

## BRIEF REPORT

# Randomized, double-blind, phase III study to evaluate the efficacy and safety of once-daily treatment with alogliptin and metformin hydrochloride in Japanese patients with type 2 diabetes

Kohei Kaku<sup>1</sup> | Shuuji Sumino<sup>2</sup> | Masafumi Katou<sup>2</sup> | Yuya Nishiyama<sup>2</sup> |  
Yoshinobu Kinugawa<sup>2</sup>

<sup>1</sup>Department of Internal Medicine, Kawasaki Medical School, Okayama, Japan

<sup>2</sup>Takeda Development Center Japan, Takeda Pharmaceutical Company Limited, Osaka, Japan

**Correspondence**

Dr. Kohei Kaku, Department of Internal Medicine, Kawasaki Medical School, 577, Matsushima, Kurashiki-shi, Okayama 701-0192, Japan.

Email: kka@med.kawasaki-m.ac.jp

**Funding information**

This study was sponsored by Takeda Pharmaceutical Company Ltd. Medical writing support was provided by BlueMomentum, a division of Ashfield Healthcare Communications (a UDG Healthcare plc company), and was funded by Takeda Pharmaceutical Company Ltd.

[The copyright line for this article has been changed on 31 August 2017, after original online publication].

This randomized, double-blind, phase III study evaluated the efficacy and safety of once-daily treatment with alogliptin (25 mg once daily), alone or with metformin hydrochloride (500 mg once daily or 250 mg twice daily), in Japanese patients with type 2 diabetes. The primary endpoint was change in glycated haemoglobin (HbA1c) from baseline to the end of treatment (week 24). The least squares (LS) mean (standard error) change in HbA1c from baseline to the end of treatment (week 24) was 0.16 (0.072)% in alogliptin alone, -0.49 (0.049)% in alogliptin/metformin once daily, and -0.60 (0.049)% in alogliptin/metformin twice daily. The LS mean difference in HbA1c change from baseline between alogliptin/metformin once daily and alogliptin alone (alogliptin/metformin once daily minus alogliptin alone) was -0.65% (95% confidence interval [CI] -0.821, -0.480) and between alogliptin/metformin once daily and twice daily (once daily minus twice daily) was 0.11% (95% CI -0.026, 0.247). The overall frequency of adverse events was similar among the groups. This study showed that the efficacy of alogliptin/metformin once daily was superior to alogliptin alone and non-inferior to alogliptin/metformin twice daily, and that alogliptin/metformin once daily was safe and well tolerated in Japanese patients with type 2 diabetes.

**KEYWORDS**

antidiabetic drug, DPP-IV inhibitor, metformin, phase III study, randomized trial, type 2 diabetes

## 1 | INTRODUCTION

Alogliptin benzoate is a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor. As a result of the inhibition of DPP-4 activity, the level of glucagon-like peptide-1 (GLP-1) increases, stimulating glucose-dependent insulin secretion from pancreatic  $\beta$  cells, thereby improving glucose homeostasis.<sup>1</sup>

Metformin is a biguanide antihyperglycaemic agent that suppresses the release of glucose from the liver and improves insulin sensitivity in peripheral tissues. Additionally, it suppresses intestinal absorption of glucose. These pharmacological actions produce a blood glucose-lowering effect.

Combination therapy of alogliptin and metformin is a reasonable treatment approach because these compounds have different mechanisms of action that improve glucose metabolism (ie, alogliptin stimulates glucose-dependent insulin secretion and metformin improves insulin sensitivity in peripheral tissues). Indeed, the effectiveness of this combination therapy has been reported in Japanese patients with type 2 diabetes whose blood glucose was not adequately controlled with metformin alone<sup>2</sup>; however, the effectiveness of alogliptin and metformin combination therapy has not been confirmed in Japanese patients with type 2 diabetes whose blood glucose is inadequately controlled with alogliptin treatment alone.

In general, the recommendation in Japan is to dose with metformin two or three times a day. Increasing the frequency of dosing is considered to have a negative impact on treatment adherence in patients with chronic disease including type 2 diabetes,<sup>3</sup> therefore, once-daily dosing of metformin with alogliptin would be expected to improve adherence. It has not yet been established, however, whether or not different co-administration methods of metformin (once daily or twice daily) with alogliptin (once daily) affect treatment efficacy and safety in the Japanese population.

