The Unique Pharmacological and Pharmacokinetic Profile of Teneligliptin: Implications for Clinical Practice

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Abstract
Teneligliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that was approved for the treatment of type 2 diabetes mellitus (T2DM) in Japan and Korea and is being researched in several countries. Teneligliptin is a potent, selective, and long-lasting DPP-4 inhibitor with a t1/2 of approximately 24 h and unique pharmacokinetic properties: it is metabolized by cytochrome P450 (CYP) 3A4 and flavin-containing monooxygenase 3 (FMO3), or excreted from the kidney in an unchanged form. Because of its multiple elimination pathways, dose adjustment is not needed in patients with hepatic or renal impairment, and it is considered to have a low potential for drug–drug interactions. Clinical studies and postmarketing surveillance show that teneligliptin, administered as monotherapy and/or in combination with antihyperglycemic agents, is effective and well tolerated in T2DM patients, including in elderly patients and those with renal impairment. Furthermore, teneligliptin has antioxidative properties, which induce the antioxidant cascade, as well as ·OH scavenging properties. In addition, it has shown endothelial protective effects in several non-clinical and clinical studies. From its unique profile and clinical data, teneligliptin represents a potential therapeutic option in a wide variety of patients, including elderly diabetic patients and those with renal impairment. The fixed-dose combination (FDC) tablet of teneligliptin and canagliflozin has been approved in Japan; this is the first FDC tablet of a DPP-4 inhibitor and sodium glucose co-transporter 2 inhibitor in Japan, and the third globally. The FDC tablet may also provide additional prescribing and adherence benefits.

1 Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. In 2017, it was estimated that 451 million people aged 18–99 years had diabetes, and that the disease was responsible for approximately 5.0 million deaths in that year [1]. There are different trends in diabetes prevalence by age group, income, and region. For example, in low- and middle-income countries, diabetes predominantly affects individuals aged ≤ 65 years (prevalence 88% and 77%, respectively); however, in high-income countries, almost half (44%) of all individuals with diabetes are aged > 65 years [1].

In Japan, more than 60% of T2DM patients are estimated to be over 65 years of age [2]. Another report suggested that approximately 8.8 million people in Japan had T2DM in 2015, with the disease affecting approximately 20% of men and 10% of women aged ≥ 60 years [3]. With the population aging in Japan, the prevalence of T2DM is predicted to rise substantially over the next two decades, affecting 9.7 million people by 2030 [3]. In elderly T2DM patients, careful treatment is needed because of the high risk of hypoglycemia and drug adverse events (AEs) due to the altered pharmacokinetic profile associated with aging and polypharmacy [4–6]. Therefore, the treatment of elderly T2DM patients is a growing problem in several countries, including Japan.

Hyperglycemia is an important cause of morbidity and mortality in T2DM and is associated with both macrovascular (coronary artery disease, peripheral arterial disease, and stroke) and microvascular (diabetic nephropathy, neuropathy,
Teneligliptin is a potent, selective, and long-lasting DPP-4 inhibitor with a unique pharmacokinetic profile (multiple elimination pathways); no dose adjustment is needed in patients with hepatic or renal impairment and it is considered to have a low potential for drug–drug interactions.

Teneligliptin has antioxidative properties and has shown endothelial protective effects in several non-clinical and clinical studies.

Teneligliptin provides a therapeutic option for a broad range of T2DM patients, including elderly subjects and those with renal impairment.

Teneligliptin, a DPP-4 inhibitor, was approved for the treatment of T2DM in Japan in 2012 and in Korea in 2014, and is being researched in several countries [23]. The approved dose of teneligliptin is 20 mg once daily. In Japan, the dosage can be increased to 40 mg/day, with close monitoring of the clinical course if efficacy is insufficient [24, 25]. In July 2017, Japan’s first DPP-4 inhibitor/sodium glucose co-transporter 2 (SGLT2) inhibitor combination drug, a fixed-dose combination (FDC) tablet of teneligliptin/canagliflozin, was approved for the treatment of T2DM.

This review summarizes non-clinical, pharmacokinetic, and clinical data for teneligliptin, and discusses the role of teneligliptin in clinical practice, in light of the drug’s novel chemical structure, pharmacokinetic profile, and pleiotropic effects.

PubMed and Scopus searches were performed using the key word ‘teneligliptin’. In addition, the prescribing information for teneligliptin and the other DPP-4 inhibitors was searched via the Pharmaceuticals and Medical Devices Agency (PMDA) home page using the drug name (e.g. teneligliptin) or brand name (e.g. Tenelia) as keywords.

