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ORIGINAL ARTICLE

Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial with an open-label, long-term extension study

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Aims: To evaluate the efficacy and safety of alogliptin added to metformin versus metformin monotherapy in Japanese patients with type 2 diabetes who achieved inadequate glycaemic control on metformin (500 or 750 mg/day) + diet/exercise.

Methods: In a randomized, double-blind trial, 288 patients with type 2 diabetes mellitus T2DM received either 12.5 or 25 mg alogliptin once daily + metformin or placebo + metformin for 12 weeks. Thereafter, 276 patients continued on one of the two alogliptin dosages + metformin in an open-label extension for 40 weeks. The primary efficacy endpoint in the randomized, double-blind phase was the change in HbA1c from baseline (week 0) to the end of treatment (week 12). The primary endpoint during the long-term extension phase was adverse events.

Results: After 12 weeks both dosages of alogliptin + metformin produced significantly greater changes from baseline in HbA1c than placebo (metformin monotherapy: with changes in LS means − 0.55 and − 0.64% vs. 0.22%, respectively; $p < 0.0001$). Incidences of adverse effects were comparable between groups, with no increases in hypoglycaemia. Over 52 weeks, there were no safety or tolerability concerns with alogliptin when added to metformin.

Conclusions: Alogliptin 12.5 and 25 mg once daily was safe and effective when added to metformin (500 or 750 mg/day) in Japanese patients with inadequately controlled type 2 diabetes on metformin alone.

Keywords: alogliptin, clinical trial, Japanese patients, metformin, type 2 diabetes mellitus

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Introduction

Optimal management of patients with type 2 diabetes mellitus (T2DM) requires implementation of all relevant components of care (dietary measures, exercise, self-management education, pharmacological interventions, careful clinical monitoring) to achieve individualized glycaemic goals and hence reduce the morbidity and mortality [1,2]. As T2DM is characterized by insulin resistance and a decline in pancreatic insulin secretion, sulphonylureas and glinides, which stimulate insulin secretion, and metformin, which improves insulin sensitivity primarily by inhibiting hepatic glucose production, are widely used to achieve glucose control. Metformin, an effective antihyperglycaemic agent in patients with T2DM [3–5], is advocated in current clinical guidelines in Western countries [1,2] as a first-line medication. It can be used alone [e.g. when glycosylated haemoglobin (HbA1c) levels are in the range 6.5–7.5%] or in combination with another antihyperglycaemic agent acting via a different mechanism (e.g. an insulin secretagogue) for patients with higher HbA1c levels or whenever metformin alone fails to achieve glycaemic control.

Metformin does not stimulate insulin secretion and therefore, does not generally produce hypoglycaemia except when caloric intake is deficient, in elderly, debilitated, or malnourished patients, and potentially during concomitant use with other glucose-lowering agents (such as sulphonylureas) [6–8]. Metformin does not cause hyperinsulinaemia and insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease with metformin therapy. Insulin secretagogues are most commonly used for treating type 2 diabetes in Japan and despite its good efficacy and safety profile, metformin is not generally chosen as a first-line therapy in Japanese patients. Metformin is, however, widely used in combination with sulphonylureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors globally [8,9].

Alogliptin is a potent and highly selective DPP-4 inhibitor [9] and, as with other members of this class, represents a new treatment approach in patients with T2DM [10,11]. DPP-4 rapidly degrades the incretin hormone glucagon-like peptide-1 (GLP-1) which is secreted into the blood

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from the gastrointestinal tract and has an important role in glucose metabolism. GLP-1 improves glucose homeostasis by enhancing glucose-dependent stimulation of insulin secretion, suppressing glucagon secretion, and delaying gastric emptying [12–14]. Recent improvement in incretin immunoassays revealed that circulating levels of active GLP-1 in T2DM are much less than previously reported, and DPP-4 inhibitors significantly increase active GLP-1 levels in T2DM patients [15–17]. These lines of evidence suggest that DPP-4 inhibitors are effective antidiabetic agents for T2DM. Furthermore, it has been recently shown that DPP-4 inhibitors improve β-cell function [18,19].

In patients with T2DM, alogliptin has been found to reduce HbA1c and fasting plasma glucose (FPG) concentrations, and to be well tolerated with a low risk of hypoglycaemia [9,20,21]. A multicenter, randomized, double-blind clinical trial in Western populations reported that combined alogliptin and metformin was more effective than metformin monotherapy in decreasing HbA1c and FPG concentrations in patients with T2DM who were inadequately controlled on metformin monotherapy [22]. However, the efficacy and safety of this combination has not yet been studied in Japanese patients.

This clinical efficacy and safety assessment of alogliptin combined with metformin, as an adjunct to diet and exercise therapy, is based on a phase 3 clinical trial in Japanese patients with T2DM comprising an initial 12-week, randomized, double-blind, placebo-controlled study, followed by a long-term, open-label study (total duration of combination treatment: 52 weeks). Alogliptin dosages used (12.5 and 25 mg once daily) were previously found to be significantly more effective than placebo and voglibose in reducing HbA1c and FPG concentrations in a 12-week study involving 480 Japanese patients with T2DM [23]. An HbA1c limit of 6.9% was chosen for inclusion of study patients, based on Japan Diabetes Society recommendations [24] that levels below this are the target of blood glucose control to prevent the development or progression of microangiopathy; a 12-week metformin run-in period was adopted on the basis that changes in HbA1c plateau over this time [25] and metformin would be expected to have stable effects thereafter.

