin 10 mg (n = 66) + metformin Glimepiride (n = 65) + metformin Placebo (n = 71) + metformin Total: 12 weeks	Primary: A1c Secondary: FPG A1c < 7.0% A1c lowered by >0.5% Body weight
Haak et al ¹⁵ R, PC, DB, PG Patients with type 2 diabetes not controlled who were either treatment-naïve or had been treated with one other ADT	Linagliptin 2.5 mg BID + metformin 500 mg BID (n = 143) Linagliptin 2.5 mg BID + metformin 1000 mg BID (n = 143) Linagliptin 5 mg daily (n = 142) Metformin 500 mg BID (n = 144) Metformin 1000 mg BID (n = 147) Placebo (n = 72) Total: 24 weeks	Primary: A1c Secondary: FPG Body weight
Owens et al ¹⁶ R, PC, DB, PG Patients with type 2 diabetes not controlled with metformin plus a sulfonylurea	Linagliptin 5 mg daily + metformin + sulfonylurea (n = 792) Placebo + metformin + sulfonylurea (n = 263) Total: 24 weeks	Primary: A1c Secondary: FPG A1c < 7.0% A1c lowered by >0.5% Body weight

Efficacy results

At week 24:

	A1c change (%)	FPG change (mg/dL)	PPG change (mg/dL)
Linagliptin 5 mg	-0.64 ^{a,b}	-21.62 ^{a,b}	-66.7 ^{a,b}

Notes: ^a*P* < 0.0001; ^bplacebo-corrected.

Among patients with a baseline A1c $\geq$ 7%, 26% of individuals treated with linagliptin versus 9% of those in the placebo group achieved A1c < 7% at 24 weeks (*P* = 0.0001). Similarly, in those patients with a baseline HbA1c $\geq$ 6.5%, 10% with linagliptin versus 2% with placebo achieved A1c < 6.5% at 24 weeks (*P* = 0.0016).

The percentage of patients achieving an A1c reduction $\geq$ 0.5% at 24 weeks was 50% with linagliptin and 22% with placebo (*P* < 0.0001).

At week 12:

	A1c change (%)	FPG change (mg/dL)	Body weight change (kg)
1 mg	-0.39 ^{a,e}	-19.8 ^{d,e}	-0.15
5 mg	-0.75 ^{b,e}	-34.2 ^{c,e}	-0.57
10 mg	-0.73 ^{b,e}	-30.6 ^{c,e}	-1.27
Glimepiride	-0.90 ^{c,e}	NR	+0.73

Notes: ^a*P* = 0.005; ^b*P* < 0.001; ^c*P* < 0.0001; ^d*P* = 0.002; ^eplacebo-corrected.

A greater proportion of patients who received linagliptin (43.8%–53.2%) showed reductions in A1c $\geq$ 0.5% versus placebo at 12.9%. Only 1.4% of patients in the placebo group achieved A1c $\leq$ 7% versus 15%–21% of the patients who received linagliptin therapy.

At week 24:

	A1c change (%)	FPG change (mg/dL)	Body weight change (kg)
LIN 2.5 mg + MET 1000 mg	-1.7 ^{a,b}	-59.46 ^{a,b}	-0.8
LIN 2.5 mg + MET 500 mg	-1.3 ^{a,b}	-43.24 ^{a,b}	-0.1
MET 1000 mg	-1.2 ^{a,b}	-41.44 ^{a,b}	-0.5
MET 500 mg	-0.8 ^{a,b}	-25.23 ^{a,b}	-0.7
Linagliptin 5 mg	-0.6 ^{a,b}	-18.02 ^{a,b}	+0.2
Placebo	N/A	N/A	-0.7

Notes: ^aPlacebo-corrected; ^b*P* < 0.0001.

At week 24:

	A1c change (%)	FPG change (mg/dL)
Linagliptin	-0.62 ^{a,b}	-12.61 ^{a,b}

Notes: ^aPlacebo-corrected; ^b*P* < 0.0001.

Among patients with a baseline A1c $\geq$ 7%, 29.2% of individuals treated with linagliptin versus 8.1% of those in the placebo group achieved A1c < 7% at 24 weeks (*P* < 0.0001). The percentage of patients achieving an A1c reduction $\geq$ 0.5% at 24 weeks was 58.2% with linagliptin and 30.2% with placebo.

