Linagliptin: A Novel Xanthine-Based Dipeptidyl Peptidase-4 Inhibitor for Treatment of Type II Diabetes Mellitus

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Abstract: Type 2 diabetes mellitus causes significant morbidity and mortality on account of its progressive nature and results in considerable burden on healthcare resources. Current treatment strategies have only limited long-term efficacy and tolerability given the progressive nature of the disease leading to inadequate glycemic control and are also associated with undesirable side effects such as weight gain, hypoglycemia and gastrointestinal distress. In the light of these existing limitations, exploring new treatment targets and new therapies have become the need of the hour at present. The incretin pathway, in particular, glucagon-like peptide (GLP-1), plays an important pathological role in the development of type 2 diabetes mellitus, and treatments targeting the incretin system have recently generated surmount interest. These can mainly be categorized into two broad classes; GLP-1 agonists/analogs (exenatide, liraglutide), and dipeptidyl peptidase- 4 inhibitors (sitagliptin, vildagliptin). The gliptins act by prolonging the action of incretins, the gut hormones which can boost insulin levels. Linagliptin is the latest dipeptidyl peptidase-4 inhibitor to complete pivotal phase III trials, which have demonstrated its superiority to its competitors based on its low therapeutic dose, long-lasting inhibition of DPP-4 activity and a good safety/tolerability profile. One of the unique characteristics of linagliptin is its primarily non-renal route of excretion. The drug has recently been approved by the US Food and Drug Administration and has been portrayed as a promising treatment option for patients in whom metformin and the other DPP-4 inhibitors are either contraindicated or require dose adjustment because of moderate to severe renal impairment.

Keywords: Linagliptin, DPP-4 inhibitors, Incretin, Plasma glucose, Type II diabetes mellitus.

INTRODUCTION

Diabetes mellitus refers to a group of metabolic diseases characterized by hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Himsworth *et al* in 1930s was the first to recognize that two types of diabetes mellitus exist- one due to insufficiency of insulin (type 1); the other due to resistance to the action of insulin (type 2) [1].

Type II diabetes mellitus (T2DM) is the most common endocrine disorder worldwide, characterized by fasting and postprandial hyperglycemia and relative insulin insufficiency [2]. Untreated hyperglycemia may cause long-term microvascular and macrovascular complications, such as nephropathy, neuropathy, retinopathy, and atherosclerosis and is associated with co morbidities, such as obesity, hypertension, hyperlipidemia (increased VLDL, triglycerides and decreased HDL cholesterol), and cardiovascular disease, which taken together, comprise the 'Metabolic Syndrome' [3].

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Emerging as an epidemic of the 21st century T2DM has become a major health problem throughout the globe. It is noteworthy that India has the largest population of patients with T2DM and the International Diabetes Federation (IDF) estimates the number of people with diabetes in India to reach to 80 million by 2025 [4]. Another report by the IDF states that the T2DM epidemic now affects a staggering 246 million people worldwide, with 46% of all those affected in the 40-59 age group and it is estimated that the total number of people living with diabetes will skyrocket to 380 million within 20 years if significant steps are not taken well in time [3].

Obesity, mainly when fat is distributed largely at the abdominal level is the main risk factor for T2DM. For T2DM patients, excess weight can increase the risk of mortality; up to 8-fold for those with weight >40% above ideal target weight [5]. Also, the worldwide trend of developing societies shifting away from an agrarian existence to city living and less physically demanding office and factory jobs also is taking its toll [6].

The natural history of diabetes usually begins with obesity leading to insulin resistance which in turn promotes a state of compensatory hyperinsulinemia leading to other adverse sequelae [7]. Initially, normoglycemia is maintained

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because of compensatory increase in insulin secretion by the ß-cell. Ultimately insulin secretion and insulin concentration fall leading to increased hepatic glucose production and overt diabetes. Beta-cell function continues to decline in the presence of continued insulin resistance making treatment complex and achievement of therapeutic targets difficult [8]. Hence, the failure of ß-cells to secrete sufficient insulin to overcome insulin resistant (IR) (i.e., ß-cell dysfunction) is the crucial step in the development and progression of T2DM. Based on the current understanding of the pathophysiology of T2DM, multiple pharmacological and nonpharmacological interventions have been developed over the past five decades to improve glycemic control and slow disease progression [9]. However, gradual loss in drug efficacy over time due to progressive deterioration in beta-cell function is the main limitation as most of the observed initial improvements in glycemic control are not sustained [2]. Furthermore, most of these treatments have undesired side effects: sulfonylureas increase insulin secretion, but are associated with hypoglycemia and weight gain; metformin reduces hepatic glucose output, is weight neutral, and is not associated with hypoglycemia, but has a relatively high frequency of gastrointestinal side effects; thiazolidinediones improve ß-cell function and reduce IR, but are associated with weight gain and can cause peripheral edema; meglitinides improve insulin secretion from ß-cells, but increases the incidence of hypoglycemia and weight gain compared with metformin; finally, insulin therapy produces sustainable glycosylated hemoglobin A1c (HbA1c) reductions and might improve ß-cell function, but causes hypoglycemia and weight gain. Hence, interventions that can slow and/or reverse ß-cell decline, which result in weight loss and do not result in hypoglycemia, might be expected to have a significant sustained impact in patients with T2DM [10]. Incretin-based therapies are new class of anti-diabetic medication that may address some of the abovementioned shortfalls of current treatments [9]. The major advantages of this class of drugs are that they are generally well tolerated, and that the risk of hypoglycemia is less than that of traditional diabetes medication. A further benefit is a neutral, or even reductive, effect on body weight [2].

