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Linagliptin plus metformin : pharmacokinetic and pharmacodynamic evaluation

SUMMARY

Introduction : The first-choice drug therapy in the management of type 2 diabetes is metformin. However, most patients require a combined therapy to reach and/or maintain targets of glucose control. Dipeptidylpeptidase-4 (DPP-4) inhibitors, commonly referred to as gliptins, offer new options for combined therapy with metformin. Linagliptin is the most recent launched gliptin, with a unique pharmacokinetic profile characterized by negligible renal excretion, and is now also available as a fixed-dose combination (FDC) with metformin.

Area covered: An extensive literature search was performed to analyze the potential pharmacokinetic (PK) and pharmacodynamic (PD) interactions between linagliptin and metformin. Linaglipin and metformin may be administered together, either separately or as FDC supported by bioequivalence studies. Linagliptin and metformin are not prone to PK drug-drug interactions. Their co-administration improves blood glucose control more potently than either compound separately, without hypoglycemia and without increasing metformin-related gastrointestinal side effects.

Expert Opinion : The combination linaglitpin plus metformin, if not contraindicated (renal failure), may be used as first-line or second-line therapy in the management of type 2 diabetes.

Key-words : DPP-4 inhibitor – Fixed-dose combination – Linagliptin – Metformin – Pharmacokinetics –Type 2 diabetes mellitus

1. Introduction

The management of hyperglycemia in patients with type 2 diabetes mellitus (T2DM) becomes more and more complex[1-3]. After failure of metformin monotherapy, several pharmacological options may be considered[3-6], among which the addition of a selective inhibitor of dipeptidyl peptidase-4 (DPP-4) occupies an increasing place in clinical practice[7-9]. Indeed, a progressive deterioration of the glycemic control is generally observed over years in patients with T2DM, which essentially results from an unavoidable decline of insulin secretion[10] and imposes a stepwise increasing use of combined therapies[2, 3]. Even if metformin is unanimously considered as the first-line drug therapy in T2DM[3, 11-13], which treatment to be added after metformin failure remains a quite challenging issue [14]. Indeed, whatever the mode of action, almost all second-drug therapies offer quite similar efficacy regarding glycated hemoglobin (HbA1c) lowering effect[4, 12]. However, T2DM is often accompanied by other conditions and risk factors, on which the various glucose-lowering agents may exert different effects that may have an impact on long-term clinical outcomes and, thereby, may influence physician's drug choice[15, 16]. Classical insulin secretagogues include sulfonylureas (still recommended because of their low cost)[3], but these glucose-lowering agents expose to a risk of potentially severe hypoglycemia[4, 9, 17, 18], weight gain [4, 9, 18-20] and pharmacokinetics (PK) interactions[21], which may worsen outcomes[16]. In this regard, DPP-4 inhibitors, which inhibit the inactivation of glucagon-like peptide- 1 (GLP-1), may offer new opportunities in the management of T2DM[8, 9, 20, 22]. Indeed, GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner, which explains the minimal risk of hypoglycemia associated with such incretin-based therapies[8]. Furthermore, GLP-1 contributes to appetite regulation and thereby may avoid or at least limit weight gain despite improvement of glucose control in T2DM patients, in contrast to what is generally observed with other glucose-lowering therapies[19, 20]. However, the positioning of DPP-4 inhibitors in the management of T2DM, especially their place compared to either sulfonylureas[23-25] or injectable GLP-1 receptor agonists[26, 27], is still a matter of debate.

Several DPP-4 inhibitors are already available since many years (sitagliptin, saxagliptin, vildagliptin except in US, alogliptin only in Japan)[8, 9, 28]. Despite a similar mode of action, i.e. selective inhibition of DPP-4 resulting in a physiological increase in active GLP-1 levels, they differ by some PK properties[29, 30]. Most of them are also available as fixed dose combination (FDC) with metformin, especially vildagliptin[31, 32], sitagliptin[33, 34] and saxagliptin[35]. FDC can offer convenience, reduce the pill burden and simplify administration regimens for the patient, all conditions that may improve adherence to therapy[36-38].

Linagliptin is the newest DPP-4 inhibitor and is characterized by specific PK properties as summarized in numerous recent reviews[30, 39-43]. The most clinically relevant specificity, relative to other already available DPP-4 inhibitors, is that linagliptin has a minimal renal excretion and instead a predominant biliary excretion[29, 44]. Thus, it may be used in patients with chronic kidney disease (CKD) without dose adjustment[44]. This contrasts with other DPP-4 inhibitors, for which a dose reduction is recommended according to the decrease of the estimated glomerular filtration rate (eGFR)[45]. Therefore, linagliptin may be considered as a valuable alternative in T2DM patients with impaired renal function in whom metformin

may be contraindicated[46, 47]. However, in T2DM patients who may receive metformin (because of acceptable renal function and good gastrointestinal tolerance), linagliptin may also be added to the biguanide to reach HbA1c targets in case of failure of monotherapy. Thus, linagliptin may be used in dual therapy with metformin, a well-known positioning for all DPP-4 inhibitors[7, 23], or even in triple therapy when added to metformin plus sulfonylurea[48, 49]. A linagliptin plus metformin hydrochloride fixed-dose combination (FDC : Jentadueto®) has been accepted in 2012 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Even in combination, linagliptin may be used without dose adjustment in case of renal impairment, which contrasts with the dose reduction recommended for other DPP-4 inhibitors in T2DM patients with mild to moderate CKD[45], as recently reviewed for the saxagliptin plus metformin combination[50].

The present paper provides a PK/ pharmacodynamic (PD) evaluation of linagliptin plus metformin and an updated review of the randomized clinical trials and of the bioequivalence studies that have assessed the efficacy and tolerability/safety of this linaglitin-metformin combination. To identify relevant studies, an extensive literature search of MEDLINE was performed from January 2008 to October 2012, with the two key-words "metformin" and "linagliptin". No language restrictions were imposed. Reference lists of original studies, narrative reviews, and previous systematic reviews were also scrutinized. The European Public Assessment Report (EPAR) of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) of the FDC Juntadueto®[51] and the approval document of Juntadueto® by the Food and Drug Administration (FDA)[52] have been examined too.