The aim of the present study was to evaluate the efficacy and safety of a 24-week treatment with metformin 500 mg once daily added to alogliptin 25 mg once daily compared with metformin 500 mg twice daily added to alogliptin 25 mg once daily and alogliptin 25 mg once daily alone in Japanese patients with type 2 diabetes who have inadequate glycaemic control, despite treatment with once-daily alogliptin 25 mg in addition to diet and exercise therapy.

## 2 | METHODS

This was a phase III, randomized, double-blind, parallel-group, multi-centre study, conducted at 34 sites in Japan. The study was conducted in compliance with the protocol and ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice. The study included a 12-week screening period (visits every 4 weeks, including evaluations of eligibility, glycosylated haemoglobin [HbA1c] and safety) and a 24-week treatment period.

Patients aged  $\geq 20$  to  $< 75$  years were eligible for enrolment in the 12-week screening period if they were diagnosed with type 2 diabetes and had no hepatic, cardiovascular or pulmonary impairment.

On completion of the screening period, patients were randomized to the treatment period if they met the following criteria: HbA1c level  $\geq 6.9\%$  and  $< 10.5\%$  at week -4 (8 weeks after the start of the screening period); no more than 10% difference in HbA1c level between week -8 and -4; and on a stable diet and exercise therapy with alogliptin treatment (25 mg/d administered after breakfast) throughout the screening period.

Patients who used antidiabetic agents other than alogliptin during the screening period or had evident renal impairment were excluded before the treatment period.

During the 12-week screening period, all patients took 1 tablet of alogliptin 25 mg. After the screening period, the eligibility of each patient was evaluated at week 0, and the inclusion/exclusion criteria (including the HbA1c data) were also assessed during the screening period. Eligible patients were randomized to receive treatment with alogliptin 25 mg once daily alone, combination therapy of alogliptin 25 mg once daily and metformin 500 mg once daily, or combination therapy of alogliptin 25 mg once daily and metformin 250 mg twice daily (500 mg/d).

The primary endpoint was the change in HbA1c from baseline to the end of the treatment period (week 24). For the primary analysis, an analysis of covariance model was used with the change in HbA1c from baseline to the end of the treatment period (week 24) as a dependent variable and HbA1c at baseline and treatment group as independent variables; the least squares (LS) mean, the standard error

(s.e.) values and 2-sided 95% confidence intervals (CIs) of the LS means were calculated for each treatment group. Last observation carried forward imputation was used for missing values. A secondary analysis of the primary endpoint was performed without correction for baseline HbA1c level. The superiority of alogliptin/metformin once daily over alogliptin alone and non-inferiority of alogliptin/metformin once daily to alogliptin/metformin twice daily were also assessed. Secondary endpoints included HbA1c, fasting plasma glucose (FPG) and assessment of safety.

