

Efficacy and safety of teneligliptin in combination with pioglitazone in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

Aim: To confirm the efficacy and safety of teneligliptin in combination with pioglitazone in Japanese patients with type 2 diabetes mellitus inadequately controlled with pioglitazone monotherapy.

Materials and Methods: In an initial 12-week, double-blind, placebo controlled, parallel-group study, patients ($n = 204$) were randomized to teneligliptin 20 mg or placebo once daily added to their stable pioglitazone therapy. This was followed by a 40-week, open-label period during which all patients received teneligliptin once daily. The primary end-point was the change in hemoglobin A1c (HbA_{1c}) from baseline to week 12.

Results: Patients in the teneligliptin group showed significantly greater reductions in HbA_{1c} compared with the placebo group at week 12 ($P < 0.001$). The changes in HbA_{1c} from baseline to week 12 were $-0.9 \pm 0.0\%$ (least-squares mean \pm standard error) in the teneligliptin group and $-0.2 \pm 0.0\%$ in the placebo group. The change in fasting plasma glucose from baseline to week 12 was greater in the teneligliptin group than in the placebo group ($P < 0.001$). The blood glucose lowering effects of teneligliptin were sustained throughout the 40-week open-label period. Adverse events and adverse drug reactions occurred slightly more frequently in the teneligliptin group than in the placebo group, although the incidence of hypoglycemia was low. Bodyweight was unchanged in the double-blind period, but was slightly increased in the open-label period.

Conclusions: Add-on therapy with teneligliptin was effective and generally well tolerated throughout the study period in Japanese patients with type 2 diabetes mellitus inadequately controlled with pioglitazone monotherapy. This trial was registered with ClinicalTrials.gov (no. NCT01026194). (*J Diabetes Invest*, doi: 10.1111/jdi.12092, 2013)

KEY WORDS: Dipeptidyl peptidase 4 inhibitors, Pioglitazone, Type 2 diabetes mellitus

INTRODUCTION

The incretin hormone, glucagon-like peptide-1 (GLP-1), plays a critical role in the regulation of blood glucose level¹. GLP-1 stimulates postprandial insulin secretion and inhibits postprandial glucagon secretion in a glucose-dependent manner, thereby controlling postprandial glucose (PPG) levels². GLP-1 also has a variety of favorable effects that might be relevant for patients with type 2 diabetes mellitus, such as the enhancement of pancreatic β -cell mass, which was observed in animal studies^{3,4}, as well as the inhibition of gastric emptying and reduction of food intake, which were observed in clinical studies^{5,6}. However, it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4)^{7,8}, inhibition of which is now gaining attention as a reasonable mode of enhancing blood glucose lowering in a glucose-dependent manner.

Teneligliptin is a novel DPP-4 inhibitor that has been shown to produce significant increases in plasma active GLP-1 concentration after breakfast, lunch and dinner⁹. The PPG lowering effects of once-daily teneligliptin are sustained throughout the day⁹. We previously found that teneligliptin monotherapy produced significant reductions in hemoglobin A1c (HbA_{1c}) in Japanese patients with type 2 diabetes mellitus, with placebo-adjusted decreases (least-squares [LS] mean) of -0.9 , -0.9 and -1.0% in patients treated with teneligliptin 10, 20 and 40 mg, respectively. All three doses also improved fasting plasma glucose (FPG) levels. Teneligliptin was generally well tolerated (Kadowaki and Kondo, 2013, in press). The peroxisome proliferator-activated receptor- γ agonist, pioglitazone, improves blood glucose levels by raising insulin sensitivity in muscle, liver and adipose tissue, and by controlling glucose release from the liver^{10,11}. Thus, it is widely used to treat type 2 diabetes mellitus in Japan.

When treating type 2 diabetes mellitus, and especially patients who cannot achieve adequate glycemic control by monotherapy, it is helpful to consider combination therapies. Indeed, the majority of patients with type 2 diabetes mellitus will require combination therapy in their long-term treatment history. When

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considering the most appropriate drug combination, selecting drugs with different mechanisms of actions is recommended¹². Therefore, the combination of teneligliptin and pioglitazone is expected to be a clinically beneficial combination.

The present study was designed to confirm the efficacy and safety of teneligliptin added to pioglitazone in Japanese patients with type 2 diabetes mellitus inadequately controlled with pioglitazone monotherapy.

MATERIALS AND METHODS

Study Design and Procedure

The present study was a randomized, double-blind, placebo-controlled, parallel-group, phase III study designed to confirm the efficacy and safety of teneligliptin added to pioglitazone. The study was carried out at 39 sites in Japan (see Appendix), and consisted of four phases: (i) a 4-week single-blind run-in period in which patients received a placebo; (ii) a 12-week randomized double-blind period in which patients were treated with teneligliptin 20 mg or a placebo; (iii) a 40-week open-label period in which patients were treated with teneligliptin 20 or 40 mg; and (iv) a 2-week follow-up observation period in which patients did not take study drugs and were monitored. There were a total of 18 visits over the study period (weeks -4, -2, 0, 2, 4, then at 4-week intervals through to week 52 and week 54). The study drug was taken orally before breakfast every morning during the study. The dose of pioglitazone was unchanged throughout the study period.