2 Chemical Structure

Teneligliptin is a prolylthiazolidine-based DPP-4 inhibitor characterized by a unique, rigid, ‘J-shaped’ structure of five consecutive rings (Fig. 1) [25–27]. DPP-4 inhibitors are categorized into three groups, based on interactions with DPP-4 binding subsites. Like sitagliptin, teneligliptin is a class 3 DPP-4 inhibitor and binds to S1, S2, and S2 extensive subsites on DPP-4; however, teneligliptin demonstrates fivefold higher activity than sitagliptin. While sitagliptin and teneligliptin appear to bind to subsites in the same manner, there are three potential factors that may account for differences in potency. First, the unique, rigid ‘J-shaped’ structure of teneligliptin, formed by five rings, leads to a small entropy loss upon binding to DPP-4 [27]. Second, the affinity of teneligliptin to the S2 subsite of DPP-4 is derived from the formation of a hydrogen bond between the carbonyl group of teneligliptin and the side chain of Asn710 at the S2 subsite [27]. Finally, teneligliptin binds with the S2 extensive subsite of DPP-4 via strong hydrophobic interactions mediated by an ‘anchor lock domain’ [25, 27]. These interactions may be related to the potency of inhibition and the duration of action of teneligliptin observed in vivo [27].

3 Pharmacological Properties

3.1 In Vitro Studies

Teneligliptin is a potent, selective, and long-lasting DPP-4 inhibitor that has approximately 700- to 1500-fold greater...
The Unique Pharmacological and Pharmacokinetic Profile of Teneligliptin

The Unique Pharmacological and Pharmacokinetic Profile of Teneligliptin

affinity for DPP-4 than other DPP enzymes, such as DPP-8 and DPP-9 [26]. Teneligliptin inhibits recombinant human DPP-4 and human plasma DPP-4 in a concentration-dependent manner: concentrations producing half maximal inhibition (IC$_{50}$) are 0.889 nmol/L and 1.75 nmol/L, respectively [28]. In these respects, teneligliptin is more potent than sitagliptin (6.74 nmol/L and 4.88 nmol/L, respectively) and vildagliptin (10.5 nmol/L and 7.67 nmol/L, respectively), as demonstrated by lower IC$_{50}$ values [28].

3.2 In Vivo Studies

In rats, single oral administration of teneligliptin inhibited plasma DPP-4 in a dose-dependent manner, with a median effective dose of 0.41 mg/kg, compared with 27.3 and 12.8 mg/kg for sitagliptin and vildagliptin, respectively [28]. At 24 h after drug administration, inhibition of DPP-4 persisted with teneligliptin 10 mg/kg (≥ 50% inhibition), but did not persist with sitagliptin or vildagliptin 100 mg/kg (< 3% and < 15% inhibition, respectively) [28]. The effect of teneligliptin in an oral mixed meal tolerance test showed that teneligliptin 0.1 mg/kg had nearly maximum effects for reducing glucose excursion and increasing active GLP-1/insulin. Plasma DPP-4 inhibition was ≥ 40% for the entire treatment period of the oral mixed meal tolerance test, suggesting that 40% DPP-4 inhibition was required for sufficient efficacy [28].

The effects of teneligliptin on hyperglycemia and hypertriglyceridemia were evaluated in Zucker fatty rats [28]. A single dose of teneligliptin 1 mg/kg reduced PPG, free fatty acid, and triglyceride excursions after carbohydrate and fat loading. After repeated administration of teneligliptin for 2 weeks, glucose excursions after carbohydrate loading were reduced, as were non-fasting levels of free fatty acids and triglycerides [28].

4 Pharmacokinetic Properties

4.1 Non-Human Study

Oral administration of teneligliptin (0.1, 0.3, or 1.0 mg/kg) in rats showed rapid absorption, with mean peak plasma concentration (t$_{max}$) reached in 0.75–0.88 h [26]. After oral administration of [$^{14}$C]teneligliptin to Sprague–Dawley rats, teneligliptin was predominantly distributed in the kidney and liver, followed by the lung, spleen, and pituitary gland [29]. It was reported that tissue DPP-4 activity was greatest in the kidney, followed by the lung, adrenal gland, jejunum, and liver [30]. The elimination of [$^{14}$C]teneligliptin from tissues with high DPP-4 activity (kidney, liver, and lung) was slower in wild-type Fisher rats than in DPP-4-deficient rats, although there was no marked difference in low DPP-4 activity tissues (the heart and pancreas). This suggests that the high binding affinity of teneligliptin for DPP-4 has some influence on tissue distribution of the drug [29]. Among DPP-4 inhibitors, teneligliptin and linagliptin have high tissue distribution properties, especially in the kidney. The hydrophobic properties of both drugs may influence the high tissue distribution [29].

