Pharmacokinetic, Pharmacodynamic, and Tolerability Profiles of the Dipeptidyl Peptidase-4 Inhibitor Linagliptin: A 4-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase IIa Study in Japanese Type 2 Diabetes Patients*

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ABSTRACT

Background: The dipeptidyl-peptidase-4 (DPP-4) inhibitor linagliptin is under clinical development for treatment of type 2 diabetes mellitus (T2DM). In previous studies in white populations it showed potential as a once-daily oral antidiabetic drug.

Objectives: In compliance with regulatory requirements for new drugs intended for use in the Japanese population, this study investigated the pharmacokinetics, pharmacodynamics, and tolerability of multiple oral doses of linagliptin in Japanese patients with T2DM.

Methods: In this 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 (1:1:1:1 ratio) once daily for 28 days. For analysis of pharmacokinetic properties, linagliptin concentrations were determined from plasma and urinary samples obtained throughout the treatment phase, with more intensive samplings on days 1 and 28. DPP-4 inhibition, glycosylated hemoglobin A1c (HbA_{1c}) levels, and plasma glucose and glucagon-like peptide-1 (GLP-1) levels were compared by mixed effect model. Tolerability was assessed throughout the study by physical examination, including blood pressure and pulse rate measurements, 12-lead ECG, and laboratory analysis.

Results: Baseline demographic characteristics were well balanced across the 4 treatment groups (mean [SD] age, 59.7 [6.4] years in the placebo group, 60.8 [9.2] years in the 0.5 mg group, 60.2 [6.4] years in the 2.5 mg group, and 59.1 [8.6] years in the 10 mg group; mean [SD] weight, 67.2 [10.0] kg in the placebo group, 64.5 [9.0] kg in the 0.5 mg group, 69.6 [9.4] kg in the 2.5 mg group, and 63.5 [12.2] kg in the 10 mg group; mean [SD] duration of T2DM diagnosis, 5.1 [4.2] years in the placebo group, 5.2 [4.7] years in the 0.5 mg group, 5.9 [4.8] years in the 2.5 mg group, and 2.6 [2.3] years in the 10 mg group). The majority of the patients treated were male (76.4%). Use of previous antidiabetic medication was more common in the 2.5 mg linagliptin group (44%) than in the 0.5 or 10 mg linagliptin (15.8% and 22.2%, respectively) or placebo groups (35.3%). Total systemic exposure in terms of linagliptin AUC and C_{max} (which occurred at 1.25–1.5 hours) increased in a less than dose-proportional manner. The terminal half-life was long (223–260 hours) but did not reflect the accumulation half-life (10.0–38.5 hours), resulting in a moderate accumulation ratio of <2.9 that decreased with increasing dose.

*Data from this study were presented, in part, at the American Diabetes Association, 68th Scientific Sessions, San Francisco, California, June 9–13, 2008 (poster 0533P), and at the 52nd Annual Meeting of the Japan Diabetes Society, Osaka, Japan, May 21–24, 2009 (poster III-P-95).

Accepted for publication June 3, 2011.
doi:10.1016/j.clinthera.2011.06.005
0149-2918/$ - see front matter

Urinary excretion increased with linagliptin doses but was <7% at steady state for all dose groups. Inhibition of plasma DPP-4 at 24 hours after the last dose on day 28 was approximately 45.8%, 77.8%, and 89.7% after linagliptin 0.5, 2.5, and 10 mg, respectively. At steady state, linagliptin was associated with dose-dependent increases in plasma GLP-1 levels, and the postprandial GLP-1 response was enhanced. Statistically significant dose-dependent reductions were observed in fasting plasma glucose levels at day 29 for all linagliptin groups (–11.5, –13.6, and –25.0 mg/dL for the 0.5, 2.5, and 10 mg groups, respectively; $P < 0.05$ for all linagliptin groups). Linagliptin also produced statistically significant dose-dependent reductions from baseline for glucose area under the effect curve over 3 hours after meal tolerance tests (–29.0 to –68.1 mg × h/dL; $P < 0.05$ for all 3 linagliptin groups). For the 0.5 and 10 mg linagliptin-treated groups, there were statistically significant reductions in HbA_{1c} from baseline compared with placebo, despite the relatively low baseline HbA_{1c} (7.2%) and small sample size ($P < 0.01$ for both groups). The greatest reduction in HbA_{1c} (–0.44%) was seen in the highest linagliptin dose group (10 mg). On dosing for up to 28 days, linagliptin was well tolerated with no reported serious adverse events or symptoms suggestive of hypoglycemia. Overall, fewer adverse events were reported by patients after linagliptin than after placebo (11 of 55 [20%] vs 6 of 17 [35%]).

