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ORIGINAL ARTICLE

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

K. Kaku[1], T. Itayasu[2], S. Hiroi[2], M. Hirayama[2] & Y. Seino[3]

[1]*Diabetes and Endocrine Division, Kawasaki Medical School, Okayama, Japan*
[2]*Takeda Pharmaceutical Company, Osaka, Japan*
[3]*Kansai Electric Power Hospital, Osaka, Japan*

Aim: To assess the efficacy and safety of alogliptin added to pioglitazone versus pioglitazone monotherapy, in Japanese patients with type 2 diabetes who achieved inadequate glycaemic control on pioglitazone plus diet/exercise.

Methods: Patients were stabilized on pioglitazone 15 or 30 mg/day plus diet/exercise during a 16-week screening period. Patients with HbA1c of 6.9–10.4% were randomized to 12 weeks' double-blind treatment with alogliptin 12.5 or 25 mg once daily or placebo, added to their stable pioglitazone regimen. The primary endpoint was the change in HbA1c from baseline to week 12. Patients had an option to continue in a 40-week, open-label extension study, with those originally randomized to alogliptin remaining on the same dosage regimen while patients treated with placebo were randomly allocated to alogliptin 12.5 or 25 mg (added to their stable pioglitazone).

Results: The change from baseline in HbA1c after 12 weeks was significantly greater with alogliptin 12.5 mg added to pioglitazone and alogliptin 25 mg added to pioglitazone than with placebo added to pioglitazone (−0.91 and −0.97% vs. −0.19%; $p < 0.0001$). Responder rates (HbA1c <6.9% and HbA1c <6.2%) and changes in fasting and postprandial blood glucose levels showed a similar positive trend in terms of glycaemic control. The benefits seen with alogliptin were sustained during the 40-week extension period. Alogliptin added to pioglitazone was generally well tolerated; hypoglycaemia was infrequent and increases in body weight were minor.

Conclusions: Once-daily alogliptin was effective and generally well tolerated when given as add-on therapy to pioglitazone in Japanese patients with type 2 diabetes who achieved inadequate glycaemic control on pioglitazone plus lifestyle measures. Clinical benefits were maintained for 52 weeks.

Keywords: alogliptin, DPP-4 inhibitors, Japanese patients, pioglitazone, type 2 diabetes

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Introduction

Diabetes mellitus is a major cause of morbidity and mortality worldwide [1]. Oral antidiabetic agents are a key element of the treatment of type 2 diabetes, which accounts for the majority of cases of diabetes [2,3]. However, although these drugs improve glycaemic control, they do not correct all the glucoregulatory mechanisms affected in diabetes and it can be difficult to maintain adequate control of blood glucose levels in the long term, particularly with monotherapy [4].Consequently, there is often a need for combination therapy, using drugs with different mechanisms of action [2,5].

Key pathophysiological elements that treatment must address include pancreatic β-cell dysfunction and insulin resistance [4]. In addition, the role of impaired incretin hormone activity in diabetes has become apparent and several therapies now target this pathway [3,4]. The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are secreted in the intestine in response to food and stimulate insulin secretion from pancreatic β-cells and suppress glucagon secretion in a glucose-level-dependent manner [3,6,7]. Early studies reported that GLP-1 secretion was impaired following ingestion of a meal or glucose load in patients with type 2 diabetes, and this suggests that a lack of incretin effects is at least partly due to GLP-1 deficiency [8–10]. Measurement of intact GLP-1 in patients with type 2 diabetes, however, revealed no defects in GLP-1 secretory responses [8–10]. Yabe et al. noted that GLP-1 concentrations were very low in Japanese persons, including those with type 2 diabetes [8]. GLP-1 also appears to provide a protective effect for pancreatic β-cell function [6]. However, GLP-1 and GIP are rapidly deactivated by dipeptidyl peptidase IV (DPP-IV) [3]. Elevation of GLP-1 to physiological levels, by inhibiting the inactivating enzyme DPP-IV, is therefore expected to have antidiabetic effects in patients with type 2 diabetes who still maintain some degree of β-cell function.

Correspondence to: Prof. Kohei Kaku, Kawasaki Medical School, 577, Matsushima, Kurashiki-shi, Okayama 701-0192, Japan.
E-mail: kka@med.kawasaki-m.ac.jp

Alogliptin is a highly selective DPP-IV inhibitor, which prevents the degradation of GLP-1 and GIP. In particular, the resulting increase in GLP-1 levels enhances insulin secretion and reduces glucagon secretion [11]. Alogliptin has been shown to be effective in the treatment of Japanese patients with type 2 diabetes, both as monotherapy and as combination therapy with an α-glucosidase inhibitor [12]. This study was designed to evaluate the efficacy and safety of alogliptin as add-on therapy in Japanese patients with inadequate glycaemic control, despite treatment with thiazolidinedione.