4.2 Healthy Subjects

Pharmacokinetic data for teneligliptin (20 and 40 mg) in Japanese healthy subjects are outlined in Table 1. Single oral doses of teneligliptin (2.5, 10, 20, 40, 80, and 160 mg) or placebo were administered under fasting conditions, and dose-dependent increases in the maximal plasma concentration (C$_{max}$) and area under the plasma concentration–time curve (AUC) of teneligliptin were observed. The t$_{max}$ and mean elimination half-life (t$_{1/2}$) of teneligliptin 20 mg were 1.8 and 24.2 h, respectively. After repeated doses of teneligliptin 20 or 80 mg, no remarkable changes were observed in the pharmacokinetic profile, and teneligliptin reached steady state by day 7 [24]. The pharmacokinetic profile did not differ between Japanese and Caucasian subjects [24, 31, 32].

The mass balance study using [$^{14}$C]teneligliptin indicated that teneligliptin was metabolized or excreted from the kidney, with metabolism and renal excretion contributing to 65.6% and 34.4%, respectively, of total body clearance [24]. Teneligliptin was the most abundant radioactive component in plasma (71.1%); the most abundant metabolite in plasma was a thiazolidine-1-oxide derivative (designated as M1, 14.7%). The main enzymes responsible for teneligliptin metabolism are cytochrome P450 (CYP) 3A4 and flavin-containing monoxygenase 3 (FMO3), with equal contribution [33] (Fig. 2). Because of its elimination via multiple pathways, teneligliptin is considered a suitable treatment...
option for patients with hepatic or renal impairment, and is considered to have a low potential for drug–drug interactions, as described below.

### 4.3 Special Subject Populations

The pharmacokinetic properties of teneligliptin in special populations were evaluated in Caucasian subjects.

#### 4.3.1 Subjects with Renal Impairment/Hepatic Impairment

The pharmacokinetic properties of teneligliptin have been evaluated in subjects with normal renal function and renal impairment (Table 2) [34]. Patients were assigned to one of four groups based on their renal function [mild, moderate, severe renal impairment, as assessed using Cockcroft–Gault estimates of creatinine clearance [35], or end-stage renal disease (ESRD)] and two groups of matched healthy subjects. In individuals with mild, moderate, or severe renal impairment, or ESRD, who received a single dose of teneligliptin 20 mg, no greater than a twofold increase in teneligliptin AUC from time zero to infinity (AUC∞) relative to healthy controls was observed. Changes in Cmax and t½ were unremarkable. Dialysis is not expected to affect the pharmacokinetic profile of teneligliptin; the removal of teneligliptin after dialysis was 15.6% [34].

The pharmacokinetics of teneligliptin were compared in three groups of eight subjects who were categorized according to their degree of hepatic impairment [two groups with chronic (> 6 months), stable, mild (Child–Pugh score 5–6), or moderate (Child–Pugh score 7–9) hepatic impairment, and one group of matched healthy subjects] (Table 2) [36]. Hepatic impairment was associated with a mild increase in Cmax and overall exposure (AUC∞) relative to healthy controls; however, no greater than a twofold increase was observed [36]. Collectively, pharmacokinetic changes were unremarkable; thus, no dose adjustment of teneligliptin is required in patients with renal or hepatic impairment.

#### 4.3.2 Elderly Subjects

In a placebo-controlled, randomized, double-blind, parallel-group comparative study in 40 healthy adult patients [21 non-elderly (aged ≥ 45 and < 65 years) and 19 elderly (aged ≥ 65 and ≤ 75 years) individuals] who received a single dose of placebo or teneligliptin 20 or 80 mg, the ratio (elderly/non-elderly) of the geometric least square (LS) means of Cmax, AUC from time zero to time t (AUCt), and t½ of plasma teneligliptin was approximately 1.0 across all parameters, demonstrating a similar pharmacokinetic profile between elderly and non-elderly individuals. The results of teneligliptin 20 mg administration are shown in Table 2 [31].

### 4.4 Drug–Drug Interactions

The results from drug–drug interaction studies are presented in Table 3. Teneligliptin is metabolized by CYP3A4 and is a

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Table 1 Pharmacokinetic profile of teneligliptin in healthy Japanese subjects [24, 31]

| Category       | Day | Dose (mg/day) | n  | tmax (h)a | Cmax (ng/mL)b | AUC∞ (ng·h/mL)b | t½ (h)b |
|----------------|-----|--------------|----|-----------|---------------|----------------|--------|
| Single-dose    | 1   | 20           | 6  | 1.8 (1.0, 2.0) | 187.20 (44.70) | 2028.9 (459.5) | 24.2 (5.0) |
|                | 1   | 40           | 6  | 1.0 (0.5, 3.0) | 382.40 (89.83) | 3705.1 (787.0) | 20.8 (3.2) |
| Multiple-dose  | 1   | 20           | 7  | 1.0 (0.4, 2.0) | 160.60 (47.26) | 1627.9 (427.8) | 25.8 (4.9) |
|                | 7   | 20           | 7  | 1.0 (1.0, 1.0) | 220.14 (59.86) | 2641.4 (594.7) | 30.2 (6.9) |