Methods

Patients

Participants were outpatients with T2DM aged ≥20 and <65 years, with an HbA1c value between ≥6.9 and <10.4% after 8 weeks of observation (with <10% variation between weeks 4 and 8), for which they had been receiving metformin at a stable dosage for at least 12 weeks, plus specific dietary and exercise therapies. Exclusion criteria: administration of any investigational drug, other than metformin, within 12 weeks of study initiation; patients requiring insulin; a history/symptoms of lactic acidosis; hypersensitivity to metformin or biguanides; dialysis; patients with severe cardiovascular or pulmonary function impairment; dehydration; gastrointestinal disorders; malignant tumours; elevated blood pressure (≥180/≥110 mmHg); hepatic/renal impairment; serious cardiac, cerebrovascular, pancreatic or haematological diseases; history of drug abuse/dependency or habitual consumption; pregnant or lactating women.

Study Design, Procedures and Treatment

Initially, a randomized, double-blind, parallel-group study was conducted over 24 weeks (12-week observation period plus 12-week treatment period) at 30 Japanese centres between August 2008 and April 2009. Following completion of this study, a long-term (40-week), open-label extension was commenced in consenting subjects (total treatment duration 52 weeks). The study was approved by Institutional Review Boards (IRBs) at each study centre, and was conducted in accordance with the Declaration of Helsinki, ICH GCP [26], and all applicable local laws and regulations. All patients provided written informed consent. This trial was registered with Clinical trials.gov (identifier: NCT01318109).

During the 12-week observation period, patients received metformin (Glycoran®, Nippon Shinyaku Co. Ltd, Kyoto, Japan) 500 mg/day (in two divided doses) or 750 mg/day (in three divided doses) after meals, plus instructions on diet/exercise therapies. On the day following completion of the observation period, patients were randomized equally (via an interactive voice or web-activated response system) to 12 weeks of treatment with: (1) alogliptin (Takeda Pharmaceutical Co. Ltd, Osaka, Japan) 12.5 mg once daily before breakfast plus metformin; (2) alogliptin 25 mg once daily before breakfast plus metformin; or (3) a matching placebo tablet once daily before breakfast plus metformin. The metformin dosage remained stable throughout the observation and treatment periods.

On completion of the 12-week treatment phase, consenting patients entered the long-term, open-label extension study. Patients who had received alogliptin + metformin combinations continued on the same regimens; metformin monotherapy recipients were randomized equally to alogliptin 12.5 mg once daily before breakfast plus metformin (500 or 750 mg/day) or alogliptin 25 mg once daily before breakfast plus metformin (500 or 750 mg/day) for 40 weeks. During this extension phase, dosage adjustments of metformin were allowed on an as-needed basis according to individual plasma glucose control.

During the randomized, double-blind study, patients were required to visit their study centre every 4 weeks during the 12-week observation period (weeks −12 to 0), every 2 weeks during the first 4 weeks of the treatment phase (weeks 0–4), then every 4 weeks for the remainder of this phase (weeks 4–12), a total of eight visits. At these visits, the following were assessed: physical examination, clinical laboratory tests (including various glycaemic and lipid parameters; see below), vital signs, treatment compliance, adverse events. A 12-lead electrocardiogram (ECG) was performed at study entry and at week 12. Meal tolerance tests were performed at the beginning and end of treatment (weeks 0 and 12), by taking blood samples before a meal and at 0.5, 1 and 2 h after the start of the meal.

During the long-term extension, patients were required to visit their study centre every 4 weeks from weeks 12 to 52. At each visit, the following were assessed: physical examination, clinical laboratory parameters, vital signs, body weight, compliance, adverse events. HbA1c and FPG concentrations were measured at each clinic visit; other glycaemic parameters

were measured at weeks 24, 36 and 52 or at weeks 24 and 52 only. Fasting serum lipids were measured at weeks 24, 36 and 52, and meal tolerance tests were performed at weeks 24 and 52.

Treatment compliance was monitored throughout the study by returned tablet counts. Patients were withdrawn from the study if they had taken <20% of their assigned medication during the period since the last visit. Compliance with diet and exercise therapies was also monitored and rated on a 4-point scale: fully compliant, almost fully compliant, occasionally compliant, or rarely compliant.

Efficacy Assessments

The primary efficacy endpoint in the randomized, double-blind phase was the change in HbA1c from the completion of the observation period (week 0; baseline) to the completion of the treatment period (week 12). Secondary endpoints included HbA1c and FPG concentrations at each assessment point, and plasma glucose concentrations measured during meal tolerance tests. Other endpoints included: (1) fasting C-peptide, fasting insulin, fasting glucagon, glycoalbumin, 1,5-anhydroglucitol (1,5-AG), fasting proinsulin, fasting serum lipids [total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), free fatty acids (FFA)], body weight, abdominal circumference, HOMA-R (homeostasis model assessment of insulin resistance), HOMA-β (homeostasis model assessment of β-cell function), insulinogenic index and proinsulin/insulin ratio at each assessment point; and (2) insulin, C-peptide, glucagon, and active GLP-1 concentrations measured during meal tolerance tests. Active GLP-1 concentrations were measured using extracted plasma samples as described previously [16]. In the extension phase, the same efficacy endpoints were evaluated. All HbA1c values in this study have been reported according to the published 2010 diagnostic criteria proposed by the Japan Diabetes Society (JDS) [27,28].

The number of patients achieving HbA1c levels <6.9% at week 12 was assessed based upon a current proposal of the JDS and was a secondary endpoint of this study. Achieving HbA1c levels <6.9% during the treatment phase represents the treatment efficacy standard consistent with good glycaemic control.

Safety Assessments

Safety was assessed by recording all adverse events (primary endpoint: long-term extension phase), vital signs, 12-lead ECG, and laboratory tests (haematology, serum chemistry and urinalysis parameters). All adverse events were coded using the MedDRA (Medical Dictionary for Regulatory Activities; version 12.0) classification, and the likely relationship to the study medications was assessed by the attending physician as definite, probable, possible or not related.