Patients and Methods

Study Design

This randomized, double-blind, placebo-controlled trial was designed to assess the efficacy and safety of 12 weeks of therapy with alogliptin in combination with pioglitazone compared with pioglitazone monotherapy, in patients with type 2 diabetes. It was followed by a 40-week, open-label extension study. On the basis of the findings of a large multinational clinical trial, dosages of alogliptin 12.5 and 25 mg were chosen for this study [13].

The study was performed at 33 centres in Japan (32 for the extension study) in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline on Good Clinical Practice (GCP), and was approved by the Institutional Review Boards at each study site. All subjects provided written informed consent. The randomized study was performed between November 2007 and October 2008, while the extension study ran from May 2008 to August 2009.

Patients

Patients were aged $\geq$20 years with type 2 diabetes and had poor glycaemic control despite treatment with diet, exercise and a stable dose of pioglitazone (15 or 30 mg/day) for at least 16 weeks. Poor glycaemic control was defined as glycated haemoglobin (HbA1c) $\geq$6.9 to 10.4% after 14 weeks of screening, with a maximum allowable variation in the HbA1c level of 10% between weeks 6 and 2.

The main exclusion criteria were administration of an antidiabetic drug (other than pioglitazone) within 16 weeks; requirement for insulin; history of cardiac failure; systolic/diastolic blood pressure $\geq$180/110 mmHg; hepatic or renal impairment (aspartate aminotransferase or alanine aminotransferase $\geq$2.5 $\times$ upper limit of normal or serum creatinine $\geq$2 mg/dl); serious cardiovascular, cerebrovascular, pancreatic or haematological disorders; any malignancy; drug abuse or dependency or excessive alcohol consumption; hypersensitivity to pioglitazone; treatment with any investigational drug within 12 weeks; and pregnancy or lactation (for women of child-bearing age).

Treatment

Eligible patients were randomized in a ratio of 1 : 1 : 1 to receive alogliptin 12.5 or 25 mg or placebo once daily, in addition to their existing stable dose of pioglitazone 15 or 30 mg/day, for 12 weeks. Randomization was stratified based on the dose of pioglitazone. The randomization schedule was generated by independent personnel and the code was kept in a secure facility. Double-blinding was maintained using identical alogliptin and placebo tablets.

Patients who completed the 12-week double-blind period could continue immediately into a 40-week open-label extension study comparing alogliptin 12.5 and 25 mg in combination with pioglitazone. Patients who had received alogliptin plus pioglitazone during the double-blind phase continued on the same treatment and dose during the extension phase, while those who had been receiving pioglitazone monotherapy (plus placebo) were randomized to either alogliptin 12.5 or 25 mg plus pioglitazone.

Assessments

During the screening period, assessments included demographic characteristics, medical and medication histories, physical examination, vital signs, clinical laboratory tests, 12-lead electrocardiogram, HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, fasting C-peptide, glycoalbumin, 1,5-anhydroglucitol (1,5-AG), fasting proinsulin, fasting serum lipids, total and high molecular weight (HMW) adiponectin, high-sensitive C-reactive protein (CRP), and monocyte chemoattractant protein-1 (MCP-1). The evaluations listed above (except demographic characteristics, medical and medication histories) were performed during the study treatment period, as were several additional assessments, including a meal tolerance test, abdominal circumference, DPP-IV activity, homeostasis model assessment of insulin resistance and β-cell function (HOMA-R and HOMA-β), insulinogenic index, proinsulin/insulin ratio, and active GLP-1, plasma drug concentration, and adverse events. Patients were assessed at weeks 2, 4, 8 and 12 during the double-blind phase, and at 4- to 12-week intervals during the extension phase. Laboratory assessments were all performed at an independent central laboratory (Mitsubishi Chemical Medience Corporation).

Endpoints

The primary endpoint in the double-blind study was the change in HbA1c from baseline (start of double-blind period) to the end of treatment (week 12). Secondary endpoints included HbA1c and fasting blood glucose at each timepoint, and blood glucose measured during a meal tolerance test. In addition, other measures of glycaemic and metabolic control, as listed above, were also recorded. The primary endpoint in the extension study was adverse events, while secondary endpoints were the same as glycaemic measures described for the double-blind study. For both parts of the study, safety variables included adverse events, vital signs, 12-lead ECG findings and clinical laboratory parameters. All HbA1c values in this study have been reported according to the published 2010 diagnostic criteria proposed by the Japan Diabetes Society (JDS) [14,15].

