Abstract: Dipeptidyl peptidase-4 (DPP-4) inhibitors have recently emerged as a new class of antidiabetic that show favorable results in improving glycemic control with a minimal risk of hypoglycemia and weight gain. Teneligliptin, a novel DPP-4 inhibitor, exhibits a unique structure characterized by five consecutive rings, which produce a potent and long-lasting effect. Teneligliptin is currently used in cases showing insufficient improvement in glycemic control even after diet control and exercise or a combination of diet control, exercise, and sulfonylurea- or thiazolidine-class drugs. In adults, teneligliptin is orally administered at a dosage of 20 mg once daily, which can be increased up to 40 mg per day. Because the metabolites of this drug are eliminated via renal and hepatic excretion, no dose adjustment is necessary in patients with renal impairment. The safety profile of teneligliptin is similar to those of other available DPP-4 inhibitors. However, caution needs to be exercised when administering teneligliptin to patients who are prone to QT prolongation. One study has reported that the postprandial blood glucose-lowering effects of teneligliptin administered prior to breakfast were sustained throughout the day, and the effects observed after dinner were similar to those observed after breakfast or lunch. Thus, although clinical data for this new drug are limited, this drug shows promise in stabilizing glycemic fluctuations throughout the day and consequently suppressing the progression of diabetic complications. However, continued evaluation in long-term studies and clinical trials is required to evaluate the efficacy and safety of the drug as well as to identify additional indications for its clinical use.

Keywords: teneligliptin, DPP-4 inhibitor, diabetes

Introduction
Incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), are released from enteroeendocrine cells and enhance insulin secretion. Incretins are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4), and have a very short half-life as a result. DPP-4 inhibitors increase the levels of active GLP-1 and GIP by inhibiting DPP-4 enzymatic activity; thus, in patients with diabetes, these inhibitors improve hyperglycemia in a glucose-dependent manner by increasing serum insulin levels and decreasing serum glucagon levels. Therefore, incretin-related agents such as DPP-4 inhibitors are promising drugs that can decrease glucose fluctuations in diabetic patients and have emerged as a new class of antidiabetic. The effect of these inhibitors on glycemic control when administered as monotherapy or in combination with other drugs has been investigated in multiple trials. Moreover, DPP-4 inhibitors have shown favorable results in improving glycemic control with a minimal risk of hypoglycemia and weight gain.
In this review, a novel chemotype prolylthiazolidine-based DPP-4 inhibitor, teneligliptin (generic name: teneligliptin hydrobromide hydrate) is characterized. Teneligliptin was originally synthesized by Mitsubishi Tanabe Pharma Corporation (Osaka, Japan) and was the first drug of its kind to be synthesized in Japan. Mitsubishi Tanabe Pharma Corporation and Daiichi Sankyo Co, Ltd, (Tokyo, Japan) jointly sell the drug under the brand name TENERIA®.

**Chemistry of teneligliptin**

Despite their common mechanism of action, DPP-4 inhibitors show marked structural heterogeneity (Figure 1). DPP-4 inhibitors may be classified into peptidomimetic (ie, sitagliptin, vildagliptin, saxagliptin, and anagliptin) and non-peptidomimetic (ie, alogliptin and linagliptin) subtypes. Teneligliptin, \{2S,4S\}-4-[4-(3-methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-yl\} (1,3-thiazolidin-3-yl) methanone hemipentahydrobromide hydrate exhibits a unique structure that is characterized by five consecutive rings (Figure 2) and is peptidomimetic. An X-ray co-crystal structure of teneligliptin with DPP-4 demonstrates that the key interaction occurs between the phenyl ring on the pyrazole and the S2 extensive subsite of DPP-4, which not only enhances the potency of the drug but also increases its selectivity.

According to the product information provided by the pharmaceutical company, teneligliptin inhibits human plasma DPP-4 activity and recombinant human DPP-4 activity in a concentration-dependent manner with half-maximal inhibitory concentrations (IC50) of 1.75 (95% CI, 1.62–1.89) nmol/L and 0.889 (95% CI, 0.812–0.973) nmol/L, respectively. Furthermore, the IC50 values of teneligliptin for DPP-8, DPP-9, and fibroblast activation protein (FAP) are 0.189, 0.150, and >10 µmol/L, respectively, all of which are more than 160 times the value for recombinant human DPP-4.