AUC∞ area under the plasma concentration-time curve from time zero to infinity, Cmax maximal plasma concentration, tmax time to reach Cmax, t½ elimination half-life

aMedian (minimum, maximum)
bMean (standard deviation)
The Unique Pharmacological and Pharmacokinetic Profile of Teneligliptin

The Unique Pharmacological and Pharmacokinetic Profile of Teneligliptin

weak substrate of P-glycoprotein. The effects of the CYP3A4 and P-glycoprotein inhibitor ketoconazole on teneligliptin pharmacokinetics in healthy adults were investigated in an open-label, fixed-sequence study conducted in 16 healthy volunteers (14 of whom were included in the pharmacokinetic analysis set) in Germany [37]. Exposure to teneligliptin, when administered in combination with ketoconazole, was less than twice the exposure to teneligliptin alone, which suggests that drugs and foods that inhibit CYP3A4 are unlikely to markedly increase exposure to teneligliptin [37]. No clinically relevant drug–drug interactions were observed when teneligliptin was coadministered with metformin, canagliflozin, glimepiride, or pioglitazone [31, 38, 39].

5 Pharmacokinetic/Pharmacodynamic Data in Type 2 Diabetes Mellitus

A pharmacokinetic/pharmacodynamic (PK/PD) study was conducted in Japanese patients with T2DM [40]. Ninety-nine patients were administered teneligliptin 10 or 20 mg or placebo before breakfast for 4 weeks in a randomized, double-blind, placebo-controlled, parallel-group study. Both teneligliptin-treated groups showed significantly decreased PPG after each meal, 24-h mean glucose, and fasting plasma glucose (FPG) values compared with the placebo group. The differences between the teneligliptin 20 mg and placebo groups in changing 2-h PPG [LS means ± standard error (SE)] after each meal were −38.1 ± 7.8, −28.6 ± 9.2, and −36.1 ± 7.5 mg/dl at breakfast, lunch, and dinner, respectively (p < 0.001, p < 0.01, and p < 0.001, respectively). Both doses of teneligliptin increased postprandial plasma active GLP-1 concentrations compared with placebo after each meal, and DPP-4 inhibition was sustained over 24 h, with slightly stronger inhibition observed with the 20 mg dose. The pharmacokinetic profile was similar to that observed in healthy subjects. These PK/PD data provided the evidence required to support the dosing of teneligliptin 20 mg once daily [40].

6 Clinical Studies in Japan

6.1 Monotherapy

Efficacy data from relevant clinical trials are summarized in Table 4. The efficacy of teneligliptin was confirmed in

\[\text{Table 2 Pharmacokinetic profile of teneligliptin in special populations}\]