TREATMENT OF T2DM WITH INCRETIN BASED THERAPIES

Two gut derived peptides, glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) account for over half the incretin effect after a meal [11]. T2DM is due to little or no incretin-mediated augmentation of insulin secretion, which can be attributed to a decreased secretion of GLP-1 and loss of the insulinotropic effects of GIP. GLP-1, however, retains the insulinotropic effects and effectively improves metabolism in T2DM patients [12]. Moreover, published reports with assays that cross-react with substances in plasma that are unrelated to GIP, have suggested elevated, decreased and unchanged concentrations of GIP in patients with T2DM [13]. In a large group of type 2 diabetic subjects, Toft-Nielsen *et al.* observed a pronounced impairment of the postprandial GLP-1 response, particularly during the later postprandial phase [14]. Although similar findings were reported in subsequent studies [15], some studies could not confirm decreased GLP-1 responses in T2DM [16, 17]. GLP-1 has shown to have trophic effects on ß-cells: not only does it stimulate ß-cell proliferation but it also enhances the differentiation of new ß-cell from progenitor cells in the pancreatic duct epithelium [18]. The incretin hormones also affect glucagon secretion. GIP has thus been demonstrated to stimulate glucagon secretion, whereas GLP-1 inhibits glucagon secretion. Both incretins inhibit gastric emptying [19]. These actions render GLP-1 highly attractive as a therapeutic agent, but an extremely rapid enzymatic degradation of the molecule makes it unsuitable for injection therapy. This metabolism, which is attributable to the actions of the ubiquitous enzyme dipeptidyl peptidase IV (DPP-4), results in a half-life for GLP-1 of only about two minutes; furthermore, the actions on metabolism of single subcutaneous injection are short-lived. The conclusion drawn was that GLP-1 based therapy has unusually attractive potential in diabetes treatment. Therefore, two strategies have been pursued. One strategy is the development of DPP-4 resistant GLP-1 analogues. Exetinide, isolated from the saliva of the lizard Gila monster is such a molecule. It is 53% homologous to GLP-1 (but it is not the GLP-1 of the Gila monster) and is cleared from the plasma at a rate of 1.8 ml/kg/min, which is similar in magnitude to the normal glomerular filteration rate [18]. Twice daily exenatide, another GLP-1 analogue with a half-life of 2–3 h, is approved for the treatment of type 2 diabetes. Liraglutide is a once daily human GLP-1 analogue with a half-life of 13 h, and provides 24-h glycemic control with one daily injection. Another approach is to inhibit the action of DPP-4 and thereby prolong and increase the levels of endogenously released GLP-1 two to four times (e.g., sitagliptin, vildagliptin, saxagliptin) [20].

DPP-4 is a ubiquitous enzyme that can be detected in the endothelium of different organs, and which demonstrates measurable circulating enzymatic activity in plasma. In addition to GLP-1 and GIP, peptides such as pituitary adenylate cyclase-activating polypeptide and gastrin-releasing peptide are substrates of DPP-4; however, the affinity of DPP-4 is higher for GLP-1 than for these other peptides, including GIP [21]. An increase in levels of uncleaved, biologically active GLP-1 caused by DPP-4 inhibitors offers an alternative therapeutic option in type 2 diabetes [22]. Recently, another study has demonstrated that high levels of GLP-1 should be maintained for 24 h for optimal glycemic control [23]. Thus, in addition to focusing on potency and selectivity, development of long acting inhibitors is also desirable that could potentially provide maximal efficacy, particularly in patients suffering from severe diabetes (e.g., HbA1c >9%). Structurally, two distinctive classes, for example, peptidomimetic and non-peptidomimetic DPP-4 inhibitors have been reported. The peptidomimetic class can be subdivided into (a) glycine-based (α-series A) and (b) ß-alanine-based (ß -series B) inhibitors. Interactions of α - and ß -series with the DPP-4 enzyme do not follow the same pattern [24]. Studies in animals have demonstrated DPP-4 inhibitors to be effective in enhancing endogenous levels of GLP-1, resulting in improved glucose tolerance in glucose-intolerant and diabetic animal models. Also, clinical studies of 3–12 months duration in patients with type 2 diabetes, proved DPP-4 inhibitors efficacious, both as monotherapy and when given in combination with metformin. Fasting and postprandial glucose concentrations were reduced, leading to

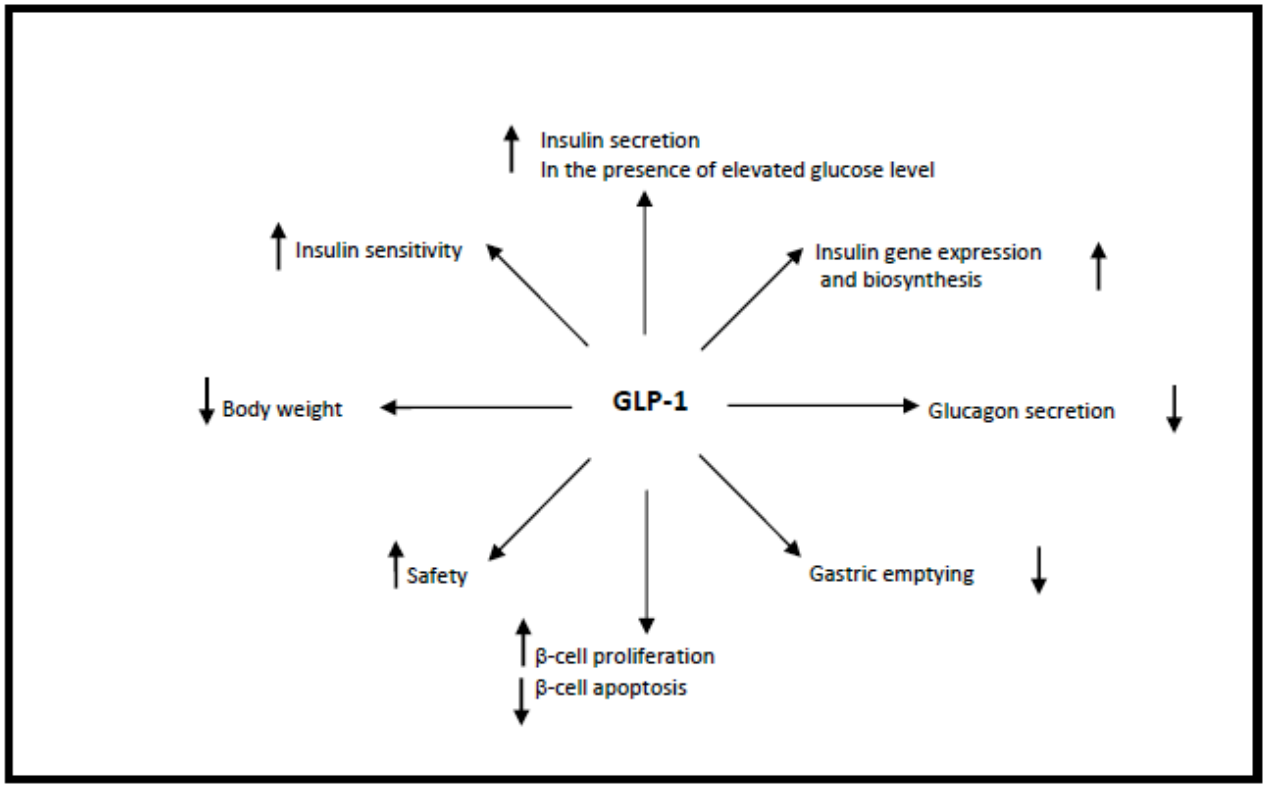


Fig. (1). Effect of DPP – 4 Inhibition.

reductions in glycosylated hemoglobin levels, while ß-cell function was preserved. Current information suggests DPP-4 inhibitors are body weight neutral and are well tolerated [25]. Fig. (**1**) highlights the various effects resulting from DPP – 4 Inhibition.