Sample Size and Statistical Methods

According to a previous study, mean changes in HbA1c after 12 weeks' treatment with alogliptin 12.5 mg, 25 mg and placebo

were assumed to be −0.50, −0.50 and 0.0%, respectively, and standard deviation [s.d.] was assumed to be 0.80% for each treatment. On the basis of these assumptions, 65 patients per group were needed to provide a 90% simultaneous power of detecting a statistically significant difference between the pioglitazone monotherapy group and the alogliptin combination groups at a significance level of 2.5% (one-sided) in the double-blind study. Allowing for drop-outs, it was therefore planned to randomize 80 patients per treatment group (total of 240 patients).

The main efficacy analysis in the double-blind study was performed on the full analysis set (FAS), which included patients who were randomized and received at least one dose of study medication. Efficacy analysis was based on a last observation carried forward (LOCF) methodology: if no evaluable data were available at the completion of the observation period (week 0) or at any assessment point after the start of the treatment period, then these data would be replaced by the last evaluable data. Safety analyses were performed on the safety analysis set, which included all patients who received at least one dose of study medication.

In the double-blind study, summary statistics (number of patients, mean, s.d., maximum, minimum and quartile values) and two-sided 95% confidence intervals (CIs) of the means were calculated per group. Point estimates were calculated for between-group differences. Based on an analysis of covariance (ANCOVA) model using a closed testing procedure, with change in HbA1c as a dependent variable, pioglitazone dose as a block factor, HbA1c at the end of the screening phase as a covariate, and treatment group as an independent variable, adjusted least square (LS) means, standard errors (s.e.) and two-sided 95% CIs of the LS means were calculated by treatment group for the primary endpoint. A comparison between each alogliptin combination group and the pioglitazone monotherapy group was also performed in accordance with a closed testing procedure using the ANCOVA model. Area under the curve (AUC) time profiles were evaluated for parameters measured during meal tolerance tests.

In the open-label long-term extension study, summary statistics (number of patients, mean, s.d., maximum, minimum and quartile values) and two-sided 95% CIs of the means were calculated per group. For patients who received alogliptin throughout the study, the efficacy comparison was made between weeks 0 and 52. However, for patients who received placebo during the 12-week double-blind phase, the efficacy comparison was made between weeks 12 and 52. AUC time profiles were again evaluated for parameters measured during meal tolerance tests. Adverse events were coded using the MedDRA system and summarized using preferred term and organ class.

Results

Patient Disposition and Baseline Characteristics

The disposition of patients is summarized in figure 1. Of the 460 enrolled patients, 339 were randomized in the double-blind phase (111 to alogliptin 12.5 mg, 113 to alogliptin 25 mg and 115 to placebo). There were no clinically relevant differences in baseline characteristics among the groups (Table 1).

Efficacy

After 12 weeks of treatment, the change from baseline in HbA1c (primary endpoint; LS mean ± s.e.) was significantly greater in the alogliptin 12.5 mg plus pioglitazone group and the alogliptin 25 mg plus pioglitazone group than in the placebo plus pioglitazone (pioglitazone monotherapy) group (−0.91 and −0.97% vs. −0.19, respectively; for both comparisons $p < 0.0001$). The reduction in HbA1c was significantly greater for both combination therapy groups compared with the placebo group at all timepoints from week 2 to week 12, and a significantly higher proportion of patients treated with alogliptin achieved HbA1c <6.9 and <6.2% compared with the placebo group (Table 2).

Changes from baseline in HbA1c were analysed with stratification according to baseline subject characteristics [HbA1c, age, gender, body mass index (BMI), duration of diabetes, pioglitazone dosage during the observation period, fasting C-peptide, 2-h postprandial blood glucose, HOMA-R and HOMA-β]. A subgroup analysis according to baseline HbA1c showed that greater reductions in HbA1c occurred in the alogliptin combination groups compared with pioglitazone monotherapy in all patient subgroups and that larger decreases were associated with higher baseline values of HbA1c. In addition, slightly larger reductions in HbA1c were associated with higher pioglitazone dose, higher baseline values of 2-h postprandial blood glucose level and lower baseline levels of fasting C-peptide level, HOMA-R and HOMA-β. Age, gender, BMI and duration of diabetes had no effect on the reduction seen in HbA1c.

