



Comparison of the Effectiveness of Once-Daily Alogliptin/Metformin and Twice-Daily Anagliptin/Metformin Combination Tablet in a Randomized, Parallel-Group, Open-Label Trial in Japanese Patients with Type 2 Diabetes

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ABSTRACT

Introduction: The combination tablets of dipeptidyl peptidase-4 (DPP-4) inhibitors and metformin are used for both once-daily and twice-daily agents in Japan. If there is no difference in effectiveness between the once-daily and twice-daily DPP-4 inhibitor/metformin combination tablets, the once-daily agent is advantageous in terms of frequency of administration. The aim of this study was to compare the effectiveness of once-daily alogliptin/metformin combination tablet (alogliptin 25 mg/metformin 500 mg) and twice-daily anagliptin/metformin combination tablet low dose (LD) (anagliptin 100 mg/metformin 250 mg).

Methods: Forty-eight Japanese patients with type 2 diabetes whose metformin administration of 250 mg twice daily had remained unchanged for at least 8 weeks, except when

using DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists, or insulin, were randomized to either the once-daily alogliptin/metformin combination tablet group or the twice-daily anagliptin/metformin combination tablet LD group. The primary endpoint was the difference in glycosylated hemoglobin (HbA1c) levels from baseline to week 12 of administration, whereas the secondary endpoints were fasting blood glucose, body mass index (BMI), and adherence.

Results: Forty-four patients completed the study, and intention-to-treat analyses were performed. The adjusted mean value (standard error) for the change in HbA1c from week 0 to 12, was -0.75 (0.109)% for the once-daily alogliptin/metformin combination tablet group and -0.65 (0.109)% for the twice-daily anagliptin/metformin combination tablet LD group, with an intergroup difference of -0.10 % (95% confidence interval, CI -0.407 , 0.215). The upper limit of the bilateral 95% CI was 0.215 %, below the 0.40 % pre-defined as the non-inferiority margin. Fasting blood glucose, BMI, and adherence were not significantly different between the groups.

Conclusions: The once-daily alogliptin/metformin combination tablet was non-inferior to the twice-daily anagliptin/metformin combination tablet LD in Japanese patients with type 2 diabetes.

Trial Registration: University Hospital Medical Information Network Clinical Trial Registry

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Keywords: Alogliptin; Anagliptin; Combination tablet; Dose frequency; Metformin

Key Summary Points

Why carry out this study?

Combination tablets of dipeptidyl peptidase-4 (DPP-4) inhibitors and metformin are widely used for the treatment of type 2 diabetes in Japan.

There are two types of combination tablets of DPP-4 inhibitors and metformin: once-daily and twice-daily.

What did the study ask?

Is the once-daily alogliptin/metformin combination tablet (alogliptin 25 mg/metformin 500 mg) non-inferior to the twice-daily anagliptin/metformin combination tablet low dose (LD) (anagliptin 100 mg/metformin 250 mg)?

What was learned from the study?

The once-daily alogliptin/metformin combination tablet was non-inferior to the twice-daily anagliptin/metformin combination tablet LD.

The alogliptin/metformin combination tablet is useful in terms of dose frequency.

promoting blood glucose level-dependent insulin secretion and inhibiting glucagon secretion [5]. However, GLP-1 is catabolized rapidly by dipeptidyl peptidase-4 (DPP-4), thereby losing its physiological activity [6]. DPP-4 inhibitors are drugs that inhibit DPP-4 activity and GLP-1 inactivation, thus promoting insulin secretion and exhibiting antihyperglycemic activity [7]. In contrast, metformin inhibits glucose release from the liver while increasing sensitivity to insulin in peripheral tissues (mainly in the muscles) and thus improving blood glucose levels [8, 9]. Combining DPP-4 inhibitors, insulin secretagogues, with metformin, an insulin sensitizer, is considered a reasonable therapeutic approach in diabetes. Metformin also has a GLP-1 secretagogue action [10], and its combined use with a DPP-4 inhibitor inhibits the breakdown of GLP-1, which is increased by metformin, with an additive effect that has the potential to enhance the antihyperglycemic effects [11].