LINAGLIPTIN-INTRODUCTION

Linagliptin (chemical name: 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3- methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione) is a potent and highly selective oral DPP-4 inhibitor based upon a xanthine scaffold structure, which is being developed as an oral once-daily tablet by Boehringer Ingelheim Corp., USA as the company's lead diabetes compound [26]. In August 2008, Boehringer Ingelheim announced that all phase III clinical trials required for the registration of linagliptin had been initiated [27]. In June 2009, new phase II data results for linagliptin (BI 1356, Tradjenta™), were presented at the 69th Annual American Diabetes Association (ADA) Scientific Sessions in New Orleans, USA [28]. The compound is currently being studied in a number of pivotal, multi-centre, randomised, placebo-controlled, double-blind, phase III clinical trials including more than 4,000 patients to investigate the efficacy, safety and tolerability. These trials are fully recruited and underway globally and in many states across the U.S [29]. This will certainly lead to the enhancement of the product profile of linagliptin.

CHEMISTRY

Linagliptin, a xanthine derivative containing quinazoline and aminopiperidine moieties, with a molecular formula $C_{25}H_{28}N_8O_2$ and a molecular weight of 472.5 Da., was synthesized via sequential alkylation of the 7, 1 and 8 positions of the parent 7-benzyl-8-piperazinylxanthine molecule with appropriate halides. It was identified and optimized from a compound originally discovered by high-throughput screening as a potent DPP-4 inhibitor in the low micromolar range.

X-ray crystallography analysis of linagliptin in complex with human DPP-4 has highlighted that its butynyl substituent occupies the S1 hydrophobic pocket of the enzyme. The aminopiperidine substituent at C(8) of the xanthine scaffold occupies the S2 subsite, and its primary amine interacts with the key amino acid residues on Glu205, Glu206 and Tyr662 by the formation of three charge-reinforced hydrogen bonds, involved in the recognition of the amino terminus of the peptide substrates of DPP-4 [30]. A fourth hydrogen bond formation takes place between the C(6) carbonyl group of the xanthine scaffold and the backbone amide of residue Tyr631.

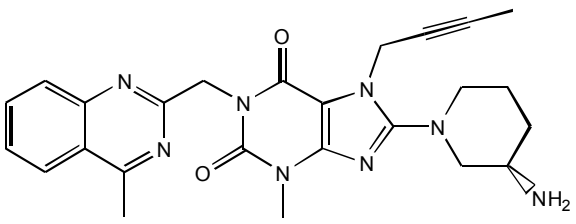


Fig. (2). Chemical structure of linagliptin

PRE-CLINICAL DEVELOPMENT

In vitro investigation of the potency, selectivity, mechanism, and duration of action of linagliptin (BI 1356) and subsequent comparison with other DPP-4 inhibitors in

an enzyme inhibition assay, showed linagliptin to be 19-, 24-, 50- and 62-fold more potent than sitagliptin, alogliptin, saxagliptin and vildagliptin, respectively in a direct head-to-head comparison [31]. Moreover, evidences from kinetic studies in Caco2 cells demonstrated that linagliptin is a competitive reversible inhibitor with a slower rate of dissociation from the enzyme, indicating the longer association with DPP-4 compared to vildagliptin [31]. Kinetic dissociation rates for other DPP-4 inhibitors were however not provided.

Single doses of linagliptin (0.1, 0.3, 1, 3 and 10 mg/kg p.o.) inhibited plasma DPP-4 activity in a dose-dependent manner within 30 min of administration in normal Han-Wistar rats, by > 70% with 1 mg/kg and by ~ 90% with 3- and 10-mg/kg doses at 7 h post dose [31]; with a persistent inhibitory activity observed until 24 h after dosing. Similar results were obtained in beagle dogs and rhesus monkeys as well, wherein; linagliptin (1 mg/kg p.o.) demonstrated a strong and sustained inhibition of plasma DPP-4 activity, with > 70% inhibition for > 7 h after dosing [30].

In C57BL/6J mice, a single-dose linagliptin (1 mg/kg p.o) exerted a longer-lasting effect on glucose tolerance with glucose excursion reduced by approximately 20 to 30% when an oral glucose tolerance test (OGTT) was conducted at 16 h after dosing. On the other hand, a 10-fold increase in the dose of sitagliptin and saxagliptin was able to cause such effects comparable with linagliptin 16 h following dosing [31, 32].

In obese, insulin-resistant Zucker rats, linagliptin (3 mg/kg p.o.) reduced the total glucose excursion by 29% following an OGTT conducted 30 min after dosing. An OGTT, when conducted 24 h after dosing, was associated with 77% increase in peak GLP-1 and 26% increase in peak insulin levels, thereby highlighting on the correlation between the inhibition of DPP-4 activity and an increase in active GLP-1 levels, resulting in an increase in plasma insulin levels and an improved glucose tolerance [31].

In diabetic db/db mice model, single- doses of linagliptin (0.1, 0.3 and 1 mg/kg, p.o.) dose-dependently reduced plasma glucose excursion by 15, 44 and 66% respectively, following an OGTT conducted 45 min after dosing. An OGTT, when conducted 30 min after dosing, was associated with a 76% inhibition of DPP-4 activity at the 1-mg/kg dose [33].