Statistical Analysis

Efficacy analyses were performed on the full analysis set (FAS; all randomized patients who received at least one dose of study medication) and the per-protocol set (PPS, patients in the FAS who had no major protocol violations and who were evaluable for the primary endpoint). Safety was analyzed in the safety analysis set (all patients who received at least one dose of study medication). For the initial double-blind assessment, analyses were based on the last observation carried forward (LOCF) method if no data were available at any assessment point during the study.

In the randomized, double-blind study, the primary efficacy analysis (change in HbA1c from baseline to week 12 in the FAS), summary statistics (means, standard deviations) and two-sided 95% confidence intervals (CIs) were calculated for each treatment group. Based on an analysis of covariance (ANCOVA) model, with HbA1c change at week 12 from baseline as a dependent variable, HbA1c at baseline as a covariate, the daily dose of metformin during the observation period (500 or 750 mg/day) as a block factor, and treatment group as an independent variable, adjusted means [least square (LS) means], standard errors (SE) and two-sided 95% CIs of the LS mean were calculated for each treatment group. In addition, assessment of the efficacy of the two alogliptin + metformin regimens versus placebo plus metformin (metformin monotherapy) was performed with a closed testing procedure. The same analyses were performed on the PPS to assess the robustness of the analytical results. For each secondary efficacy endpoint, summary statistics and two-sided 95% CIs of the mean were calculated for each treatment group of the FAS at each assessment point, including meal tolerance data (before a meal and at 0.5, 1 and 2 h after the start of the meal). These measurements were performed upon completion of the observation and treatment period to depict the time profile of means and standard deviations in figures for each group. For adverse events, incidences were calculated for each treatment group for all-cause adverse events and those classified as related to study medication.

In the long-term extension study, efficacy and safety analyses compared data at 52 weeks with data at week 0 in the groups randomized to alogliptin + metformin in the randomized, double-blind study, and at 52 weeks with data at week 12 (completion of the treatment period) in the metformin monotherapy group. Efficacy and safety analyses performed in the long-term extension were similar to those performed in the randomized, double-blind study.

Results

As outlined in figure 1, 428 patients were screened, 3 of whom voluntarily withdrew and 425 entered the observation (run-in) phase. Of these, 288 were randomized to treatment; 129 did not meet entry criteria, 2 withdrew voluntarily, 1 had a major protocol violation, and 5 had pretreatment/adverse events (figure 1). All 288 randomized patients received at least one dose of study drug, and comprised the FAS and the safety analysis set. All except 4 patients completed the study, 1 withdrawing voluntarily, 2 (both in the alogliptin 25 mg + metformin group) discontinuing due to adverse events, and 1 due to other reasons. No major differences between the groups were found in any baseline demographic characteristics (Table 1). There were no major differences in the proportions of patients with diabetic