In pharmacotherapy for type 2 diabetes, if monotherapy is insufficiently effective, an additional drug with a different mechanism of action is recommended. As polypharmacy has become an issue in recent years, combinatorial therapeutics using formulated combination drugs have been created to combat the issue. Compared to the use of two drugs, formulated combination drugs reportedly lead to better adherence [12]. Various formulated drugs, such as combination tablets of DPP-4 inhibitors and metformin, are available for use in Japan. Of these, alogliptin/metformin combination tablet (alogliptin 25 mg + metformin 500 mg) is administered once daily, whereas anagliptin/metformin combination tablet low dose (LD) (anagliptin 100 mg + metformin 250 mg) is administered twice daily. No previous large-scale clinical study has directly compared the effectiveness of alogliptin and anagliptin; however, the results from a network meta-analysis have shown that 25 mg of alogliptin has equivalent effectiveness to sitagliptin 100 mg, which was the first developed DPP-4 inhibitor [13]. Moreover, twice-daily anagliptin 100 mg has been shown to be non-inferior to sitagliptin 100 mg in a randomized controlled trial [14]. Once-daily alogliptin 25 mg and twice-daily

INTRODUCTION

The development of type 2 diabetes is associated with a decline in insulin secretion with concomitant resistance to insulin [1–4]. Oral antidiabetics include insulin secretagogues, insulin sensitizers, and other drugs with different mechanisms of action. Glucagon-like peptide-1 (GLP-1), a hormone secreted in the digestive tract, improves blood glucose levels by

anagliptin 100 mg are therefore considered to be highly likely to have equivalent effectiveness. Regarding metformin, the recommended prescription in Japan is at least twice-daily, but a study with a small sample size showed that switching from twice-daily metformin 250 mg to once-daily 500 mg did not negatively impact glycemic control [15]. Although combining a DPP-4 inhibitor and metformin reportedly produces an additive increase in GLP-1 secretion [11], the short half-life of metformin, of approximately 5 h [16], indicates that even with equivalent overall daily dosages of metformin, different frequencies of administration of fixed-dose combination tablets of DPP-4 inhibitors and metformin may yield different effectiveness between once- and twice-daily dosages. If there were no difference in effectiveness between once-daily and twice-daily fixed-dose combination tablets of DPP-4 inhibitors and metformin, a once-daily tablet has an advantage in terms of frequency of medication. The more often an oral antidiabetic needs to be taken, the greater the reported decrease in adherence [17, 18].

However, no previous reports have confirmed non-inferiority of once-daily alogliptin/metformin combination tablet to twice-daily anagliptin/metformin combination tablet LD. This study aimed to fill this knowledge gap by comparing the effectiveness of once-daily alogliptin/metformin combination tablet and twice-daily anagliptin/metformin combination tablet LD in Japanese patients with type 2 diabetes who had insufficient glycemic control when administered twice-daily metformin 250 mg. We hypothesized that the once-daily treatment is non-inferior to twice-daily for HbA1c.

METHODS

The present study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments, and was approved by the Fujisawa City Hospital Ethics Committee (approval number F2018049) and was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (registration number: UMIN000034951).

Written informed consent was obtained from all the subjects, and case registration was conducted from December 2018 to October 2020.

This was a single-center, randomized, parallel-group controlled, open-label study conducted on outpatients with type 2 diabetes at the Department of Diabetes and Endocrinology of Fujisawa City Hospital. The selection criteria were as follows: (1) Patients taking metformin 250 mg twice daily for at least 8 weeks, and with HbA1c of 7.0–11.0%; (2) Patients aged 20–75 years; and (3) Patients with no changes in their oral antidiabetic agents for at least 8 weeks. Patients were excluded for any of the following criteria: (1) Patients currently using DPP-4 inhibitors, GLP-1 receptor agonists, or insulin; (2) Patients with eGFR < 30 ml/min/1.73 m²; (3) Patients with severe liver disorders; (4) Patients with severe infection, pre-/post-surgery, or severe trauma; (5) Patients currently using steroids; (6) Patients who are pregnant or breastfeeding, or who may be pregnant; (7) Patients with a history of hypersensitivity to metformin/DPP-4 inhibitors; and (8) Patients who were otherwise deemed ineligible to participate in the study for various medical reasons by the principal investigator or co-investigator.