In a non-genetic multiple-dose model of type 2 diabetes in male high-fat diet/streptozotocin-induced diabetic mice, chronic administration of linagliptin (1, 3 or 10 mg/kg p. o. once daily for 4 weeks) dose dependently reduced plasma DPP-4 activity by 59, 78 and 87% at the respective doses. The steady state of enzyme inhibition was achieved on day 27. Glucose excursion on day 17 following an OGTT 16 h after the 3-mg/kg dose was significantly reduced, however; all doses were associated with improvements in HbA1c after 4 weeks. Active GLP-1 levels 16 h after drug administration were also dose dependently increased by up to threefold on day 28, with significance achieved in the 3- and 10-mg/kg dose groups [34].

In a primarily genetic model of type 2 diabetes involving male Zucker diabetic fatty (ZDF) rats, once-daily administration of linagliptin (3 mg/kg p.o, qd for 5 weeks) increased intact GLP-1 levels and resulted in similar improvements in oral glucose tolerance as vildagliptin (50% reduction in glucose excursion), when an OGTT was conducted 15 min after dosing on day 34. However, examination of 24-h glucose profiles revealed that, unlike vildagliptin, linagliptin reduced the overall glucose AUC by 10%, and was associated with a 0.4% decrease in HbA1c levels compared with controls, although the difference was statistically unremarkable in either treatment group [34].

A recent study in a genetic model of diabetic ob/ob mice has also shown Linagliptin (3 mg/kg p.o for 12 days) to reduce DPP-4 activity by 85.5%. Furthermore, glucose excursion was significantly reduced by 25% following an oral glucose challenge. Histological analysis demonstrated that linagliptin improved diabetes-impaired wound healing, leading to reduced wound size and improved wound morphology and re-epithelialization. This was supplemented by a reduction in the infiltration and accumulation of polymorphonuclear neutrophils, suggesting an improvement in wound inflammation [35].

TOXICITY PROFILE

Toxicological profile of linagliptin in a 26-week study in rats revealed lack of toxicity at plasma concentrations up to 300-fold greater than the therapeutic C_{max} value [36]. Similar results were obtained in a 52-week study in monkeys, in which no toxicity was observed with concentrations up to 150-fold greater than the therapeutic C_{max} value. Furthermore, there was no evidence of skin lesions in monkeys up to and including > 1000-fold the therapeutic exposure. On the whole, toxicological studies on linagliptin reported so far, demonstrated a sufficiently large safety margin for the therapeutically effective dose of the compound [36].

HUMAN PHARMACOKINETICS

Linagliptin was previously shown to exhibit nonlinear pharmacokinetics due to target-mediated, concentration dependent changes in binding to DPP-4 [37-39].

The pharmacokinetic profile of single-dose linagliptin (0.5, 2.5 and 10 mg iv, or 5 mg iv + 10 mg p.o) was assessed in healthy volunteers (n = 28) using a three-compartment model, with time-dependent protein binding in the central compartment and DPP-4 binding in the plasma and tissues in one peripheral compartment [40]. The absolute bioavailability of linagliptin was estimated to be approximately 30%, which is lower than that of sitagliptin (~ 87%) or vildagliptin (85%) [41, 42].

The single-dose pharmacokinetic profile of linagliptin (2.5, 5, 25, 50, 100, 200, 400 and 600 mg p.o), assessed in young (mean age 38 years), healthy, lean (mean BMI 24.8 kg/m^2) healthy male volunteers (n = 64), showed the drug to be rapidly absorbed, with time to peak plasma concentration (T_{max}) values occurring 0.7 – 3 h post dose [39, 43]. The elimination half-life ranged from 70 to 80 h for doses < 50 mg, and from 128 – 184 h for doses > 50 mg. < 1% of the dose was excreted in the urine for the 5-mg dose, but increased to 32.7% for the 600-mg dose.

The multiple-dose pharmacokinetic profile of linagliptin (1, 2.5, 5 and 10 mg p.o, qd for 12 days) was evaluated in patients with T2DM (n = 47) [38]. The T_{max} value ranged from 1 – 3 h post dose following both single and multiple dosing, and plasma exposure (linagliptin AUC) and maximal concentration (C_{max}) values increased less than dose proportionately. Steady state was attained by day 2 with the 10-mg dose and by days 4 to 6 at the other doses, with only modest drug accumulation (accumulation ratio: 1.18 – 2.03). The $t_{1/2}$ value at steady state was 113 to 131 h. Renal excretion of linagliptin was < 1% on day 1 at all doses, and remaining below 6% by day 12. Linagliptin was reported to be excreted primarily unchanged in the bile [36].

These results observed in the Caucasians were in concordance with that in healthy Japanese volunteers receiving multiple oral doses (1, 2.5, 5 and 10 mg q.d.) for 12 days and in a 4-week study of linagliptin (0.5, 2.5 or 10 mg q.d.) in Japanese subjects (n = 72) with T2DM [44, 45]. The studies revealed non-linear pharmacokinetics exhibited by linagliptin, with exposure increasing less than dose-proportionally. The terminal $t_{1/2}$ value was 97 to 175 h in the 12 day study; while a longer terminal $t_{1/2}$ value (223 to 260 h) was observed in the 4-week study. The dominant $t_{1/2}$ value ranged from approximately 10 to 15 h and from 10 to 40 h respectively in both the studies. Urinary excretion was always < 7% at steady state in all dose groups.

CLINICAL EFFICACY

Phase I Trials

A phase I, randomized, double-blind, placebo-controlled clinical trial in healthy male volunteers (n = 64) showed that plasma DPP-4 activity was inhibited by 73% following 2.5 mg linagliptin, with single doses of 25 – 600 mg giving > 95% inhibition [39]. Maximal inhibition was attained between 3 h (2.5 mg) and 0.7 h (≥200 mg) post dose. The inhibition of DPP-4 activity was long-lasting till 96 h after dosing. Decreases in DPP-4 activity exhibited direct correlation with the plasma concentration of linagliptin, wherein, 50 and 80% inhibition were attained at linagliptin concentrations of 2 – 4 and 4 – 6 nM, respectively.

Similar results were obtained in another phase I, randomized, double-blind, placebo-controlled clinical trial in healthy Japanese volunteers after both single (1, 2.5, 5 and 10 mg po; n = 32) and multiple oral doses of linagliptin (2.5, 5 and 10 mg/day po, for 12 days; n = 24), wherein plasma DPP-4 activity was suppressed dose-dependently and postprandial plasma GLP-1 levels were significantly increased in the treatment cohorts compared to the placebo [44].