Patients who completed the double-blind period entered the open-label period. Of these, patients who had taken a placebo during the double-blind period received teneligliptin 20 mg in the open-label period (P/T group), and patients who had taken teneligliptin 20 mg during the double-blind period continued medication with the same dose in the open-label period (T/T group). Patients with HbA_{1c} >7.3% after week 24 underwent dose titration to teneligliptin 40 mg at their next visit if they had no safety concerns. The teneligliptin dose remained stable from week 40 to the end of the study period. The decision to increase the teneligliptin dose to 40 mg after week 24 was based on the results of a prior study (Kadowaki and Kondo, unpublished data, 2013), in which teneligliptin (10, 20 and 40 mg) dose-dependently inhibited plasma DPP-4 activity, and tended to reduce HbA_{1c} and FPG in a dose-dependent manner at doses ≥20 mg. However, considering the slight increase in adverse drug reactions (ADRs) with teneligliptin 40 mg, we limited its use to patients with an inadequate response to lower doses and who had no safety concerns.

Meal tolerance tests were carried out at weeks 0, 12, 24 and 52 to assess postprandial efficacy. Patients took the study drug and pioglitazone before consuming a standard meal comprising one Calorie Mate[®] bar, one pack of Calorie Mate[®] jelly and one can of Calorie Mate[®] drink (all from Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). The ready-made meals were to be consumed within 15 min. Total caloric content was approximately 500 kcal, with 60% as carbohydrate, 15% as protein and 25% as fat.

The study was carried out in compliance with Good Clinical Practice. The protocol was approved by institutional review boards at each participating site. Written informed consent was obtained from all patients before enrolment. This trial was registered with ClinicalTrials.gov (no. NCT01026194).

Patients

Japanese patients aged 20–75 years with type 2 diabetes mellitus were eligible to participate if they had inadequate glycemic control (HbA_{1c} 6.8–10.3% at weeks -4 and -2) with pioglitazone (15 or 30 mg/day) monotherapy for at least 12 weeks, and had not taken any other oral antihyperglycemic agents for at least 8 weeks before week -4. Additional inclusion criteria were maximum change in HbA_{1c} ≤0.5% between weeks -4 and -2 and FPG ≤270 mg/dL (15.0 mmol/L) at week -4. Patients with any of the following were excluded: type 1 diabetes, arrhythmic treatment, serious diabetic complications, severe hepatic disorder or severe renal disorder, serum creatinine levels at week -4 >2.0 mg/dL, and aspartate aminotransferase or alanine aminotransferase at week -4 ≥2.5 times the upper limit of normal.

End-Points

The primary efficacy end-point was the change in HbA_{1c} from baseline to week 12. Secondary efficacy end-points included changes in FPG, 2-h PPG after a standard meal, and the areas under the curve from 0 to 2 h (AUC_{0–2h}) for PPG from baseline to week 12. Other end-points included the change in fasting insulin, fasting glucagon, proinsulin/insulin ratio, homeostasis model assessment of insulin resistance (HOMA-R), homeostasis model assessment of β-cell function (HOMA-β), postprandial insulin AUC_{0–2h}, and postprandial glucagon AUC_{0–2h} assessed at weeks 12 and 52.

Hemoglobin A1c was measured by high-performance liquid chromatography using a reference standard approved by the USA National Glycohemoglobin Standardization Program (NGSP). In Japan, HbA_{1c} (Japan Diabetes Society [JDS]) values <6.5 and <7.0% (equivalent to HbA_{1c} <6.8 and <7.3% in NGSP units using JDS Lot 2 as an internal control¹³) are used as indices of glycemic control. Glucagon was initially measured using a glucagon kit from TFB, Inc. (Tokyo, Japan) in the present study. However, as the distribution of this kit was discontinued, because of exhaustion of the anti-glucagon polyclonal antibody, a new kit was obtained from Millipore Corp. (Billerica, MA, USA). The method was changed immediately after starting the study, as just two pretrial values in two patients were measured using the old kit; all of the other samples were measured using the new kit. The central laboratory, Mitsubishi Chemical Medicine Corporation, (Tokyo, Japan) established the following regression equation to convert glucagon levels: glucagon concentration (new kit) = 0.3837 × glucagon concentration (old kit) + 26.407 (*r* = 0.672).

Safety was evaluated on the basis of adverse event (AE) reports, including episodes of hypoglycemia, as well as assess-

ments of vital signs, 12-lead electrocardiogram (ECG) and laboratory measurements (hematology, blood chemistry and urinalysis). AEs were monitored from week 0 through to the 2-week follow-up observation period, and were evaluated by the investigators in terms of their intensity and relationship to the study drug. Patients were provided with self-monitored blood glucose (SMBG) devices and diaries to record the symptoms of hypoglycemia and the results of SMBG. Hypoglycemia was confirmed by the investigators based on examination, the patient's diary and SMBG data.

