Clinical Medicine Insights: Endocrinology and Diabetes

REVIEW

Linagliptin—A Novel Dipeptidyl Peptidase Inhibitor for Type 2 Diabetes Therapy

Baptist Gallwitz

Department of Medicine IV, Eberhard-Karls-University, Otfried-Müller Strasse 10, 72976 Tübingen, Germany.
Corresponding author email: baptist.gallwitz@med.uni-tuebingen.de

Abstract: Incretin based therapies have been introduced into the treatment options of type 2 diabetes a few years ago. Among them, the orally active DPP-4 inhibitors have established themselves as insulinotropic agents. Their advantage is the glucose-dependent insulinotropic action without an intrinsic risk for causing hypoglycemia. Additionally DPP-4 inhibitors have a glucose dependent glucagonostatic action contributing to improved glucose control. They are weight neutral and show a good safety and tolerability profile with comparable efficacy to sulfonylureas. Linagliptin is a novel DPP-4 inhibitor with a distinct pharmacological profile. In contrast to the other approved DPP-4 inhibitors it is eliminated by a hepatic/biliary route rather than a renal route. Therefore no dose adjustment is recommended in patients with type 2 diabetes and renal impairment. In clinical studies, it has been shown to be non-inferior to sulfonylurea treatment regarding glycemic parameters, but to possess favourable safety advantages regarding hypoglycemia frequency, body weight development and effects on cardioavascular parameters. This article gives an overview on the pharmacology of linagliptin as well as on the clinical data available.

Keywords: linagliptin, oral antidiabetics, DPP-4 inhibitors, incretin based therapies, type 2 diabetes

Clinical Medicine Insights: Endocrinology and Diabetes 2012:5 1–11

doi: 10.4137/CMED.S7274

This article is available from http://www.la-press.com.

Introduction

Type 2 diabetes is increasing world-wide and it is expected that by the year 2030 at least 400 million people will suffer from this chronic and progressive disease that is characterized by severe and often fatal micro- and macrovascular complications.[1] Efficacious and safe therapies are needed to improve the burden of type 2 diabetes. In this respect, agents that are easy to use and do not require regular glucose monitoring or dose adjustments seem advantageous. Dipeptidyl-peptidase-IV (DPP-4) inhibitors are a drug class that was introduced in 2006 and that seems to fulfill these requirements. Furthermore, DPP-4 inhibitors have a good safety profile and are well tolerated. Fixed dose combinations of DPP-4 inhibitors with metformin are feasible and in practice patient adherence has been good to the fixed dose combinations. Therefore, this drug class has been perceived as an important addition to the oral antidiabetic treatment options.

DPP-4 inhibitors are an oral drug class with a mode of action based on incretin physiology. The gastrointestinal hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are secreted from the intestinal L- and K-cells after a meal, respectively. They enhance insulin secretion under hyperglycemic conditions and are responsible for around 70% of the postprandial insulin secretion. GLP-1 and GIP mediate the so called incretin effect that describes the phenomenon that orally ingested glucose leads to a higher insulin response than an isoglycemic intravenous glucose administration.[2] In type 2 diabetes, the incretin effect is diminished,[3] but supraphysiological concentrations of GLP-1still exert insulinotropic and glucagonostatic actions in a glucose dependent manner, while GIP has lost its insulinotropic action.[2,4] DPP-4 is they key enzyme involved in the initial cleavage of GLP-1 (and GIP).[5,6] In vivo, the biological half-life of GLP-1 is only 1–2 minutes due to DPP-4 action.[6] The prevention of GLP-1 degradation by DPP-4 inhibition leads to an elevation of endogenous GLP-1 plasma concentrations that contribute significantly to the stimulation of insulin secretion and inhibition of glucagon secretion in a glucose dependent manner.[2,6] A first proof of principle of the effectiveness of DPP-4 inhibition in type 2 diabetic patients was demonstrated in 2002.[7] Besides the described insulinotropic and glucagonostatic actions, animal studies in rodents with a high beta cell replication rate and—turn over have shown favourable effects of DPP-4 inhibitor administration on beta cell function and an increase in beta cell mass of these animals.[2]

Sitagliptin was the first DPP-4 inhibitor that was approved for type 2 diabetes therapy in 2006, vildagliptin and saxagliptin followed later.[8] According to many guidelines, DPP-4 inhibitors have now established themselves as insulinotropic agents without hypoglycemia risk predominantly as add on therapy after metformin failure.[9,10] Most DPP-4 inhibitors are given with a standard dose once daily, fixed dose combinations with metformin are available.[8–10] Recently, linagliptin was approved by the FDA (Food and Drugs Administration) and the EMA (European Medicines Agency). This article is focused on the pharmacology and the clinical development of linagliptin.