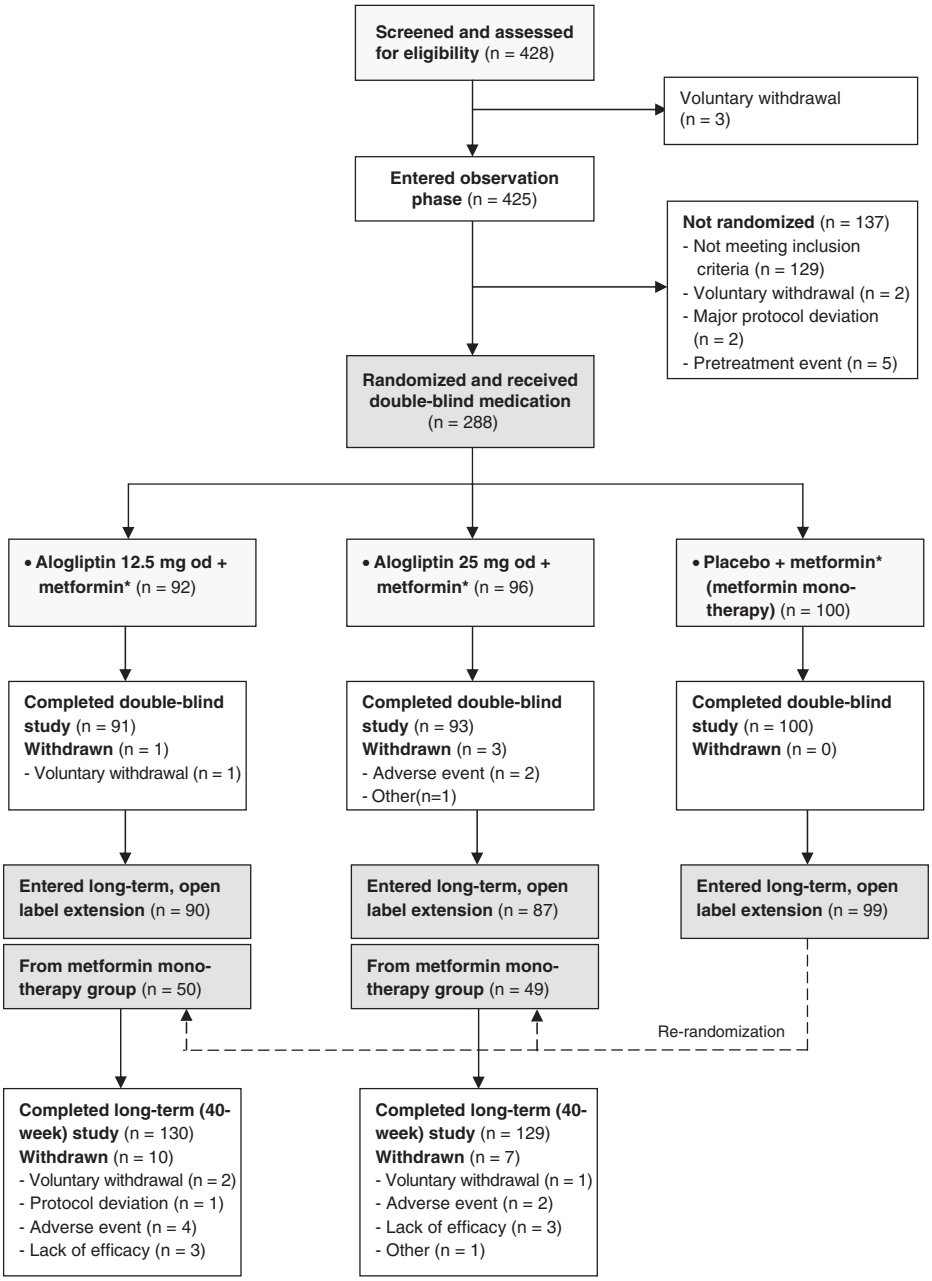

Figure 1. Patient disposition. *The dosage of metformin remained stable throughout the double-blind study (500 or 750 mg/day) and on an as needed basis in the long-term extension study.

nephropathy, diabetic neuropathy or diabetic retinopathy, or in those receiving concomitant medications. Most patients in each treatment group (>98.9%) had >90% compliance with treatment, and >85% in each group were 'fully compliant' or 'almost compliant' with diet therapy.

Efficacy

Changes in HbA1c from week 0 (baseline) to week 12 (LS mean ± s.e.) in the FAS were: −0.55% ± 0.058 (two-sided 95% CI −0.67 to −0.44%) [alogliptin 12.5 mg + metformin]; −0.64% ± 0.056 (95% CI −0.75 to −0.53%) [alogliptin 25 mg + metformin] and 0.22% ± 0.055 (95% CI 0.11 to 0.33%) [metformin monotherapy]. Both alogliptin combination groups achieved significantly greater reductions in HbA1c compared with the metformin monotherapy group ($p < 0.0001$) (figure 2a). Analyses conducted in the PPS (n = 284) yielded comparable results to the FAS, indicating the robustness of these findings.

The proportion of patients who achieved HbA1c levels below 6.9% at week 12 was also statistically significantly higher with the two alogliptin + metformin combinations (28.3 and 27.1% with the 12.5 and 25 mg dosages, respectively) compared with metformin monotherapy (2.0%).

Table 1. Baseline demographic characteristics of patients randomized to treatment in the double-blind study (n = 288).

Characteristic	Alogliptin 12.5 mg od + metformin* (n = 92)	Alogliptin 25 mg od + metformin* (n = 96)	Metformin monotherapy* (n = 100)	Total (n = 288)
Age, years (mean ± s.d.)	53.4 (±8.80)	52.3 (±8.02)	52.1 (±8.05)	52.6 (±8.28)
Gender				
Male (n, %)	60 (65.2)	66 (68.8)	72 (72.0)	198 (68.8)
Female (n, %)	32 (34.8)	30 (31.3)	28 (28.0)	90 (31.3)
Body weight, kg (mean ± s.d.)	69.47 (±12.46)	69.65 (±12.67)	69.89 (±14.23)	69.68 (±13.12)
Height, cm (mean ± s.d.)	164.5 (±8.16)	164.1 (±8.63)	163.3 (±8.56)	163.9 (±8.44)
BMI, kg/m^2 (mean ± s.d.)	25.63 (±4.10)	25.79 (±3.70)	26.14 (±4.58)	25.86 (±4.14)
Duration of diabetes, years (mean ± s.d.)	6.34 (±5.39)	6.62 (±4.80)	6.04 (±4.36)	6.33 (±4.84)
HbA1c, % (mean ± s.d.)	7.89 (±0.82)	8.02 (±0.73)	8.00 (±0.86)	7.97 (±0.80)
Fasting C-peptide, ng/ml (mean ± s.d.)	1.72 (±0.69)	1.90 (±0.93)	1.89 (±0.80)	1.84 (±0.82)
2-h postprandial plasma glucose, mg/dl (mean ± s.d.)	241.6 (±54.70)	252.9 (±48.55)	244.4 (±52.70)	246.4 (±52.06)

BMI, body mass index; HbA1c, glycosylated haemoglobin; od, once daily; s.d., standard deviation.
* The dosage of metformin remained stable throughout the observation and treatment periods (500 or 750 mg/day).

Mean changes in other glycaemic and lipid parameters, and in body weight and abdominal circumference from baseline to week 12 in all treatment groups are shown in Table 2. Mean changes from week 0 to 12 with both alogliptin + metformin dosages were significantly greater than those with metformin monotherapy for FPG (figure 2b), glycoalbumin, 1,5-AG, HOMA-β and proinsulin/insulin ratio; and for fasting glucagon and fasting proinsulin (for alogliptin 25 mg + metformin). Changes in other parameters failed to reach statistical significance with both alogliptin + metformin combinations compared with metformin monotherapy. Although there was a minor increase in body weight in the alogliptin 12.5 mg + metformin group (mean rise 0.17 ± 1.38 kg) versus minor decreases in the other two groups, the increase was not considered clinically significant.

Changes in meal tolerance test parameters with combined alogliptin + metformin were significantly greater than those with metformin monotherapy for 2-h postprandial plasma glucose, glucose $AUC_{0\text{-}2h}$, insulin $AUC_{0\text{-}2h}$, C-peptide $AUC_{0\text{-}2h}$ and active GLP-1 $AUC_{0\text{-}2h}$, but not for glucagon $AUC_{0\text{-}2h}$ (Table 2).