Changes in glycaemic/metabolic parameters including the primary, secondary and other endpoints after 12 weeks are summarized in Table 2. Compared with placebo, alogliptin 12.5 and 25 mg were associated with significantly greater mean changes from baseline in fasting blood glucose (−2.4, −14.9 and −18.9 mg/dl, respectively), glycoalbumin (−0.11, −2.73 and −2.79%), 1,5-AG (0.48, 4.31 and 4.76 μg/ml), proinsulin/insulin ratio (0.034, −0.275 and −0.398), HOMA-β (0.06, 5.48 and 6.99%), DPP-IV (0.2404, −9.6336 and −10.0062 nmol/min/ml), serum lipids [free fatty acid: (0.039, −0.022 and −0.037 mEq/l)] and body weight (−0.03, 0.48 and 0.46 kg; although this change was small and not considered clinically relevant).

Statistically significant differences between placebo and alogliptin 12.5 and 25 mg measured during a meal tolerance test included 2-h postprandial blood glucose (−4.5, −31.8 and −41.5 mg/dl), glucose $AUC_{0-2\,h}$ (−7.0, −55.7 and −68.2 mg·h/dl), 2-h active GLP-1 (0.573, 4.733 and 4.786 pmol/l) and active GLP-1 $AUC_{0-2\,h}$ (0.915, 10.275 and 11.453 pmol·h/l). There were no significant between-group differences for other endpoints including HOMA-R (−0.11, −0.14 and −0.20).

Results from the open-label extension study showed that HbA1c and fasting blood glucose were significantly lower than baseline at all timepoints throughout the 52-week treatment period, in both alogliptin combination therapy groups (figure 2). Likewise, 2-h postprandial glucose values