Development and Basic Characteristics of Linagliptin

The substance, a xanthine-based DPP-4 inhibitor was developed by Boehringer Ingelheim Pharmaceuticals (Ingelheim, Germany) and was first named BI1356. Linagliptin has a molecular mass of 472.5 Da. The structural formula of the molecule is shown in Figure 1. It inhibits the enzymatic activity of DPP-4 in a competitive and reversible manner with a slow rate of dissociation from the active center of the DPP-4 molecule.[11] The maximal efficacy for DPP-4 inhibition in vitro is similar to that of other DPP-4 inhibitors available. Linagliptin has the highest potency for inhibiting DPP-4 of all the approved DPP-4 inhibitors with an IC_{50} of approximately 1 nM (compared to 19 nM for sitagliptin, 62 nM for vildagliptin, 50 nM for saxagliptin). The selectivity of linagliptin for DPP-4 is 40,000-fold higher than

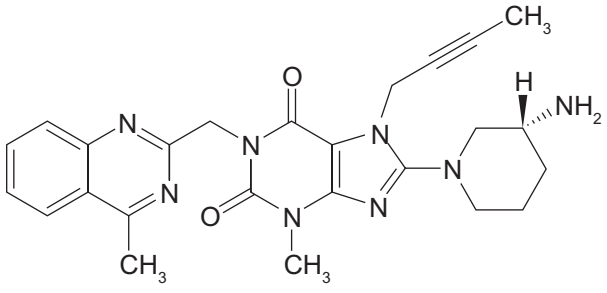

Figure 1. Chemical structure of linagliptin.

towards DPP-8 and >10,000-fold higher than towards DPP-9. Linagliptin shows only little interaction with other protease enzymes such as aminopeptidase N or –P, plasmin, prolyl-oligopeptidase, thrombin and trypsin.[11] Furthermore, linagliptin has no significant inhibitory effect on the CYP 450 enzymes (IC_{50} > 50 μM).[12,13]

Pharmacokinetics and Pharmacodynamics of Linagliptin

The oral bioavailability of linagliptin in animal studies amounted to 51% in rats and monkeys, the biological half-life is approximately 36 hours.[12,14] In vivo, linagliptin is hardly metabolized and approximately 90% of the compound are excreted in unchanged form by a hepatobiliary route via the feces.[15,16] Linagliptin avidly binds to plasma proteins in vivo so that most of the drug is protein bound at therapeutic concentrations in humans.[16] It also shows high-affinity binding to the target DPP-4 in different tissues, predominantly in the kidney resulting in a long biological half-life there. However, tissue accumulation of linagliptin does not occur after repetitive oral administration because the tissue binding capacity is limited at low doses already.[15] In humans, the bioavailability of linagliptin is about 30%, which is lower than that of vildagliptin (85%) or sitagliptin (approximately 87%).[17–19] After oral intake, linagliptin is rapidly absorbed and the T_{max} was determined at a time interval of 0.7–3 hours after administration. The T_{max} did not differ between healthy and type 2 diabetic subjects after single and multiple doses of linagliptin. The elimination is rather slow with a half-life of 70–80 hours for doses <50 mg.[20] Approximately 1%–6% of the compound are eliminated via a renal route and excreted with the urine when standard doses of 5 mg are given.[20,21] Steady-state concentrations of linagliptin are reached within 2–5 days after once daily administration. Only modest drug accumulation and an elimination half-life between 113 and 130 hours was observed. These pharmacokinetic data are valid for all different ethnic groups studied.[17,22]

The plasma DPP-4 activity was already inhibited effectively by 73% in healthy volunteers after doses of 2.5 mg linagliptin. The maximal DPP-4 inhibition was reached between 3 hours (with doses of 2.5 mg) and 0.7 hours (after doses of ≥200 mg) after administration and was sustained for up to 96 hours. At linagliptin plasma concentrations of 10 nM, DPP-4 in plasma was fully inhibited. The 50% and 80% inhibitory doses for linagliptin were calculated to be in the ranges of 2–4 and 4–6 nM, respectively.[17,20,22] Linagliptin given once daily to patients with type 2 diabetes led to a maximal DPP-4 inhibition of >90% with doses of 5 mg and 10 mg at steady state with approximately 85% inhibition still remaining after 24 hours post dose. Plasma concentrations of intact GLP-1 concomitantly increased about 3-fold and glucose concentrations consecutively improved.[21]

Potential Drug-Drug Interactions

Linagliptin is not likely to interfere with drugs metabolized by the CYP 450 enzymatic system because it neither inhibits CYP 450 nor is it metabolized through this system.[12,16] Since DPP-4 inhibitors are predominantly used in combination therapy with metformin, the potential interactions of linagliptin and metformin were investigated. In a study in healthy individuals, no significant effect of linagliptin on the exposure to metformin was observed. Likewise, metformin did not interact with linagliptin and did not change the extent of DPP-4 inhibition.[23] Due to this lack of drug-drug interaction both, metformin and linagliptin can be given in combination without dose adjustments.[23] In a similar way, the possible interactions of pioglitazone and linagliptin were investigated in healthy subjects. Again, no relevant drug-drug interactions between linagliptin and pioglitazone were detected, so that this combination can also be used without dose adjustments for either compound.[24] Another study investigated the possibility of pharmacological interactions of linagliptin and digoxin in healthy volunteers. In this study, no clinically significant changes in the steady-state pharmacokin etic parameters of digoxin were observed when it was co-administered with linagliptin and pharmacokinetic properties of digoxin were not altered, indicating that linagliptin does not inhibit P-glycoprotein or other transporters relevant for digoxin pharmacokinetics and dose adjustments will not be necessary in a therapy with both drugs.[25]

Phase III Clinical Study Programme

The clinical study programme used for application for approval with the FDA and EMA is shown in Table 1.

Table 1. Clinical studies with linagliptin (registered on clinicaltrials.gov [search date Oct. 2011]).