Laboratory assays were carried out at a central laboratory (Mitsubishi Chemical Medience Corporation).

Statistical Methods

Efficacy

All patients who entered the double-blind period were included in the efficacy analysis set and safety analysis set.

Efficacy end-points were assessed using descriptive statistics. Changes in HbA_{1c} from baseline to week 12 were calculated in each group. Changes in HbA_{1c} from baseline to week 12 were compared between the groups using analysis of covariance (ANCOVA) with HbA_{1c} at baseline as a covariate; a point estimate and the 95% confidence interval (CI) for the difference between the placebo and teneligliptin groups were calculated based on the LS mean \pm standard error (SE). If any end-point data were missing at week 12, the evaluated values at the previous measurement point were used as the data at week 12 according to the last observation carried forward (LOCF) procedure.

In the open-label period, the baseline for the T/T group was set to week 0, whereas that for the P/T group was set to week 12. Data from all time-points in the T/T group were included in the analysis; by contrast, in the P/T group, data from all time-points except the 12-week period during which they had taken placebo were included. Changes in HbA_{1c} from baseline to each measurement point were calculated based on mean \pm standard deviation (SD) in each group; we also calculated their 95% CIs. HbA_{1c} values at each measurement point were compared with those at baseline in each group using a paired *t*-test. If any end-point data were missing at week 52, the evaluated values at the previous measurement point were used as the data at week 52 according to the LOCF procedure.

Safety

The incidences of and 95% CIs for AEs and hypoglycemia in the double-blind and open-label periods were calculated for each group. Data from the double-blind period were compared between the placebo and teneligliptin groups. The incidences of AEs and hypoglycemia were evaluated only during the teneligliptin treatment periods for each group.

RESULTS

The disposition of patients is summarized in Figure 1. Of the 246 patients who started the run-in period; 204 patients were randomized to either teneligliptin ($n = 103$) or a placebo

($n = 101$), and entered the double-blind period. Of these, 196 patients (98 in each group) entered the open-label period, and 179 patients subsequently completed the study (91 in the P/T group and 88 in the T/T group). Patient characteristics are listed in Table 1, and were generally similar in the two groups. The mean baseline values for HbA_{1c}, duration of diabetes, body mass index, and bodyweight for all patients were 8.0%, 7.4 years, 25.9 kg/m² and 68.8 kg, respectively.

Efficacy

The changes in HbA_{1c}, FPG, 2-h PPG and other end-points from baseline are shown in Table 2. The changes in HbA_{1c} (LS mean \pm SE) from baseline to week 12 were $-0.9 \pm 0.0\%$ in the teneligliptin group and $-0.2 \pm 0.0\%$ in the placebo group. The change in HbA_{1c} was significantly greater in the teneligliptin group than in the placebo group ($P < 0.001$).

The changes in FPG, 2-h PPG and PPG AUC_{0-2h} from baseline to week 12 were significantly greater in the teneligliptin group than in the placebo group ($P < 0.001$ for all parameters). Among other end-points, the proinsulin/insulin ratio, HOMA- β , and postprandial glucagon AUC_{0-2h} were all significantly improved in the teneligliptin group compared with the placebo group. The change in fasting glucagon from baseline to week 12 was not significantly different between the teneligliptin and placebo groups.

In the open-label period, the changes in HbA_{1c} (mean \pm SD) from baseline to week 52 were $-0.9 \pm 0.7\%$ in the T/T group and $-0.7 \pm 0.7\%$ in the P/T group. HbA_{1c} at week 52 was significantly decreased compared with baseline in both groups (both $P < 0.001$). The HbA_{1c} lowering effect observed at week 12 was sustained throughout the study (Figure 2).

Fasting plasma glucose, 2-h PPG, PPG AUC_{0-2h}, proinsulin/insulin ratio, HOMA- β and postprandial glucagon AUC_{0-2h} at week 52 were all significantly improved compared with baseline in both groups. Although postprandial insulin AUC_{0-2h} was increased in both groups, a statistically significant difference from baseline was observed only in the T/T group. Fasting glucagon increased slightly in the T/T group, but the fasting glucagon level at week 52 was similar to that at week 12.

Five of 29 patients (17.2%) in the T/T group and eight of 23 patients (34.8%) in the P/T group showed a decrease in HbA_{1c} of $\geq 0.1\%$ at 12 weeks after being uptitrated to teneligliptin 40 mg. Furthermore, 12 of 29 patients (41.4%) in the T/T group and 11 of 23 patients (47.8%) in the P/T group experienced a decrease in FPG at 12 weeks after being uptitrated to teneligliptin 40 mg.