| Dose (mg/day) | n | C\text{max} (ng/mL)\text{a} | AUC\text{∞} (ng·h/mL)\text{a} | t\text{½} (h)\text{a} | Ratio to normal subjects (90% CI)\text{b} |
|---------------|---|-----------------------------|-----------------------------|----------------|---------------------------------------------|
|               |   |                             |                             |                | C\text{max}                          | AUC\text{∞} | t\text{½} |
| Renal impairment [34] |   |                             |                             |                |                                         |            |          |
| Normal        | 20| 8                           | 176.50 (38.42)              | 1772.7 (657.3) | 26.1 (5.0)                               | 1.08 (0.86, 1.35) | 1.25 (1.01, 1.54) | 1.00 (0.76, 1.31) |
| Mild          | 20| 8                           | 207.96 (53.31)              | 2234.2 (278.6) | 27.7 (7.9)                               | 1.12 (0.89, 1.40) | 1.68 (1.36, 2.07) | 1.36 (1.04, 1.79) |
| Moderate      | 20| 8                           | 203.63 (42.33)              | 3090.3 (868.6) | 36.0 (11.0)                               | 1.04 (0.82, 1.32) | 1.49 (1.19, 1.86) | 1.02 (0.77, 1.37) |
| Severe        | 20| 8                           | 191.63 (49.07)              | 2833.3 (652.3) | 29.8 (11.0)                               | 1.10 (0.82, 1.46) | 1.32 (1.06, 1.65) | 1.31 (0.98, 1.75) |
| Renal impairment with ESRD [34] |   |                             |                             |                |                                         |            |          |
| Normal        | 20| 8                           | 195.75 (43.28)              | 1843.1 (450.0) | 18.3 (5.7)                               | 0.85 (0.64, 1.13) | 1.17 (0.94, 1.47) | 1.19 (0.89, 1.59) |
| Pre-dialysis  | 20| 8                           | 164.45 (78.85)              | 2162.5 (488.1) | 22.7 (7.7)                               | 1.25 (0.97, 1.62) | 1.46 (1.22, 1.74) | 1.22 (0.94, 1.57) |
| Post-dialysis | 20| 8                           | 219.00 (118.91)             | 2472.9 (599.7) | 23.6 (5.8)                               | 1.38 (1.07, 1.78) | 1.59 (1.33, 1.90) | 1.38 (1.07, 1.78) |
| Hepatic impairment [36] |   |                             |                             |                |                                         |            |          |
| Normal        | 20| 8                           | 185.88 (84.65)              | 1548.8 (209.1) | 24.8 (6.4)                               | 1.01 (0.87, 1.16) | 1.09 (0.98, 1.22) | 1.05 (0.91, 1.22) |
| Mild          | 20| 8                           | 229.25 (86.16)              | 2207.9 (790.0) | 27.9 (7.1)                               | 1.12 (0.89, 1.40) | 1.68 (1.36, 2.07) | 1.36 (1.04, 1.79) |
| Moderate      | 20| 8                           | 247.63 (112.95)             | 2418.9 (505.8) | 30.9 (6.6)                               | 1.04 (0.82, 1.32) | 1.49 (1.19, 1.86) | 1.02 (0.77, 1.37) |
| Age (years) [31] |   |                             |                             |                |                                         |            |          |
| ≥45 to < 65   | 20| 12                          | 143.6c                      | 1637.6c         | 33.8c                                    | 1.01 (0.87, 1.16) | 1.09 (0.98, 1.22) | 1.05 (0.91, 1.22) |
| ≥65 to ≤ 75   | 20| 12                          | 142.7c                      | 1502.8c         | 32.1c                                    | 1.01 (0.87, 1.16) | 1.09 (0.98, 1.22) | 1.05 (0.91, 1.22) |

\[AUC\text{∞} \text{ area under the plasma concentration-time curve from time zero to infinity, } C\text{max} \text{ maximal plasma concentration, } ESRD \text{ end-stage renal disease, } t\text{½} \text{ elimination half-life, } CI \text{ confidence interval}\]

\[\text{aMean (standard deviation)}\]

\[\text{bResults are reported as ratios of geometric means and the respective 90% CIs}\]

\[\text{cData are expressed as least square means as these were the only data available}\]
two randomized, double-blind, placebo-controlled, parallel-group studies (phases II and III) in Japanese patients with T2DM inadequately controlled by diet and exercise [24, 25, 41]. In the phase II study (3000-A4), 324 patients were randomized to receive teneligliptin 10, 20, or 40 mg, or placebo, once daily before breakfast for 12 weeks [41]. The primary endpoint was the change in HbA1c from baseline to week 12. A significantly greater reduction in HbA1c was observed in all teneligliptin-treated groups compared with the placebo group from weeks 2 to 12. Differences between the teneligliptin 10, 20, or 40 mg groups and the placebo group for change in HbA1c {LS mean [95% confidence intervals (CIs)]} were − 0.9% (− 1.0, − 0.7), − 0.9% (− 1.1, − 0.7), and − 1.0% (− 1.2, − 0.9), respectively (all p < 0.001; baseline HbA1c values in the placebo, teneligliptin 10, 20, and 40 mg groups were 8.0%, 7.9%, 7.8%, and 7.7%, respectively). FPG and PPG were also significantly improved at week 12 [41].

The phase III study (3000-A5) [24, 25] sought to confirm the efficacy and safety of once daily, oral teneligliptin. Patients were randomized to teneligliptin 20 mg or placebo in a 12-week, double-blind phase. The difference [LS mean (95% CI)] between the teneligliptin and placebo groups for change in HbA1c (primary endpoint) was − 0.79% (− 0.94, − 0.64). FPG and 2-h PPG were also improved significantly at week 12 [24, 25]. The incidence of AEs and serious AEs did not differ significantly between the teneligliptin and placebo groups in both studies (Table 5a). In addition, adverse drug reactions (ADRs) did not increase in the teneligliptin versus placebo groups in both studies. Hypoglycemia was the only ADR reported by ≥ 3% (3000-A4 study), being 2.5% (n = 2), 0% (n = 0), 0% (n = 0), and 3.7% (n = 3) in the placebo and teneligliptin 10, 20, and 40 mg groups, respectively.