Clinicaltrials.gov identifier/reference	Study title	Status of study	Linagliptin dose(s)	Comparator/ combination substance(s)
NCT01189201	Relative bioavailability of BI10773/linagliptin FDC Tbl, comparison with mono-components, with a second FDC tablet and influence of food	Completed	5 mg qd	FDC with BI10773 (SGLT2 inhibitor)
NCT01383356	Comparison of the bioavailability of metformin between medium dose linagliptin/metformin tablets and medium dose glucophage tablet given with linagliptin tablet	Recruiting	2.5 mg qd	FDC with 500 mg metformin
NCT01276327	Bioequivalence of a fixed dose combination tablet linagliptin/pioglitazone compared with its mono-components	Completed	5 mg qd	FDC with 30 mg pioglitazone
NCT00935220	Pharmacokinetics and pharmacodynamics trial with linagliptin (BI1356) 5 mg in African American type 2 diabetic patients	Completed	5 mg qd	None
NCT01216397	Relative bioavailability of two different batches of a linagliptin/metformin combination tablet in healthy volunteers	Completed	2.5 mg	Metformin 1000 mg
NCT01012037	Linagliptin 2.5 mg twice daily versus 5 mg once daily as add-on therapy to twice daily metformin in type 2 diabetes	completed	2.5 mg bid vs. 5 mg od	Baseline: metformin
NCT00309608	Efficacy and safety of BI1356 bs (linagliptin) in combination with metformin in patients with type 2 diabetes	Completed	1 mg, 5 mg or 10 mg qd	Baseline: metformin, comparator glimepiride
NCT01342484	Finding a safe and effective dose of linagliptin in peadiatric patients with type 2 diabetes	Recruiting	1 or 5 mg qd	None
NCT00716092	The effect of linagliptin (BI1356) on 24h-glucose control and various biomarkers in type 2 diabetic patients	Completed	5 mg qd	Comparator: sitagliptin 100 mg qd, placebo
NCT00328172[21]	Efficacy and safety of 3 doses of BI1356 (linagliptin) in type 2 diabetes patients	Completed	0.5 mg, 2.5 mg and 5.0 mg qd	Comparator: metformin/placebo
NCT00915772[29]	Treatment of type 2 diabetes with linagliptin 2.5 mg bid + metformin 500 or 1000 mg bid and metformin 1000 mg bid	Completed	2.5 mg bid	Plus 500 mg or 1000 mg metformin bid
NCT01422876	Efficacy and safety of BI10773/BI1356 fixed dose combination in treatment naïve and metformin treated type 2 diabetes patients	Recruiting	5 mg qd	FDC with BI10773 (10 mg or 25 mg)
NCT01087502	Safety and efficacy of linagliptin in type 2 diabetes mellitus patients with moderate to severe renal impairment	Ongoing, but not recruiting	5 mg qd	Comparator: glimepiride
NCT01084005	Efficacy and safety of linagliptin in elderly patients with type 2 diabetes	Completed	5 mg qd	None
NCT00996658	Linagliptin versus placebo in type 2 diabetic patients with inadequate glycaemic control on metformin in combination with pioglitazone	Ongoing, but not recruiting	5 mg qd	Baseline: metformin and pioglitazone
NCT01204294	Linagliptin open label comprehensive safety trial	Ongoing, but not recruiting	5 mg qd	Baseline: metformin

NCT01243424	CAROLINA: cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes	Recruiting	5 mg qd	Comparator: glimepiride
NCT00954447	Efficacy and safety of linagliptin in combination with insulin in patients with type 2 diabetes	Completed	5 mg qd	
NCT01194830	Efficacy and safety of linagliptin (BI1356) in Black/African Americans with type 2 diabetes with a MTT sub-study	Completed	5 mg qd	
NCT00601250[28]	Efficacy and safety of BI1356 (linagliptin) vs. placebo added to metformin background therapy in patients with type 2 diabetes	Completed	5 mg qd	Placebo
NCT01183013	30 week parallel group comparison study of linagliptin + pioglitazone (5 + 15, 5 + 30 and 5 + 45 mg) qd versus respective monotherapies, followed by 54 week comparison of 5 mg + 30 mg and 5 mg + 45 mg versus respective monotherapies in type 2 diabetes	Recruiting	5 mg qd	Pioglitazone 15; 30 or 45 mg qd (partly FDC)
NCT00602472	BI1356 (linagliptin) in combination with metformin and a sulphonylurea in type 2 diabetes	Completed	5 mg qd	Placebo
NCT01215097	Efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy	Recruiting	5 mg qd	Placebo
NCT01214239	Efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated type 2 diabetic patients with insufficient glycaemic control	Recruiting	5 mg qd	Placebo
NCT00621140[17]	Efficacy and safety of BI1356 (linagliptin) versus placebo in type 2 diabetic patients with insufficient glycemic control	Completed	5 mg qd	Placebo
NCT00740051	A randomised, db, placebo-controlled study of BI1356 for 18 weeks followed by a 34 week double-blind extension period (placebo patients switched to glimepiride) in type 2 diabetic patients for whom treatment with metformin is inappropriate	Completed	5 mg qd	Comparator: placebo/glimepiride
NCT00641043	Efficacy vs. placebo as initial combination therapy with pioglitazone	Completed	5 mg qd	Comparator: placebo/pioglitazone (30 mg)
NCT00798161[29]	Safety and efficacy of linagliptin (BI1356) plus metformin in type 2 diabetes, factorial design	Completed	5 mg qd or 2.5 mg bid	Plus 500 mg or 1000 mg metformin bid
NCT00819091	Randomized, double-blind (db), placebo-controlled 18 week study of linagliptin (BI1356) in type 2 diabetic patients with insufficient glycaemic control on a sulfonylurea drug	Completed	5 mg qd	Placebo
NCT00736099	Safety and efficacy of BI1356 as monotherapy or in combination in type 2 DM	Completed	5 mg qd	Pioglitazone 30 mg
NCT00654381[27]	Japanese P III vs. voglibose and placebo	Completed	5 mg or 10 mg qd	Comparator volglibose 0.6 mg or placebo
NCT01438814	Linagliptin in combination with metformin in treatment naive patients with type 2 diabetes mellitus and insufficient glycaemic control	Not yet open for recruitment	5 mg qd	Metformin

Abbreviations: FDC, fixed dose combination; MTT, meal tolerance test.