Safety

A summary of the safety evaluation is shown in Table 3. The incidences of AE and ADRs were slightly higher in the teneligliptin group than in the placebo group at week 12. The most commonly observed AEs in the teneligliptin group were gastrointestinal disorders and skin disorders. The severities of these AEs were primarily mild, and no patients in the teneligliptin

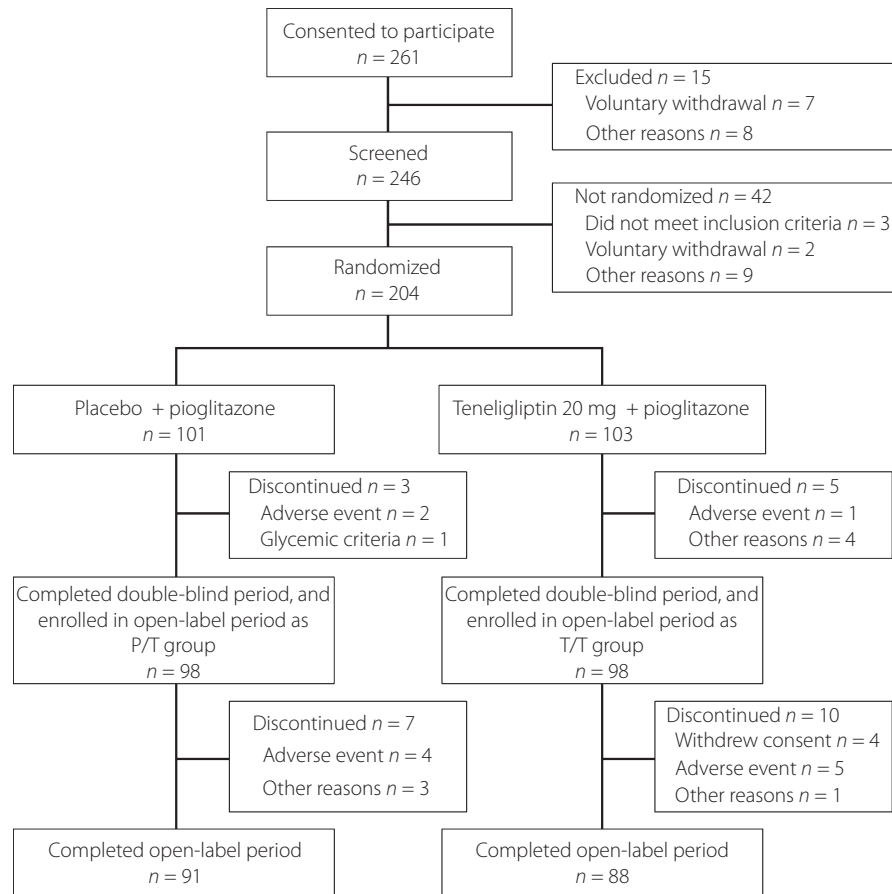


Figure 1 | Flow diagram of patients participating in the trial. P/T, patients who had taken a placebo during the double-blind period and then received teneligliptin 20 mg in the open-label period; T/T, patients who had taken teneligliptin 20 mg during the double-blind period and then continued medication with the same dose in the open-label period.

Table 1 | Patient characteristics

	Placebo (n = 101)	Teneligliptin (n = 103)	All patients (n = 204)	P-value*
Sex, n (%)				
Male	76 (75.2)	68 (66.0)	144 (70.6)	0.1681
Female	25 (24.8)	35 (34.0)	60 (29.4)	
Age (years)	61.1 (8.9)	59.7 (9.7)	60.4 (9.3)	0.2863
Bodyweight (kg)	67.7 (13.0)	70.0 (16.6)	68.8 (14.9)	0.2808
BMI (kg/m ²)	25.6 (3.7)	26.2 (5.2)	25.9 (4.5)	0.3861
Duration of diabetes (years)	7.7 (6.1)	7.2 (4.8)	7.4 (5.5)	0.4794
Baseline HbA _{1c} (%)	7.9 (0.8)	8.1 (0.9)	8.0 (0.9)	0.0896
Baseline FPG (mg/dL)	145.7 (26.5)	150.7 (28.1)	148.2 (27.4)	0.1900

Values are expressed as means (standard deviation). *P-values are for comparisons between the placebo and teneligliptin groups. BMI, body mass index; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A1c.

group discontinued the study drug as a result of gastrointestinal disorders or skin disorders. Specific AEs occurring at an incidence of $\geq 5\%$ included nasopharyngitis in both groups, as well

as peripheral edema and the presence of glucose in the urine in the placebo group (Table 3).

Hypoglycemia was reported in two patients (1.9%) in the teneligliptin group at week 12. No cases of severe hypoglycemia were reported, and all episodes of hypoglycemia were mild in severity.

The incidences of serious AEs were similar in both groups at week 12, and there were no drug-related serious AEs in either group. One patient (1.0%) in the teneligliptin group (spinocerebellar disorder) and two patients (2.0%) in the placebo group (gastric cancer, skin exfoliation) discontinued because of AEs, but none of these AEs was considered to be drug related by the investigator.

Edema and bodyweight gain are known drug reactions to pioglitazone. Peripheral edema was reported in two patients (1.9%) in the teneligliptin group and six patients (5.9%) in the placebo group at week 12. The changes in bodyweight (LS mean \pm SE) from baseline to week 12 were 0.2 ± 0.2 kg in the teneligliptin group and 0.0 ± 0.2 kg in the placebo group. There was no clinically significant change in bodyweight at week 12.