Conclusions: Linagliptin demonstrated a nonlinear pharmacokinetic profile in these Japanese patients with T2DM consistent with the findings of previous studies in healthy Japanese and white patients. Linagliptin treatment resulted in statistically significant and clinically relevant reductions in HbA_{1c} as soon as 4 weeks after starting therapy in these Japanese patients with T2DM, suggesting that clinical studies of longer duration in Japanese T2DM patients are warranted. (*Clin Ther*. 2011;33:973–989)

Key words: BI 1356, dipeptidyl-peptidase-4, incretin, linagliptin, pharmacodynamics, pharmacokinetics, type 2 diabetes.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic progressive disease caused by a combination of insulin resistance and β-cell dysfunction, resulting in hyperglycemia.[1] Dipeptidyl-peptidase-4 (DPP-4) inhibitors are a class of oral antihyperglycemic agents that have been introduced as a new treatment option for monotherapy and combination therapy use in T2DM.[2,3] DPP-4 inhibitors lower blood glucose by preventing the degradation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide.[4] These peptides, released by gut endocrine cells in response to food intake, play an important role in glucose homeostasis by stimulating glucose-dependent insulin secretion from pancreatic islet β-cells. Prolonging the effects of endogenous GLP-1 by inhibition of DPP-4 was clinically validated as a glucose-dependent therapeutic approach to improve fasting and postprandial plasma glucose levels, leading to decreases in glycosylated hemoglobin (HbA_{1c}).[2]

Linagliptin is an orally active DPP-4 inhibitor[5] that was approved in the US for the treatment of T2DM.[6,7] In preclinical studies, linagliptin exhibited high-potency inhibition of DPP-4 (K_i ~1 nM)[8] and improved glycemic homeostasis in a variety of rodent models of T2DM.[8,9] Linagliptin showed high selectivity for DPP-4 versus DPP-8 (40,000-fold) and DPP-9 (>10,000-fold).[8] In a Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study in 64 healthy white male volunteers, single oral doses of linagliptin up to 120 times the proposed clinically effective dose level (ie, 5 mg/d) were well tolerated with an adverse event (AE) profile similar to that of placebo.[10] Compared with other DPP-4 inhibitors, linagliptin showed a unique PK and PD profile with a mainly nonrenal route of elimination.[11,12] In a multiple dose study in 48 white male patients with T2DM, once-daily dosing of linagliptin for 12 days (1–10 mg) resulted in maximal inhibition of plasma DPP-4 of >90% with the 5 and 10 mg doses at steady state, with ~85% inhibition remaining at 24 hours post-dose (5 mg).[13] In studies performed in T2DM patients in Europe and North America, oral dosing with linagliptin was well tolerated and resulted in significant improvements of glucose parameters ($P < 0.05$).[6,7,14] Guidance from the Pharmaceutical and Medical Devices Agency in Japan requires that the dose–response relationship for any new drug is confirmed in the Japanese population and that treatment is evaluated in "adequate numbers of Japanese cases."[15] In a Phase I study of 56 healthy male Japanese volunteers, the tolerability, PK, and PD profiles of linagliptin were consistent with previous observations in white patients[10,13,16]; however, these profiles have not