Patients were randomly assigned to the once-daily alogliptin/metformin combination tablet group (administered after breakfast) or the twice-daily anagliptin/metformin combination tablet LD group (administered after breakfast and dinner), and medication was continued up to 12 weeks after the intervention. SY, TT, and KT enrolled participants. The random assignment of participants was performed by ST using the envelope method, and the assignment was blinded. The randomization code was generated by a computerized random number table. After the analyses were completed, the randomization codes were revealed. After each group reached ten patients, dynamic random assignment was performed using the minimization method with the following items as assignment adjustment factors. (1) HbA1c ($\geq 8\%$, < 8%); and (2) body mass index (BMI) (≥ 25 kg/m², < 25 kg/m²) to prevent possible bias that might influence the effectiveness of DPP-4 inhibitors in lowering blood glucose levels [19]. The computed minimization method was

performed by web-based software (Mujinwari, Iruka System, Tokyo, Japan). Previously obtained HbA1c and BMI information for each group was included in the minimization method, and ST entered this information into the web-based software. Adjustment factor assignment information was kept confidential to the investigators during the course of the study to reduce selection bias in the minimization method as much as possible.

The sample size was calculated as follows. In a clinical trial involving 25 mg alogliptin given to patients with type 2 diabetes being treated with 500–750 mg metformin per day, the change in HbA1c was -0.64% (adjusted mean) with a standard error of 0.057 [20]. In another clinical trial involving 100 mg anagliptin given twice daily to patients with type 2 diabetes receiving 250 mg metformin twice daily, the change in HbA1c was $-0.43 \pm 0.63\%$ (mean \pm SD) [21]. Furthermore, in a study comparing the effectiveness of administering a DPP-4 inhibitor teneligliptin at different frequencies (every day versus every other day) in Japanese patients with type 2 diabetes, the non-inferiority margin was less than 0.4% [22]. Based on these studies, we assumed the difference in HbA1c change between the alogliptin/metformin combination tablet group and the anagliptin/metformin combination tablet LD group to be 0.21% ($= 0.64 - 0.43\%$) and the standard deviation of HbA1c change to be 0.63%, and estimated that a non-inferiority margin of 0.4% with a one-sided significance level of 5% would result in a requirement of 14 patients per group to obtain 80% power. Assuming a dropout rate of 10%, the required number of recruited patients was determined to be at least 16 in each group.

HbA1c, fasting blood glucose levels, and BMI were measured at 0, 4, 8, and 12 weeks after the intervention. Blood samples were analyzed at the clinical laboratory of Fujisawa City Hospital. Adherence was calculated based on the difference between the prescribed number of tablets and the remaining number of tablets by asking the subjects to bring the remaining tablets to the hospital at week 12. The primary endpoint was the difference in HbA1c levels from baseline to week 12 of drug administration. Fasting

blood glucose levels, BMI, and adherence were assessed as secondary endpoints. Intention-to-treat (ITT) analyses were performed. Missing follow-up data were compensated for using the last observation carried forward (LOCF) method, and estimates were calculated and tested.

To determine the change in HbA1c levels, an analysis of covariance (ANCOVA) model was applied with the amount of change in HbA1c at the end of the intervention (week 12) as the dependent variable and the HbA1c levels at the start of the intervention (week 0) and administration group as the independent variables. The non-inferiority of once-daily alogliptin/metformin combination tablet to twice-daily anagliptin/metformin combination tablet LD was deemed valid if the upper limit of the bilateral 95% confidence interval (CI) of the intergroup difference in adjusted mean values of the change in HbA1c fell below 0.40%. To determine the change in fasting blood glucose levels, ANCOVA analysis was applied with the amount of change in the fasting blood glucose levels at the end of the intervention (week 12) as the dependent variable and the fasting blood glucose levels at the start of the intervention (week 0) and the administration group as independent variables.

A paired *t* test was used to assess HbA1c and fasting blood glucose levels at weeks 4, 8, and 12 by comparing values obtained at weeks 4, 8, and 12 with those obtained at week 0 followed by the Bonferroni correction. Differences in BMI between the two groups were assessed using Student's *t* test at weeks 4, 8, and 12. Adherence was assessed using the Mann–Whitney *U* test. The level of statistical significance was set at $p < 0.05$. SPSS statistics version 23.0 (IBM Japan, Ltd., Tokyo, Japan) was used for analyses.