Decreases in HbA1c were maintained with continued treatment during the extension phase (figure 3). Changes in both HbA1c and FPG from baseline were statistically significant for each dosage of alogliptin + metformin at all assessment points from week 2 to 52. In the FAS, mean changes in HbA1c and FPG from week 0 to study end were: −0.44% and −16.4 mg/dl, respectively [alogliptin 12.5 mg + metformin], and −0.58% and −17.7 mg/dl, respectively [alogliptin 25 mg + metformin].

Changes in 2-h postprandial plasma glucose concentrations and glucose $AUC_{0\text{-}2h}$ values were also statistically significant versus baseline for both alogliptin + metformin groups at each assessment at weeks 12, 24 and 52 in the extension phase (data not shown).

Safety

The incidence of adverse events was comparable in all treatment groups during the 12-week treatment period. Approximately 50% of patients in each group reported adverse events, although only 8 to10% experienced events that were considered related to the study medications. None of the treatment-related events was serious or necessitated treatment discontinuation (Table 3). Most adverse events were mild in severity. Nasopharyngitis was the most commonly reported adverse event (alogliptin 12.5 mg + metformin: 19.6%; alogliptin 25 mg + metformin: 22.9%; metformin monotherapy: 20.0%), followed by headache, diarrhoea and constipation (Table 3).

Mild skin eruptions were reported by two patients in the alogliptin 12.5 mg + metformin group, in three patients in the alogliptin 25 mg + metformin group and in no patients in the metformin monotherapy group. Adverse events classified as 'skin and subcutaneous tissue disorders' and that were assessed as drug related were erythema annulare in one subject and seborrhoeic dermatitis in one subject in the alogliptin 12.5 mg combination group. None of these adverse events were classified as serious or led to discontinuation of treatment.

The incidence of abnormal laboratory values was low and similar between treatment groups and none was clinically significant. No clinically significant changes in vital signs or 12-lead ECG findings were observed.

Safety data recorded during long-term treatment with alogliptin + metformin are presented in Table 3. The incidence of adverse events was comparable with the two regimens. Around 78% of patients in each group reported adverse events, but only 18 to 20% had adverse events that were considered treatment-related. Most events were mild in severity, although three patients receiving alogliptin 12.5 mg + metformin required treatment discontinuation because of treatment-related adverse events, and one patient in each group experienced a serious treatment-related adverse event (infectious enteritis: alogliptin 12.5 mg + metformin; cardiac failure: alogliptin 25 mg + metformin group). No cases of pancreatitis were observed during this clinical trial.

Adverse events occurring in ≥3% of patients with 12.5 or 25 mg alogliptin + metformin included nasopharyngitis (31.0 and 36.6%, respectively), headache (6.3 and 2.1%), constipation (4.9 and 5.5%), back pain (6.3 and 4.1%),

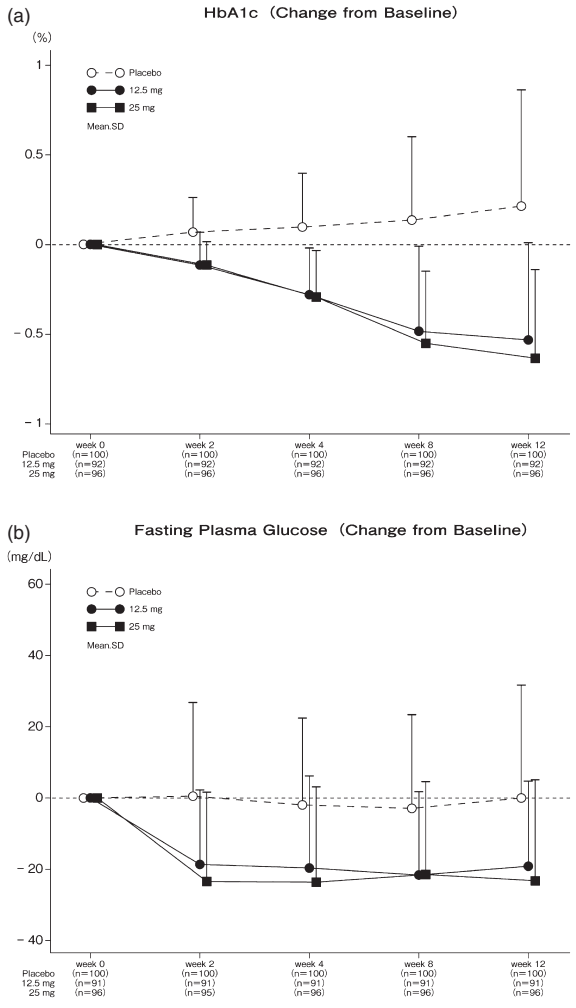

Figure 2. Time profiles of mean + s.d changes in HbA1c (a) and fasting plasma glucose (b) from baseline to week 12 in the alogliptin 12.5 mg, alogliptin 25 mg and placebo groups in a randomized, double-blind trial.

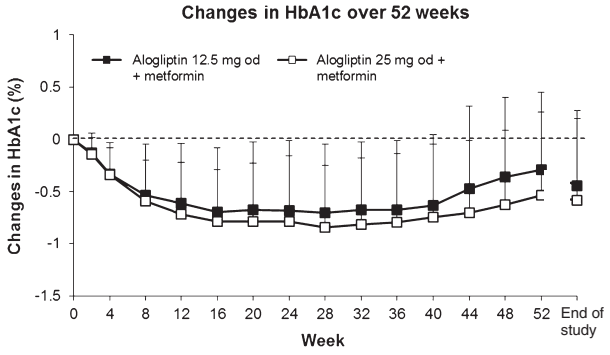

Figure 3. Mean (+ s.d.) changes in HbA1C values from week 0 (baseline) over 52 weeks in patients treated with alogliptin 12.5 or 25 mg once daily + metformin and who received treatment for up to 1 year (full analysis sets). For patients assigned to placebo + metformin in the randomized, double-blind study, values were based on data recorded between weeks 13 and 52 of the long-term, open-label extension.

eczema (4.9 and 4.1%) and diarrhoea (4.2 and 2.1%) (Table 3). Hypoglycaemia occurred in three patients during the study (alogliptin 12.5 mg + metformin [n = 1], alogliptin 25 mg + metformin [n = 2]); all cases were mild in intensity (there were no severe cases) and causality was assessed as not related to study treatment (two patients).