### 6.2 Combination Therapy/Long-Term Therapy

In phase III studies, the efficacy and safety of teneligliptin 20 mg in combination with a sulfonylurea (glimepiride; 3000-A6) [42] or pioglitazone (3000-A7) [43] were evaluated in randomized, double-blind, placebo-controlled, parallel-group studies (12 weeks); thereafter, all patients received teneligliptin once daily for a 40-week period. The phase IV study investigating teneligliptin in combination with insulin (3000-A15) was conducted in a similar manner, except that the double-blind period was 16 weeks followed

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**Table 3** Drug–drug interactions: effect on teneligliptin pharmacokinetics

| Combination | Dose (mg/day) | n | $C_{\text{max}}$ (ng/mL)$^a$ | $AUC_{\infty}$ (ng·h/mL)$^a$ | $t_{\frac{1}{2}}$ (h)$^a$ | Ratio to teneligliptin alone (90% CI)$^b$ |
|-------------|--------------|---|----------------|----------------|----------------|---------------------------------------------|
|             |              |   |                        |               |                | $C_{\text{max}}$ | $AUC_{\infty}$ | $t_{\frac{1}{2}}$ |
| Ketoconazole [37] |              |   |                        |               |                |               |               |               |
| Teneligliptin alone | 20           | 14 | 222.8 (43.5) | 2039.6 (265.3) | 20.7 (4.2) |               |               |               |
| Teneligliptin + ketoconazole | 20           | 14 | 308.8 (77.6) | 3064.1 (523.5) | 21.8 (3.9) | 1.37 (1.25, 1.50) | 1.49 (1.39, 1.60) | 1.06 (0.95, 1.18) |
| Metformin [38] |              |   |                        |               |                |               |               |               |
| Teneligliptin alone | 40           | 19 | 446.3 (62.7) | 3352.0 (538.5)$^c$ |               | 0.91 (0.85, 0.97) | 1.04 (1.00, 1.09) |
| Teneligliptin + metformin | 40           | 19 | 405.7 (63.9) | 3477.9 (459.7)$^c$ |               |               |               |               |
| Glimepiride [31] |              |   |                        |               |                |               |               |               |
| Teneligliptin alone | 40           | 16 | 545.4 (169.0) | 3970.0 (710.5) | 22.6 (5.9) |               |               |               |
| Teneligliptin + glimepiride | 40           | 16 | 523.1 (134.9) | 3663.6 (604.9) | 24.9 (5.5) | 0.97 (0.87, 1.09) | 0.93 (0.89, 0.96) | 1.10 (0.97, 1.26) |
| Pioglitazone [31] |              |   |                        |               |                |               |               |               |
| Teneligliptin alone | 40           | 16 | 503.3 (151.0) | 3820.2 (440.6) | 24.7 (5.5) |               |               |               |
| Teneligliptin + pioglitazone | 40           | 16 | 549.7 (109.0) | 3836.1 (412.1) | 22.7 (5.3) | 1.12 (0.98, 1.27) | 1.01 (0.97, 1.05) | 0.92 (0.82, 1.03) |
| Canagliflozin [39] |              |   |                        |               |                |               |               |               |
| Teneligliptin alone | 40           | 18 | 458.3 (78.8) | 3781.2 (646.3) | 24.0 (6.5) |               |               |               |
| Teneligliptin + canagliflozin | 40           | 18 | 444.9 (66.6) | 3699.5 (743.6) | 22.1 (4.8) | 0.98 (0.90, 1.06) | 0.98 (0.93, 1.02) | 0.93 (0.82, 1.06) |

$AUC_{\infty}$ area under the plasma concentration time-curve from time zero to infinity, $AUC_{24}$ AUC from time zero to 24 h, $C_{\text{max}}$ maximal plasma concentration, $t_{\frac{1}{2}}$ elimination half-life, CI confidence interval

$^a$Mean (standard deviation)

$^b$Results are reported as ratios of geometric means and the respective 90% confidence intervals