2. Pharmacokinetic evaluation

2.1. Metformin

Metformin hydrochloride has an absolute oral bioavailability of 40 to 60%, and gastrointestinal absorption is apparently complete within 6 hours of ingestion[53, 54]. An inverse relationship is observed between the dose ingested and the relative absorption with therapeutic doses ranging from 0.5 to 1.5 g, suggesting the involvement of an active, saturable absorption process. Food decreased the extent and slightly delays the absorption of metformin, with a 40% lower plasma peak concentration (C_{max}), a 24% decrease in area under the plasma concentration time curve (AUC) and a 37-minute prolongation of time to peak plasma concentration (t_{max}) following administration of a dose of 850 mg metformin with a meal instead after an overnight fast[55]. However, the clinical relevance of these changes is unknown.

Metformin is rapidly distributed following absorption and does not bind to plasma proteins. No metabolites or conjugates of metformin have been identified. Metformin undergoes renal excretion and has a mean plasma elimination half-life ($t_{1/2}$) after oral administration of between 4.0 and 8.7 hours[53, 54]. This elimination is prolonged in patients with CKD and correlates with creatinine clearance[56].

Recent studies showed that organic cation transporters (OCTs) are responsible for the intestinal, hepatic and renal transport of metformin[57]. In vitro observations showed that OCT1 is responsible for the hepatic uptake as well as playing a role in the intestinal uptake of metformin[58]. Other *in vitro* findings suggested that metformin is a superior substrate for renal

OCT2 rather than hepatic OCT1, and renal OCT2 plays a dominant role for metformin PK[59]. Genetic polymorphisms in OCT1 and OCT2 have been found to be associated with changes in PK/PD responses to substrate drugs, including metformin, although the results are still controversial[60].

Only limited drug-drug interactions (DDIs) have been described with metformin both in healthy volunteers and in T2DM patients[21, 53, 61]. Linagliptin showed inhibitory potency to OCT1 and OCT2[62]. However, considering the low therapeutic plasma concentration of linagliptin, available *in vitro* data clearly suggest a very low risk for transporter-mediated DDIs on comedications, including metformin, in clinical practice[62].

2.2. Linagliptin

The most clinically specificity of linagliptin compared with other available DPP-4 inhibitors concerns its minimal renal excretion[29, 44]. We have reviewed the PK properties of linagliptin, as compared with those of other DPP-4 inhibitors, emphasizing its negligible renal excretion and its low potential of DDIs[29, 63]. Furthermore, the PK and PD characteristics of linagliptin have been extensively reviewed in two recent papers[64, 65].

In vitro studies demonstrated that linagliptin is a substrate of OCT2 and P-glycoprotein (P-gp), suggesting that OCT2 and P-gp may play a role in the disposition of linagliptin in vivo[62].

2.2.1. Healthy volunteers

A single rising-dose (2.5 up to 600 mg) study investigated the PK/PD profiles of linagliptin in healthy men[66]. Linagliptin was rapidly absorbed, with t_{max} values ranging from 0.7 to 3 hours. Exposure of linagliptin increased less than proportionally from 2.5 mg to 5 mg, more than proportionally from 25 mg to 100 mg and approximately proportionally for doses from 100 mg to 600 mg. The geometric mean terminal $t_{1/2}$ ranged from 128 to 184 hours. Renal excretion was low and almost complete after 24 hours. The fraction of dose excreted unchanged in urine was dose-dependent and increased from below 1% in the 5 mg group up to about 33% in the 600 mg group. The PK and metabolism of linagliptin were investigated further in healthy volunteers[67]. The 10- and 5-mg ^{14}C-labeled drug was administered orally or intravenously, respectively. Fecal excretion was the dominant excretion pathway with 84.7% and 58.2% of the dose, while renal excretion accounted for 5.4% and 30.8% of the dose, after oral and intravenous administration, respectively. Several metabolites were identified but it was concluded that they only play a minor role in the overall disposition and elimination of the drug[67].

A single rising-dose, randomized, four-group, placebo-controlled study was performed in healthy men to investigate PK and PD of linagliptin after intravenous administration (0.5 mg, 2.5 mg, 10 mg) and to determine the absolute bioavailability of the drug (comparison between 5 mg intravenous and 10 mg oral administration)[68]. Linagliptin showed nonlinear PK after intravenous infusion of 0.5-10 mg, with a less than dose-proportional increase in exposure. Renal excretion of the unchanged parent compound increased with increasing plasma concentrations from 2.72% in the 0.5 mg dose group to 23.0% in the 10 mg dose

group. Although unbound linagliptin is cleared efficiently, the concentration-dependent binding is responsible for the long terminal $t_{1/2}$ (126-139 hours across dose groups) of linagliptin and its nonlinear PK, independent of the mode of administration (intravenous or oral). By a modelling approach avoiding the problem of a nonlinear PK, the absolute bioavailability of the 10 mg linagliptin tablet was estimated to be about 30%. The model demonstrated that the target binding to DPP-4 has a major impact on linagliptin PK and largely explains its nonlinear pattern[69]. Furthermore, results from modeling and simulation support a stable antidiabetic effect of linagliptin over 24 h at steady state and further indicate a low risk for off-target side effects[70]. These PK characteristics obtained in Caucasian people were confirmed in other populations such as Japanese[71] or Chinese[72] healthy adult male volunteers, both after a single oral administration and short-term multiple dosing.

Even if bioavailability of metformin is slightly reduced by food[55], it is generally recommended to take metformin with a meal in order to improve gastrointestinal tolerance. Therefore, in the context of a linagliptin plus metformin FDC, it is of interest to analyze the effect of a meal on the PK parameters of linagliptin. To evaluate this food effect, 32 healthy subjects received in a randomized order a single dose of 5 mg linagliptin after an overnight fast of at least 10h or immediately after the ingestion of a high-fat high-calorie breakfast[73]. Comparable bioavailability was established based on linagliptin AUC_{0-72}. The concurrent intake of food increased T_{max} by approximately 2 hours and reduced C_{max} by about 15% (GMR 84.7%; 90% CI, 75.9%-94.6%). Since adequate drug exposure for inhibition of DPP-4 was still given for the entire 24-hour dosing interval, this result was considered to be of no clinical relevance. Intake of a high-fat meal reduced the rate of linagliptin absorption but had no influence on the extent of absorption; this finding suggests that food has no relevant influence on the efficacy of linagliptin and that linagliptin can be given together with metformin during a meal.