## 3 | RESULTS

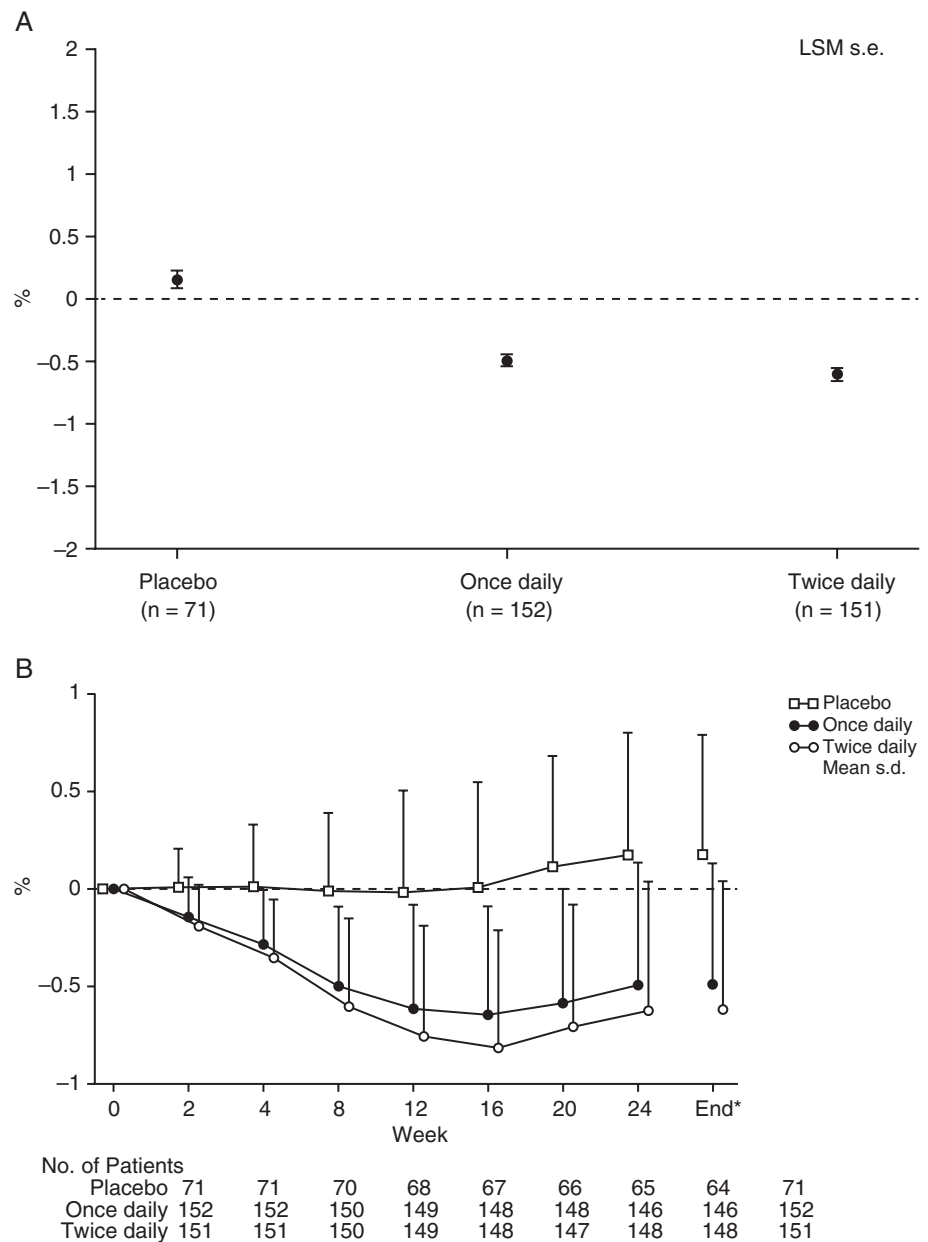
Of 524 patients undergoing screening, 374 were randomly assigned to treatment with alogliptin alone ( $n = 71$ ), alogliptin/metformin once daily ( $n = 152$ ) or alogliptin/metformin twice daily ( $n = 151$ ), and were included in the efficacy and safety populations (Figure S1). Patient demographic and clinical characteristics for the randomized population were similar between study groups (Table S1, Appendix S1). Mean values of HbA1c at the beginning (week -12) and end (week 0) of the screening period for the 374 patients who entered the treatment period are shown in Table S2.

### 3.1 | Efficacy

The primary analysis showed that the LS mean change (s.e.) in HbA1c from baseline to the end of treatment period (week 24) was 0.16 (0.072)% with alogliptin alone, -0.49 (0.049)% with alogliptin/metformin once daily and -0.60 (0.049)% with alogliptin/metformin twice daily (Figure 1A). The difference in LS mean change in HbA1c from baseline to the end of treatment period between alogliptin/metformin once daily and alogliptin alone (alogliptin/metformin once daily - alogliptin alone) was -0.65% (2-sided 95% CI -0.821, -0.480) and the difference in LS mean change between alogliptin/metformin once daily and alogliptin/metformin twice daily (alogliptin/metformin once daily - alogliptin/metformin twice daily) was 0.11% (2-sided 95% CI -0.026, 0.247). These results demonstrated the superiority of alogliptin/metformin once daily vs alogliptin alone and the non-inferiority of alogliptin/metformin once daily vs alogliptin/metformin twice daily.

A reduction in mean HbA1c level was observed with alogliptin/metformin once daily and alogliptin/metformin twice daily at each time point assessed, but this was not seen with alogliptin alone. The reduction observed with alogliptin/metformin once daily and alogliptin/metformin twice daily was similar after week 20 (Figure 1B). The proportion of patients whose HbA1c level was  $\geq 7.0\%$  at baseline and  $< 7.0\%$  at the end of treatment period (week 24) was 4.8% (3/63) with alogliptin alone, 35.0% (48/137) with alogliptin/metformin once daily and 34.3% (48/140) with alogliptin/metformin twice daily (Table 1).