In patients with T2DM (n = 47), a phase Ib, randomized, double-blind, placebo-controlled clinical trial showed that once-daily dosing of linagliptin for 12 days (1 – 10 mg) resulted in > 90% inhibition of plasma DPP-4 with the 5- and 10-mg doses at steady state, with approximately 85% inhibition at 24 h post dose (5 mg) [38]. This was associated with dose-dependent reductions in the glucose excursion following an OGTT conducted 24 h after the last dose with all but the lowest dose of linagliptin. Other significant observations in the study included an approximate 4-fold increase in plasma levels of GLP-1 in the treated group and a 10% decrease in fructosamine levels in the 10-mg dose cohort.

According to the National Institute of Health (NIH) clinical trials registry, another phase I, open-label clinical trial (ClinicalTrials.gov identifier: NCT00935220, 1218.55) to investigate the pharmacokinetics and pharmacodynamics of linagliptin (BI 1356) 5mg after single and multiple oral administration in African American Type 2 Diabetic Patients (n = 41) for 7 days has been completed in August 2010 for the measurement of primary outcomes.

Phase II Trials

Linagliptin (2.5, 5 and 10 mg p.o, qd for 4 weeks) has been investigated in a phase IIa, randomized, double-blind, placebo-controlled multiple-dose study in obese patients with T2DM (n = 77) [46]. After 4 weeks, mean GLP-1 plasma levels increased by up to fourfold following a meal tolerance test in all treatment groups and glucagon concentrations were suppressed by 17.2, 23.6 and 8.0% from baseline in the 2.5-, 5- and 10-mg dose cohorts, respectively. Similarly, glucose levels were significantly reduced with all linagliptin doses (45.3, 46.2 and 39.3% for the respective doses) after 1 day of therapy, with the 5-mg dose cohort clearly demonstrating the greatest efficacy. After 4 weeks, a placebo-corrected mean change in HbA1c levels of -0.31%, -0.37% and -0.28% was observed in the 2.5-, 5- and 10-mg dose cohorts, respectively.

Similar results were replicated in a phase IIa, randomized, double-blind, placebo-controlled clinical trial with linagliptin (0.5, 2.5 and 10 mg po, qd for 28 days) in Japanese patients with T2DM (n=72), wherein inhibition of plasma DPP-4 activity increased with the plasma concentration of linagliptin along with a dose-dependent increase in the steady-state GLP-1 levels [45]. Furthermore, the fasting plasma glucose levels also decreased in a dose-dependent manner and HbA1c levels were significantly reduced (0.44%) from baseline in the 10-mg dose cohort.

Another phase IIb, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial assessed linagliptin (1, 5 and 10 mg p.o, qd for 12 weeks) as an add-on to the failing metformin therapy in patients with T2DM (n = 333) [47]. An additional non-blinded treatment arm of patients comprised of glimepiride (1 to 3 mg po, qd) added to the failing metformin therapy. Linagliptin was found to significantly reduce HbA1c levels, with highest reduction (0.73%) being observed in the 10-mg dose cohorts. A better response (mean placebo-corrected reduction in HbA1c = 0.90%) was however observed in the glimepiride cohort. Furthermore, fasting plasma glucose levels were significantly reduced at week 12 in all the three dose cohorts.

These studies showed linagliptin to be well tolerated in T2DM patients with no reports of hypoglycemia and serious adverse events related to study medication [45, 47].

The NIH clinical trials registry has reports of some additional phase II, randomized, double-blind, placebo-controlled clinical trials on linagliptin. The first (ClinicalTrials.gov Identifier: NCT00328172, 1218.5) was a randomized, double-Blind, placebo-controlled, five parallel group study investigating the efficacy and safety of BI 1356 BS (0.5 mg, 2.5 mg and 5.0 mg administered orally once

daily) over 12 weeks in drug naive and treated T2DM patients (n = 302) with insufficient glycemic control (study also included an open-label treatment arm with metformin).

The second (ClinicalTrials.gov Identifier: NCT00716092, 1218.37) was a 4-week, randomized, double blind, double dummy, placebo controlled, parallel group study comparing the influence of BI 1356 (5 mg) and sitagliptin (100 mg) administered orally once daily on various biomarkers in T2DM patients (n = 121) with inadequate glycemic control. At the time of publication, no data had been reported from either of the above mentioned trials.

Another phase II, 12 week, randomized double-blind study (ClinicalTrials.gov Identifier: NCT01012037, 1218.62) that is currently recruiting participants, aims to investigate the efficacy and safety of linagliptin 2.5 mg twice daily compared to 5 mg once daily compared to placebo given orally for 12 weeks as add-on therapy to metformin in patients with T2DM with insufficient glycemic control. It is planned to show the non-inferiority of linagliptin 2.5 mg twice daily compared to 5 mg once daily and each treatment's superiority over placebo.

Phase III Trials

At the time of this publication, seven phase III clinical trials involving linagliptin have been listed as completed on the NIH clinical trials registry [www.clinicaltrials.gov], ten studies are currently active and recruiting participants, while five studies, although active, are not currently recruiting.

The completed clinical trials were designed as randomized, double-blind, placebo-controlled, 24-week study to assess the efficacy and safety of linagliptin (5 mg p.o, qd) on HbA1c levels in patients with T2DM and insufficient glycemic control, when compared to a placebo (ClinicalTrials.gov Identifier: NCT00621140, 1218.16; n = 503), as an add-on therapy to metformin (ClinicalTrials.gov Identifier: NCT00601250, 1218.17; n = 702) and as an add-on to metformin plus either sulfonylurea (ClinicalTrials.gov Identifier: NCT00602472, 1218.18; n = 1058) or pioglitazone therapy (30 mg p.o, qd) (ClinicalTrials.gov Identifier: NCT00641043, 1218.15; n = 389).

An open-label, non-randomized 78-week extension trial (ClinicalTrials.gov Identifier: NCT00736099, 1218.40), recently completed, was aimed to investigate the long-term safety and tolerability of linagliptin (5 mg p.o, qd) as monotherapy or in combination with other antidiabetic medications in Type 2 diabetic patients, including patients who had participated in any of the above four trials (estimated n = 2133). The therapy regimen was planned to be a continuation of the previous trial, with patients receiving placebo switched to active therapy.