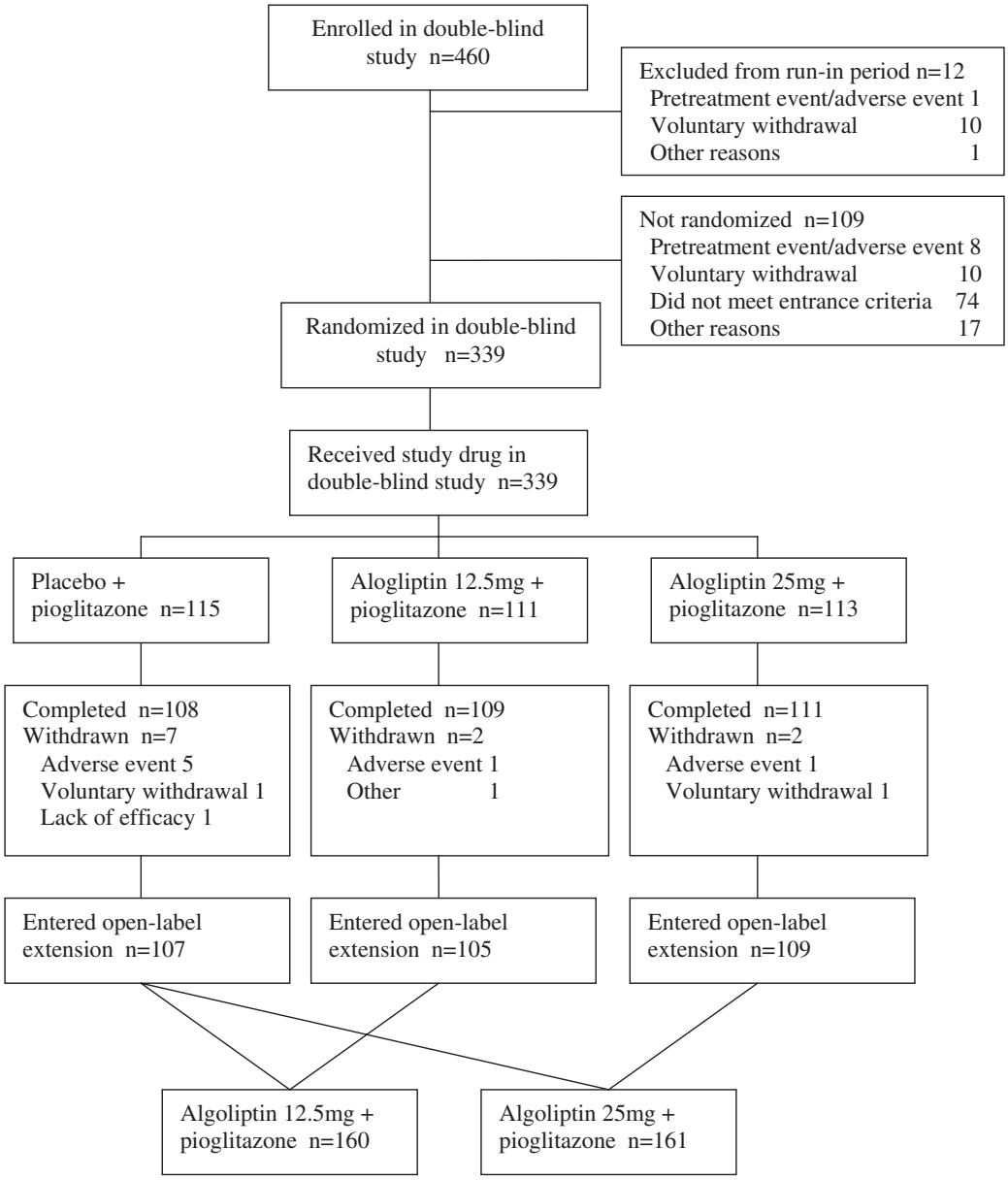

Figure 1. Disposition of patients in the 12-week double-blind study and 40-week open-label extension.

measured during a meal tolerance test were significantly reduced at all timepoints in the alogliptin groups. The mean change in HbA1c from baseline to week 52 was −0.65% for both groups. Changes from baseline in glucose AUC_{0-2h} (meal tolerance test), glycoalbumin, 1,5-AG, HOMA-β, active GLP-1, DPP-IV activity and proinsulin/insulin ratio were also significantly different to baseline in both groups at all assessment points throughout the study (data not shown).

Safety

During the 12-week double-blind study, 37.8% of the alogliptin 12.5 mg plus pioglitazone group, 45.1% of the alogliptin 25 mg plus pioglitazone group and 47.8% of the placebo plus pioglitazone group experienced an adverse event. The incidence of drug-related adverse events in these groups was 7.2, 8.8 and 6.1%, respectively, while serious events occurred in 0.9, 1.8 and 4.3% of patients and adverse events leading to drug discontinuation occurred in 0.9, 1.8 and 3.5%. Only one serious adverse event was considered possibly drug-related (dizziness in the placebo plus pioglitazone group).

The most common adverse event in each group was nasopharyngitis (4.5, 12.4 and 5.2% for alogliptin 12.5 mg plus pioglitazone, alogliptin 25 mg plus pioglitazone and placebo plus pioglitazone), which was mild in severity and not considered related to study medication. Mild hypoglycaemia was reported for one patient in each of the alogliptin combination groups. Oedema-related events were oedema (3.5%), peripheral oedema (2.7%) and facial oedema (0.9%) in the alogliptin 25 mg plus pioglitazone group, while no

Table 1. Baseline characteristics (12-week double-blind study).

	Placebo + pioglitazone n = 115	Alogliptin 12.5 mg + pioglitazone n = 111	Alogliptin 25 mg + pioglitazone n = 113
12-Week double-blind study			
Male/Female (n)	76/39	67/44	70/43
Age (years)	60.1 (9.7)	60.8 (8.8)	59.3 (10.7)
Weight (kg)	69.0 (14.4)	66.50 (12.9)	68.07 (13.0)
Height (cm)	161.4 (9.8)	160.2 (9.3)	161.3 (9.0)
BMI (kg/m^2)	26.4 (4.4)	25.91 (4.7)	26.07 (3.7)
Diabetes duration (years)	6.7 (5.3)	6.51 (5.0)	6.80 (5.7)
HbA1c (%)	7.92 (0.85)	7.91 (0.82)	7.89 (0.73)
Pioglitazone dose 15 mg/30 mg (n)	62/53	62/49	60/53

Values shown are mean (s.d.). BMI, body mass index.

Table 2. Changes in glycaemic/metabolic parameters from baseline (12-week double-blind study).