**Metabolism and excretion**

CYP3A4, a cytochrome P450 isozyme and flavin-containing monoxygenases (FMO1 and FMO3) play major roles in the metabolism of teneligliptin. In vitro, teneligliptin exhibits a weak inhibitory effect for CYP2D6, CYP3A4, and FMO; however, it demonstrates no inhibitory effect for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1. In addition, teneligliptin does not induce the expression of CYP1A2 or CYP3A4.

About 34.4% of teneligliptin is excreted unchanged via the kidney and the remaining 65.6% teneligliptin is metabolized and eliminated via renal and hepatic excretion; 216 hours after the administration of 14C-labeled teneligliptin (20 mg), the cumulative excretion percentages of radioactive teneligliptin in urine and feces were 45.4% and 46.5%, respectively.

**Clinical use**

Since September 2012, teneligliptin has been commercially sold in Japan and has been used for the treatment of type 2 diabetes mellitus when patients do not show sufficient improvement after diet control and exercise or a combination of diet control, exercise, and sulfonylurea- or thiazolidine-class drugs. In adults, 20 mg of teneligliptin may be orally administered once daily. If this dosage is insufficient, the dosage is increased to 40 mg once daily.
Effects of teneligliptin on glycemic parameters
Teneligliptin is still a relatively new drug, and published clinical studies concerning this drug are sparse. However, a report by Eto et al\textsuperscript{22} provides important novel data, particularly the finding that teneligliptin significantly improved 24-hour blood glucose control in Japanese patients with type 2 diabetes. Hereafter, the results of this particular report are summarized.

Effects on blood glucose level
To assess blood glucose control over 24 hours and the safety of teneligliptin at 10 and 20 mg doses, a randomized, double-blind, placebo-controlled, parallel-group study was conducted at four locations in Japan.\textsuperscript{22} Japanese patients with type 2 diabetes mellitus that was inadequately controlled with diet and exercise were eligible to participate in the study. Among the 99 patients who participated, 32 were treated with a placebo, 34 were treated with teneligliptin at a dose of 10 mg, and 33 were treated with teneligliptin at a dose of 20 mg before breakfast for 4 weeks. The results revealed that both teneligliptin-treated groups showed significantly smaller 2-hour postprandial glucose (PPG), 24-hour mean glucose (MG), and fasting plasma glucose (FPG) values than the placebo group when the values at week 4 were compared to the baseline values.

The differences in the changes in 2-hour PPG after each meal between the teneligliptin (10 mg) and placebo groups were $-50.7 \pm 7.8$, $-34.8 \pm 9.2$, and $-37.5 \pm 7.5$ mg/dL at breakfast, lunch, and dinner, respectively (least squares [LS] mean $\pm$ standard error [SE], $P < 0.001$ for all comparisons). The corresponding LS means $\pm$ SE for teneligliptin (20 mg) versus the placebo were $-38.1 \pm 7.8$, $-28.6 \pm 9.2$, and $-36.1 \pm 7.5$ mg/dL, respectively ($P < 0.001$, $P < 0.01$, and $P < 0.001$, respectively). Importantly, the postprandial blood glucose-lowering effects of teneligliptin administered before breakfast were sustained throughout the day, and the effects observed after dinner were similar to those observed after breakfast or lunch.

The changes in the 24-hour MG level from baseline were $-34.7 \pm 3.9$, $-30.9 \pm 4.0$, and $-5.4 \pm 4.0$ mg/dL in the groups receiving 10 and 20 mg of teneligliptin and the placebo groups, respectively. Therefore, the differences between the teneligliptin-treated and placebo groups were $-29.3 \pm 5.3$ and $-25.5 \pm 5.3$ mg/dL for teneligliptin at doses of 10 and 20 mg, respectively (LS mean $\pm$ SE). These findings demonstrate that the 24-hour MG values significantly decreased in both teneligliptin-treated groups in comparison with the placebo group (both teneligliptin-treated groups, $P < 0.001$).