Another recently concluded trial (ClinicalTrials.gov Identifier: NCT00654381, 1218.23) was a randomized, double-blind study in Japanese patients with T2DM and insufficient glycemic control (n = 441), comparing the effects of linagliptin (5 and 10 mg p.o, qd) with placebo on HbA1c levels for 12 weeks before patients receiving placebo were switched to voglibose (0.6 mg) for 26 weeks. Furthermore, long-term safety was evaluated with an extension treatment to 52 weeks.

Another randomized, double-blind, active-controlled, 2-year trial (ClinicalTrials.gov Identifier: NCT00622284, 1218.20) compared the efficacy, safety and tolerability of BI 1356 (5.0 mg daily) with glimepiride given for 104 weeks as add-on therapy to preferably > 1500 mg metformin in patients with T2DM with insufficient glycemic control, with the primary endpoint designated as the change from baseline in HbA1c levels after 104 weeks.

Other active ongoing phase III randomized, double-blind, placebo-controlled, parallel group trials on linagliptin, include:

Investigation of the efficacy, safety and tolerability of linagliptin (5 mg / once daily) compared to placebo during long term treatment (52 weeks and longer) in combination with basal insulin in patients with (T2DM) with insufficient glycemic control (ClinicalTrials.gov Identifier: NCT00954447, 1218.36).

An extension study to investigate the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg versus monotherapy with metformin 1000 mg twice daily over 54 weeks in T2DM patients previously completing the double-blind part of a similar 24 week study (ClinicalTrials.gov Identifier: NCT00798161, 1218.46; NCT00915772, 1218.52).

Identification of the safe and effective dose of linagliptin in pediatric patients with T2DM. Other efficacy objectives include the comparison of the lowering effect of linagliptin low dose, high dose and placebo on the fasting plasma glucose observed after 12 wk of treatment. Furthermore, the study also plans to investigate the pharmacokinetics (PK), the pharmacodynamics (PD) and the PK/PD relationship of linagliptin in the paediatric population (ClinicalTrials.gov Identifier: NCT01342484, 1218.56)

Investigation of the efficacy, safety and tolerability of Linagliptin (5 mg once daily) compared to placebo given for 24 weeks as add on therapy to metformin in combination with pioglitazone in patients with (T2DM) with insufficient glycemic control (ClinicalTrials.gov Identifier: NCT00996658, 1218.61).

Investigation of the efficacy, safety and tolerability of linagliptin (5 mg / once daily) compared to placebo given for 24 weeks as add-on therapy to stable treatment in elderly patients with T2DM with insufficient glycemic control (HbA1c >= 7.0) Despite Metformin and/or Sulphonylurea and/or Insulin Therapy (ClinicalTrials.gov Identifier: NCT01084005, 1218.63).

Investigation of the efficacy, safety and tolerability of linagliptin (5 mg / once daily) compared to placebo given over 12 weeks in drug naive or previously treated T2DM patients with moderate to severe renal impairment and insufficient glycemic control. In addition, safety in this patient population with longer term (40 week) treatment in comparison to sulfonylurea drug (glimepiride) is also planned to be assessed (ClinicalTrials.gov Identifier: NCT01087502, 1218.64).

Comparison of the safety and efficacy of 5 mg of linagliptin administered orally once daily with a placebo after 24 weeks of treatment as add-on therapy to metformin

in patients with T2DM and insufficient glycemic control (ClinicalTrials.gov Identifier: NCT01215097, 1218.65).

Comparison of the safety and efficacy of 5 mg of linagliptin administered orally once daily with a placebo after 24 weeks of treatment in monotherapy in patients with T2DM and insufficient glycemic control (ClinicalTrials.gov Identifier: NCT01214239, 1218.66).

Investigation of the long term impact on cardiovascular morbidity and mortality, relevant efficacy parameters (e.g., glycemic parameters) and safety (e.g., weight and hypoglycemia) of treatment with linagliptin in patients with T2DM at elevated cardiovascular risk receiving usual care, and subsequent comparison of the outcome against glimepiride (ClinicalTrials.gov Identifier: NCT01243424, 1218.74).

Assessment of the efficacy and safety of linagliptin (BI 1356) in Black/African American patients with T2DM with a MTT sub-study (ClinicalTrials.gov Identifier: NCT01194830, 1218.75).

Investigation of the safety and efficacy of linagliptin (5mg / once daily) given for 52 weeks as add-on therapy to patients with type 2 diabetes mellitus and insufficient glycemic control despite diet, exercise, and treatment with the approved antidiabetic drug, metformin (ClinicalTrials.gov Identifier: NCT01204294, 1218.78).

Demonstration of a superior glycemic control (HbA1c reduction) of linagliptin/pioglitazone (5/15, 5/30 and 5/45 mg) versus the respective individual monotherapies of pioglitazone (15 mg, 30 mg, or 45 mg, administered orally once daily), and linagliptin (5 mg, administered orally once daily). In addition, durability of treatment effect and safety under chronic treatment conditions is also being planned to be investigated (ClinicalTrials.gov Identifier: NCT01183013, 1264.3).

Recent Results from Phase III Trials

Phase III data presented at the 70th Scientific Sessions of the American Diabetes Association (ADA) in June 2010, indicated that linagliptin achieved significant, sustained and clinically meaningful reductions in blood glucose as evident from the HbA_{1c}, fasting plasma glucose and postprandial glucose concentrations [48-53]. Fig. (**3**) depicts some of the key efficacy results from phase III pivotal trials of linagliptin (5 mg once daily) in terms of mean placebo-adjusted changes in HbA_{1c} from baseline over 24 weeks in type 2 diabetes mellitus patients with insufficient glycaemic control [48-51].