RESULTS

Of the initial 52 patients screened for this study, four refused to participate and the remaining 48 patients were randomly assigned to each group. Each group had two dropouts: once-daily alogliptin/metformin combination tablet group had two dropouts for protocol violations; twice-

daily anagliptin/metformin combination tablet LD group had one dropout for nausea and one for abdominal aortic aneurysm surgery (Fig. 1). Baseline characteristics (age, sex, BMI, diabetes disease duration, HbA1c levels, and fasting blood glucose levels) of the two groups are presented in Table 1. The therapeutic profiles of the randomized groups are presented in Table 2. Patient outcome measures at each of the four time points are provided in Table 3. Post-intervention, HbA1c (Fig. 2) and fasting blood glucose levels (Fig. 3) decreased significantly compared to those at the start of the intervention in both groups. There were no significant intergroup differences in BMI nor in adherence (Table 3).

The adjusted mean value (standard error) for the change in HbA1c from week 0 to week 12, was -0.75 (0.109)% for the once-daily alogliptin/metformin combination tablet group and -0.65 (0.109)% for the twice-daily anagliptin/metformin combination tablet LD group, with an intergroup difference (once-daily alogliptin/metformin combination tablet group – twice-daily anagliptin/metformin combination tablet LD group) of -0.10% (95% CI $-0.407, 0.215$) (Fig. 4). The upper limit of the bilateral 95% CI

was 0.215%, falling under 0.40%, which was the set non-inferiority margin; thus, the once-daily alogliptin/metformin combination tablet was non-inferior to the twice-daily anagliptin/metformin combination tablet LD.

The adjusted mean value (standard error) for the change in fasting blood glucose levels from week 0 to week 12 was -14.9 (4.01) mg/dl for the once-daily alogliptin/metformin combination tablet group and -23.1 (4.01) mg/dl for the twice-daily anagliptin/metformin combination tablet LD group. The difference between the groups was 8.1 mg/dl (95% CI $-3.3, 19.6$), which was non-significant (Fig. 5). As for adverse events, nausea was observed in one patient in the twice-daily anagliptin/metformin combination tablet LD group. There were no severe adverse events in either group.

DISCUSSION

In the present study, the effectiveness of once-daily alogliptin/metformin combination tablet and twice-daily anagliptin/metformin combination tablet LD was compared in Japanese patients with type 2 diabetes. The most

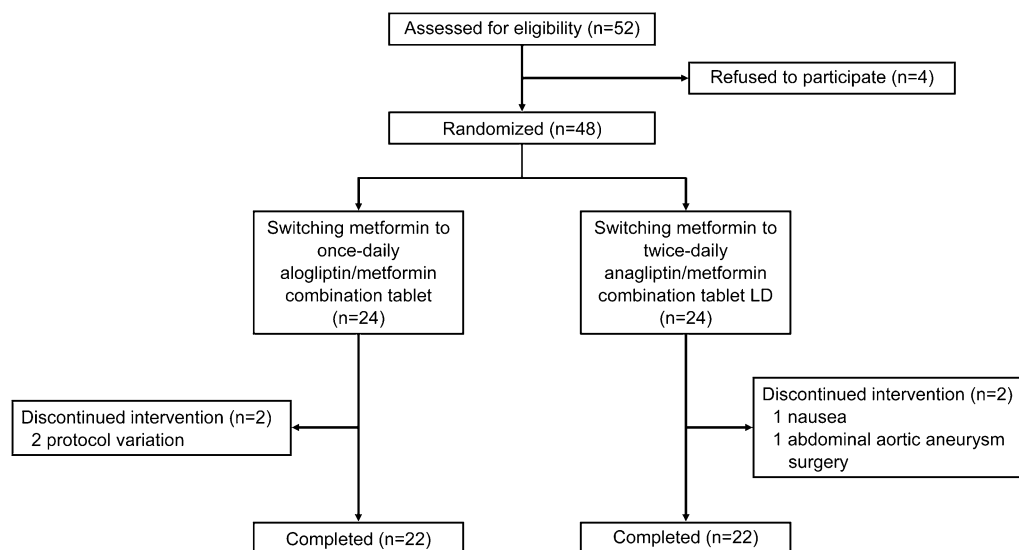


Fig. 1 Flow chart of the study. A total of 52 patients were assessed for eligibility, with four refusing to participate and the remaining 48 were randomly assigned to the once-daily alogliptin/metformin combination tablet group or the

twice-daily anagliptin/metformin combination tablet LD group. Forty-four patients completed the study