Tolerability results

Most common:

Hyperglycemia (5.2% linagliptin versus 14.7% placebo)
Nasopharyngitis (5.2% linagliptin versus 5.1% placebo)
Minor hypoglycemia (0.6% linagliptin versus 2.3% placebo)
No major hypoglycemia events

Body weight did not differ significantly from baseline in either group (-0.5 kg placebo; -0.4 kg linagliptin)

Most common:

Nasopharyngitis (reported in 10%, 6%, 8%, 8%, 6% for placebo, 1 mg, 5 mg, 10 mg and glimepiride, respectively)
Diarrhea (reported in 4%, 2%, 3%, 3%, 5% for placebo, 1 mg, 5 mg, 10 mg, and glimepiride respectively)
Nausea (reported in 4%, 0%, 6%, 5%, 0% for placebo, 1 mg, 5 mg, 10 mg, and glimepiride respectively)
Hypoglycemia was not reported with linagliptin or placebo
Hypoglycemia was reported in 4.6% of patients taking glimepiride

Most common:

Diarrhea (7.7% in LIN 2.5 mg + metformin 1000 mg BID)
Nasopharyngitis (8.4% in LIN 2.5 mg + MET 500 mg BID)
Hypoglycemia:
LIN + HD MET – 0%
LIN + MD MET – 3.5%
MET 1000 mg BID – 3.4%
MET 500 mg BID – 1.4%
LIN 5 mg daily – 0%
Placebo – 0%

No pancreatitis reported

No clinically meaningful change in body weight was noted in any of the treatment groups

Most common:

Hypoglycemia (22.7% linagliptin versus 14.8% placebo)
Severe hypoglycemia occurred in 2.7% linagliptin versus 4.8% placebo

Neither group showed significant changes in weight from baseline

(Continued)

Table 2 (Continued)

Authors and study design	Dose, patients (n)	Study parameters
Gallwitz et al ¹⁷ R, DB, PG, AC, NI Patients with type 2 diabetes not controlled on metformin alone or with metformin and one other ADT	Linagliptin 5 mg daily + metformin (n = 764) Glimepiride 1–4 mg once daily (initially 1 mg) + metformin (n = 755) Total: 104 weeks	Primary: A1c Secondary: Hypoglycemic episodes Body weight FPG PPG A1c < 7.0% and <6.5% A1c lowered by >0.5%
Gomis et al ¹⁸ R, PC, DB, PG Drug-naïve or previously treated patients with uncontrolled type 2 diabetes	Linagliptin 5 mg daily + pioglitazone 30 mg daily (n = 259) Placebo + pioglitazone 30 mg daily (n = 130) Total: 24 weeks	Primary: A1c Secondary: FPG A1c < 7.0% A1c lowered by >0.5%
Gomis et al ¹⁹ R, PC, DB, open-label extension Trial participants who had completed one of the four 24-week parent trials ^{12,13,16,18}	Linagliptin monotherapy Linagliptin + metformin Linagliptin + metformin + sulfonylurea Linagliptin + pioglitazone Group A (n = 1349) received linagliptin as monotherapy or combination during previous trials and remained on the same treatment in extension phase Group B (n = 531) received placebo during the previous studies and were switched to linagliptin monotherapy in the extension phase Total: 102 weeks (24 weeks with a 78-week, open-label extension)	Primary: Long-term safety and tolerability of linagliptin given alone or in combination with other ADT Secondary: A1c FPG A1c < 7.0% A1c lowered by >0.5% Body weight

Abbreviations: AC, active controlled; A1c, glycosylated hemoglobin; ADT, antidiabetic therapy; BID, twice daily; BW, body weight; CV, cardiovascular; DB, double-blind; FPG, fasting plasma glucose; GLIM, glimepiride; HD MET, high dose metformin; LIN, linagliptin; MD MET, moderate dose metformin; MET, metformin; MC, multicenter; NI, noninferiority; NR, not reported; PG, parallel-group; PIO, pioglitazone; PC, placebo-controlled; PPG, postprandial plasma glucose; R, randomized; RR, relative risk; SU, sulfonylurea; TZD, thiazolidinediones.