In monotherapy, in one randomized, double-blind, placebo-controlled study in obese patients with type 2 diabetes and a baseline HbA1c ranging from 6.8%–7.3%, GLP-1 plasma concentrations increased up to 4-fold during meal tests. The glucagon plasma concentrations were consecutively lowered by 24%. These effects led to a significant reduction of the meal-related glucose excursions by linagliptin. The placebo-subtracted changes of HbA1c were –0.31%, –0.37% and –0.28% for the doses of 2.5 mg, 5 mg and 10 mg linagliptin, respectively.[17] A similarly designed study in Japanese patients demonstrated comparable results, with placebo-subtracted HbA1c reductions of 0.27%, 0.27% and 0.42% for the doses of 2.5 mg, 5 mg and 10 mg linagliptin at week 4 of the study.[17,22] In another monotherapy study in type 2 diabetic patients who were either drug-naïve or washed out from previously used oral antidiabetic drugs for 6 weeks, a dose of 5 mg linagliptin once daily significantly reduced the HbAc by –0.69% compared to placebo after 24 weeks ($P < 0.0001$). The patient cohort, that had a baseline HbA1c ≥ 9% profited from an even more pronounced reduction in HbA1c (–1.01%, $P < 0.0001$). Along with the HbA1c reductions, fasting plasma glucose and 2-hour postprandial glucose also improved significantly (–1.3 mmol/L; $P < 0.0001$ and –3.2 mmol/L; $P < 0.0001$, respectively). Regarding parameters for beta cell function, significant improvements for the HOMA B (Homeostasis Model Assessment-%B) ($P = 0.049$) and the disposition index ($P = 0.0005$) as well as for the proinsulin/insulin ratio ($P = 0.025$) were observed compared to placebo.[26] In a study carried out in Japanese patients with type 2 diabetes, daily doses of either 5 mg or 10 mg of linagliptin were compared to placebo- or voglibose treatment.[27] Preliminary results after 12 weeks of treatment the maximal HbA1c reduction was –0.9%. The complete results of this study have not been published yet.

As add on to metformin in patients with type 2 diabetes not adequately controlled with a monotherapy with metformin, a 24 week study investigated the efficacy and safety of a daily dose of 5 mg linagliptin compared to placebo. Linagliptin significantly reduced the HbA1c from a baseline of 8.1% by –0.49% compared to placebo (–0.155). In line with these changes fasting plasma glucose and postprandial glucose were lowered significantly (fasting glucose baseline 9.4 mmol/L; –0.59 for the linagliptin add on group, vs. +0.58 mmol/L for the placebo group, $P < 0.0001$; 2-hour postprandial glucose –2.7 for linagliptin vs. 1.0 mmol/L for placebo, $P < 0.0001$). Hypoglycemic events occurred rarely with an incidence of 0.6% in linagliptin treated patients and 2.8% in the placebo treated patients. In both arms, body weight did not change significantly (–0.4 kg in the linagliptin arm, –0.5 kg in the placebo arm).[28]

The efficacy and safety of an initial combination of metformin and linaglitpin was also investigated in a study 791 patients with type 2 diabetes. This study contained an open arm for patients with poor glycemic control. The study had a total of six treatment arms with two arms being treated with a free combination of linagliptin (2.5 mg linaglitpin plus 500 mg metformin, both b.i.d. or 2.5 mg linaglitpin plus 1000 mg metformin, both b.i.d.). The other four arms were monotherapy arms with linagliptin 5 mg q.d., metformin 500 mg or 1000 mg b.i.d., or placebo, resectively. A total of 66 patients with a baseline HbA1c = 11% received an open-label combination therapy with linagliptin 2.5 mg b.i.d. plus metformin 1000 mg b.i.d.. The mean baseline HbA1c ranged from 8.5%–8.7% in the five arms without poor control, in the arm with poor control that was open label, the initial HbA1c was 11.8%. For the initial combination of linagliptin (2.5 mg linagliptin plus 500 mg metformin, both b.i.d. or 2.5 mg linaglitpin plus 1000 mg metformin, both b.i.d.) the placebo-corrected reduction in HbA1c amounted to –1.3% and –1.7%, respectively. The combination therapy was superior to the monotherapy treatments. In the poorly controlled open label arm, the HbA1c reduction amounted to –3.7%. The adverse event rate was low and comparable to other studies with linaglitpin and also, the number of hypoglycemic episodes associated with combination treatment was low (1.8%, 5 patients receiving the initial combination). The linagliptin/metformin combination was weight neutral (–0.23 kg in the group with 2.5 mg linagliptin and 1000 mg metformin, both b.i.d.).[29]

A therapy with linagliptin as add on to metformin was compared to a therapy with glimepiride and metformin in a 2 year study. Patients not well controlled on metformin monotherapy with a baseline HbA1c of 7.7% either received 5 mg linagliptin once daily (n = 764) or glimepiride 1–4 mg daily (n = 755).