Table 1 Patient demographics of the randomized groups

	Alo/Met (n = 24)	Ana/Met (n = 24)
Age (years)	58.7 ± 9.8	57.8 ± 12.7
Sex (male/female)	15/9	13/11
BMI (kg/m ²)	27.7 ± 6.0	27.5 ± 6.0
Disease duration (years)	4.0 ± 4.3	4.3 ± 3.7
HbA1c (%)	8.17 ± 1.05	8.17 ± 1.01
Fasting blood glucose (mg/dl)	176.0 ± 44.2	166.4 ± 41.8

Data other than sex are presented as mean ± standard deviation

Alo/Met alogliptin/metformin combination tablet group, *Ana/Met* anagliptin/metformin combination tablet low dose (LD) group, *BMI* body mass index, *HbA1c* glycosylated hemoglobin

Table 2 Therapeutic profile of patients in the randomized groups

	Alo/Met (n = 24)	Ana/Met (n = 24)
No other antihyperglycemic drugs	20	19
Other antihyperglycemic drugs	4	5
SGLT2 inhibitors	1	4
SGLT2 inhibitor + SU	1	0
SGLT2 inhibitor + α -GI	1	0
SGLT2 inhibitor + SU + α -GI	0	1
Glinides	1	0

Data are presented as number of patients

Alo/Met alogliptin/metformin combination tablet group, *Ana/Met* anagliptin/metformin combination tablet low dose (LD) group, *SGLT2* sodium-glucose cotransporter 2, *SU* sulfonylurea, α -*GI* α -glucosidase inhibitor

important finding was that in the patients receiving twice-daily metformin 250 mg with insufficient glycemic control, switching to once-daily alogliptin/metformin combination tablet or switching to twice-daily anagliptin/metformin combination tablet LD yielded an equivalent amount of change in HbA1c levels after 12 weeks. As HbA1c is reflective of the mean blood glucose levels of the past 1–2 months, the effectiveness of once-daily alogliptin/metformin combination tablet and twice-daily anagliptin/metformin combination tablet LD would be equivalent.

Although the present study showed no significant difference in adherence between the

once-daily alogliptin/metformin combination tablet group and the twice-daily anagliptin/metformin combination tablet LD group, more frequent administration of oral antidiabetics has been reported to result in decreased adherence in the long term [17, 18]. Moreover, glycemic control has been reported to be significantly correlated with adherence to drugs for treating diabetes [23]. It is therefore important to have drug therapies that take adherence into consideration to produce favorable glycemic control, and once-daily alogliptin/metformin combination tablet appears to be useful in terms of frequency of administration.

Table 3 Patient outcome measures at each of the four time points

	Week 0		Week 4		Week 8		Week 12	
	Alo/Met	Ana/Met	Alo/Met	Ana/Met	Alo/Met	Ana/Met	Alo/Met	Ana/Met
HbA1c (%)	8.17 ± 1.05	8.17 ± 1.01	7.80*** ± 0.88	7.78*** ± 0.87	7.52*** ± 0.73	7.60*** ± 0.86	7.42*** ± 0.71	7.52*** ± 0.78
Fasting blood glucose (mg/dl)	176.0 ± 44.2	166.4 ± 41.8	156.7** ± 35.6	144.5* ± 34.2	155.0*** ± 36.8	146.9** ± 26.4	158.8* ± 34.2	145.7** ± 23.5
BMI (kg/m ²)	27.7 ± 6.0	27.5 ± 6.0	27.6 ± 6.1	27.4 ± 5.7	27.7 ± 6.1	27.4 ± 5.7	27.8 ± 6.2	27.6 ± 5.7
Adherence over 12 weeks (%)							97.3 ± 5.1	95.8 ± 8.1

Data are presented as mean ± standard deviation. Intention-to-treat (ITT) analyses were performed. Missing follow-up data were compensated for using the last observation carried forward (LOCF) method, and estimates were calculated and tested. HbA1c and fasting blood glucose levels at weeks 4, 8, and 12 were assessed by paired *t* test followed by Bonferroni correction, comparing values obtained at weeks 4, 8, and 12 with those obtained at week 0. Differences in BMI between the two groups were assessed using Student's *t* test at weeks 4, 8, and 12. Adherence was assessed using the Mann–Whitney *U* test. **p* < 0.05 compared to week 0; ***p* < 0.01 compared to week 0; ****p* < 0.001 compared to week 0