concentrations of 7.5%–11.0% (mean 8.6%) and a body mass index ≤ 40 kg/m². Patients pretreated with oral antidiabetic therapies underwent a 6-week washout period that included an open-label placebo run-in phase in the last 2 weeks. For treatment-naïve patients, only the 2-week

run-in phase was required. Eligible subjects were then randomized to receive pioglitazone 30 mg once daily and linagliptin 5 mg once daily or pioglitazone 30 mg once daily and placebo for 24 weeks. The primary endpoint was change from baseline HbA1c, adjusted for baseline HbA1c and

Efficacy results

At week 104:

	A1c change (%)	FPG change (mg/dL)	PPG change (mg/dL)
Linagliptin	-0.16 ^a	-2.34 ^b	-28.47 ^c
Glimepiride	-0.36 ^a	-8.65 ^b	-18.74 ^c

Notes: ^aTreatment difference was 0.20%; $P = 0.0004$, < 0.0125 (one-sided); ^btreatment difference was 6.31 mg/dL; $P = 0.0012$, < 0.05 (two-sided); ^ctreatment difference was 9.73 mg/dL; $P = 0.0918$.

The treatment difference in the adjusted mean change in A1c from baseline was 0.20% and met the prespecified noninferiority criterion of $< 0.35\%$ with a one-sided $\alpha = 0.0125$.

A total of 30% of patients achieved an A1c target of $< 7\%$ with linagliptin versus 35% with glimepiride, while 12% achieved an A1c of $< 6.5\%$ with linagliptin versus 16% with glimepiride ($P < 0.0001$). The percentage of patients achieving $\geq 0.5\%$ reduction in A1c was 26% with linagliptin and 34% with glimepiride.

At week 24:

	A1c change (%)	FPG change (mg/dL)	Body weight change (kg)
Linagliptin	-1.06 ^a	-32.43 ^b	2.3 ^c
Placebo	-0.56 ^a	-18.02 ^b	1.2 ^c

Notes: ^aTreatment difference was 0.51%; $P < 0.0001$; ^btreatment difference was -14.41 mg/dL; $P < 0.0001$; ^ctreatment difference was 1.1 kg; $P = 0.014$.

A total of 42.9% of patients achieved an A1c target of $< 7\%$ with linagliptin versus 30.5% with placebo ($P = 0.0051$). The percentage of patients achieving $\geq 0.5\%$ reduction in A1c was 75% with linagliptin and 50.8% with placebo.

At week 102:

	A1c change (%)
Group A	-0.8 ^a
Group B	-0.9
LIN monotherapy	-0.5
LIN + MET	-0.7
MET + LIN + SU	-0.7
LIN + PIO	-1.5

Note: ^aCoefficient of durability per 78 weeks, 0.14% ($P < 0.0001$, noninferiority 0.3%).

A total of 42% of subjects in group A and 46.1% of those in group B reached the A1c target of $< 7.0\%$ at week 78 of the extension phase. The percentage of subjects with A1c lowering by $\geq 0.5\%$ at week 78 was twice that in group B compared with group A (46.9% versus 17.1%, respectively).

Tolerability results

Most common:

Hypoglycemia (7% linagliptin vs 36% glimepiride; $P < 0.0001$)
Nasopharyngitis (16% in both linagliptin and glimepiride)
Back pain (9% linagliptin versus 8% glimepiride)
Severe hypoglycemia: one versus 12 patients with linagliptin and glimepiride, respectively
BW: -1.4 kg linagliptin versus +1.3 kg glimepiride with treatment difference of -2.7 kg ($P < 0.0001$)
CV events: 12 (2%) patients with linagliptin versus 26 (3%) patients with glimepiride ($RR = 0.46$, $P = 0.0213$)
One patient experienced pancreatitis with linagliptin

Most common:

Weight gain: 2.3% with linagliptin + pioglitazone versus 0.8% with pioglitazone + placebo
Hypoglycemia: 1.2% with linagliptin + pioglitazone vs 0% with pioglitazone + placebo
BW: mean weight increased in both groups; LIN + PIO was lower than placebo + PIO at baseline (78.3 kg and 82.7 kg, respectively) and at week 24 (80.8 kg and 84 kg, respectively)