In addition, when the 24–hour MG profiles were plotted, treatment with teneligliptin suppressed the increases in blood glucose levels over a 24-hour period in comparison with the effect of the placebo at week 4.

The changes in the FPG values from baseline were $-20.7 \pm 2.7$, $-20.5 \pm 2.8$, and $-6.9 \pm 2.8$ mg/dL in the 10 mg and 20 mg groups of teneligliptin and the placebo groups, respectively. These results indicate the differences between the teneligliptin-treated and placebo groups, which were $-13.8 \pm 4.0$ and $-13.6 \pm 4.0$ mg/dL for teneligliptin at doses of 10 and 20 mg, respectively (LS mean $\pm$ SE). The decreases in the FPG values with teneligliptin at doses of 10 and 20 mg (both, $P < 0.001$) were statistically significant, compared with the placebo. However, there were no significant differences in the 2-hour PPG values after each meal, as well as in the 24-hour MG or FPG values between the 10 and 20 mg teneligliptin groups. These results indicate that the once-daily administration of teneligliptin before breakfast improved blood glucose control, even at dinnertime.

Effects on insulin
The area under the curve (AUC)\textsubscript{0-2h} values for the postprandial insulin levels significantly increased after dinner in the teneligliptin 10 mg group ($P < 0.05$), in comparison with the corresponding values in the placebo group, but not at other times in either group. The relative insulin concentrations were higher in the teneligliptin-treated groups because of the decreased blood glucose concentrations of the patients in these groups.

Effects on glucagon
In this study, the AUC\textsubscript{0-2h} for the postprandial glucagon levels significantly decreased after breakfast and lunch as well as after dinner in the 20 mg teneligliptin group compared with the corresponding values in the placebo group. In addition, there were no significant differences in the insulin or glucagon concentrations between the two teneligliptin-dosage groups, although glucagon secretion was lower with teneligliptin treatment at 20 mg, particularly after dinner. Thus, the study concluded that teneligliptin effectively suppressed postprandial glucagon secretion after meals and improved postprandial hyperglycemia.

Pharmacokinetic and pharmacodynamic properties of teneligliptin
The plasma concentrations of teneligliptin after the administration of teneligliptin at dosages of 10 or 20 mg once
Safety and tolerability

The incidence of adverse events (AEs) was not significantly different between the teneligliptin and placebo groups in the study conducted by Eto et al. When AEs were rated by the investigators for intensity and potential relationship to the study drug, two drug-related AEs, increased levels of alanine aminotransferase and γ-glutamyltransferase, were observed in one patient (2.9%) treated with 10 mg of teneligliptin. No drug-related AEs occurred in the placebo or 20 mg teneligliptin groups. Furthermore, none of the patients in any of the groups experienced hypoglycemic symptoms or serious AEs. In addition, a pharmaceutical company provided information regarding domestic clinical studies that included 1183 patients, of which 118 patients (10.0%) experienced AEs, including abnormalities in clinical examination values such as levels of liver and kidney function, blood cell count, creatinine phosphokinase, and electrolytes. The main AEs included hypoglycemia (35 patients: 3.0%) and constipation (eleven patients: 0.9%). The pharmaceutical company also warned of serious AEs such as hypoglycemia, which could occur when other antidiabetic drugs were coadministered. In addition, they cautioned that intestinal obstruction could occur with an unknown frequency. GLP-1 is involved in gastrointestinal motility, and the patients with intestinal obstruction had a past medical history of intestinal obstruction or abdominal surgery. Therefore, we should be cautious when administering incretin-related agents to patients with a history of these conditions. Continued assessment of AEs previously reported in clinical trials and post-market monitoring is required to determine the benefit/risk ratio for the drug.

According to a strict QT/QTc evaluation study and clinical studies for type 2 diabetes conducted in Japan and other countries, no AEs related to QT prolongation were detected with 40 mg/day of teneligliptin, which is the maximal dosage used in clinical practice. However, because when 160 mg/day of the drug was administered, slight prolongation of the QTc interval was detected temporally at the high concentrations of the drug (around t max level), and also because some patients with diabetes have comorbid arrhythmia or ischemic heart diseases, teneligliptin may be used for a longer period, and thus special caution is required in the administration of teneligliptin to patients who are prone to QT prolongation. In addition, the coadministration of teneligliptin with drugs known to cause QT prolongation on their own, such as class IA or class III antiarrhythmic drugs, should be performed with caution.