Table 2 | Effects of teneligliptin and placebo

	Week 0		Week 12†		Week 52		Change from Week 0 to Week 12		Teneligliptin vs placebo at Week 12		Change from baseline to Week 52	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	LS mean (SE)	95% CI	LS mean (SE)	95% CI	Mean (SD)	95% CI
HbA _{1c} (%)												
Placebo	7.9 (0.8)	7.8 (0.8)	7.8 (0.8)	7.8 (0.8)	7.2 (0.7)	7.0 (0.5)	-0.2 (0.0)	-	-	-	-	-
Teneligliptin (†/†)	8.1 (0.9)	7.1 (0.7)	7.1 (0.7)	7.8 (0.8)	7.2 (0.7)	7.0 (0.5)	-0.9 (0.0)	-0.7 (0.1)	-0.7 (0.1)	(-0.9, -0.6)***	-0.9 (0.7)	(-1.0, -0.7)***
P/T	-	7.8 (0.8)	7.8 (0.8)	7.8 (0.8)	7.0 (0.5)	7.0 (0.5)	-	-	-	-	-0.7 (0.7)	(-0.9, -0.6)***
FPG (mg/dL)												
Placebo	145.7 (26.5)	140.8 (27.6)	140.8 (27.6)	140.8 (27.6)	138.6 (27.9)	131.8 (21.7)	-4.5 (2.0)	-	-	-	-	-
Teneligliptin (†/†)	150.7 (28.1)	128.3 (20.6)	128.3 (20.6)	140.8 (27.6)	138.6 (27.9)	131.8 (21.7)	-21.0 (1.9)	-16.4 (2.8)	-16.4 (2.8)	(-21.9, -11.0)***	-12.1 (26.2)	(-17.2, -6.9)***
P/T	-	140.8 (27.6)	140.8 (27.6)	140.8 (27.6)	131.8 (21.7)	131.8 (21.7)	-	-	-	-	-9.1 (20.6)	(-13.2, -4.9)***
Fasting insulin (μU/mL)												
Placebo	5.4 (3.0)	5.5 (3.1)	5.5 (3.1)	5.5 (3.1)	7.4 (4.5)	6.0 (3.1)	0.7 (0.5)	-	-	-	-	-
Teneligliptin (†/†)	6.6 (4.7)	6.7 (4.4)	6.7 (4.4)	5.5 (3.1)	7.4 (4.5)	6.0 (3.1)	0.4 (0.5)	-0.3 (0.7)	-0.3 (0.7)	(-1.8, 1.1)	0.8 (2.8)	(0.2, 1.3)**
P/T	-	5.5 (3.1)	5.5 (3.1)	5.5 (3.1)	6.0 (3.1)	6.0 (3.1)	-	-	-	-	0.5 (2.1)	(0.1, 0.9)*
Proinsulin/insulin ratio												
Placebo	0.3 (0.2)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.0 (0.0)	-	-	-	-	-
Teneligliptin (†/†)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	-0.1 (0.0)	0.0 (0.0)	0.0 (0.0)	(-0.1, 0.0)***	-0.1 (0.1)	(-0.1, 0.0)***
P/T	-	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	-	-	-	-	0.0 (0.1)	(-0.1, 0.0)***
HOMA-R												
Placebo	2.0 (1.1)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)	2.6 (1.8)	2.0 (1.1)	0.4 (0.3)	-	-	-	-	-
Teneligliptin (†/†)	2.5 (1.7)	2.2 (1.6)	2.2 (1.6)	1.9 (1.2)	2.6 (1.8)	2.0 (1.1)	-0.2 (0.3)	-0.6 (0.5)	-0.6 (0.5)	(-1.5, 0.3)	0.1 (1.1)	(-0.1, 0.4)
P/T	-	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)	2.0 (1.1)	2.0 (1.1)	-	-	-	-	0.0 (0.9)	(-0.1, 0.2)
HOMA-β												
Placebo	25.9 (16.5)	28.0 (17.9)	28.0 (17.9)	28.0 (17.9)	37.9 (26.6)	34.4 (19.9)	2.8 (1.4)	-	-	-	-	-
Teneligliptin (†/†)	29.8 (27.7)	38.9 (27.5)	38.9 (27.5)	28.0 (17.9)	37.9 (26.6)	34.4 (19.9)	9.7 (1.3)	6.9 (1.9)	6.9 (1.9)	(3.2, 10.7)***	8.1 (14.8)	(5.2, 11.0)***
P/T	-	28.0 (17.9)	28.0 (17.9)	28.0 (17.9)	34.4 (19.9)	34.4 (19.9)	-	-	-	-	6.4 (11.5)	(4.0, 8.7)***
Fasting glucagon (pg/mL)												
Placebo	61.0 (14.1)	66.0 (14.4)	66.0 (14.4)	66.0 (14.4)	66.7 (16.5)	67.6 (14.5)	4.6 (1.1)	-	-	-	-	-
Teneligliptin (†/†)	63.2 (17.9)	67.6 (17.6)	67.6 (17.6)	66.0 (14.4)	66.7 (16.5)	67.6 (14.5)	4.9 (1.1)	0.4 (1.6)	0.4 (1.6)	(-2.7, 3.5)	3.5 (12.0)	(1.1, 5.8)**
P/T	-	66.0 (14.4)	66.0 (14.4)	66.0 (14.4)	67.6 (14.5)	67.6 (14.5)	-	-	-	-	1.6 (10.3)	(-0.5, 3.7)
PPG, 2 h (mg/dL)												
Placebo	221.5 (55.3)	218.8 (56.0)	218.8 (56.0)	218.8 (56.0)	190.2 (48.6)	177.4 (43.1)	-5.6 (3.6)	-	-	-	-	-
Teneligliptin (†/†)	230.9 (57.9)	172.5 (40.0)	172.5 (40.0)	218.8 (56.0)	190.2 (48.6)	177.4 (43.1)	-56.9 (3.6)	-51.3 (5.2)	-51.3 (5.2)	(-61.4, -41.1)***	-37.5 (47.1)	(-47.5, -27.5)***
P/T	-	218.8 (56.0)	218.8 (56.0)	218.8 (56.0)	177.4 (43.1)	177.4 (43.1)	-	-	-	-	-41.5 (46.6)	(-51.2, -31.8)***
PPG AUC _{0-2h} (mg·h/dL)												
Placebo	427.2 (75.3)	417.0 (83.3)	417.0 (83.3)	417.0 (83.3)	380.3 (73.5)	360.4 (65.8)	-13.7 (5.1)	-	-	-	-	-
Teneligliptin (†/†)	441.0 (81.0)	354.1 (57.2)	354.1 (57.2)	417.0 (83.3)	380.3 (73.5)	360.4 (65.8)	-85.0 (5.1)	-71.3 (7.3)	-71.3 (7.3)	(-85.7, -57.0)***	-57.0 (63.3)	(-70.5, -43.5)***
P/T	-	417.0 (83.3)	417.0 (83.3)	417.0 (83.3)	360.4 (65.8)	360.4 (65.8)	-	-	-	-	-55.8 (64.8)	(-69.3, -42.3)***