2.2.2. T2DM patients

The PK and PD properties of multiple oral doses of linagliptin were investigated in 47 Caucasian patients with T2DM[74]. They received linagliptin 1, 2.5, 5 or 10 mg, or placebo, once daily for 12 days. Linagliptin exposure (AUC and C_{max}) increased less than proportionally with dose. Accumulation $t_{1/2}$ was short (8.6-23.9 hours), resulting in rapid attainment of steady state (2-5 days) and little accumulation (range: 1.18-2.03). The long terminal $t_{1/2}$ (113-131 hours) led to a sustained inhibition of DPP-4 activity. Renal excretion was below 1% on day 1 in all dose groups.

In a randomized, double-blind, placebo-controlled multiple dose study, 72 Japanese patients with T2DM were assigned to receive oral doses of linagliptin 0.5, 2.5, or 10 mg or placebo once daily for 28 days[75]. Total systemic exposure in terms of linagliptin AUC and C_{max} increased in a less than dose-proportional manner. The terminal $t_{1/2}$ was rather long (223-260 hours) but did not reflect the accumulation $t_{1/2}$ (10.0-38.5 hours), resulting in a moderate accumulation ratio of <2.9 that decreased with increasing dose. Urinary excretion increased with linagliptin doses but was <7% at steady state for all dose groups. Thus, linagliptin PK profile in these Japanese patients with T2DM was consistent with the findings of previous studies in healthy Japanese and white patients.

2.3. Linagliptin plus metformin

A randomized, open-label, two-way crossover design study was conducted in 16 healthy male subjects to investigate the potential PK or PD interactions between linagliptin and metformin[76]. Linagliptin (10 mg/day) and metformin (850 mg three times daily) were each administered alone and concomitantly (3-9 days to steady-state). Co-administration of linagliptin had no apparent effect on metformin exposure (metformin $AUC_{\tau,ss}$). GMR co-administration:individual administration was 101%; 90% CI was 89, 114%. Effects on maximum concentration at steady-state ($C_{max,ss}$) were small (GMR: 89%; 90% CI: 78, 100). Co-administration of metformin did not significantly affect $C_{max,ss}$ of linagliptin (GMR: 103%; 90% CI: 86, 124), but slightly increased $AUC_{\tau,ss}$ by 20% (GMR: 120%; 90% CI: 107, 134). Metformin alone had no effect on DPP-4 activity, and the inhibition of DPP-4 caused by linagliptin was not affected by concomitant administration of metformin. Thus, in this small, multiple dose study carried out in healthy subjects, co-administration of linagliptin with metformin did not have a clinically relevant effect on the PK or PD of either agent[76].

Three bioequivalence studies with a similar design (open-label, randomized, single dose, two-way crossover, trials, in 94-96 healthy volunteers each) were performed with three different linagliptin/metformin FDC tablet strengths (2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg). The results demonstrated that linagliptin/metformin hydrochloride 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg FDC tablets are bioequivalent to coadministration of corresponding doses of linagliptin and metformin as individual tablets (Table 1)[51]. Finally, the effect of food on bioavailability of linagliptin/metformin FDC was evaluated with the higher strength of metformin. Administration of linagliptin 2.5 mg/metformin hydrochloride 1000 mg fixed-dose combination with a fat meal resulted in no change in overall exposure of linagliptin. There was no change in metformin AUC; however, mean peak serum concentration of metformin was decreased by 18% when administered with food. A delayed time-to-peak serum concentrations by 2 hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant[51].

3. Pharmacodynamic evaluation

3.1. Potential synergistic activity

The potential synergistic activity of the two glucose-lowering agents metformin and linagliptin in the treatment of T2DM is illustrated in Figure 1.

The mechanism of action of metformin mainly involves suppression of hepatic glucose output and modestly reduction of insulin resistance[77]. The inhibition of hepatic glucose production is mostly through a mild and transient inhibition of the mitochondrial respiratory chain complex I. The resulting decrease in hepatic energy status activates AMPK (AMP-activated protein kinase), a cellular metabolic sensor, providing a generally accepted mechanism for the action of metformin on hepatic gluconeogenesis[78]. Interestingly, almost 10 years ago already, metformin was shown to increase GLP-1 release in obese patients without or with T2DM[79, 80]. A more recent study confirmed that three months or more of metformin monotherapy in obese patients with T2DM was associated with increased postprandial

GLP-1 levels, including its active form, over a 6-h period following a standard mixed meal, without changes in DPP-4 activity[81]. These data confirmed that metformin-induced increase in GLP-1 levels is independent of DPP-4 inhibition after a meal[82, 83]. The mechanisms of action explaining why metformin may promote GLP-1 secretion from L cells are rather complex[84]. A recent study demonstrated that metformin protects against lipoapoptosis (possibly by blocking JNK2 activation), and enhances GLP-1 secretion from GLP-1-producing cells in vitro[85]. These direct effects of the drug might explain the elevated plasma GLP-1 levels seen in diabetic patients on chronic metformin therapy[81]. When taken together, the combination of a DPP-4 inhibitor and metformin led to greater increases in active GLP-1 than either treatment alone[82, 86], which may represent a further argument in favor of this combination[87].

In contrast to metformin, which does not exert any direct effect on the endocrine pancreas, the DPP-4 inhibitor linagliptin, by increasing GLP-1 and GIP (glucose-dependent insulinotropic polypeptide) concentrations, targets pancreatic defects present in T2DM. Indeed, in a glucose-dependent manner, it stimulates insulin secretion (decreased in T2DM) and inhibits glucagon secretion (increased in T2DM), two hormonal effects that contribute to reduce liver gluconeogenesis and hepatic glucose production. Thus, the combined effects of metformin and linagliptin result in a better control of both fasting and postprandial hyperglycemia in patients with T2DM (Figure 1).