For the mean (standard deviation [s.d.]) change in fasting blood glucose from baseline to the end of the treatment period (week 24), the reduction was greater with alogliptin/metformin once daily (-7.6 [26.41] mg/dL) than alogliptin alone (7.4 [26.89] mg/dL), but smaller than alogliptin/metformin twice daily (-18.2 [25.41] mg/dL; Table 1). Regarding other endpoints, the mean changes from baseline in fasting insulin, fasting glucagon, homeostatic model assessment of insulin



**FIGURE 1** Change in HbA1c from baseline to the end of the treatment period (week 24). A, LS mean change ( $\pm$  s.e.). B, Mean change ( $\pm$  s.d.). \*End of treatment period (week 24).

resistance and body weight through to the end of the treatment period (week 24) were similar among the treatment groups (Table 1). The remaining endpoint, mean change in homeostatic model assessment of  $\beta$ -cell function, was greater with alogliptin/metformin once daily than alogliptin alone and similar between alogliptin/metformin once daily and alogliptin/metformin twice daily (Table 1).

### 3.2 | Safety

The overall frequency of adverse events (AEs) was similar among all treatment groups, with incidences of 57.7% (41/71) with alogliptin alone, 50.7% (77/152) with alogliptin/metformin once daily, and 52.3% (79/151) with alogliptin/metformin twice daily (Table S3, Appendix S1). Across all treatment groups, nasopharyngitis was the most common AE and the only AE with an incidence  $\geq 5\%$  in all 3 groups (11.3%, 14.5% and 12.6% with alogliptin alone, alogliptin/metformin once daily and alogliptin/metformin twice daily, respectively). No patients developed serious hypoglycaemia or acute

pancreatitis, both of which are AEs of special interest for this combination therapy.

## 4 | DISCUSSION

This phase III, randomized trial showed that alogliptin/metformin once daily is superior to alogliptin alone and non-inferior to alogliptin/metformin twice daily with regard to reducing HbA1c over a period of 24 weeks in Japanese patients with type 2 diabetes.

In the once-daily alogliptin/metformin group there was a greater reduction in HbA1c and FPG levels, and a greater proportion of patients achieving HbA1c  $< 7.0\%$  compared with alogliptin alone. Alogliptin/metformin once daily also led to a similar reduction in HbA1c and proportion of patients achieving HbA1c  $< 7.0\%$  at 24 weeks as with alogliptin/metformin twice daily

Although a reduction in FPG at week 24 with alogliptin/metformin twice daily was higher than that achieved with alogliptin/

**TABLE 1** Secondary and other efficacy endpoints

	Alogliptin once daily (n = 71)	Alogliptin once daily/metformin once daily (n = 152)	Alogliptin once daily/metformin twice daily (n = 151)	Point estimate for treatment difference (95% CI)	
				Alogliptin once daily/metformin once daily vs alogliptin once daily alone	Alogliptin once daily/metformin once daily vs alogliptin once daily/metformin twice daily
Number patients evaluable	71	149 <sup>1</sup> or 152	151		
Number of patients with HbA1c <7.0% at week 24, n (%)	3 (4.8)	48 (35.0)	48 (34.3)	30.3 (20.7, 39.8)	0.8 (-10.5, 12.0)
Mean changes from baseline to week 24, mean (s.d.)					
Fasting glucose, mg/dL	7.4 (26.9)	-7.6 (26.4)	-18.2 (25.4)	-14.9 (-22.5, -7.4)	10.6 (4.7, 16.5)
Fasting insulin, $\mu$ U/mL	-0.1 (4.0)	-0.2 (4.0)	-0.6 (4.2)	-0.1 (-1.2, 1.1)	0.3 (-0.6, 1.3)
Fasting glucagon, pg/mL	-0.6 (15.1)	1.9 (18.4)	-0.8 (18.6)	2.5 (-2.4, 7.5)	2.7 (-1.5, 6.9)
HOMA-IR	0.2 (2.1)	-0.3 (2.0)	-0.6 (2.0)	-0.5 (-1.1, 0.1)	0.3 (-0.1, 0.8)
HOMA- $\beta$	-3.4 (13.2)	3.2 (17.4)	4.8 (15.4)	6.6 (2.0, 11.2)	-1.6 (-5.3, 2.2)
Body weight, kg	-0.1 (1.5)	0.0 (1.5)	0.0 (1.7)	0.1 (-0.3, 0.5)	0.0 (-0.4, 0.4)

Abbreviations: HOMA- $\beta$ , homeostatic model assessment of  $\beta$ -cell function; HOMA-IR, homeostatic model assessment of insulin resistance; s.d., standard deviation.