Table 2 | (Continued)

	Week 0		Week 12†		Week 52		Change from Week 0 to Week 12		Teneligliptin vs placebo at Week 12		Change from baseline to Week 52	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	LS mean (SE)	LS mean (SE)	LS mean (SE)	95% CI	Mean (SD)	95% CI
Postprandial insulin AUC _{0-2h} (μU·h/mL)												
Placebo	57.8 (28.5)	56.2 (28.5)	–	–	–	–	–1.0 (2.0)	–	–	–	–	–
Teneligliptin (T/T)	62.5 (39.0)	65.0 (38.7)	–	–	66.5 (40.7)	–	2.7 (2.0)	3.7 (2.9)	(–2.0, 9.3)	4.0 (17.0)	(0.4, 7.7)*	
P/T	–	56.2 (28.5)	–	–	60.1 (28.0)	–	–	–	–	3.1 (20.2)	(–1.2, 7.3)	
Postprandial glucagon AUC _{0-2h} (pg·h/mL)												
Placebo	153.9 (34.8)	161.8 (33.5)	–	–	–	–	7.5 (2.0)	–	–	–	–	–
Teneligliptin (T/T)	151.0 (36.7)	145.9 (35.4)	–	–	143.1 (33.8)	–	–4.9 (2.0)	–12.5 (2.8)	(–18.1, –6.8)***	–5.9 (21.7)	(–10.5, 1.3)*	
P/T	–	161.8 (33.5)	–	–	146.5 (31.3)	–	–	–	–	–15.2 (20.2)	(–19.4, –11.0)***	

****p* < 0.001 vs placebo, ***p* < 0.01 vs placebo, **p* < 0.05 vs placebo. †Did not complement the missing data by last observation carried forward. AUC_{0-2h}, areas under the curve from 0 to 2 h; CI, confidence interval; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A1c; HOMA-R, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; LS mean, least squares mean; PPG, postprandial glucose; P/T, patients who had taken a placebo during the double-blind period and then received teneligliptin 20 mg in the open-label period; SD, standard deviation; SE, standard error; T/T, patients who had taken teneligliptin 20 mg during the double-blind period and then continued medication with the same dose in the open-label period.

Specific AEs occurring in ≥5% of any group during the teneligliptin treatment periods are also shown in Table 3. Five patients (4.9%) in the T/T group and four patients (4.1%) in the P/T group discontinued because of AEs. ADRs were reported in 15 patients (14.6%) in the T/T group and eight patients (8.2%) in the P/T group.

Hypoglycemia was reported in two patients in the T/T group and one patient in the P/T group. No patient discontinued because of hypoglycemia.