Most common:

Hyperglycemia (24.4% group A versus 20.5% group B)
Hypoglycemia (LIN + MET + SU 11%, LIN + MET 2.1%, LIN monotherapy 0.5%, LIN + PIO 0.2%)
Severe hypoglycemia: 0.6% overall
No clinically relevant change in body weight observed
Pancreatitis: 4 patients in group A (0.2% of the overall treatment set experienced pancreatitis) (2 acute cases and 4 chronic cases)

baseline antidiabetic therapy, after 24 weeks of treatment. At the end of the study, the adjusted mean change in HbA1c from baseline for linagliptin plus pioglitazone was -1.06% compared with -0.56% for placebo plus pioglitazone. The placebo-corrected difference in HbA1c was 0.51%. Changes

in fasting plasma glucose were assessed as a secondary endpoint, showing a significantly greater reduction for linagliptin plus pioglitazone than for placebo plus pioglitazone. Changes in postprandial plasma glucose were not addressed in this study (see Table 2).

Open-label extension: linagliptin monotherapy or in combination with other oral antidiabetic therapies

A 78-week open-label extension conducted by Gomis et al evaluated participants who had previously completed one of the four 24-week, randomized, double-blind, placebo-controlled parent trials.¹⁹ These subjects received either linagliptin monotherapy, linagliptin plus metformin, linagliptin plus metformin and sulfonylurea, or linagliptin plus pioglitazone. All patients receiving one of these treatments during a previous trial continued the same treatment for an additional 78 weeks ($n = 1532$). Those patients previously treated with placebo were switched to linagliptin monotherapy ($n = 589$). Overall, the cohort of patients had a mean age of 57.7 years and mean baseline HbA1c of 7.5%. This extension study was conducted primarily to assess the long-term safety and tolerability of linagliptin. Secondary efficacy outcomes evaluated the changes in HbA1c and fasting plasma glucose from baseline to 102 weeks. In participants randomized to treatment with linagliptin in the four previous trials, the mean change from baseline HbA1c during the initial 24 weeks of treatment was -0.8% . This was maintained over the 78 weeks of the extension study, with a change from baseline HbA1c of -0.8% . The largest observed reduction in HbA1c from baseline to week 102 was in the group receiving linagliptin plus pioglitazone at -1.5% . This was followed by those patients receiving metformin and metformin plus a sulfonylurea in combination with linagliptin (-0.7%). Lastly, patients receiving linagliptin monotherapy showed a reduction of 0.5% at week 102. Similarly, fasting plasma glucose values already reduced during the previous trials further decreased during the extension period. In subjects randomized to placebo in the previous trials and switched to linagliptin monotherapy in the extension phase, the change in mean HbA1c was -0.90% . Fasting plasma glucose values also decreased from baseline over the study period (see Table 2).

Safety and tolerability

Most adverse events with linagliptin were considered to be mild to moderate in nature. Adverse reactions that occurred in $\geq 2\%$ of patients treated with linagliptin included nasopharyngitis, diarrhea, cough, urinary tract infection, and hypertriglyceridemia (in combination with sulfonylurea therapy), hyperlipidemia, and weight increase (in combination with pioglitazone).¹ Weight changes were reported or addressed in each of the studies above. No significant changes with regard to body weight were found when linagliptin was given as monotherapy. With regard to sulfonylurea therapy, two of the studies revealed an increase in body weight in patients