<sup>1</sup> Three randomized patients were not evaluable for evaluation of fasting insulin, HOMA-IR or HOMA- $\beta$ .

metformin once daily, the HbA1c results, which reflect glycaemic control during the previous 1 or 2 months as a whole, indicate that alogliptin/metformin once daily provides clinically meaningful efficacy in glycaemic control. Moreover, alogliptin and metformin can each increase GLP-1 levels, and the combination of them has the potential for a synergistic or additive effect, resulting in increased GLP-1 levels.<sup>4</sup> Indeed, alogliptin/metformin once daily led to a -0.49% reduction in HbA1c in this study.

No serious hypoglycaemia or acute pancreatitis were reported in any treatment group and all treatments were generally well tolerated, with a similar overall frequency of AEs among the treatment groups.

Because alogliptin/metformin once daily led to a similar HbA1c reduction to alogliptin/metformin twice daily and was well tolerated in the present study, this once-daily treatment regimen should be beneficial for patients with type 2 diabetes who usually take several medications including antidiabetic drugs multiple times a day. Decreasing medication frequency within a day has a remarkable impact on improving medication adherence in patients with type 2 diabetes.<sup>5</sup> Indeed, patients with chronic disease, including type 2 diabetes, have a greater adherence to once-daily treatment than to more frequent dosing schedules.<sup>3</sup> Furthermore, improving medication adherence is also associated with better glycaemic control<sup>6,7</sup>; combination therapy with alogliptin 25 mg once daily and metformin 500 mg once daily, therefore, would be expected not only to improve medication adherence but also to provide better glycaemic control in patients currently treated with multiple doses of alogliptin and metformin within a day.

The main limitation of the present study is that patients aged <20 or  $\geq$ 75 years, or with evident liver or renal impairment were excluded and, therefore, the effectiveness of the combination therapy was not confirmed in these patients. In addition, this study was conducted in Japanese patients with type 2 diabetes within a

treatment environment in Japan, therefore expansion of these findings to other populations needs careful consideration.

In conclusion, treatment with alogliptin/metformin once daily was superior in efficacy to alogliptin alone and non-inferior to alogliptin/metformin twice daily. This once-daily combination was safe and well tolerated in Japanese patients with type 2 diabetes who had inadequate glycaemic control with alogliptin 25 mg monotherapy.

## Conflict of interest

K.K. has been an advisor to, received honoraria for lectures from, and received scholarship grants from Astellas, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical, MSD, Kowa, Kissei, Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim, Daiichi Sankyo, Fuji Film Pharma and Sanofi. S.S., M.K., Y.N. and Y.K. are employees of Takeda.

## Author contributions

K.K., S.S. and M.K. contributed to the design of the study. K.K., Y.N. and Y.K. contributed to study conduct/data collection. S.S. and M.K. contributed to data analysis. All authors contributed to writing the manuscript.

## REFERENCES

- Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. *J Diabetes Invest.* 2010;1:8-23.
- Seino Y, Fujita T, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, dose-ranging comparison with placebo, followed by a long-term extension study. *Curr Med Res Opin.* 2011;27:1781-1792.

3. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm.* 2012;18:527-539.
4. Mulherin AJ, Oh AH, Kim H, et al. Mechanisms underlying metformin-induced secretion of glucagon-like peptide-1 from the intestinal L cell. *Endocrinology.* 2011;152:4610-4619.
5. Dezii CM, Kawabata H, Tran M. Effects of once-daily and twice-daily dosing on adherence with prescribed glipizide oral therapy for type 2 diabetes. *South Med J.* 2002;95:68-71.
6. Rozenfeld Y, Hunt JS, Plauschinat C, Wong KS. Oral antidiabetic medication adherence and glycemic control in managed care. *Am J Manag Care.* 2008;14:71-75.
7. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. *Diabetes Care.* 2002;25:1015-1021.

## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Kaku K, Sumino S, Katou M, Nishiyama Y and Kinugawa Y. Randomized, double-blind, phase III study to evaluate the efficacy and safety of once-daily treatment with alogliptin and metformin hydrochloride in Japanese patients with type 2 diabetes, *Diabetes Obes Metab*, 2017;19(3):463-467.