The adjusted mean (±SE) HbA1c changes from baseline were −0.4% (± 0.04%) for linagliptin 5 mg/d and −0.5% (±0.04%) for glimepiride in the per protocol analysis. The mean dose of glimepiride was 3 mg/d. Linagliptin was non-inferior to glimepiride. The hypoglycemia incidence was much lower with linagliptin than with glimepiride (7.5% vs. 36.1%; $P < 0.0001$). Additionally, the body weight was decreased with linagliptin and increased with glimepiride (−1.4 kg vs. + 1.3 kg; adjusted mean difference, −2.7 kg; $P < 0.0001$). Cardiovascular events occurred in 13 (1.7%) patients treated with linagliptin vs. 26 (3.4%) patients on glimepiride revealing a significant 50% reduction in the relative risk for a combined cardiovascular endpoint (RR, 0.50; 95% CI, 0.26–0.96; $P = 0.04$).[30]

Likewise, the efficacy and safety of an initial combination therapy of linagliptin and pioglitazone was investigated in a 24 week study with a total of 389 participants with type 2 diabetes. Patients received either the combination of 30 mg pioglitazone with 5 mg linagliptin once daily, 30 mg pioglitazone as monotherapy or placebo. At the end of the study, the HbA1c was lowered by −1.06% in the patients treated with the initial combination therapy, whereas the patients on pioglitazone monotherapy demonstrated a reduction in HbA1c by −0.56%. In parallel with the HbA1c reductions, the fasting plasma glucose reductions were significantly greater for linagliptin plus pioglitazone than with placebo plus pioglitazone; −1.8 and −1.0 mmol/L, respectively, corresponding to a treatment difference of −0.8 mmol/L (95% CI −1.2, −0.4; $P < 0.0001$). The rate of mild hypoglycaemic events was low with 1.2% and all episodes occurred in the linagliptin plus pioglitazone goup, no severe hypoglycemia was reported. The parameters of beta cell function HOMA-IR and disposition index improved.[31]

Also the combination of linagliptin with a sulfonylurea (glyburide) was investigated in a randomized, open label, cross over study with three periods in healthy subjects to study the possible effects of linagliptin on the pharmacokinetics of glyburide and vice versa. The coadministration of single doses of 1.75 mg glyburide daily to 5 mg of linagliptin did not significantly change the steady state PKs and C_{max} of either drug.[32]

Another study investigated potential drug-drug interactions between linagliptin and the novel sodium glucose cotransporter-2 (SGLT-2) inhibitor BI10773 (empagliflozin) in healthy volunteers at doses of 5 mg linagliptin q.d. and 50 mg BI10773 q.d. The combined administration of linagliptin had no effect on the extent of BI10773 absorption ($AUC_{\delta,ss}$ geometric mean ratio [GMR] 101.7%; 90% CI 96.5%, 107.2%). There was a slight, clinically non-significant reduction in the rate of absorption ($C_{max,ss}$ GMR 88.3%; 90% CI 78.8%, 98.9) of BI10773. Co-administration of BI10773 had no effect on the extent ($AUC_{\delta,ss}$ GMR 103.3%; 90% CI 96.1%, 111.1%) or rate ($C_{max,ss}$ GMR 101.5%; 90% CI 86.9%, 118.5%) of linagliptin absorption. BI10773 alone and in combination with linagliptin led to a clinical relevant excretion of glucose in urine due to the action of the SGLT-2 inhibitor BI10773. DPP-4 inhibition was similar following linagliptin administration with BI10773 or alone. Both BI10773 and linagliptin were well tolerated. These data support co-administration of BI10773 and linagliptin in future clinical trials without dose adjustments.[33]

Safety and Adverse Events with Linagliptin

In the studies performed, linagliptin was well tolerated and not associated with specific side effects in doses up to >100-fold of the therapeutic dose of 5 mg. The most frequently reported adverse events for linagliptin versus placebo were headache (21% vs. 38%), influenza-like illness (11% vs. 4%) and nausea (4% vs. 6%). No changes in laboratory parameters have been observed in the clinical studies and since approval so far.

As expected for a therapy with a DPP-4 inhibitor, the hypoglycemia incidence was not increased during linagliptin treatment in the studies as long as linagliptin was not given in a combination with a sulfonylurea.[17,20]

Meanwhile, a large pooled-analysis of 3572 patients with type 2 diabetes on linagliptin was performed to extend the safety- and tolerability data from the clinical studies with linagliptin. In this database, 2523 received linagliptin 5 mg daily and 1049 patients received placebo. The total incidence rate of adverse events (AEs) or serious AEs with linagliptin was comparable to placebo (AEs 55.0% vs. 55.8%; serious AEs 2.8% vs. 2.7%). The overall aggregated infection rates were 19.5% for linagliptin and 21.4% for placebo. Fewer or similar rates of AEs vs. placebo

were seen with linagliptin for upper respiratory tract infection (3.3% vs. 4.9%), headache (2.9% vs. 3.1%), urinary tract infection (2.2% vs. 2.7%), blood and lymphatic disorders (1.0% vs. 1.2%), hypersensitivity (0.1% vs. 0.1%), hepatic enzyme increase (0.1% and 0.1%), and serum creatinine increase (0.0% and 0.1%). There was a slight increased frequency of nasopharyngitis (5.9% vs. 5.1%) and cough (1.7% vs. 1.0%) with linagliptin. In general, hypoglycemia rates were similar with linagliptin (8.2%) and placebo (5.1%). Incidence of hypoglycemia was increased in patients with background sulfonylurea therapy (linagliptin 20.7%), which is in agreement with other reports where DPP-4 inhibitors were added to a sulfonylurea therapy. Overall, the hypoglycemic event rate with linagliptin was very low (<1.0%) when used without sulfonylureas. This metaanalysis provides further evidence that linagliptin is well tolerated and more data are continuously being generated.[34]