treated with glimepiride versus those receiving linagliptin.^{14,17} However, in a study in which all patients received metformin and sulfonylurea therapy and were then randomized to placebo or linagliptin, no significant changes in body weight were seen.¹⁶ When patients received pioglitazone and either placebo or linagliptin, both groups showed an increase in body weight from baseline. The amount of weight gain was larger in patients receiving linagliptin, but the mean weight for patients receiving linagliptin was lower than that in patients receiving placebo at baseline.¹⁸ In general, linagliptin showed a low propensity to cause hypoglycemia. When used as monotherapy, no patients experienced hypoglycemia in the two studies reviewed.^{11,15} One study reviewing linagliptin as monotherapy versus placebo reported hypoglycemia occurring in one patient in each group.¹² When combined with metformin and sulfonylurea, a higher percentage of patients receiving linagliptin experienced hypoglycemia versus placebo. However, a smaller percentage of patients experienced severe hypoglycemia when compared with placebo.¹⁶ Three studies discussed or reported the occurrence of pancreatitis. One study reported zero cases¹⁵ while another study reported one case of pancreatitis in a patient receiving linagliptin.¹⁷ A 78-week, open-label extension study, which included 2121 subjects, reported four cases of pancreatitis in patients who had received linagliptin for a total of 102 weeks, with two cases being acute and two chronic. This was an incidence of 0.2% in the overall treated set.¹⁹ According to the prescribing information, pancreatitis was reported more often in patients treated with linagliptin (21.9 per 10,000 patient years) versus placebo (eight per 10,000 patient years).¹ One study prospectively assessed cardiovascular safety for linagliptin versus sulfonylurea (e.g. glimepiride). Major cardiovascular events occurred in 2% of patients treated with linagliptin and 3% treated with glimepiride ($P = 0.0213$). This finding was mainly attributable to a significantly lower number of nonfatal strokes with linagliptin compared with glimepiride, without any relation to hypoglycemia.¹⁷

Discussion

Data from the clinical trials suggest that linagliptin administered as monotherapy or in combination with other antidiabetic therapies improves HbA1c and reduces fasting plasma glucose.^{11–19} When used as monotherapy, linagliptin resulted in a placebo-corrected change in HbA1c ranging from -0.28% to 0.69% .^{11,12} When linagliptin was added to metformin or metformin and a sulfonylurea, similar HbA1c reductions ranging from 0.39% to 0.75% were observed.^{13,14,16} When comparing linagliptin with glimepiride as add-on therapy

to metformin, a numerically greater response was seen with glimepiride, but this was not statistically significant. However, when linagliptin was used in combination with pioglitazone, larger reductions in placebo-corrected HbA1c of 1.06% were seen.¹⁸ Those studies that evaluated the impact of linagliptin therapy on postprandial plasma glucose also reported an improvement.^{11–13} When used as monotherapy, linagliptin decreased postprandial plasma glucose in the range of 27.2–57.7 mg/dL, and when used in combination with metformin, postprandial plasma glucose decreased by 66.7 mg/dL.^{11–13} With this, the data suggest linagliptin used as monotherapy or in combination with other antidiabetic therapies offers improvement in glycemic control. Specific populations that may particularly benefit from linagliptin therapy should also be considered. In patients experiencing renal impairment precluding the use of metformin, linagliptin may have a niche in managing glycemia because it does not require dose adjustment in renal compromise. Several of the studies discussed in this review stratified the change in HbA1c according to the baseline value. Reduction in HbA1c was greater in patients with a baseline HbA1c > 9%, offering another possible niche for linagliptin therapy.

DPP-4 inhibitors as a class are generally well tolerated. A minimal risk of hypoglycemia when used as monotherapy and lack of weight gain are some of the desirable characteristics of this class of medications. Overall, linagliptin has been shown to be well tolerated, with adverse events similar to others within its class. It is important to note that although linagliptin offers a low risk of hypoglycemia, this risk increases when this agent is combined with secretagogue therapy. Linagliptin used in combination with thiazolidinediones also offers augmentation of weight gain. Pancreatitis is also of concern and is a class effect of DPP-4 inhibitors, although the risk of the condition seems very low with this medication. A long-term safety and efficacy study evaluated linagliptin therapy in over 2000 patients for a total of 102 weeks and found an overall incidence of 0.2%.¹⁹ However, recent discussions have noted that the prevalence of pancreatitis among patients with type 2 diabetes is similar to that seen with incretin hormones. A study published in 2009 by Noel et al found that patients with type 2 diabetes had an almost three-fold greater risk of pancreatitis than those patients without diabetes.²⁰ This information suggests that there may not be an increased risk of pancreatitis with incretin therapy.

Linagliptin has several differences compared with the other currently available DPP-4 inhibitors. It has a long half-life and undergoes less renal excretion, avoiding the need for dose adjustments in patients with renal impairment.^{6,9}

However, to date, there are no head-to-head studies comparing the efficacy of this agent with other DPP-4 inhibitors in its class.