There were no clinically significant changes in any laboratory test parameters, and no clinically significant differences were found in vital signs or 12-lead ECG findings.

Discussion

This randomized, double-blind, placebo-controlled trial in Japanese patients with T2DM inadequately controlled by metformin monotherapy plus diet and exercise therapies has confirmed the findings of an earlier, similarly designed study in Western populations [22], demonstrating that combinations of alogliptin 12.5 or 25 mg once daily + metformin have comparable clinical efficacy and produce significantly better glycaemic control than metformin. Over the 12-week treatment period, the two alogliptin/metformin combinations significantly reduced HbA1c compared with metformin monotherapy at weeks 2, 4, 8 and 12. At week 12, LS mean baseline HbA1c values were reduced in the two combination groups, compared with an increase with metformin monotherapy ($p < 0.0001$). Further, the proportion of patients who achieved HbA1c levels <6.9% at week 12 was statistically significantly higher with alogliptin + metformin combinations.

As well as HbA1c and FPG, other glycaemic parameters that were significantly improved at week 12 with both alogliptin/metformin combinations compared with metformin monotherapy were glycoalbumin, 1,5-AG, HOMA-β, proinsulin/insulin ratio, and most meal tolerance tests parameters (including the 2-h postprandial glucose concentration, glucose $AUC_{0\text{-}2h}$, insulin $AUC_{0\text{-}2h}$, C-peptide $AUC_{0\text{-}2h}$ and active GLP-1 $AUC_{0\text{-}2h}$). DPP-4 inhibitors and metformin have complementary mechanisms of action and additive effects with respect to increasing the concentrations of active GLP-1 [29]. Fasting glucagon and fasting proinsulin were also significantly improved versus metformin monotherapy with the alogliptin 25 mg + metformin regimen; other endpoints such as fasting C-peptide, fasting insulin, fasting lipids, HOMA-R, and the insulinogenic index, showed no significant differences with either combination regimen versus metformin monotherapy. There were no significant differences in abdominal circumferences between the three groups, and body weight changes were comparable, although there was a slight (clinically non-significant) mean increase of 0.17 kg in the 12.5 mg alogliptin + metformin group compared with slight decreases (0.09 and 0.23 kg, respectively) in the 25 mg alogliptin + metformin and metformin monotherapy groups.

Reductions from baseline in HbA1c and FPG concentrations achieved with the two combination regimens in the 12-week study were maintained over 52 weeks of treatment, at least until week 40 when they appeared to diminish slightly. However, this open-label phase of the study did not include a control group (metformin alone).

Our study shows that alogliptin 12.5 and 25 mg once daily are effective as add-on therapy in Japanese patients with

Table 2. Changes in efficacy parameters (mean values ± s.d.) from week 0 (baseline) to week 12 (full analysis set; LOCF analysis).

Efficacy parameter	Alogliptin 12.5 mg od + metformin† (n = 92)	Alogliptin 25 mg od + metformin† (n = 96)	Metformin monotherapy† (n = 100)
HbA1c, %	−0.54 (±0.56)*	−0.64 (±0.49)*	0.21 (±0.64)
Fasting plasma glucose (FPG), mg/dl	−19.0 (±23.23)*	−23.1 (±27.84)*	−0.8 (±32.20)
Fasting C-peptide, ng/ml	−0.08 (±0.52)	−0.11 (±0.64)	−0.17 (±0.57)
Fasting insulin, μU/ml	−0.05 (±3.55)	−0.27 (±4.11)	−0.57 (±4.43)
Fasting glucagon, pg/ml	24.2 (±314.10)	−6.3 (±29.23)*	−14.7 (±28.22)
Glycoalbumin, %	−2.53 (±1.93)*	−2.70 (±1.79)*	0.56 (±2.77)
1,5-AG, μg/ml	3.70 (±2.77)*	3.68 (±2.86)*	−0.08 (±1.77)
Fasting proinsulin, pmol/l	−2.75 (±4.61)	−3.55 (±6.93)*	−1.76 (±3.83)
Fasting total cholesterol, mg/dl	−2.3 (±26.67)	−1.7 (±25.61)	−4.4 (±23.18)
Fasting triglyceride, mg/dl	−6.6 (±140.19)	−23.1 (±117.01)	−10.3 (±118.04)
Fasting HDL-C, mg/dl	−2.0 (±8.24)	−1.2 (±7.09)	−0.5 (±7.69)
Fasting LDL-C, mg/dl	−4.3 (±20.26)	−0.5 (±21.09)	−5.3 (±21.07)
Fasting free fatty acids, mEq/l	−0.025 (±0.217)	−0.028 (±0.225)	0.008 (±0.216)
Body weight, kg	0.17 (±1.38)*	−0.09 (±1.29)	−0.23 (±1.37)
Abdominal circumference, cm	−0.20 (±3.35)	−0.54 (±3.59)	0.14 (±2.54)
HOMA-R (score)	−0.32 (±1.77)	−0.55 (±2.23)	−0.34 (±2.14)
HOMA-β, %	6.05 (±17.42)*	6.46 (±14.43)*	0.34 (±18.88)
Insulinogenic index‡	0.04 (±0.33)	0.07 (±0.38)	0.08 (±1.01)
Proinsulin/insulin ratio	−0.413 (±0.486)*	−0.476 (±0.662)*	−0.209 (±0.747)
Meal tolerance test parameters			
2-h postprandial plasma glucose, mg/dl	−33.6 (±37.56)*	−42.9 (±36.11)*	−3.1 (±43.33)
Glucose $AUC_{0\text{-}2h}$, mg h/dl	−57.0 (±55.33)*	−69.6 (±54.96)*	0.5 (±77.50)
Insulin $AUC_{0\text{-}2h}$, μU h/ml	3.48 (±14.13)*	4.03 (±16.86)*	−2.28 (±14.32)
C-peptide $AUC_{0\text{-}2h}$, ng h/ml	0.18 (±1.35)*	0.08 (±1.24)*	−0.48 (±1.25)
Glucagon $AUC_{0\text{-}2h}$, pg h/ml	34.6 (±593.38)	−22.9 (±53.80)	−31.0 (±46.37)
Active GLP-1 $AUC_{0\text{-}2h}$, pmol h/l	9.61 (±11.14)*	13.08 (±12.11)*	0.27 (±3.99)