	Week	Placebo + pioglitazone (n = 115)	Alogliptin 12.5 mg + pioglitazone (n = 111)	Alogliptin 25 mg + pioglitazone (n = 113)
ΔHbA1c (%)	12	−0.19 (0.55)	−0.91 (0.44)*	−0.97 (0.52)*
Responders (%): HbA1c <6.9%	12	20.0 [13.1, 28.5]	49.5* [39.9, 59.2]	49.6* [40.0, 59.1]
Responders (%): HbA1c <6.2%	12	0.0 [0.0, 3.2]	6.3* [2.6, 12.6]	4.4* [1.4, 10.0]
Δ Fasting blood glucose (mg/dl)	12	−2.4 (26.8)	−14.9* (18.4)	−18.9* (21.0)
Δ Glycoalbumin (%)	12	−0.11 (2.18)	−2.73* (1.74)	−2.79* (1.91)
Δ1, 5−AG (μg/ml)	12	0.48 (1.96)	4.31* (2.77)	4.76* (3.02)
Δ Insulinogenic index	12	−0.04 (0.46)	0.07 (0.33)	0.04 (0.33)
Δ DPP-IV activity (nmol/min/ml)	12	0.24 (1.25)	−9.63* (2.02)	−10.01* (2.33)
Δ HOMA-R	12	−0.11 (1.54)	−0.14 (0.77)	−0.20 (1.13)
Δ HOMA-β (%)	12	0.06 (9.68)	5.48* (11.91)	6.99* (11.22)
Δ Body weight (kg)	12	−0.03 (1.52)	0.48* (1.26)	0.46* (1.42)
Meal tolerance test				
Δ Blood glucose 2-h (mg/dl)	12	−4.5 (48.1)	−31.8* (38.2)	−41.5* (39.2)
Δ Blood glucose $AUC_{0-2\,h}$ (mg·h/dl)	12	−7.0 (66.6)	−55.7 (50.9)	−68.2* (58.3)
Δ Active GLP-1 concentrations during meal tolerance test 2-h (pmol/l)	12	0.6 (1.9)	4.7 (3.4)	48 (7.6)
Δ Active GLP-1 $AUC_{0-2\,h}$ during meal tolerance test (pmol·h/l)	12	0.9 (4.7)	10.3* (5.6)	11.4* (16.2)
Serum lipids				
Δ Total cholesterol (mg/dl)	12	0.3 (24.3)	−4.5 (22.6)	−5.7* (21.1)
Δ LDL-cholesterol (mg/dl)	12	0.1 (20.4)	−2.5 (18.1)	−4.0 (18.4)
Δ HDL-cholesterol (mg/dl)	12	−0.8 (9.6)	−1.4 (8.0)	−2.4 (8.2)
Δ Triglycerides (mg/dl)	12	7.6 (79.3)	−7.8 (54.9)	−6.8 (56.8)
Δ Free fatty acids (mEq/l)	12	0.04 (0.21)	−0.02* (0.22)	−0.04* (0.20)

Values shown are mean (s.d.) or % [95% CI]; Δ, change from baseline. 1,5-AG, 1,5-anhydroglucitol; $AUC_{0-2\,h}$, area under the blood glucose concentration time curve from 0 to 2 h; DPP-IV, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; HOMA-β, homeostasis model assessment of β-cell function; HOMA-R, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.
*$p < 0.05$ versus placebo.

oedema-related events (0%) were observed in the alogliptin 12.5 mg plus pioglitazone group. Peripheral oedema (1.7%) was reported in the placebo plus pioglitazone group. Oedema-related events were generally considered drug-related and were mild in severity. No clinically relevant changes in body weight or vital signs were observed during the study. Isolated cases of hypertension (n = 1, 12.5 mg group) and cardiac disorders (n = 1, placebo group) were all considered mild and unrelated to alogliptin treatment.

Based on the extension study, the incidence of adverse events in the alogliptin 12.5 mg plus pioglitazone group and the alogliptin 25 mg plus pioglitazone group during a total of up to 52 weeks of treatment were 87.3 and 89.1% for total adverse events, 18.1 and 25.5% for drug-related adverse events, 7.2 and 7.9 for adverse events leading to discontinuation, and 8.4 and 6.7% for serious adverse events. One patient died (25 mg group) from a myocardial infarction that was not considered related to study medication. Most adverse events were mild in severity.

Adverse events that occurred at an incidence of ≥5% in either group during the 52-week treatment period included nasopharyngitis (32.5% for the alogliptin 12.5 mg plus pioglitazone group and 33.3% for alogliptin 25 mg plus pioglitazone group), increased blood creatine phosphokinase