$^c$AUC$_{24}$
| Study name | Phase | Monotherapy/concomitant therapy | Treatment period (weeks) | Design | Dose | N  | Baseline, mean (SD) or mean [95% CI] | Change from baseline, LS mean (SE) or mean [95% CI] | Difference in HbA1c from placebo, LS mean [95% CI] | p value (vs. placebo) | ClinicalTrial.gov registration number |
|------------|-------|-------------------------------|--------------------------|--------|------|-----|-------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------|---------------------------------|
| 3000-A4 [41] | II | Monotherapy | 12 | Double-blind | Placebo | 80 | 8.0 (0.7) | 0.1 (0.1) | -0.9 | [-1.0, -0.7] | <0.001 | NCT00628212 |
| 3000-A5 [24, 25] | III | Monotherapy | 12 | Double-blind | Placebo | 104 | NDd | 0.17 (0.05) | -0.62 (0.05) | -0.79 | [-0.94, -0.64] | <0.0001 | NCT00998881 |
| 3000-A6 [42] | III | Add on to glimepiride | 12 | Double-blind | Placebo | 98 | 8.4 (0.8) | 0.3 (0.1) | -0.7 | [-1.0, -1.2, -0.9] | <0.001 | NCT00974090 |
| 3000-A7 [43] | III | Add on to pioglitazone | 12 | Double-blind | Placebo | 101 | 7.9 (0.8) | -0.2 (0.0) | -0.7 | [-1.0, -0.9] | <0.001 | NCT01026194 |
| 3000-A8/A14 [45] | III | Monotherapy/combination therapy | 52 | Open-label | All patientsb | 702 | 7.87 (0.77) | -0.72 [-0.77, -0.67] | -0.63 [-0.70, -0.57] | NCT02314637/ NCT01301833 |
| 3000-A15 [44] | IV | Add on to insulin | 16 | Double-blind | Placebo | 71 | 8.73 (0.81) | -0.07 (0.08) | -0.80 | [-1.0, -0.58] | <0.001 | NCT02081599 |
| 3000-A10 [46] | IV | Monotherapy | 16 | Double-blind | Placebo | 77 | 8.70 (0.81) | -0.87 (0.08) | -0.88 | [-1.08, -0.68] | <0.001 | NCT00988881 |
| 3000-A11 | IV | Add on to insulin | 16 | Double-blind | Placebo | 36 | 8.70 (0.81) | -0.88 | [-1.08, -0.68] | <0.001 | NCT00988881 |
| 3000-A12 | IV | Add on to insulin | 16 | Double-blind | Placebo | 52 | 8.70 (0.81) | -0.88 | [-1.08, -0.68] | <0.001 | NCT00988881 |
Table 4 (continued)

| Study name       | Phase | Monotherapy/concomitant therapy | Treatment period (weeks) | Design      | Dose          | N       | Baseline, mean (SD) or mean [95% CI] | Change from baseline, LS mean (SE) or mean [95% CI] | Difference in HbA1c from placebo, LS mean [95% CI] | p value (vs. placebo) | ClinicalTrial.gov registration number |
|------------------|-------|---------------------------------|--------------------------|-------------|---------------|---------|--------------------------------------|------------------------------------------------|---------------------------------------------------|-----------------------|--------------------------------------|
| MP_C301 [48]     | III   | Add on to biguanide             | 16                       | Double-blind | Placebo/TNL 20 mg | 68      | 7.72 (0.65)                         | −0.12 (0.09)                                     | −0.78 [−0.95, −0.61]                                        | <0.0001               | NCT01805830 |
|                  |       |                                 |                          |             | TNL 20 mg       | 136     | 7.79 (0.80)                         | −0.90 (0.07)                                     |                                                   |                      |                                      |
| MP_C302 [47]     | III   | Monotherapy                     | 24                       | Double-blind | Placebo/TNL 20 mg | 43      | 7.77 (0.81)                         | 0.03 (0.12)                                      | 0.94 [−1.22, −0.65]                                       | <0.0001               | NCT01798238 |
|                  |       |                                 |                          |             | TNL 20 mg       | 99      | 7.63 (0.69)                         | −0.90 (0.09)                                     |                                                   |                      |                                      |
| MP-513-E07 [49]  | II    | Add on to biguanide             | 24                       | Double-blind | Placebo/TNL 20 mg | 88      | 7.88 [6.1, 9.8]                     | −0.28 (0.07)                                     | 0.48 [−0.67, −0.29]                                       | <0.001                | NCT00971243 |
|                  |       |                                 |                          |             | TNL 20 mg       | 91      | 7.96 [6.7, 10.0]                    | −0.76 (0.07)                                     |                                                   |                      |                                      |
| MT2412-J02 [50]  | III   | for FDC                        | 24                       | Double-blind | Placebo/TNL 20 mg | 77      | 8.09 (0.85)                         | 0.00 (0.08)                                      | −0.94 [−1.16, −0.72]                                      | <0.001                | NCT02354222 |
|                  |       |                                 |                          |             | TNL 20 mg       | 77      | 7.98 (0.80)                         | −0.94 (0.08)                                     |                                                   |                      |                                      |

αGI α-glucosidase inhibitor, CI confidence interval, FDC fixed-dose combination, JDS Japan Diabetes Society, LS least square, ND no data, NGSP National Glycohemoglobin Standardization Program, SD standard deviation, SE standard error, TNL teneligliptin

* Patients who completed the double-blind period entered the open-label period, in which placebo was switched to TNL 20 mg (placebo/TNL group) or TNL was continued (TNL/TNL group). Patients with HbA1c ≥ 7.3% after week 24, regardless of prior treatment with placebo or TNL, were uptitrated to TNL 40 mg at the next visit if there were no safety concerns. The TNL dose remained stable from week 40 to the end of the study period.