Serious AEs were reported in 11 patients (10.7%) in the T/T group and three patients (3.1%) in the P/T group. A serious AE considered related to teneligliptin was reported in one patient (1.0%, ovarian cancer) in the P/T group. The patient was a 48-year-old woman who was diagnosed with ovarian cystoma before the study. After 160 days of teneligliptin treatment, the patient underwent magnetic resonance imaging (MRI) for routine follow up of her ovarian cystoma. The MRI showed that the ovarian cystoma had grown, and a solid area was detected in part of the cystoma. Pathological tests showed that it was stage 1 right ovarian cancer. Because the event occurred after the administration of teneligliptin, the investigator considered it to be related to teneligliptin, but a causal relationship with pioglitazone was ruled out.

The incidences of AEs in patients uptitrated to teneligliptin 40 mg were 80.6% in the T/T group and 92.6% in the P/T group. The incidences of AEs in patients who were not uptitrated were 88.9% in the T/T group and 90.1% in the P/T group. No hypoglycemia was observed in the patients that received the increased dose of teneligliptin.

Peripheral edema was reported in four patients (3.9%) in the T/T group and four patients (4.1%) in the P/T group, although in none of these patients was the peripheral edema considered related to teneligliptin by the investigators. The incidences of peripheral edema were low in both groups and did not increase, even with increased dosage period. The changes in bodyweight (mean ± SD) from baseline to week 52 were 1.5 ± 2.9 kg in the T/T group and 1.2 ± 2.1 kg in the P/T group. Bodyweight was slightly increased in both groups, although the amount of increase was small.

DISCUSSION

The addition of teneligliptin to pioglitazone therapy for 12 weeks provided a significant reduction in HbA_{1c} relative to the addition of a placebo in Japanese patients with type 2 diabetes mellitus inadequately controlled with pioglitazone monotherapy. In addition, the improvement in HbA_{1c} was sustained throughout the 52 weeks.

Add-on therapy with teneligliptin provided a significant reduction in FPG, 2-h PPG and PPG AUC_{0-2h} compared with the placebo at week 12. These blood glucose lowering effects were sustained throughout the study. The mean 2-h PPG values in the teneligliptin group at week 12 met the target level of <180 mg/dL, which is used as an index of glycemic control in Japan¹².

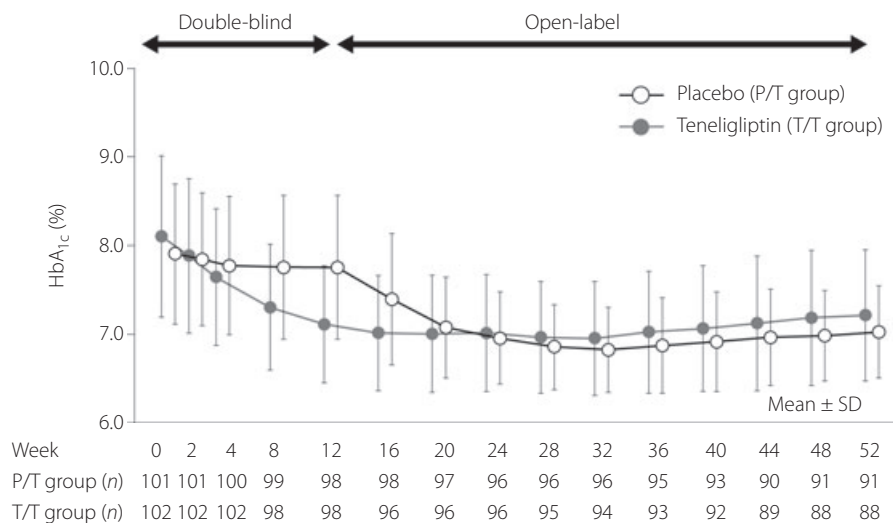


Figure 2 | Time course of hemoglobin A1c (HbA_{1c}) in Japanese patients with type 2 diabetes mellitus. Values are means \pm standard deviation. P/T, patients who had taken a placebo during the double-blind period and then received teneagliptin 20 mg in the open-label period; T/T, patients who had taken teneagliptin 20 mg during the double-blind period and then continued medication with the same dose in the open-label period.

These results show superior glycemetic control with the addition of teneagliptin, and the improvement in glycemetic control was sustained throughout the study.

The add-on therapy with teneagliptin provided significant improvements in postprandial glucagon AUC_{0-2h} in both groups. Although no significant difference in postprandial insulin AUC_{0-2h} was observed in the T/T group, postprandial insulin secretion tended to be increased. The improvement in postprandial blood glucose level observed in the present study with teneagliptin treatment was likely a result of postprandial suppression of glucagon secretion and postprandial promotion of insulin secretion, which are known effects of GLP-1. Although the glucagon assay changed during the study, as just two pretrial samples were measured using the old kit, the change in assay would not have affected the overall results.

In addition, HOMA- β , an index of pancreatic β -cell function, and the proinsulin/insulin ratio, were significantly improved by the addition of teneagliptin. In non-clinical studies, DPP-4 inhibitors were reported to promote β -cell proliferation, in addition to their β -cell protective effects (achieved by inhibiting their apoptosis), resulting in functional improvements¹⁴, and similar effects might occur in humans. The significant improvement in HOMA- β observed in the present study suggests that teneagliptin has a beneficial effect on pancreatic β -cells.