Conclusion

Linagliptin is a newly approved DPP-4 inhibitor for use as a once-daily oral medication in the treatment of type 2 diabetes. The use of linagliptin as monotherapy or in combination with metformin or pioglitazone led to reductions in HbA1c and fasting plasma glucose after 12–24 weeks of therapy. This improvement in glycemic control was shown to be maintained for up to 102 weeks. Linagliptin appears to be well tolerated in most patients. It is generally considered to be weight neutral, unless used in combination with a thiazolidinedione, and has a low risk of hypoglycemia.

Disclosure

The authors have no conflict of interest to disclose with regard to the content of this article.

References

1. Tradjenta [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2011.
2. Vilsboll T, Krarup T, Deacon CF, et al. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes*. 2001;50:609–613.
3. Baggio L, Druker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132:2131–2157.
4. Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. *Int J Clin Pract*. 2006;60:1454–1470.
5. Thomas L, Eckhardt M, Langkopf E, Tadayyon M, Himmelsbach F, Mark M. (R)-8-(3-amino-piperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydro-purine-2,6-dione (BI 1356), a novel xanthine-based dipeptidyl peptidase 4 inhibitor, has a superior potency and longer duration of action compared with other dipeptidyl peptidase-4 inhibitors. *J Pharmacol Exp Ther*. 2008;325:175–182.
6. Hüttner S, Graefe-Mody EU, Withopf B, Ring A, Dugi KA. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of BI 1356, an inhibitor of dipeptidyl peptidase 4, in healthy male volunteers. *J Clin Pharmacol*. 2008;48:1171–1178.
7. Heise T, Graefe-Mody EU, Hüttner S, Ring A, Trommeshauser D, Dugi KA. Pharmacokinetics, pharmacodynamics and tolerability of multiple oral doses of linagliptin, a dipeptidyl peptidase-4 inhibitor in male type 2 diabetes patients. *Diabetes Obes Metab*. 2009;11:786–794.
8. Retlich S, Withopf B, Greischel A, Staab A, Jaehde U, Fuchs H. Binding to dipeptidyl peptidase-4 determines the disposition of linagliptin (BI 1356) – investigations in DPP-4 deficient and wildtype rats. *Biopharm Drug Dispos*. 2009;30:422–436.
9. Blech S, Ludwig-Schwellinger E, Graefe-Mody EU, Withopf B, Wagner K. The metabolism and disposition of the oral dipeptidyl peptidase-4 inhibitor, linagliptin, in humans. *Drug Metab Dispos*. 2010;38:667–678.
10. Izucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35:1364–1379.

11. Forst T, Uhlig-Laske B, Ring A, Ritzhaupt A, Graefe-Mody U, Dugi KA. The oral DPP-4 inhibitor linagliptin significantly lowers HbA1c after 4 weeks of treatment in patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2011;13:542–550.
12. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycemic control and markers of β -cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab.* 2011;13: 258–267.
13. Taskinen MR, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2010;13:65–74.
14. Forst T, Uhlig-Laske B, Ring A, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled type 2 diabetes. *Diabet Med.* 2010;27:1409–1419.
15. Haak T, Meinicke T, Jones R, Weber S, Von Eynatten M, Woerle HJ. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2012;14:565–574.
16. Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with Type 2 diabetes inadequately controlled by a combination of metformin and sulfonylurea: a 24-week randomized study. *Diabet Med.* 2011;28:1352–1361.
17. Gallwitz B, Rosenstock J, Rauch T, et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomized, double-blind, non-inferiority trial. *Lancet.* 2012;380:475–483.
18. Gomis R, Espadero RM, Jones R, Woerle HJ, Dugi KA. Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2011;13: 653–661.
19. Gomis R, Owens DR, Taskinen MR, et al. Long-term safety and efficacy of linagliptin as monotherapy or in combination with other oral glucose-lowering agents in 2121 subjects with type 2 diabetes: up to 2 years exposure in 24-week phase III trials followed by a 78-week open-label extension. *Int J Clin Pract.* 2012;66:731–740.
20. Noel RA, Patterson RE, Braun DK, Bloomgren GL. Increased risk of pancreatitis and biliary disease observed in patients with type 2 diabetes. *Diabetes Care.* 2009;32:843–838.

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