1,5-AG, 1,5-anhydroglucitol; AUC0-2 h, area under the plasma concentration-time curve from pre-meal through 2 h after the start of the meal; GLP-1, glucagon-like peptide 1; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-b, homeostasis model assessment of b-cell function (insulin concentration × 360 / fasting plasma glucose − 63); HOMA-R, homeostasis model assessment of insulin resistance (insulin concentration × fasting plasma glucose / 405); LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; od = once daily; s.d., standard deviation.

* Statistically significant difference versus the change with metformin monotherapy.

† The dosage of metformin remained stable throughout the observation and treatment periods (500 or 750 mg/day).

‡ Insulin increment 30 min after glucose loading / plasma glucose increment 30 min after glucose loading.

T2DM inadequately controlled on metformin monotherapy plus diet and exercise, and they extend the findings of an earlier study in Japanese patients [30] which found that alogliptin 6.25, 12.5, 25 and 50 mg monotherapy produced significantly greater changes in HbA1c and FPG than placebo. In other studies in Western populations, alogliptin added to existing antihyperglycaemic therapy has also been shown to be more effective than monotherapy with these agents in patients with T2DM receiving glyburide [20], pioglitazone [31,32] and insulin (± metformin) [33], as well as metformin [22]. In the study that evaluated the addition of alogliptin to metformin in patients who were inadequately controlled on metformin alone (n = 527), once-daily alogliptin 12.5 mg and 25 mg plus metformin (≥1500 mg/day) produced significantly greater reductions from baseline in LS mean HbA1c (−0.6% [both dosages] vs. −0.1% [metformin alone]; $p < 0.001$) and FPG concentrations (−19 and − 17 mg/dl, respectively, vs. 0 mg/dl [metformin alone]; $p < 0.001$ for both alogliptin dosages) over 26 weeks. These reductions in HbA1c and FPG were similar to those achieved in our study over a shorter 12-week treatment period. The findings in the current trial, which are very similar to an international study in which alogliptin was added to metformin therapy [22], are interesting given postulated ethnic differences in the pathogenesis of type 2 diabetes and differences in body mass index. In leaner Asian patients with type 2 diabetes loss of glycaemic control is attributed to insulin deficiency rather than increased insulin resistance, and recent clinical data suggest that incretin-based therapies (such as alogliptin, sitagliptin and vildagliptin) are more effective in Japanese patients compared with Caucasian patients [14]. The effectiveness of incretin-based therapies is consistent with the reduced early insulin secretory capacity in patients with type 2 diabetes in Asian countries including Japan, and further suggests that such reduced early insulin secretory capacity could be partly due to lower levels of intact GLP-1, which has been recently revealed in Japanese subjects [14]. The effectiveness of incretin-based therapies in various races should be further investigated as more evidence becomes available.

In the 26-week study of Rosenstock et al. [33] in which once-daily alogliptin 12.5 or 25 mg was added to stable insulin

Table 3. Adverse events (n, %) occurring in ≥3% of patients in any treatment group over 12 weeks in the randomized, double-blind study and 52 weeks in the long-term, open-label extension (safety analysis sets).