These results provide support for the long-term efficacy of teneagliptin; however, more research is required to investigate the effects of DPP-4 inhibitors on pancreatic β -cell function.

The incidences of AEs and ADRs were slightly higher in the teneagliptin group than in the placebo group. AEs that showed a significant difference in incidence between the groups included gastrointestinal disorders and skin disorders, but most of the AEs were mild in severity, and no patients in the teneagliptin group withdrew from the study because of these AEs.

Furthermore, the incidences of serious AEs and hypoglycemia were low in both groups, consistent with the results in the placebo group.

After completion of the 12-week double-blind study, teneagliptin was continuously administered for 40 weeks with no increase in the incidence of certain AEs, confirming its favorable tolerability with long-term administration. In addition, because the up-titration of teneagliptin dose caused no difference in the incidence of AEs, and no patient presented with hypoglycemia after the dose increase, it was considered that there was no safety concern in increasing the dose of teneagliptin to 40 mg.

Edema and bodyweight increases are known adverse reactions to pioglitazone, and it has been reported that the incidence of edema is increased when pioglitazone is administered concomitantly with other DPP-4 inhibitors¹⁵⁻¹⁷. However, the incidence of peripheral edema at 12 weeks in the present study was consistent with that in patients receiving pioglitazone monotherapy. In addition, there was no tendency toward an increase in the incidence of peripheral edema, even if the drug was administered for a long time, and the concomitant administration of teneagliptin and pioglitazone did not result in an increase in the incidence of edema. Bodyweight was slightly increased at week 52 after teneagliptin treatment, but the amount of increase was small (1.2 kg in the P/T group and 1.5 kg in the T/T group). There are several possible explanations for this apparent discrepancy in the incidence of peripheral edema in this study compared with that in previous studies¹⁵⁻¹⁷. First, it is possible that some patients with weight gain showed mild edema that was not detected or diagnosed as such by the investigators. A second explanation is that, in our

Table 3 | Summary of adverse events

	Double-blind period		Teneligliptin treatment period	
	Weeks 0–12		Weeks 12–52	Weeks 0–52
	Placebo (n = 101)	Teneligliptin (n = 103)	P/T group (n = 98)	T/T group (n = 103)
AEs	47 (46.5)	63 (61.2)	89 (90.8)	89 (86.4)
ADRs	2 (2.0)	12 (11.7)	8 (8.2)	15 (14.6)
Serious AEs	1 (1.0)	4 (3.9)	3 (3.1)	11 (10.7)
Drug-related serious AEs	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Discontinued because of AEs	2 (2.0)	1 (1.0)	4 (4.1)	5 (4.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoglycemia	0 (0.0)	2 (1.9)	1 (1.0)	2 (1.9)
Gastrointestinal disorder	5 (5.0)	13 (12.6)	23 (23.5)	36 (35.0)
Skin disorder	3 (3.0)	11 (10.7)	10 (10.2)	18 (17.5)
AE with a frequency $\geq 5\%$				
Nasopharyngitis	8 (7.9)	12 (11.7)	33 (33.7)	33 (32.0)
Upper respiratory tract inflammation	1 (1.0)	4 (3.9)	10 (10.2)	12 (11.7)
Edema peripheral	6 (5.9)	2 (1.9)	4 (4.1)	4 (3.9)
Gastritis	0 (0.0)	2 (1.9)	4 (4.1)	6 (5.8)
Eczema	0 (0.0)	2 (1.9)	4 (4.1)	6 (5.8)
Back pain	1 (1.0)	2 (1.9)	6 (6.1)	7 (6.8)
Glucose urine present	8 (7.9)	3 (2.9)	6 (6.1)	7 (6.8)
Blood creatine phosphokinase increased	2 (2.0)	3 (2.9)	4 (4.1)	9 (8.7)
Urine ketone body present	2 (2.0)	0 (0.0)	6 (6.1)	2 (1.9)
Blood urine present	2 (2.0)	3 (2.9)	5 (5.1)	12 (11.7)
Protein urine present	1 (1.0)	4 (3.9)	3 (3.1)	9 (8.7)

Values are expressed as n (%). ADRs, adverse drug reactions; AEs, adverse events.

experience, patients might experience severe peripheral edema within a relatively short time after starting pioglitazone, and those who do might be switched to another drug. Therefore, as the patients in the present study were using stable doses of pioglitazone for at least 12 weeks before starting treatment with teneligliptin, they were less likely to experience peripheral edema within the duration of the study.

In conclusion, add-on therapy with once-daily teneligliptin improved glycemic control in Japanese patients with type 2 diabetes mellitus inadequately controlled with pioglitazone monotherapy. The improvement of glycemic control was maintained

for up to 52 weeks. Add-on therapy with teneligliptin was generally well tolerated, with only low incidences of hypoglycemia and peripheral edema.

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