In a study investigating linagliptin PK/PD after single rising-dose (2.5 up to 600 mg) of linagliptin in healthy men, all doses inhibited plasma DPP-4 activity, and single doses of 2.5 mg and 5 mg inhibited DPP-4 activity by 72.7% and 86.1% from baseline, respectively. The time to achieve maximum inhibition shifted with increasing doses from 3 hours (2.5 mg) to <0.7 hours (200 mg and above). Within the dose range tested, a direct PK/PD relationship was observed, with a profile demonstrating the potency and full 24-hour duration of action of linagliptin[66].

In patients with T2DM, inhibition of plasma DPP-4 activity correlated well with linagliptin plasma concentrations, resulting in DPP-4 inhibition >90% in the two highest dose groups (5 and 10 mg once daily for 12 days); even 24 h postdose, DPP-4 inhibition was >80%[74]. Following an oral glucose tolerance test, 24 h after the last dose, statistically significant reductions of glucose excursions were observed with linagliptin (2.5, 5 and 10 mg doses) compared with placebo[74]. In a study of longer duration, linagliptin effectively inhibited plasma DPP-4 activity in patients with T2DM, producing immediate improvements in incretin levels, glucagon suppression, and glycemic control that were maintained throughout the 4-week study period[88]. In 5 published and 4 unpublished randomized, clinical trials identified from multiple databases, linagliptin 5 mg/day for 12-24 weeks, significantly reduced HbA1c (-0.63%, $p < 0.00001$), fasting plasma glucose (FPG) (-1.01 mmol/l, $p < 0.00001$) and improved disposition index (DI, product of insulin sensitivity and acute insulin secretion) ($p = 0.0001$)[89]. However, linagliptin monotherapy was not more effective than metformin at reducing HbA1c or FPG. Therefore, linagliptin is recommended as monotherapy only if metformin is not tolerated or contra-indicated and its main use is generally in combination with metformin[90].

3.2. Addition of linagliptin to metformin monotherapy (Table 2)

3.2.1. Comparison versus placebo

The efficacy and safety of linagliptin, added to ongoing metformin therapy, were assessed in patients with T2DM who had inadequate glycemic control with metformin alone[91]. Patients (n=333) were randomized to receive double-blind linagliptin (1, 5 or 10 mg once daily) or placebo or open-label glimepiride (1-3 mg once daily). Twelve weeks of treatment resulted in a mean placebo-corrected lowering in HbA1c levels of 0.40% for 1 mg linagliptin, 0.73% for 5 mg, and 0.67% for 10 mg, compared with -0.90% for glimepiride. Adjusted and placebo-corrected mean changes in FPG were -1.1 mmol/l for linagliptin 1 mg, -1.9 mmol/l for 5 mg and -1.6 mmol/l for 10 mg. There were no hypoglycemic events for linagliptin or placebo, whereas three patients (5%) receiving glimepiride experienced hypoglycemia. Thus, the addition of linagliptin to ongoing metformin treatment in patients with T2DM was well tolerated and resulted in significant and clinically relevant improvements in glycemic control, with 5 mg linagliptin being the most effective dose[91].

A 24-week, randomized, placebo-controlled, double-blind, parallel-group study evaluated the efficacy and safety of linagliptin administered as add-on therapy to metformin (≥1500 mg/day) in patients with T2DM with inadequate glycemic control (mean baseline HbA1c of 8.1 % and mean FPG of 9.4 mmol/l)[92]. The addition of linagliptin 5 mg once daily (n = 524) showed significant reductions vs. placebo (n = 177) in adjusted mean changes from baseline of HbA1c (-0.49 vs. 0.15%), FPG (-0.59 vs. 0.58 mmol/l) and 2h postprandial glucose (-2.7 vs. 1.0 mmol/l). Rescue glycemic therapy was less used in patients treated with linagliptin 5 mg than in those receiving placebo (7.8% vs.18.9%). Such improvement in glycemic control with linagliptin occurred without weight gain or increased risk of hypoglycemia.

As metformin is administered twice daily, a fixed-dose combination of these compounds would require twice-daily administration of linagliptin. Therefore, a study evaluated whether 2.5 mg twice-daily dosing of linagliptin has comparable efficacy and safety to 5 mg once-daily dosing when given in addition to metformin twice daily in patients with inadequate glycemic control[93]. A total of 491 T2DM patients with HbA1c 7.0-10.0% were randomized to double-blind treatment with linagliptin 2.5 mg twice daily, 5 mg once daily or placebo, respectively, in addition to continuing metformin twice daily (≥1500 mg/day or maximally tolerated dose). After 12 weeks, linagliptin 2.5 mg twice daily and 5 mg once daily both significantly reduced HbA1c [placebo-adjusted changes from baseline (7.97%) -0.74% (95% CI -0.97, -0.52) and -0.80% (95% CI -1.02, -0.58), respectively, both $p < 0.0001$]. The treatment difference (twice daily - once daily) between the linagliptin regimens was 0.06 (95% CI -0.07, 0.19), the upper bound of which was less than the predefined noninferiority margin (0.35%). Hypoglycemia was rare (3.1% with linagliptin 2.5 mg twice daily, 0.9% with 5 mg once daily, 2.3% with placebo) with no severe episodes. Linagliptin 2.5 mg twice daily had non-inferior HbA1c-lowering effects after 12 weeks compared to 5 mg once daily, with comparable safety and tolerability, in T2DM patients inadequately controlled with metformin.

3.2.2. Comparison versus a sulfonylurea

Sulfonylureas are still considered as the primary add-on-therapy in several guidelines because of a lower cost compared to newer glucose-lowering agents[3]. In T2DM patients not well controlled by metformin monotherapy, the addition of a DPP-4 inhibitor such as linagliptin can be considered as a valuable alternative to the addition of a sulfonylurea, especially in those for whom the risk of hypoglycemia and weight gain is of concern[3]. In a recent network meta-analysis, HbA1c decrease was slightly greater for sulfonylureas compared with DPP-4 inhibitors [-0.12% (-0.23 to -0.03%)][18]. However, most of the trials included in that meta-analysis were rather short term, which may favor sulfonylurea-induced glucose-lowering effect as early potency with secondary failure is a common finding with such therapy, even in patients receiving a basal therapy with metformin[24, 94]. Besides a lower weight gain compared to sulfonylureas, the advantage of a gliptin is especially of interest in patients at risk of hypoglycemia[3]. A better B-cell protection is also expected with incretin-based therapies, which might result in a better durability of the glucose-lowering effect, although this remains to be proven in patients with T2DM.