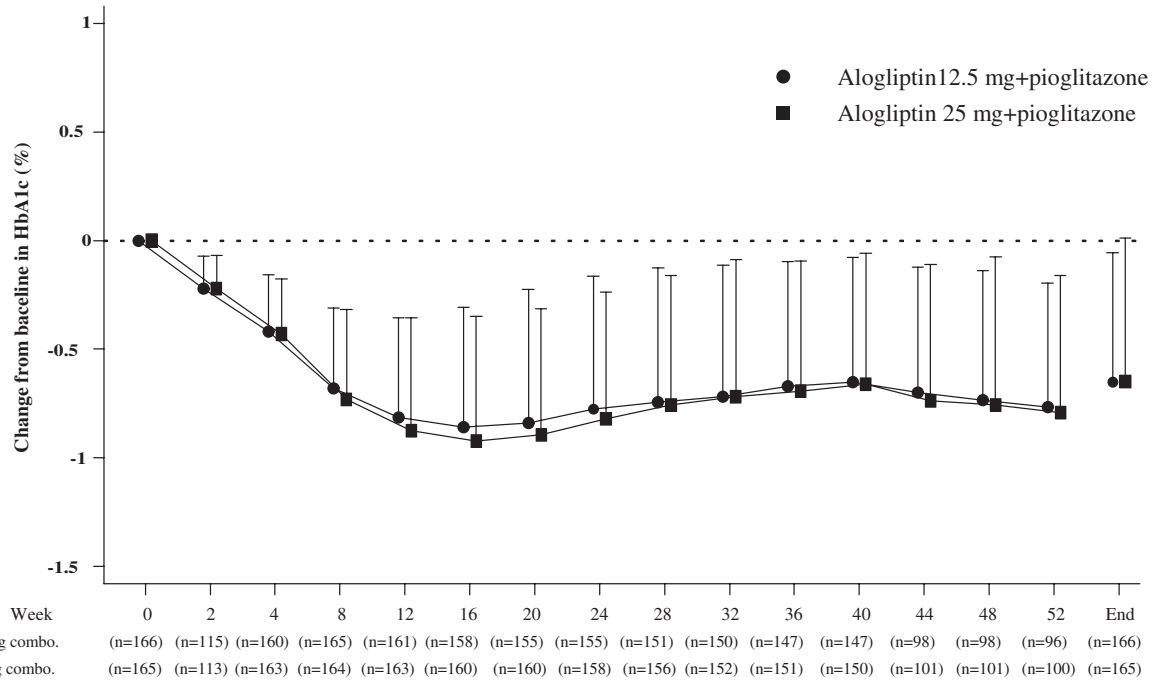

Figure 2. The change from baseline in HbA1c (mean + s.d.) throughout the entire treatment period.

(9.6 and 9.1%), arthralgia (1.2 and 9.1%), upper respiratory tract inflammation (7.8 and 5.5%), back pain (7.2 and 4.8%) and constipation (2.4 and 6.7%). The only adverse event considered drug-related that occurred at an incidence of ≥3% was oedema (3% in the alogliptin 25 mg group vs. 1.2% in the alogliptin 12.5 mg group). Hypoglycaemia was reported for two patients in the alogliptin 12.5 mg plus pioglitazone group and three in the alogliptin 25 mg plus pioglitazone group, and was generally mild, although one patient in the 12.5 mg group discontinued treatment. Oedema-related adverse events, which were reported for 6 patients in the 12.5 mg combination group and 15 in the 25 mg combination group, were generally mild, although 2 patients in the 25 mg group discontinued treatment. There were no clinically relevant changes in mean values for laboratory parameters, vital signs or 12-lead ECG during the study. At the end of the 52-week study, compared with baseline values, bodyweight was significantly ($p < 0.05$) increased by 1.24 and 1.30 kg in the alogliptin 12.5 and 25 mg groups, respectively.

Discussion

The majority of patients with type 2 diabetes will need combination therapy in the long-term [5]. This study showed that add-on therapy with alogliptin improved glycaemic control in Japanese patients with type 2 diabetes inadequately controlled on pioglitazone and diet/exercise. After 12 weeks, significantly greater reductions in the primary endpoint, HbA1c, as well as in fasting and postprandial blood glucose levels were achieved with alogliptin plus pioglitazone compared with placebo plus pioglitazone.

The proportions of patients who achieved HbA1c levels of <6.9% (the target set by the Japanese Diabetes Society) [16] and an aggressive target of <6.2% were significantly higher in the alogliptin plus pioglitazone groups than in the pioglitazone monotherapy group. The improvements in HbA1c documented for alogliptin were independent of age, sex or duration of diabetes.

The beneficial effects on glycaemic control seen with alogliptin add-on therapy were maintained over the full 52-week study period. In addition, significant improvements in HOMA-β and proinsulin/insulin ratio, both markers of β-cell function, were seen throughout the study in the alogliptin groups. In contrast, alogliptin treatment had no significant effect on HOMA-R, consistent with a lack of effect on insulin resistance. Overall, the two dosages of alogliptin produced comparable changes in glycaemic control in this cohort of Japanese patients with type 2 diabetes.