Alo/Met alogliptin/metformin combination tablet group, Ana/Met anagliptin/metformin combination tablet low dose (LD) group, HbA1c glycosylated hemoglobin, BMI body mass index

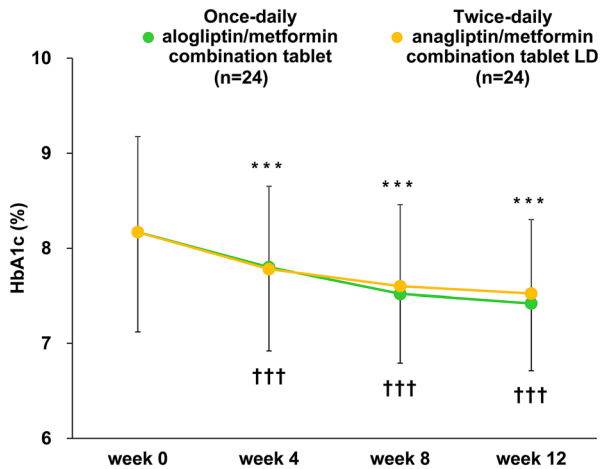


Fig. 2 Change in HbA1c levels. Data are presented as mean and standard deviation. *** $p < 0.001$, ††† $p < 0.001$ vs. week 0 (paired t test followed by Bonferroni correction)

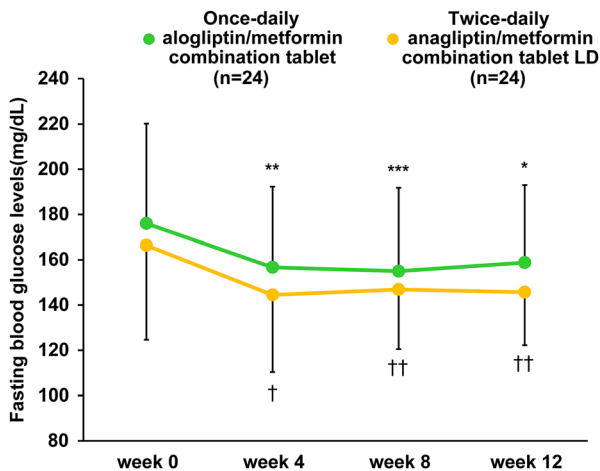


Fig. 3 Change in fasting blood glucose levels. Data are presented as mean and standard deviation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, † $p < 0.05$, †† $p < 0.01$ vs. week 0 (paired t test followed by Bonferroni correction)

A phase III clinical study of alogliptin/metformin combination tablet showed that once-daily alogliptin 25 mg plus once-daily metformin 500 mg was non-inferior to once-daily alogliptin 25 mg plus twice-daily metformin 250 mg in terms of lowering HbA1c. However, once-daily alogliptin 25 mg plus twice-daily metformin 250 mg was significantly lower than once-daily alogliptin 25 mg plus once-daily metformin 500 mg with regard to fasting blood glucose levels [24]. Thus, with alogliptin 25 mg,

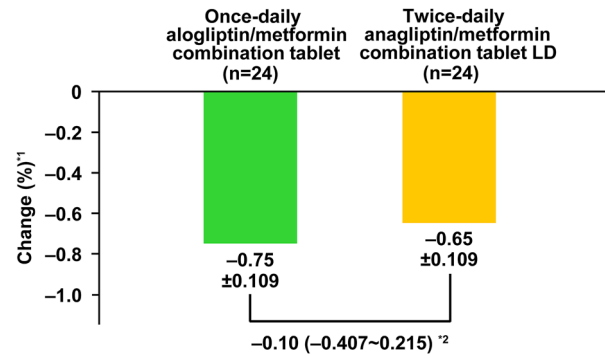


Fig. 4 Change in adjusted mean HbA1c. Data are presented as adjusted mean value \pm standard error. *1: Calculation based on analysis of covariance model with HbA1c at the end of the intervention (week 12) as the dependent variable and the start of the intervention (week 0) and the administration groups as independent variables. *2: Point estimation value (bilateral 95% confidence interval) of the difference between groups (once-daily alogliptin/metformin combination tablet group – twice-daily anagliptin/metformin combination tablet LD group) in the adjusted mean value