In a 2-year (the longest head-to-head study available yet), parallel-group, non-inferiority double-blind trial, outpatients with T2DM and HbA1c 6.5-10.0% on stable metformin alone or with one additional oral antidiabetic drug (washed out during screening) were randomly assigned to linagliptin (5 mg; n=777) or glimepiride (1-4 mg; n=775) orally once daily in addition to metformin (daily dose ≥ 1500 mg in 93% of patients)[95]. Reductions in adjusted mean HbA1c from baseline (7.69% in both groups) to week 104 were similar in the linagliptin (-0.16%) and glimepiride groups (-0.36%; difference 0.20%, 97.5% CI 0.09-0.30), meeting the predefined non-inferiority criterion of 0.35%. Fewer participants had hypoglycemia (7% vs. 36%, p<0.0001) or severe hypoglycemia (1 vs. 12 patients) with linagliptin compared with glimepiride.

3.3. Initial linagliptin-metformin combined therapy

Recent recommendations emphasized the potential benefit of early combined therapy in the management of T2DM[6]. This may be explained by the complex pathophysiology of the disease and the numerous organ defects that are involved in T2DM and may potentially be targeted by pharmacological interventions[2].

A large (n=791) 24-week, double-blind, placebo-controlled, Phase III trial evaluated the efficacy and safety of initial combination therapy with linagliptin plus metformin versus linagliptin or metformin monotherapy in patients with T2DM[96]. Two free combination therapy arms received linagliptin 2.5 mg twice daily (bid) + either low (500 mg) or high (1000 mg) dose metformin bid. Four monotherapy arms received linagliptin 5 mg once daily, metformin 500 mg or 1000 mg bid or placebo. Patients with HbA1c ≥11.0% were not eligible for randomization and received open-label linagliptin + high-dose metformin.The placebo-corrected mean (95% CI) change in HbA1c from baseline (8.7%) to week 24 was -1.7% (-2.0, -1.4) for linagliptin + high-dose metformin, -1.3% (-1.6, -1.1) for linagliptin + low-dose metformin, -1.2% (-1.5, -0.9) for high-dose metformin, -0.8% (-1.0, -0.5) for low-dose metformin and -0.6 (-0.9, -0.3) for linagliptin (all p < 0.0001). In the open-label arm, the mean change in HbA1c from baseline (11.8%) was -3.7%. Hypoglycemia occurred at a

similar low rate with linagliptin + metformin (1.7%) as with metformin alone (2.4%). Adverse event rates were comparable across treatment arms. No clinically significant changes in body weight were noted. Initial combination therapy with linagliptin plus metformin was superior to metformin monotherapy in improving glycemic control, with a similar safety and tolerability profile, no weight gain and a low risk of hypoglycemia.

3.4. Limitations regarding the efficacy of the linagliptin-metformin combination

It is noteworthy that T2DM patients included in the clinical trials having investigated the linagliptin-metformin combination, either when linagliptin was added to metformin or when the two drugs were used as initial combined therapy, had HbA1c levels below 11%. Therefore, this combination should not be recommended in patients with very poorly controlled T2DM, even if impressive results were reported in an open-label arm[96]. Furthermore, the overall HbA1c reduction with linagliptin 5 mg added to metformin averaged 0.7-0.8 % at best. However, the reduction was greater in drug-naïve patients for whom a combined linagliptin-metformin was initiated, ranging from 1.3 to 1.7 % (placebo-subtracted changes). Thus, if a HbA1c level below 7% is the target, most patients with HbA1c levels above 8.5-9 % will not reach this goal, which opens the door to other treatment strategies[3].

4. Safety profile

4.1. Overall tolerance

The safety profile of linagliptin has been analyzed in detail in previous reviews[65, 97] and is generally good and quite similar to that previously reported with other DPP-4 inhibitors[8, 98, 99]. The combination of linagliptin and metformin is generally well tolerated. The safety/tolerance profile of linagliptin-metformin coadministration is similar to that of metformin alone. The safety of concomitantly administered linagliptin (daily dose 5 mg) and metformin (mean daily dose of approximately 1800 mg) has been evaluated in 2816 patients with T2DM treated for ≥12 weeks in clinical trials. Three placebo-controlled studies with linagliptin + metformin were conducted: 2 studies were 24 weeks in duration, 1 study was 12 weeks in duration. In the 3 placebo-controlled clinical studies, adverse events which occurred in ≥5% of patients receiving linagliptin + metformin (n=875) and were more common than in patients given placebo + metformin (n=539) included nasopharyngitis (5.7% vs 4.3%)[51]. Cases of pancreatitis were exceptional. In a 24-week factorial design study, adverse events reported in ≥5% of patients receiving linagliptin + metformin were more common than in patients given placebo (nasopharyngitis : 6.3 vs. 1.4%; diarrhea : 6.3 vs. 2.8%) and only slightly higher than with either monotherapy[96]. Of note, the addition of linagliptin to metformin therapy does not appear to cause a greater incidence of gastrointestinal side effects than does metformin alone.

4.2. Body weight

Overall, no clinically relevant changes in body weight were observed with linagliptin added to metformin. In a pooled analysis of 24-week phase III trials followed by a 78-week

open-label extension, treatment with linagliptin was not associated with a clinically relevant change in body weight (-0.03 kg change in subjects previously treated with linagliptin during the initial 24-week period, 0.47 kg in those switched from placebo)[100]. In a recent two-year head-to-head comparative trial in T2DM patients treated with metformin, body weight decreased with linagliptin (−1.4 kg) but increased with glimepiride (+1.3 kg) from similar mean baseline values (86.0 *vs* 87.0 kg); the treatment difference was −2.7 kg (97.5% CI −3.2 to −2.2, p<0.0001).