	Randomized, double-blind study (12 weeks)			Open-label extension (52 weeks)*	
Adverse event (system organ class preferred term)	Alogliptin 12.5 mg od + metformin† (n = 92)	Alogliptin 25 mg od + metformin† (n = 96)	Metformin monotherapy† (n = 100)	Alogliptin 12.5 mg od + metformin† (n = 142)	Alogliptin 25 mg od + metformin† (n = 145)
Patients with AEs					
All AEs (all-cause events)	45 (48.9)	51 (53.1)	53 (53.0)	110 (77.5)	114 (78.6)
Drug-related AEs	10 (10.9)	8 (8.3)	10 (10.0)	26 (18.3)	29 (20.0)
Discontinuations due to drug-related AEs	0	0	0	3 (2.1)	0
Serious drug-related AEs	0	0	0	1 (0.7)	1 (0.7)
Specific AEs (all-cause events)‡					
Nasopharyngitis	18 (19.6)	22 (22.9)	20 (20.0)	44 (31.0)	53 (36.6)
Headache	6 (6.5)	0	0	9 (6.3)	3 (2.1)
Constipation	1 (1.1)	4 (4.2)	2 (2.0)	7 (4.9)	8 (5.5)
Diarrhoea	5 (5.4)	1 (1.0)	1 (1.0)	6 (4.2)	3 (2.1)
Eczema	0	2 (2.1)	0	7 (4.9)	6 (4.1)
Back pain	1 (1.1)	1 (1.0)	2 (2.0)	9 (6.3)	6 (4.1)
Arthralgia	0	1 (1.0)	0	2 (1.4)	6 (4.1)
Upper respiratory tract inflammation	2 (2.2)	2 (2.1)	0	6 (4.2)	6 (4.1)
Cystitis	0	1 (1.0)	0	5 (3.5)	4 (2.8)
Diabetic retinopathy	1 (1.1)	0	1 (1.0)	6 (4.2)	10 (6.9)
Hypertension	1 (1.1)	2 (2.1)	2 (2.0)	7 (4.9)	4 (2.8)
Bronchitis	0	2 (2.1)	1 (1.0)	1 (0.7)	6 (4.1)
Dental caries	0	0	2 (2.1)	1 (0.7)	7 (4.8)
Conjunctivitis, allergic	1 (1.1)	3 (3.1)	1 (1.0)	1 (0.7)	6 (4.1)
Hepatic function abnormal	1 (1.1)	1 (1.0)	0	3 (2.1)	4 (2.8)
ALT increased	0	0	0	6 (4.2)	2 (1.4)
Hepatic steatosis	0	3 (3.1)	1 (1.0)	2 (1.4)	5 (3.4)
Musculoskeletal stiffness	0	1 (1.0)	1 (1.0)	1 (0.7)	5 (3.4)
White blood cell count increased	1 (1.1)	2 (2.1)	1 (1.0)	3 (2.1)	5 (3.4)
Blood lactic acid increased	0	1 (1.0)	3 (3.0)	3 (2.1)	4 (2.8)

AE, adverse event; ALT, alanine aminotransferase; od, once daily.

* Pooled safety data for weeks 1 to 52 for patients assigned to alogliptin + metformin in the randomized, double-blind study (whether they entered the long-term extension or not), and weeks 13–52 for patients assigned to metformin monotherapy who were subsequently randomized to one of the two alogliptin + metformin groups in the long-term extension (n = 99). Patients assigned to metformin monotherapy in the randomized, double-blind study who did not receive the investigational drug in the long-term extension were excluded from this analysis.

† The dosage of metformin remained stable throughout the study (500 or 750 mg/day).

‡ Occurring in ≥3% of patients in any treatment group.

therapy (± metformin), alogliptin + insulin combinations produced significantly greater reductions from baseline in HbA1c than insulin alone (−0.63 and −0.71%, respectively, vs. −0.13% [insulin alone]; $p < 0.001$ for both alogliptin dosages), without causing weight gain or increasing the incidence of hypoglycaemia.

There were no safety or tolerability concerns with alogliptin as an add-on to metformin in our study. In the randomized, double-blind phase, the incidences of treatment emergent and treatment-related adverse events were similar in the three treatment groups, and no serious events or events necessitating withdrawal of the study medications were observed. Similarly, in the long-term extension study, the incidences of treatment emergent and treatment-related adverse events were similar in the two alogliptin/metformin groups, with no evidence of a dose relationship. No deaths occurred, and there were no clinically significant changes or events in laboratory test results, vital signs or 12-lead ECG findings. The most commonly reported adverse events in patients receiving the alogliptin/metformin combinations were nasopharyngitis, headache, constipation, back pain, eczema, and diarrhoea. Although other insulin secretagogues are associated with a risk of hypoglycaemia [6,34], only three patients in this study reported hypoglycaemic events over the 52-week treatment period, all of which were mild in severity and with two thirds considered to be not related to study medication. As lactic acidosis is a potential adverse effect of metformin, blood lactic acid levels were monitored throughout the study; increased levels were found in 3 (2.1%) patients [alogliptin 12.5 mg + metformin], and 4 (2.8%) patients [alogliptin 25 mg + metformin].

Safety data from studies in Western patients in which alogliptin was added to other antihyperglycaemic agents have also reported no major increases in the incidences of adverse effects with its use in combination with metformin [22], glyburide [20], pioglitazone [31,32] and insulin (± metformin) [33].

Alogliptin as an add-on to pioglitazone, which is categorized as an insulin sensitizer in Japanese patients with T2DM inadequately controlled on pioglitazone monotherapy plus diet and exercise was as effective and safe as the alogliptin + metformin combination used in the current study [35]. Sitagliptin, a DPP-4 inhibitor, as an add-on to pioglitazone in Japanese patients with T2DM inadequately controlled on pioglitazone monotherapy plus diet and exercise was also as effective and well tolerated as the alogliptin + metformin combination used in the current study [36]. These findings show that metformin as well as pioglitazone can be considered when selecting appropriate DPP-4 inhibitors combination therapy for Japanese patients with T2DM.

Conclusions

Alogliptin as an add-on to metformin in Japanese patients with T2DM inadequately controlled on metformin monotherapy plus diet and exercise was found to be safe and effective. In the 12-week randomized, double blind comparison with metformin monotherapy, alogliptin plus metformin produced significantly greater changes from baseline in key glycaemic parameters, with no increase in adverse events. Over 52 weeks, the incidences of adverse events were similar in the two alogliptin + metformin groups, with no evidence of a dose relationship.

In summary, alogliptin 12.5 and 25 mg once daily was safe and effective when added to metformin (500 or 750 mg/day) in Japanese patients with inadequately controlled type 2 diabetes, providing a useful therapeutic choice for improving glycaemic control.

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Conflict of Interest

K. K. has received honoraria for lectures from Takeda and has indicated no other conflicts of interest regarding the content of this article.

Y. S. and K. K. designed the study and wrote the manuscript. M. H. analyzed the data. S. H. and Y. M. contributed to conduct/data collection and wrote the manuscript.

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