Potential Pleiotropic Effects

Linagliptin, improves wound healing in the rodent model of ob/ob mice. Immunohisto-chemistry and immunoblots show a strong expression of DPP-4 in skin from healthy and diabetic (ob/ob) mice and keratinocytes. The localisation of DPP-4 protein in the skin correlates with whole body autoradiography obtained after [3H]-labelled linagliptin treatment. Analyzing DPP-4 expression in healthy mice upon full-thickness excision wounding, DPP-4 expression decreases over a period of 3 days after injury and the enzyme remaines absent in the late phase of wound repair. Skin injury leads to a strong down-regulation of DPP-4 expression in proliferating wound margin keratinocytes. In contrast, in acute wounds of diabetic mice DPP-4 expression is absent. DPP-4 protein, however, is expressed in the late phase of wound repair. This inverse regulation of DPP-4 protein in diabetic versus non-diabetic skin seems to indicate a functional basis of a potentially positive action of linagliptin in general wound healing processes.[35]

Recent data suggest that DPP-4 inhibitors may also have anti-inflammatory properties, especially in animal models of inflammatory bowel diseases.[36] The effect is possibly mediated via T-cell regulation or the inhibition of degradation of glucagon-like peptide-2 (GLP-2), which favors proliferation and repair of the colonic mucosa. In this respect, the anti-inflammatory effects of linagliptin were investigated in a model of acute dextran sulphate sodium (DSS) induced colitis in Balb/c mice. Treatment with linagliptin did not significantly alter colon length, histology, hemoccult, or stool consistency; all of which were significantly worsened by DSS administration in the animals. Linagliptin significantly reduced pro-inflammatory cytokines, elevated active GLP-2 levels, and reduced clinical changes in DSS-treated animals.[37]

Since non-alcoholic fatty liver disease (NAFLD) and hepatic steatosis are frequently observed in type 2 diabetes, the effect of linagliptin on liver tissue composition was investigated in the rodent model of DIO (diet-induced obesity) mice. Treatment of the animals with linagliptin improved glycemic parameters and reduced the liver fat content measured by MRS (magnetic resonance spectroscopy). Changes in liver fat content were visible as early as 2 weeks on treatment. The correlation between liver lipid content as measured by MRS and hepatic triglyceride levels as measured ex vivo was $r^2 = 0.565$ ($P < 0.0001$). In ob/ob mice linagliptin treatment for 2 weeks also lead to an improvement of glycemic parameters. The histological examination revealed significantly less hepatic steatosis and inflammation in the linagliptin group in comparison to control mice. In conclusion, linagliptin significantly reduces liver fat content and histological NAFLD in two different rodent models, speculating on a liver specific insulin sensitizing effect. The reversal of hepatic steatosis may support the use of linagliptin in patients with type 2 diabetes as well as NAFLD, but clinical studies with this respect have to be performed yet.[38]

Linagliptin was also investigated in an artificial myocardial ischemia model in rats. In this model, linagliptin significantly reduced the proportion of infarcted tissue relative to the total area at risk as well as the absolute infarction size. This effect was mediated by a significant elevation of endogenous GLP-1 plasma concentrations due to linagliptin mediated DPP-4 inhibition. Left ventricular left end diastolic and systolic pressure as well all echocardiography parameters were similar between groups, with a significant improvement of isovolumetric contractility indices.[39]

Further potential pleiotropic effects of linaglitpin are summarized in a recent review articles.[17,40]

Regarding clinically most important additional effects, the cardiovascular profile of linagliptin was investigated in a pre-specified metaanalysis of all cardiovascular events from a total of 8 phase III trials. Cardiovascular events were prospectively adjudicated by a blinded independent expert committee. The primary endpoint of this analysis was a composite of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction (MI), and hospitalization for unstable angina pectoris (UAP). Other secondary and tertiary CV endpoints were also assessed, including FDA-custom major adverse CV events (MACE). A total of 5239 patients were included in the metaanalysis. The mean HbA1c at baseline was 8.0%. Linagliptin was given to 3319 patients once daily (a 5 mg dose to 3159 patients, 160 patients received a dose of 10 mg q.d.). A total of 1920 patients received a comparator compound (977 patients placebo, 781 patients glimepiride, 162 patients voglibose). The overall, adjudicated primary cardiovascular events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%) receiving a comparator compound. The hazard ratio for the primary endpoint was significantly lower for linagliptin vs. comparator and the hazard ratios were similar or significantly lower with linagliptin vs. comparator for all other cardiovascular endpoints. Whether these data support a potential reduction of cardiovascular events with linagliptin will be tested prospectively in CAROLINA trial (Cardiovascular safety of linagliptin or glimepiride in subjects with type 2 diabetes mellitus at high CV risk), an ongoing outcomes trial in which linagliptin is compared to glimepiride.[41]