4.3. Hypoglycemia

The likelihood of treatment-related hypoglycemia is very low with the dual combination metformin plus linagliptin, but increased when linagliptin or linaglipin-metformin are coprescribed with a sulfonulyrea[100]. In a large (n=1058 T2DM patients) multi-centre, 24-week, randomized, double-blind, parallel-group study comparing linagliptin (5 mg once daily) and placebo when added to metformin plus sulfonylurea, symptomatic hypoglycemia occurred in 16.7 and 10.3% of the linagliptin and placebo groups, respectively[48]. Hypoglycemia was generally mild or moderate and no more severe hypoglycemia was reported with linagliptin than with placebo.

4.4. Cardiovascular events

Of potential interest, preliminary data from a 104-week trial showed a lower incidence of cardiovascular events with linagliptin added to metformin compared with the addition of a sulfonylurea (glimepiride) to metformin (12 vs. 26 patients; relative risk 0.46, 95% CI 0.23-0.91, p=0.0213)[95]. This observation is in agreement with the potential beneficial effect of DPP-4 inhibitors on cardiovascular outcomes.[101] Further information on the cardiovascular safety and efficacy of linagliptin versus glimepiride will be provided by the ongoing prospective CAROLINA ("CARdiovascular Outcome study of LINAagliptin versus glimepiride in patients with T2DM") study in which numerous patients will receive metformin as baseline therapy[102]. Meta-analyses reported that both metformin[103] and linagliptin[104] may be associated with a reduced incidence of cardiovascular events, suggesting that combination of the two drugs may be of potential interest in T2DM patients at high cardiovascular risk.

4.5. Safety in patients with CKD

One particularity of linagliptin is that this DPP-4 inhibitor may be safely and effectively used in all T2DM patients whatever the renal function (even in patients with severe CKD)[105]. In contrast, the use of metformin in patients with mild to moderate CKD is either contraindicated (as stated in the labeling) or at least limited, with dose reduction and regular careful supervision of renal function as proposed more recently[3, 46]. The safety aspects of using linagliptin and metformin in patients with mild to moderate CKD will be more extensively discussed in a further paper[106].

5. Linagliptin plus metformin FDC

Linagliptin plus metformin combination, given separately, has proven its superiority as compared to either monotherapy[96]. However, there is no study published as full peer-reviewed paper having evaluated the long-term effect of the FDC linagliptin plus metformin. The FDC (Jentadueto®) has been developed as tablets with three different dosage forms and strengths to be administered twice daily : linagliptin 2.5 mg plus metformin hydrochloride 500 mg, linagliptin 2.5 mg plus metformin hydrochloride 850 mg and linagliptin 2.5 mg plus metformin hydrochloride 1000 mg. This FDC may be prescribed when treatment with both linagliptin and metformin are appropriate. In the treatment of patients with T2DM, the FDC linagliptin plus metformin FDC (Jentadueto®) is indicated : 1) as an adjunct to diet and exercise to improve glycemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone[93]; 2) in those already being treated with the combination of linagliptin and metformin[96]; and 3) in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea[48, 49]. The recommended starting doses are as follows : in patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily; in patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g., a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily with meals); in patients already treated with linagliptin and metformin individual components may be switched to Jentadueto® FDC containing the same doses of each component. The dosage should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. Dose escalation should be gradual to reduce the gastrointestinal side effects associated with metformin use. Because of the presence of metformin, Jentadueto® is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment, although such restriction might be dampened in a near future provided that patient's careful supervision is warranted[106].

6. Conclusion

The combination of metformin, the first choice glucose-lowering drug, and a DPP-4 inhibitor such as linagliptin sounds as a valuable option in the management of patients with T2DM. Indeed the two compounds act via different, albeit complementary, mechanisms leading to an at least additive glucose-lowering activity, with overall a good safety profile. On the one hand, metformin acts predominantly by inhibiting hepatic glucose production but is also associated with a slight increased production of GLP-1 by intestinal L cells. On the other hand, linagliptin increases endogenous GLP-1 levels by inhibiting the metabolism of this incretin gut hormone, an effect that is associated with an increase in insulin secretion and a suppression of glucagon secretion in a glucose-appropriate fashion. Thus, combining both agents results in a further increase of GLP-1 levels. In addition, the modes of action of the two compounds tackle various main defects in the pathophysiology of T2DM, i.e. impaired insulin secretion, increased glucagon levels, increased hepatic glucose production and decreased insulin sensitivity. Despite the fact that both pharmacological agents are substrates of OCT1 and OCT2, there is no clinically relevant PK DDIs between linagliptin and metformin

reported so far. Linagliptin may be used in T2DM patients with any degree of renal impairment, because its almost absence of renal excretion, a characteristic that differentate the drug from other DPP-4 inhibitors. In contrast, caution is recommended with metformin use in patients with mild to moderate CKD because of the risk of drug accumulation and lactic acidosis, a rare but potentaily fatal complication. Thus, linagliptin plus metformin, either separately or as FDC, can only be prescribed when treatment with both pharmacological agents is appropriate. Statistically significant and clinically relevant reductions in plasma glucose and HbA1c levels have been described in patients not reaching individually selected HbA1c targets despite diet and exercise, metformin alone or even metformin plus sulfonylurea therapies. No adverse effects have been reported, especially no weight gain and no severe hypoglycemia. Further studies are waited to demonstrate the long-term benefit of the linagliptin plus metformin combination, especially regarding a reduction of diabetes vascular complications.

EXPERT OPINION SECTION

Type 2 diabetes (T2DM) is a complex and quite heterogeneous disease. The 2012 joint position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends a patient-centred approach in the management of hyperglycemia in patients with T2DM. It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first pharmacological agent. It is initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, individualized glycated hemoglobin (HbA1c) goals. If monotherapy alone does not achieve/maintain an HbA1c target over ~3 months, the next step would be to add a second glucose-lowering agent. On average, any second agent is typically associated with an approximate further reduction in HbA1c of ~1%. With a distinct paucity of long-term comparative effectiveness trials available, uniform recommendations on the best agent to be combined with metformin cannot be made, as stated in the ADA-EASD document. Thus, advantages and disadvantages of specific drugs for each patient should be considered. Choice is based on patient and drug characteristics, with the overriding goal of improving glycemic control while minimizing side effects. In this regard, the addition of a dipeptidyl peptidase-4 (DPP-4) inhibitor may offer potential benefits over classical sulfonylureas in T2DM patients at risk of hypoglycemia and in those overweight who fear further weight gain.