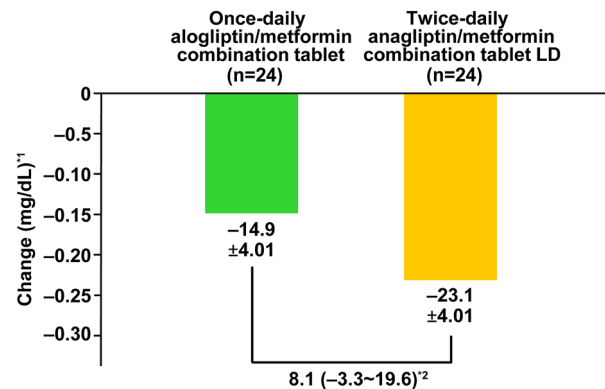


Fig. 5 Change in adjusted mean fasting blood glucose levels. Data are presented as adjusted mean value \pm standard error. *1: Calculation based on analysis of covariance model with fasting blood glucose levels at the end of the intervention (week 12) as the dependent variable and the start of the intervention (week 0) and the administration groups as independent variables. *2: Point estimation value (bilateral 95% confidence interval) of the difference between groups (once-daily alogliptin/metformin combination tablet group – twice-daily anagliptin/metformin combination tablet LD group) in the adjusted mean value

twice-daily metformin 250 mg showed a more significant decrease in fasting blood glucose

levels than once-daily metformin 500 mg. However, we found no significant difference for change in fasting blood glucose levels between the once-daily alogliptin/metformin combination tablet and the twice-daily anagliptin/metformin combination tablet LD groups. It is unknown whether these different results are due to different sample sizes or the differences between alogliptin and anagliptin; thus, further large-scale research is needed to clarify this.

A network meta-analysis showed that alogliptin 25 mg has equivalent effectiveness to sitagliptin 100 mg [13], and twice-daily anagliptin 100 mg has also been shown to be non-inferior to sitagliptin 100 mg in a randomized controlled trial [14]. Thus, although it seems highly likely that once-daily alogliptin 25 mg and twice-daily anagliptin 100 mg have equivalent effectiveness, the absence of randomized controlled trials directly comparing the two indicates a lack of solid evidence that the two are indeed equivalent. However, in Japanese patients with type 2 diabetes, once-daily alogliptin 25 mg and twice-daily anagliptin 100 mg both had equivalent rates of DPP-4 inhibitory activity and increased active GLP-1 levels to a similar extent [25]. Therefore, the effectiveness of once-daily alogliptin 25 mg and twice-daily anagliptin 100 mg is likely to be comparable. A randomized controlled trial directly comparing once-daily alogliptin 25 mg and twice-daily anagliptin 100 mg and showing that they have equivalent effectiveness in terms of glycemic control would further clarify the significance of the present study.

The present study has several limitations. First, the number of participants was relatively low, and the study period was short. Second, there was no continuous glucose monitoring or active GLP-1 measurement, and it is unclear whether the two groups had differences in circadian variation of blood glucose levels, or active GLP-1 secretion. Third, this study used the minimization method for randomization and the pill count to assess adherence, which may introduce the possibility of selection bias and information bias, respectively. Finally, we used a non-inferiority margin of 0.4% based on previous studies [14, 22], which may be within the measurement error of HbA1c [26].

Therefore, caution should be exercised when interpreting these particular results.

CONCLUSIONS

The present study has demonstrated that once-daily alogliptin/metformin combination tablet was non-inferior to twice-daily anagliptin/metformin combination tablet LD in Japanese patients with type 2 diabetes who have insufficient glycemic control when administered 250 mg metformin twice daily. Thus, once-daily alogliptin/metformin combination tablet improves glycemic control while reducing the dose frequency.

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Prior Presentation. The data in this manuscript were presented at the 64th Annual Meeting of the Japan Diabetes Society in May 2021 at Kanazawa, Japan.

Disclosures. Shunsuke Yamazaki, Tatsuro Takano, Koji Tachibana, Soichiro Takeda, and

Yasuo Terauchi declare that they have no conflict of interest.

Compliance with Ethics Guidelines. The present study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments, and was approved by the Fujisawa City Hospital Ethics Committee (approval number F2018049) and was registered at the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) (registration number: UMIN000034951). Written informed consent was obtained from all the subjects.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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