Long-term effects on glycemic control

In an independent clinical study (Phase II trial) conducted in Japan three hundred twenty-four patients with type 2 diabetes who did not achieve optimal glycemic control with diet and exercise treatment alone for more than 12 weeks were randomly allotted into the following groups: placebo, 10 mg teneligliptin, 20 mg teneligliptin, or 40 mg teneligliptin. The drugs were administered once daily for 12 weeks. After 12 weeks, the HbA1c levels in the placebo group changed by +0.11% ± 0.05%, whereas those in the 10 mg teneligliptin, 20 mg teneligliptin, and 40 mg teneligliptin groups changed by −0.77% ± 0.05%, −0.80% ± 0.05%, and −0.91% ± 0.05%, respectively (LS mean ± SE). In a Phase III trial, 20 mg of teneligliptin was administered to 151 patients with type 2 diabetes who were treated with diet control and exercise treatment alone for more than 12 weeks. The dose of teneligliptin was increased to 40 mg in patients whose HbA1c levels were greater than 7.3% at any time after week 24. At week 52, changes in the HbA1c levels (mean ± standard deviation [SD]) were −0.63% ± 0.67%, compared to baseline.

Kadowaki and Kondo conducted a double-blind, placebo-controlled, parallel-group study in 324 Japanese patients with type 2 diabetes randomized to receive different doses of teneligliptin or placebo once daily before breakfast for 12 weeks. The differences between the teneligliptin 10, 20, or 40 mg groups and the placebo group for the changes in
HbA$_1c$ levels were $-0.9$ (LS mean; 95% CI: $-1.0$, $-0.7$), $-0.9$ ($-1.1$, $-0.7$), and $-1.0$ ($-1.2$, $-0.9$)%, respectively (all, $P < 0.001$). The respective LS means for FPG were $-17.8$ ($-23.4$, $-12.1$), $-16.9$ ($-22.6$, $-11.2$), and $-20.0$ ($-25.7$, $-14.3$) mg/dL (all, $P < 0.001$). These results indicate that treatment with teneligliptin for 12 weeks provided significant and clinically meaningful reduction in the levels of HbA$_1c$ and FPG across the dose range studied.

Continued evaluation in long-term studies and clinical practice are required to assess the long-term effects of this drug.

**Effects of teneligliptin on lipid profiles**

The lipid profile is an important determinant of cardiovascular risk in type 2 diabetes. It can affect antidiabetic therapy and is important in the clinical management of patients with type 2 diabetes.$^{20,24-26}$ Meta-analyses suggested a potential beneficial effect of DPP-4 inhibitors on cholesterol, which could contribute to a reduction in cardiovascular risk.$^{16,24}$ The administration of several DPP-4 inhibitors reduces postprandial triglyceride levels in humans, mice, and hamsters; however, its effects on postprandial free fatty acid levels are a matter of debate.$^{27-30}$ Fukuda-Tsuru et al.$^{31}$ previously reported that a single administration of teneligliptin after an oral fat-loading test in Zucker fatty rats showed that teneligliptin at 1 mg/kg reduced the levels of postprandial triglycerides and free fatty acids and also increased the levels of GLP-1 and insulin.$^{32,33}$ GLP-1 inhibits the secretion of gastric lipase$^{34}$ and reduces intestinal triglyceride absorption and apo B and apo A-IV production,$^{28,35}$ and insulin suppresses lipolysis in adipose tissue, resulting in a reduction of the plasma free fatty acid levels.$^{36}$ Therefore, the study speculated that the reduction in triglyceride and free fatty acid levels could be a consequence of the elevation of active GLP-1 and insulin levels. Furthermore, in Zucker fatty rats, the repeated administration of teneligliptin for 2 weeks reduced glucose excursions in an oral carbohydrate-loading test and decreased plasma triglyceride and free fatty acid levels under nonfasting conditions. Furthermore, these results were consistent with the findings of other previous reports on DPP-4 inhibitors in various rodent models such as db/db mice and streptozocin-induced diabetic rats.$^{37-40}$