The clinical studies presented so far with the novel DPP-4 inhibitor linagliptin as add-on therapy to metformin showed clinically relevant improvement in glycemic control. Mean HbA_{1c} levels were reduced by approximately 0.65%–0.80% from a baseline of 7.9%–8.5% with linagliptin 5 mg compared to placebo. Furthermore, the combination was tolerable and safe with similar adverse events profile as placebo-treated patients given metformin alone. As with other DPP-4 inhibitors, the addition of linagliptin to metformin monotherapy was weight neutral and was not associated with any increased risk of hypoglycemia.

Linagliptin has a unique pharmacokinetic profile compared to other DPP-4 inhibitors, with a very low renal excretion and a predominant biliary excretion. This characteristic allows

use linagliptin in T2DM patients with chronic kidney disease (CKD : from mild to severe) without contra-indication and any dose adjustment. Considering the large number of patients with some degree of renal impairment (especially in the elderly population), this may represent an advantage over other DPP-4 inhibitors. Indeed, for the latter, a dose adjustment is required according to the reduction of estimated glomerular filtration rate (eGFR) that should be regularly and carefully monitored. However, the linagliptin plus metformin combination, especially the novel fixed-dose combination (FDC : Jentadueto®), can not be used in T2DM patients with renal impairment according to official guidelines because of the presence of metformin and the potential risk of lactic acidosis in case of biguanide accumulation.

The use of metformin in patients with renal impairment remains, however, controversial. According to the official label, metformin should not be used above a certain threshold of serum creatinine or when eGFR is below 60 ml/min/m². However, in clinical practice, numerous T2DM patients are currently treated with metformin despite an eGFR below this limit, without any adverse events and even, with potential benefits. There is an ongoing debate as to whether these thresholds are too restrictive and thereby not allow patients with mild-moderate renal impairment gain more benefit than harm from using metformin. In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines are less proscriptive, generally allowing use of metformin down to a GFR of 30 ml/min, with dose reduction advised at 45 ml/min. If so, the use of linagliptin plus metformin, either separately or as FDC, would be extended to a larger population of patients with T2DM and the specific advantage of linagliptin regarding its use independent of renal function would even be better appreciated in clinical practice.

In general, a FDC may offer some advantages in clinical practice. By increasing convenience, it could increase patient's adherence. Adherence to therapy is, indeed, a major concern in patients with T2DM who generally share several chronic comorbidities and thereby should receive multiple medications. However, as the classical formulation of metformin hydrochloride should be given twice daily, the linagliptin plus metformin FDC has also to be given twice daily while once daily administration of linagliptin is enough to maintain sustained DPP-4 inhibition over 24 hours. Furthermore, a FDC combination has the disadvantage not to allow an easy titration of each of the two individual agents. Because metformin should be titrated to improve gastrointestinal tolerance, various FDC forms with different strengths of metformin have been developed. However, the FDC with the lower dosage of metformin – 500 mg – will not be launched in Europe and this decision would not allow use the FDC in patients with mild renal impairment for whom metformin dosage should be reduced according to the eGFR level.

In the ADA-EASD position statement, initial combination drug therapy is limited to patients with a high baseline HbA1c (e.g. ≥9.0% [≥75 mmol/mol]) who have a low probability of achieving a near-normal target with monotherapy. It may therefore be justified to start directly with a combination of two glucose-lowering agents in this circumstance. During recent years, however, there has been a discussion of introducing initial combination therapy (instead of metformin alone) when pharmacological treatment is required for T2DM, in order to reach therapeutic goal at an earlier stage, have a better stabilisation of this evolving

disease and avoid or delay subsequent changes in therapy for the maintenance of therapeutic goal. Because the complementary effects of linagliptin and metformin lead to robust and sustained improvements in glycemic control, initial combination of the two agents may be considered as a useful treatment option for patients withT2DM. However, the durability of the glucose-lowering effect of the combination linagliptin plus metformin needs to be further explored in long-term controlled trials. Especially, its superiority regarding clinical (cardiovascular) outcomes, compared to the classical metformin-sulfonylurea combination, remains to be demonstrated in further large prospective trials, such as CAROLINA.

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Figure 1 : Synergistic effects of metformin and linagliptin on blood glucose control in patients with T2DM. AMPK : AMP-activated protein kinase. DPP-4 : dipeptidyl peptidase-4. GLP-1 : glucagon-like peptide-1. GIP : glucose-dependent insulinotropic polypeptide.

Table 1 : Results from open-label, randomized, single dose, two-way crossover, trials studying the bioequivalence between fixed-dose combinations (FDC) and separate tablets of linagliptin (2.5 mg) and three different strengths of metformin hydrochloride (1000 mg 500 mg and 850 mg) in 94-96 healthy volunteers (arithmic means and SD). Adapted from reference.[51]

Treatment	LINA/MET 2.5 mg/1000 mg FDC vs. LINA 2.5 mg + MET 1000 mg		LINA/MET 2.5 mg/500 mg FDC vs. LINA 2.5 mg + MET 500 mg		LINA/MET 2.5 mg/850 mg FDC vs. LINA 2.5 mg + MET 850 mg	
	AUC_{0-72} nmol.h/L	C_{max} nmol/L	AUC_{0-72} nmol.h/L	C_{max} nmol/L	AUC_{0-72} nmol.h/L	C_{max} nmol/L
LINAGLIPTIN PLASMA LEVELS						
FDC (test)	163 ± 45.9	5.20 ± 1.25	188 ± 50.6	5.53 ± 1.51	165 ± 42.6	5.38 ± 1.31
LINA+MET (reference)	192 ± 39.0	5.03 ± 1.20	188 ± 50.5	5.64 ± 1.56	160 ± 42.9	5.10 ± 1.19
Ratio (90% CI)	106.4 (102.7-110.2)	103.4 (100.3-106.7)	100.0 (96.7-103.4)	98.2 (94.5-102.1)	104.5 (100.6-108.5)	106.2 (102.9-109.7)
	AUC_{0-Z} ng.h/ml	C_{max} ng/ml	AUC_{0-Z} ng.h/ml	C_{max} ng/ml	AUC_{0-Z} ng.h/ml	C_{max} ng/ml
METFORMIN PLASMA LEVELS						
FDC (test)	11300 ± 2930	1740 ± 462	7530 ± 1840	1170 ± 315	11400 ± 2840	1710 ± 458
LINA+MET (reference)	10800 ± 2830	1670 ± 478	7590 ± 1910	1200 ± 329	11400 ± 3030	1730 ± 501
Ratio (90% CI)	103.6 (100.0-107.4)	104.3 (99.8-108.9)	99.4 (96.5-102.3)	97.9 (94.4-101.5)	101.0 (98.1-103.9)	100.1 (96.5-104.0)