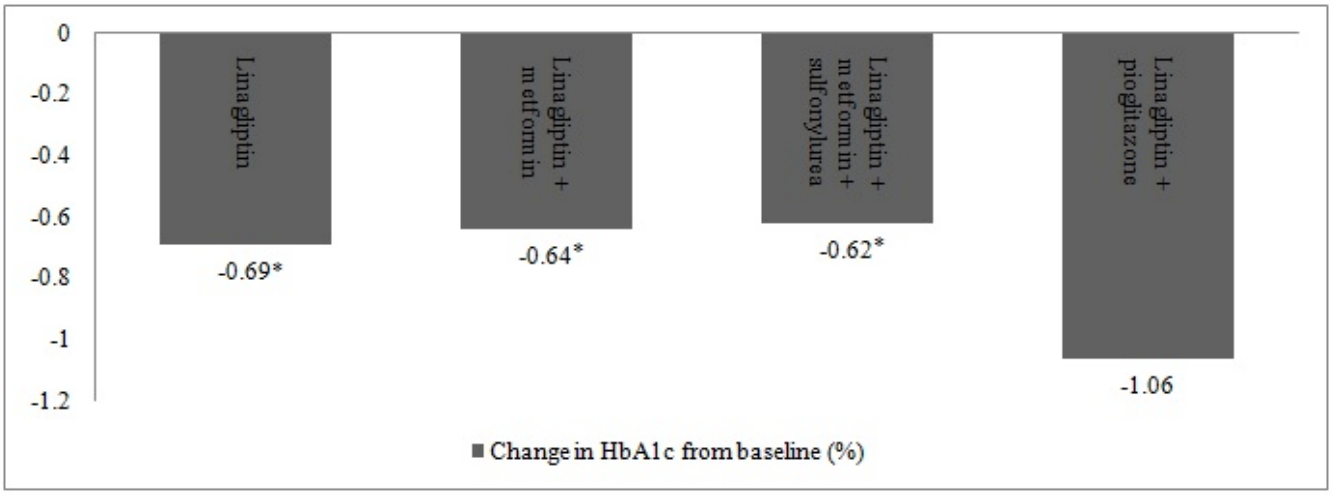
The pivotal phase III studies also suggested linagliptin to have a very favorable safety profile, with an overall rate of adverse events similar to that of placebo. In addition, linagliptin showed an excellent tolerability, was weight neutral, showed no increased risk of drug-drug interactions, including no increased risk of hypoglycemia attributed to its use in monotherapy, or in combination therapy with metformin or pioglitazone [48-53].

Remarkably, linagliptin blood plasma levels in diabetes patients with mild and moderate renal impairment were comparable to that observed in diabetes patients with normal renal function, suggesting that linagliptin, with a primarily non-renal route of excretion, would not need dose adjustment in patients with type 2 diabetes irrespective of the stage of renal impairment [48, 26].

Four multi-centric, 24 weeks, randomized, double-blind, controlled trials demonstrated statistically significant reductions in blood glucose levels with linagliptin monotherapy versus placebo and in combination with other commonly used oral anti-diabetic drugs, accompanied by significant improvements in beta-cell function [48-51].

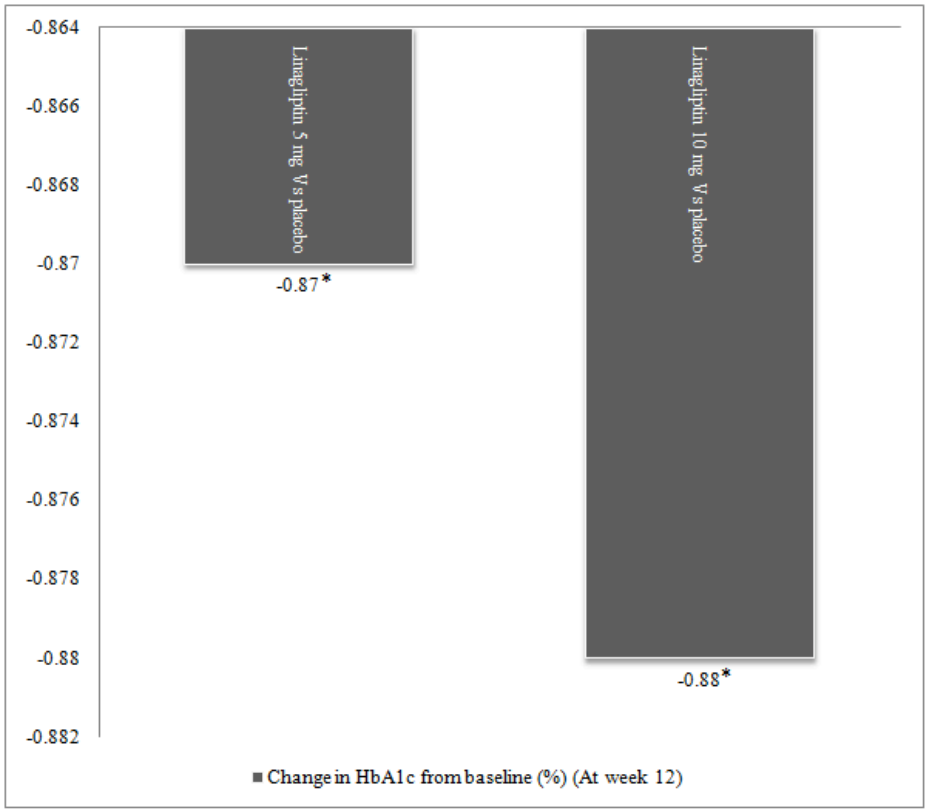
A further study documented the superiority of linagliptin monotherapy for improving glycaemic control at week 12 and week 26, versus placebo and versus voglibose, the most commonly used alpha glucosidase inhibitor in Japan [52, 53] (Figs. **4a** and **4b**). Drug-related gastrointestinal disorders were less frequent in the linagliptin groups than in the voglibose group, indicating the good tolerability of linagliptin monotherapy in Japanese patients with T2DM.

Recently presented phase III data from the linagliptin late stage clinical trial programme at the 46th Annual Meeting of



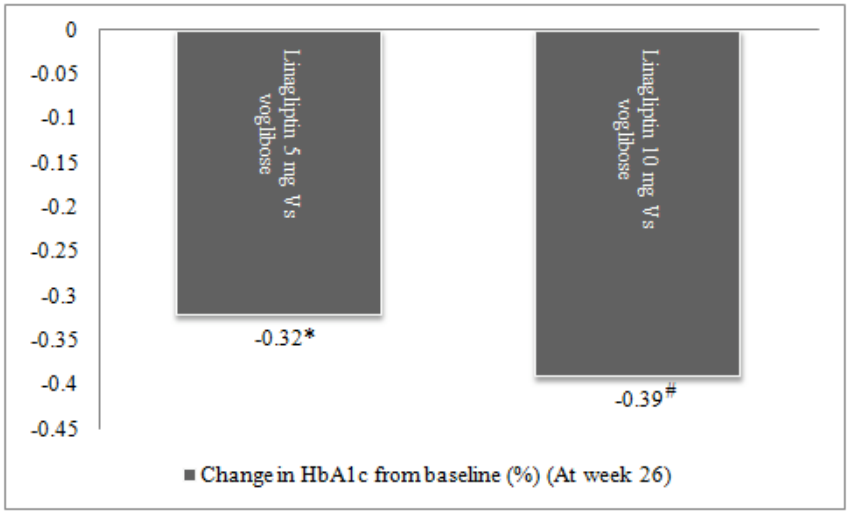
*p<0.0001 Vs placebo

Fig. (3). Mean placebo-adjusted changes in HbA1c from baseline over 24 weeks [48-51].