**Teneligliptin and renal impairment**

The single administration of teneligliptin at 20 mg in patients with renal impairment revealed no remarkable changes in $C_{\text{max}}$ and $t_{1/2}$ corresponding to the level of renal impairment. Compared with healthy adult subjects, the AUC$_{0-\infty}$ of subjects with mild renal impairment ($50 \leq \text{creatinine clearance [Ccr]} \leq 80 \text{ mL/minute}$), moderate renal impairment ($30 \leq \text{Ccr} < 50 \text{ mL/minute}$), and severe renal impairment ($\text{Ccr} < 30 \text{ mL/minute}$) was approximately 1.25 times, 1.68 times, and 1.49 times higher than that of healthy adult subjects, respectively. In addition, the AUC$_{0-48h}$ of patients with end-stage renal failure was approximately 1.16 times higher than that of healthy adult subjects. In addition, 15.6% of the total administration dose of teneligliptin was eliminated via hemodialysis.

**Teneligliptin and hepatic impairment**

A single administration of teneligliptin 20 mg in patients with hepatic impairment revealed that the $C_{\text{max}}$ of subjects with mild hepatic impairment (Child–Pugh classification:$^{41}$ total score 5–6) and moderate hepatic impairment (Child–Pugh classification: total score 7–9) was approximately 1.25 times and 1.38 times that of healthy adult subjects, respectively. Compared to healthy adult subjects, the AUC$_{0-\infty}$ of subjects with mild and moderate hepatic impairments was approximately 1.46 times and 1.59 times higher than that of healthy adult subjects, respectively. There have been no previous clinical studies using teneligliptin in patients with severe hepatic impairment (Child–Pugh classification: total score was greater than 9). Thus, specific caution is required when the drug is administered to patients with severe hepatic impairment.

**Influence on body weight**

Studies on the effect of DPP-4 inhibitors on body weight demonstrated variable results; however, these results were generally considered to be neutral.$^{14,16,42-44}$ In a Phase III trial, 20 mg of teneligliptin was administered to 151 patients with type 2 diabetes, who were previously treated with diet control and exercise treatment alone. The dose of teneligliptin was increased to 40 mg in patients with HbA$_1c$ levels greater than 7.3% at any time after week 24. The mean body weight change of the patients at week 52 (mean ± SD) was +0.18 ± 2.14 kg ($P = 0.3254$), which indicated that the effect of teneligliptin on body weight was neutral.

**Gliptins in combination with other oral antidiabetic agents**

Since DPP-4 inhibitors and metformin improve glycemic control via different, albeit potentially complementary, mechanisms, combination therapy with these two agents should
provide effective and potentially additive glycemic control. Studies using combination therapy of DPP-4 inhibitors and metformin (as one pill) showed favorable results in glycemic control because of favorable pharmacokinetic characteristics and complementary pharmacodynamic effects, which include enhanced incretin effect, suppressed hepatic glucose production, and improved peripheral insulin sensitivity. Moreover, in general, the combination of these drug into a single tablet improves patients’ compliance and often results in a lower cost of treatment. Indeed, several fixed-dose combinations have been developed and/or commercialized.

Furthermore, α-glucosidase inhibitors (α-GIs) reportedly enhanced GLP-1 responses and reduced the total GIP responses. Considering the different but complementary mechanisms of action by which α-GIs and DPP-4 inhibitors lower glucose levels and increase GLP-1 action, combination therapy using these agents may provide a valuable means of treating diabetes. Using a continuous glucose-monitoring (CGM) system, we previously reported the efficacy of combination therapy using miglitol and sitagliptin in patients with type 2 diabetes.

Several trials have also evaluated the efficacy and safety of adding a DPP-4 inhibitor to sulfonylurea, such as glimepiride or glyburide (glibenclamide), and have indicated a significant improvement in glycemic control. Because hypoglycemic events may occur with the combination of DPP-4 inhibitors and sulfonylurea, caution should be taken to reduce the dose of sulfonylurea in order to minimize the risk of hypoglycemia.