Unique Characteristics of Linagliptin

Among the class of DPP-4 inhibitors, linagliptin has the unique property of having a primarily non-renal, hepatobiliary route of elimination. The reasons for this property lie most likely in the chemical structure of the compound as well as in the high degree of protein binding in plasma and tissues. With the non-renal route of elimination, linagliptin may be used without dose adjustment in patients with renal impairment, whereas the other DPP-4 inhibitors have to be dose adjusted. On the other side, in patients with hepatic failure, dose adjustment of linagliptin may be necessary. Linagliptin is hardly metabolized and does not interact with the CYP 450 system. Therefore, pharmacokinetic interactions with other compounds that are metabolized through the liver are unlikely.[13,17] Ongoing long-term studies may possibly elucidate whether these unique characteristics of linagliptin will offer additional clinical benefits.

Conclusions and Outlook

The available DPP-4 inhibitors have different characteristics regarding their absorption, distribution, metabolism, elimination, as well as in their potency and duration of action. Linagliptin has a unique pharmacokinietic profile with a strong binding to proteins and a strong binding to DPP-4. The elimination half-life is long and linagliptin is the only DPP-4 inhibitor so far with a non-renal route of excretion, but a hepato-biliary one. This is important for the vast number of patients with the risk or already existing renal impairment as a consequence of diabetic microangiopathy. Also, older patients with declining renal function may profit from linagliptin in this respect. So far, besides the glinide repaglinide, no insulinotropic agents are available for patients with type 2 diabetes and impaired kidney function. Repaglinide, however is associated with the risk of hypoglycemia, similarly to the sulfonlyureas due to the same mode of action. Linagliptin may be used safely in these patient groups without dose adjustments. Furthermore, no monitoring of renal function for the sake of treatment safety is necessary with linagliptin therapy. In addition, linagliptin possesses a profile of potential pleiotropic effects that may additionally be favourable. Regarding cardiovascular effects, the expected outcome data from the CAROLINA study will answer the question if there is another important clinical advantage.

Disclosures

The author is a member on advisory boards for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Merck, Roche, Sanofi Aventis and Takeda and has also received honoraria from these companies for giving lectures.

References

1. International Diabetes Federation (IDF): diabetes atlas. 2009. Available from: http://www.diabetesatlas.org.
2. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696–705.