LINA = linagliptin. MET = metformin. FDC : fixed-dose combination. AUC_{0-72} : area under the plasma concentration-time curve from time zero to 72 hours. AUC_{0-Z} : area under the plasma concentration-time curve from time zero to last timepoint with a plasma concentration above the quantification limit. C_{max} : maximum plasma concentration.

Table 2 : Main randomized controlled trials assessing the efficacy of the combination linagliptin-metformin in patients with T2DM treated with metformin alone (≥ 1500 mg/day) or as initial combination therapy in patients treated with diet alone.

		Number of patients	Study Duration (weeks)	HbA_{1c} Baseline (%)	HbA1c Baseline (mmol/mol)	HbA_{1c} Change from baseline (%)	FPG Change from baseline (mmol/l)	Body weight Change from baseline (kg)
Linagliptin added to metformin monotherapy								
Comparison versus Placebo								
Forst et al 2010[91]	Linagliptin 5 mg od	66	12	8.50	69.4	-0.48	-1.22	-0.57
	Linagliptin 10 mg od	66	12	8.40	68.3	-0.42	-0.90	-1.27
	Placebo od	71	12	8.40	68.3	+0.25	+0.70	-0.84
Taskinen et al 2011[92]	Linagliptin 5 mg od	523	24	8.09	64.9	-0.49	-0.60	-0.50
	Placebo od	177	24	8.02	64.2	+0.15	+0.60	-0.40
Ross et al 2012[93]	Linagliptin 5 mg od	224	12	7.98	63.7	-0.52	-0.99*	-1.0
	Linagliptin 2.5 mg bid	223	12	7.96	63.5	-0.46	-0.76*	-0.4
	Placebo	44	12	7.92	63.1	+0.28	-	-1.1
Comparison versus Glimepiride								
Forst et al 2010[91]	Linagliptin 5 mg od	66	12	8.50	69.4	-0.48	-1.22	-0.57
	Glimepiride 1-3 mg od	65	12	8.20	66.1	-0.68	NA	+0.73
Gallwitz et al 2012[95]	Linagliptin 5 mg od	776	104	7.70	60.7	-0.16	-0.13	-1.4
	Glimepiride 1-4 mg od	775	104	7.70	60.7	-0.36	-0.48	+1.3
Initial linagliptin-metformin therapy in diet-treated patients								
Haak et al 2012[96]	Linagliptin 5mg od	135	24	8.70	71.6	-0.50	-0.50	+0.2
	Metformin 500mg bid	141	24	8.70	71.6	-0.60	-0.90	-0.7
	Metformin 1000 mg bid	138	24	8.50	69.4	-1.10	-1.80	-0.5
	Linagliptin 2.5 mg + Metformin 500 bid	137	24	8.70	71.6	-0.20	-1.80	-0.1
	Linagliptin 2.5 mg +	140	24	8.70	71.6	-1.60	-2.70	-0.8

	Metformin 1000 mg bid							
	Placebo	65	24	8.70	71.6	+0.1	+0.60	-0.7

Reduction = changes at end of follow up versus baseline (not versus comparator). FPG : fasting plasma glucose. NA : not available. Od : once daily. Bid : twice daily. *Adjusted mean difference from placebo instead of change versus baseline

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Article highlights

- Linagliptin increases glucagon-like peptide-1 (GLP-1) levels by inhibiting dipeptidyl peptidase-4 (DPP-4) and thereby enhances insulin secretion and reducing glucagon levels while metformin acts primarily by inhibiting hepatic glucose production but also promotes the secretion of GLP-1. These complementary metabolic actions result in an additive glucose-lowering activity for the management of type 2 diabetes.
- Metformin is mainly excreted by the kidneys whereas linagliptin has a negligible renal excretion (in contrast to other DPP-4 inhibitors) but has a predominant biliary excretion. Therefore, metformin is contraindicated in presence of renal impairment (or the dosage should be reduced according to the glomerular filtration rate) whereas linagliptin may be used at the same dosage of 5 mg/day whatever the level of kidney function (even in case of severe renal impairment).
- There are no pharmacokinetic drug-drug interactions between linagliptin and metformin and a fixed-dose combination (FDC) has proven to be bioequivalent compared to separate tablets. Linagliptin and metformin can be given with food either separately or as a FDC. No titration is required for linagliptin (5 mg once daily when given separately or 2.5 mg twice daily as FDC) but a initial titration of metformin is generally recommended to improve gastrointestinal tolerance (which explains the different strengths of metformin in the proposed FDCs
- When linagliptin is added to metformin, a clinically relevant reduction of glycated hemoglobin (HbA1c) of almost 0.8 % could be obtained, without weight gain and without hypoglycemia. The improvement of glucose control was non inferior to that observed with the sulfonylurea glimepiride, with a better tolerance profile. Initial combination in drug-naïve patients has also proven to be remarkably effective and more potent than either individual component.
- The use of the linagliptin plus metformin in patients with mild to moderate chronic kidney disease remains a matter of debate. Preliminary analysis suggest that linagliptin (combined with metformin) may reduced the incidence of cardiovascular events in patients with type 2 diabetes and such a protective cardiovascular effect is currently tested in the ongoing prospective trial CAROLINA comparing linagliptin with glimepiride.

This box summarizes key points contained in the article

Pivotal trials : 76,91,92,93,95,96