When 20 mg of teneligliptin was administered to 96 patients with type 2 diabetes who were treated with glimepiride (1–4 mg per day) in addition to diet and exercise treatment, the changes in HbA\textsubscript{1c} levels and fasting and 2-hour postprandial blood glucose levels (LS mean ± SE) were −0.71% ± 0.06%, −17.3 ± 2.2 mg/dL, and −43.1 ± 4.4 mg/dL, respectively, from baseline at week 12.

From a theoretical standpoint, combination of DPP-4 inhibitors, which stimulate insulin secretion in a glucose-dependent manner and do not promote weight gain, and thiazolidinedione, which enhances peripheral insulin action and may cause weight gain, is an attractive and rational approach. When 20 mg of teneligliptin was administered to 103 patients with type 2 diabetes who were treated with pioglitazone (15–30 mg per day) in addition to diet and exercise treatment, the changes in HbA\textsubscript{1c} levels and fasting and 2-hour postprandial blood glucose levels (LS mean ± SE) were −0.94% ± 0.04%, −21.0 ± 1.9 mg/dL, and −56.9 ± 3.6 mg/dL, respectively, compared with that at baseline, at week 12.

### Gliptin treatments in combination with insulin

The effectiveness of insulin injections has been previously established in various clinical studies; however, increasing the insulin dosage to achieve better glycemic control has been associated with an increased risk of hypoglycemia and weight gain. To resolve these problems, combination therapy with insulin injection and oral medication is worth considering.

**Case presentation**

A 68-year-old Japanese woman with a 7-year history of type 2 diabetes presented at our hospital (National Center for Global Health and Medicine, Tokyo, Japan) to be equipped with a CGM device (iPro\textsuperscript{®}2; Medtronic Ltd, Watford, UK). Her height was 148.6 cm and her body weight was 59.2 kg (body mass
index 26.8 kg/m²). Her hemoglobin A₁c and fasting C-peptide levels were 6.6% and 3.3 ng/mL, respectively, and she was on a treatment of 20 mg of gliclazide. On the first day of the CGM period, the patient was taking gliclazide alone. From day 2 through day 4, 20 mg of teneligliptin was also taken, before breakfast, in addition to gliclazide. During this period, she did not change her lifestyle remarkably, including the timing and amounts of her meals and the levels of her daily physical activities. Figure 3 shows the fluctuations in glucose levels measured using CGM during treatment with gliclazide alone (day 1) and gliclazide plus teneligliptin (days 2 to 4). The average and SD values of the CGM measurements on days 1, 2, 3, and 4 were 142 ± 26, 145 ± 20, 135 ± 15, and 126 ± 16 mg/dL, respectively, reflecting the attenuation of glucose fluctuations when teneligliptin was added to gliclazide. These findings clearly demonstrate the efficacy of combinatorial therapy using sulfonylurea such as gliclazide and teneligliptin in patients with type 2 diabetes.

**Conclusion**
Numerous clinical trials have demonstrated that DPP-4 inhibitors provide effective and consistent glycemic control with a good tolerability profile, including no severe hypoglycemia and weight gain.⁷,⁸,¹¹-¹⁹,⁴²-⁴⁵ Although different DPP-4 inhibitors are distinctive in their metabolic properties, excretion, recommended dosage, and daily dosage, and head-to-head clinical trials comparing the various DPP-4 inhibitors are scarce, the available data regarding indirect comparisons suggest that all available DPP-4 inhibitors have nearly the same efficacy and safety profile.¹⁴,¹⁶,⁴³ Thus, we may expect a similar efficacy and safety with the novel DPP-4 inhibitor, teneligliptin, although this drug requires careful long-term postmarketing surveillance and additional clinical trials to evaluate its efficacy and safety as well as to gain additional indications for its clinical use.

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**Disclosure**
The author reports no conflicts of interest in this work.

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Figure 3 Continuous glucose monitoring results during treatment with gliclazide alone (day 1) and gliclazide plus teneligliptin (days 2 to 4).

Notes: The symbols at the bottoms of the figures indicate the times of meals. The round symbols on or close to the wavy lines indicate the times and values of calibration.
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