*p<0.0001 Vs placebo

Fig. (4a). Mean placebo-adjusted changes in HbA_{1c} from baseline over 12 weeks [52].



*p=0.003 Vs voglibose, # p<0.0001 Vs voglibose

Fig. (4b). Mean changes in HbA_{1c} from baseline over 26 weeks [53].

the European Association for the Study of Diabetes (EASD) in September 2010, documented an improvement in glycemic control with linagliptin monotherapy in type 2 diabetes patients for whom metformin therapy is inappropriate due to contraindications and intolerability, including patients with renal impairment [54]. Another phase III 18-week, multi-centre, randomized, double-blind, placebo-controlled, parallel-group design trial confirmed the safety, efficacy and tolerability of linagliptin 5 mg as an add-on therapy to sulphonylurea (SU) in inadequately controlled type 2 diabetes patients [55]. In addition, results from a pharmacokinetic study investigating linagliptin in a special patient population with different degrees of renal impairment confirmed that decrease in renal function had only little effect on the elimination and only minor changes were observed in linagliptin exposure in patients with renal impairment [56]. The findings, along with the large safety window of linagliptin, supports the assumption that linagliptin dose adjustment may not be required in type 2 diabetes patients with any degree of renal impairment [38].

The new data add to the large body of clinical evidence demonstrating that linagliptin will not only help patients to achieve optimal blood glucose levels , but will also ensure that glucose control is stable and long-term without the traditional risk of hypoglycemia. Furthermore, the convenience with linagliptin not needing additional monitoring of kidney function and not having to adjust the dose on account of its unique pharmacokinetic profile and primarily non-renal route of excretion, could improve patient compliance and could subsequently make life easier for the health professional.

DRUG–DRUG INTERACTIONS

Literature reports suggest that linagliptin is unlikely to affect the pharmacokinetics of agents that are metabolized by the CYP450 enzymes, nor is the drug itself metabolized by this system [37, 57].

The potential pharmacokinetic interaction between linagliptin (10 mg p.o, qd for six doses to reach the steady state) and metformin (850 mg p.o, tid for seven doses to reach steady state) was assessed in a randomized, open-label, two-way crossover, single-center clinical trial in healthy male volunteers (n = 16) [58]. Linagliptin had no significant effect on the exposure (AUC) to metformin, although there was a small clinically irrelevant reduction (11%) in C_{max}, and T_{max} was delayed slightly. Metformin had no effect on the C_{max} value of linagliptin, although the AUC value was increased by 20% and the T_{max} value was modestly longer, increasing from 1 h with monotherapy to 1.5 h with combination therapy. However, the extent of inhibition of DPP-4 by linagliptin was not altered by concomitant metformin administration. The results of the study indicated that linagliptin can be administered with metformin without the need for dose adjustment of either drug.

Another possible interaction between linagliptin and pioglitazone was examined in an open-label, randomized, crossover study in healthy subjects (n = 20), wherein the subjects received linagliptin (10 mg q.d.) for 5 days followed by a combination of linagliptin (10 mg q.d.) + pioglitazone (45 mg/day) for 7 days, and pioglitazone (45 mg/day) for 7 days in a randomized order, with a washout period between the pioglitazone monotherapy and the linagliptin treatment periods. Linagliptin had no significant effect on the exposure (AUC) to pioglitazone (and its active metabolites). The T_{max} of pioglitazone was similarly unaffected by co-administration of linagliptin, although its C_{max} was moderately reduced by ~ 14%. The difference was however, not considered to be clinically significant. Hence, it was concluded that pioglitazone had no effect upon the pharmacokinetics of linagliptin, and dose adjustment will be unnecessary when both the agents are co-administered [59].

LATEST UPDATE

On May 03, 2011, linagliptin was approved by the U.S. Food and Drug Administration (FDA) as a monotherapy or in combination with other commonly prescribed medications for type 2 diabetes—such as metformin, sulphonylurea and pioglitazone — to reduce HbA1c levels by a mean of up to -0.7% as compared to placebo [50]. It is the first member of its class of DPP-4 inhibitors to be approved at one dosage strength (5 mg, once daily), regardless of kidney or liver impairment [60].

CONCLUSION

DPP-4 inhibitors represent a highly promising, novel class of oral agents for the treatment of T2DM. Their novelty lies in their dual action on 'α' and β-cell function, leading to an improved profile of glucagon and insulin secretion patterns after meal. Unlike other oral antidiabetic agents, these drugs are weight-neutral, do not provoke hypoglycemia and are not associated with gastrointestinal adverse events. Linagliptin is orally available, can be given once daily and, so far, have had an excellent safety profile. The agent fits very tightly but reversibly into the target enzyme, which results in its being the most potent DPP-4 inhibitor, with a long duration of action. Its primarily non-renal route of excretion may be an advantage in patients with renal impairment, considering that up to half of people with diabetes has mild renal impairment. Clinical trials of linagliptin have produced highly satisfactory or at least comparable data with other DPP-4 inhibitors. However, the long-term safety and additional clinical benefit of the compound remains to be confirmed by the post-marketing surveillance studies. Further investigations are warranted to validate that the unique pharmacological properties of linagliptin, together with the predominantly non-renal route of elimination, will lead to clinical benefits beyond those already observed with other agents in the DPP-4 inhibitor class. Despite such challenges, linagliptin is definitely a promising addition to the therapeutic armamentarium of T2DM, either as a monotherapy during the early stages, or as a part of a combination therapy with other drugs in the mid-to-late stages of the disease.

CONFLICT OF INTEREST

None

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