3. Nauck MA, Homberger E, Siegel EG, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab*. 1986;63:492–8.
4. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfedt W. Normalization of fasting hyperglycaemia by exogenousglucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36:741–4.
5. Mentlein R, Gallwitz B, Schmidt WE. Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum. *Eur J Biochem*. 1993;214:829–35.
6. Deacon CF, Hughes TE, Holst JJ. Dipeptidyl peptidase IV inhibition potentiates the insulinotropic effect of glucagon-like peptide 1 in the anesthetized pig. *Diabetes*. 1998;47:764–9.
7. Ahrén B, Simonsson E, Larsson H, et al. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. *Diabetes Care*. 2002;25:869–75.
8. Gallwitz B. Sitagliptin: profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes (update). *Drugs Today (Barc)*. 2007;43:801–14.
9. Gallwitz B. Sitagliptin with metformin: profile of a combination for the treatment of type 2 diabetes. *Drugs Today (Barc)*. 2007;43:681–9.
10. German Diabetes Association, Matthaei S, Bierwirth R, et al. Medical antihyperglycaemic treatment of type 2 diabetes mellitus: update of the evidence-based guideline of the german diabetes association. *Exp Clin Endocrinol Diabetes*. 2009;117:522–57.
11. 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-dihydropurine-2,6-dione (BI1356), 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;325:175–82.
12. Eckhardt M, Hauel N, Himmelsbach F, et al. 3,5-Dihydro-imidazo[4,5-d] pyridazin-4-ones: a class of potent DPP-4 inhibitors. *Bioorg Med Chem Lett*. 2008;18:3158–62.
13. Gallwitz B. Small molecule dipeptidylpeptidase IV inhibitors under investigation for diabetes mellitus therapy. *Exp Opin Invest Drugs*. 2011;20:723–32.
14. Eckhardt M, Langkopf E, Mark M, et al. 8-(3-(R)-aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methylquinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione (BI1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes. *J Med Chem*. 2007;50:6450–3.
15. Fuchs H, Binder R, Greischel A. Tissue distribution of the novel DPP-4 inhibitor BI1356 is dominated by saturable binding to its target in rats. *Biopharm Drug Dispos*. 2009;30:229–40.
16. Fuchs H, Tillement JP, Urien S, Greischel A, Roth W. Concentration-dependent plasma protein binding of the novel dipeptidyl peptidase 4 inhibitor BI1356 due to saturable binding to its target in plasma of mice, rats and humans. *J Pharm Pharmacol*. 2009;61:55–62.
17. Deacon CF, Holst JJ. Linagliptin, a xanthine-based dipeptidyl peptidase-4 inhibitor with an unusual profile for the treatment of type 2 diabetes. *Expert Opin Investig Drugs*. 2010;19:133–40.
18. Herman GA, Stein PP, Thornberry NA, Wagner JA. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: focus on sitagliptin. *Clin Pharmacol Ther*. 2007;81:761–7.
19. He YL, Sadler BM, Sabo R, et al. The absolute oral bioavailability and population-based pharmacokinetic modelling of a novel dipeptidylpeptidase-IV inhibitor, vildagliptin, in healthy volunteers. *Clin Pharmacokinet*. 2007;46:787–802.
20. Huttner S, Graefe-Mody EU, Withopf B, Ring A, Dugi KA. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of BI1356, an inhibitor of dipeptidyl peptidase 4, in healthy male volunteers. *J Clin Pharmacol*. 2008;48:1171–8.
21. 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;11:786–94.
22. Horie Y, Kanada S, Watada H, et al. Pharmacokinetic, pharmacodynamic, and tolerability profiles of the dipeptidyl peptidase-4 inhibitor linagliptin: a 4-week multicenter, randomized, double-blind, placebo-controlled phase IIa study in Japanese type 2 diabetes patients. *Clin Ther*. 2011;33:973–89.
23. Graefe-Mody EU, Padula S, Ring A, Withopf B, Dugi KA. Evaluation of the potential for steady-state pharmacokinetic and pharmacodynamic interactions between the DPP-4 inhibitor linagliptin and metformin in healthy subjects. *Curr Med Res Opin*. 2009;25:1963–72.
24. Graefe-Mody EU, Jungnik A, Ring A, Woerle HJ, Dugi KA. Evaluation of the pharmacokinetic interaction between the dipeptidyl peptidase-4 inhibitor linagliptin and pioglitazone in healthy volunteers. *Int J Clin Pharmacol Ther*. 2010;48:652–61.
25. Friedrich C, Ring A, Brand T, Sennewald R, Graefe-Mody EU, Woerle HJ. Evaluation of the pharmacokinetic interaction after multiple oral doses of linagliptin and digoxin in healthy volunteers. *Eur J Drug Metab Pharmacokinet*. 2011;36:17–24.
26. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptinmonotherapy on glycaemic control and markers of â-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab*. 2011;13:258–67.
27. Horie Y, Hayashi N, Dugi K, Takeuchi M. Design, statistical analysis and sample size calculation of a phase IIb/III study of linagliptin versus voglibose and placebo. *Trials*. 2009;10:82.
28. 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*. 2011;13:65–74.
29. Haak T, Meinicke T, Russell-Jones DL, von Eynatten M, Woerle HJ. Combination of linagliptin and metformin improves glycemic control in type 2 diabetes: a randomized trial with an open-label arm in patients with poor glycemic control. *Diabetes*. 2011;60 Suppl 1:279 OR.
30. Gallwitz B, Uhlig-Laske B, Bhattacharaya SP, Woerle HJ. Linagliptin Has Similar Efficacy to Glimepiride but Improved Cardiovascular Safety over 2 years in patients with type 2 diabetes inadequately controlled on metformin. *Diabetes*. 2011;60 Suppl 1:39-LB.
31. 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;13:653–61.
32. Graefe-Mody U, Rose P, Ring A, Zander K, Iovino M, Woerle HJ. Pharmacokinetic interaction between the novel DPP-4 inhibitor linagliptin and a sulfonylurea, glyburide, in healthy subjects. *Drug Metab Pharmacokinet*. 2011;26:123–9.
33. Friedrich C, Metzmann K, Rose P, Mattheus M, Pinnetti S, Woerle JH. Pharmacokinetics and pharmacodynamics of BI10773, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, following co-administration in healthy volunteers. *Diabetes*. 2011;60 Suppl 1:2327-PO.
34. Schernthaner G, von Eynatten M, Emser A, Patel S, Woerle HJ. Safety and tolerability of linagliptin: A pooled analysis of data from 3572 patients with type 2 diabetes. *Diabetes*. 2011;60 Suppl 1:2327-PO.
35. Schürmann C, Frank S, Greischel A, Mark M, Klein T. Linagliptin functionally counteracts a dysregulation in DPP-4 expression in diabetes-impaired wounds. *Diabetes*. 2010;59 Suppl 1:576-P.
36. Yazbeck R, Howarth GS, Abbott CA. Dipeptidyl peptidase inhibitors, an emerging drug class for inflammatory disease? *Trends Pharmacol Sci*. 2009;30:600–7.
37. Klein T, Batra A, Mark M, Siegmund B. The DPP-4 inhibitor linagliptin increases active GLP-2 and decreases colonic cytokines in a mouse inflammatory bowel disease model. *Diabetes*. 2011;60 Suppl 1:1124-P.
38. Klein T, Niessen H, Thomas L, Stiller D, Mark M. Linagliptin improves hepatic steatosis in rodent models: a magnetic resonance spectroscopy based study. *Diabetes*. 2010;59 Suppl 1:577-P.

39. Pfab T, Sharkovska Y, Alter M, et al. Effect of linagliptin on infarction size and cardiac function in rats after myocardial ischaemia reperfusion. *Diabetologia*. 2011;54 Suppl 1:A 811.
40. Kalra S, Unnikrishnan AG, Agrawal N, Singh AK. Linagliptin and newer DPP-4 inhibitors: newer uses and newer indications. *Recent Pat Endocr Metab Immune Drug Discov*. 2011;5:197–202.
41. Johansen OE, Neubacher D, von Eynatten M, Patel S, Woerle HJ. Cardiovascular risk with linagliptin in patients with type 2 diabetes: a pre-specified, prospective, and adjudicated meta-analysis from a large phase III program. *Diabetes*. 2011;60 Suppl 1:30-LB.