The results of this study are consistent with a multinational trial in which the addition of alogliptin 12.5 or 25 mg to pioglitazone for 26 weeks led to reductions in HbA1c of 0.66 and 0.80% and in fasting blood glucose of 19.7 and 19.9 mg/dl [13]. In that trial, patients were allowed to receive stable doses of metformin or sulfonylurea. A study involving Japanese patients showed that alogliptin improved glycaemic control when added to voglibose in patients with uncontrolled type 2 diabetes [17]. International trials have found similar benefits for alogliptin when added to metformin, glyburide or insulin [18–20], or used as monotherapy [21]. The results of this study are also consistent with data for other DPP-IV inhibitors [22], although head-to-head comparisons have not been performed.

Alogliptin add-on therapy with pioglitazone was generally safe and well tolerated throughout this 52-week study. In particular, it did not increase the risk of hypoglycaemia

compared with pioglitazone monotherapy. The overall incidence of adverse events was comparable in the alogliptin 12.5 and 25 mg groups with no dose-related differences in tolerability. Oedema and increased body weight are recognized adverse effects associated with pioglitazone [23]. In this study, the addition of alogliptin to pioglitazone was associated with small increases in body weight and abdominal circumference, but neither was considered clinically relevant.

Oedema-related adverse events were more frequent in the group receiving 25 mg alogliptin plus pioglitazone than in the pioglitazone monotherapy group, but were not reported for the 12.5 mg alogliptin combination group in the double-blind phase. Oedema was also more common in the alogliptin 25 mg plus pioglitazone group than in the 12.5 mg group. However, oedema-related events were generally mild and few patients discontinued therapy. In the multinational study of alogliptin added to pioglitazone, the incidence of peripheral oedema did not differ between the alogliptin 12.5 or 25 mg groups and the placebo group [16]. However, an increase in oedema has been reported in some other studies of DPP-IV inhibitors added to pioglitazone [24,25].

In conclusion, add-on therapy with alogliptin improved glycaemic control in Japanese patients with type 2 diabetes uncontrolled on pioglitazone, and was generally well tolerated. Based on results related to efficacy and safety in this study, alogliptin 12.5 mg appears to be the optimal dosage in patients not attaining optimal glycaemic control with pioglitazone monotherapy in addition to lifestyle measures (diet and exercise therapy). The benefits of combination therapy were maintained over a 1-year period.

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Conflict of Interest

K. K. and Y. S. were the independent medical experts for this study and interpreted the clinical findings and contributed to the discussion and writing of the manuscript. T. I., S. H. and M. H. were responsible for day-to-day organizational issues, monitoring, collection of data and data analysis.

All authors contributed to the preparation and/or review of the manuscript with full access to all the clinical data.

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Appendix

List of Investigators/Institutions

Yoshitaka Aiso, Aiso-naika; Yasuo To, Aiwa Clinic; Shin Aoki, Aoki-naika; Tomoyuki Arisaka, Arisaka Naika Clinic; Hideo Ayame, Ayame Medical Clinic; Shigeru Fujii, Fukuoka Shin Mizumaki Hospital; Kiyoshi Gondo, Gondo Clinic; Yasunori Sawayama, Harasanshin Hospital; Daigaku Uchida, Hotaruno Central Naika; Kiyomitsu Ikeoka, Ikeoka Clinic; Hideaki Jinnouchi, Jinnouchi Hospital; Hiroshi Kono, Jusendo General Hospital; Mitsutoshi Kato, Kato Clinic; Makoto Kunisaki, Kunisaki Makoto Clinic; Satomi Hayashi, Kurashiki Kinen Hospital; Hideki Kuribayashi, Kuribayashi Clinic; Otoya Miho, Miho-Clinic; Hideo Takahashi, Minamiakatsuka Clinic; Atsuko Murakami, Murakami Clinic; Nobuyuki Abe, Abe Clinic; Keita Ato, Nikko Memorial Hospital; Tetsuji Okuno, Nippon Kokan Fukuyama Hospital; Kazunori Ogino, Ogino Clinic; Hiroaki Miyaoka, Saiseikai Matsuyama Hospital; Hiroaki Seino, Seino Internal Medicine Clinic; Tatsuhide Inoue, Shizuoka General Hospital; Masahiro Sugawara, Sugawara Clinic; Akira Yamauchi, Suruga Clinic; Yuzo Yoshimi, The Veritas Hospital; Madoka Taguchi, Toshiba General Hospital; Makoto Sugiura, Touei Hospital; Hiroichi Ichimasu, Yashio Central General Hospital; Kotaro Shimokawa, Yutenji Medical Clinic.