* In patients with HbA1c ≥ 7.3% (3000-A8) or ≥ 7.4% (3000-A14) after week 24, TNL was uptitrated to 40 mg at the next visit if there were no safety concerns. The TNL dose remained stable from week 40 to the end of the study period.

* Patients who completed the double-blind period entered the open-label period, in which placebo was switched to TNL 20 mg (placebo/TNL group) or TNL was continued (TNL/TNL group). Patients with HbA1c ≥ 7.5% after week 28, regardless of prior treatment with placebo or TNL, were uptitrated to TNL 40 mg at the next visit if there were no safety concerns. The TNL dose remained stable from week 40 to the end of the study period.

* The baseline HbA1c data (National Glycohemoglobin Standardization Program [NGSP] value) are not available: the mean (SD) of HbA1c (Japan Diabetes Society [JDS] value) is 7.58 (0.85) and 7.53 (0.78) in the placebo and TNL group, respectively.

* Last observation carried forward was used in all studies except MP_C302.

* Change from week 12, switching to TNL in the placebo group, to week 52.

* Change from week 16, switching to TNL in the placebo group, to week 52.
by a 36-week open-label period [44]. Patients with HbA1c ≥ 7.3% after week 24 (3000-A6, A7) [42, 43] or ≥ 7.5% after week 28 (3000-A15) [44] were uptitrated to teneligliptin 40 mg at the next visit if there were no safety concerns. Teneligliptin as an add-on therapy to these drugs produced greater HbA1c-lowering activity than placebo, with sustained glucose-lowering effects maintained throughout the studies (up to 52 weeks). The safety profile did not differ between the placebo and teneligliptin groups, although hypoglycemia was somewhat higher when teneligliptin was administered with insulin (Table 5a).

Two long-term, open-label studies were performed in Japanese T2DM patients. The first was a long-term study of teneligliptin, both as monotherapy and in combination with glimepiride (3000-A8), and the second was a long-term study of teneligliptin, both as monotherapy and in combination with a glinide, biguanide, or α-glucosidase inhibitor (3000-A14). A post hoc pooled analysis using data from two phase III clinical studies involving 702 Japanese patients (3000-A8/A14) was performed [45]. The long-term use of teneligliptin as monotherapy or combination therapy significantly improved hyperglycemia in Japanese patients with T2DM, with glucose-lowering effects maintained over 52 weeks (Table 4). No change or a slight increase in body weight at the end of 52 weeks was observed.

As for long-term safety, the incidence of hypoglycemia was higher when teneligliptin was used in combination with sulfonylurea or insulin (10.7% and 20.0%, respectively) compared with teneligliptin monotherapy or in other combination therapies (1.1–5.0%) [42–45]. Overall, the long-term treatment of teneligliptin was well tolerated (Table 5b).

In a post hoc pooled analysis of two 52-week, open-label, phase III clinical trials (3000-A8/A14) that examined the treatment response when teneligliptin dose was increased

Table 5  Summary of key clinical trial results: teneligliptin safety

| Study type | Phase II (monotherapy) | Phase III (monotherapy) | Phase III (combination therapy) | Phase IV (combination therapy) |
|------------|-----------------------|-------------------------|---------------------------------|-------------------------------|
|            | 3000-A4 [41] [n (%)]  | 3000-A5 [24] [n (%)]  | 3000-A6 [42] [n (%)]  | 3000-A7 [43] [n (%)]  | 3000-A15 [44] [n (%)]  |
| Placebo    | TNL                   | Placebo                | SU                              | SU + TNL                    | INSULIN                  |
| N          | 80                    | 79                     | 104                             | 99                           | 101                      | 103                      |
| AE         | 44 (55.0)             | 40 (50.6)              | 66 (63.5)                       | 62 (62.6)                   | 61 (62.2)                | 62 (64.6)                |
| ADR        | 6 (7.5)               | 2 (2.5)                | 5 (4.8)                         | 1 (1.0)                     | 6 (6.1)                  | 8 (8.3)                  |
| SAE        | 1 (1.3)               | 0 (0.0)                | 4 (3.8)                         | 0 (0.0)                     | 2 (2.0)                  | 0 (0.0)                  |
| Discontinued because of AE | 2 (2.5) | 1 (1.3) | 2 (1.9) | 2 (2.0) | 2 (2.0) | 1 (1.0) |
| Hypoglycemia | 3 (3.8)             | 1 (1.3)                | 1 (1.0)                         | 1 (1.0)                     | 1 (1.0)                  | 1 (1.0)                  |

| Study type | Phase III (combination therapy) | Phase III (combination therapy) |
|------------|---------------------------------|---------------------------------|
|            | 3000-A8/A14 [45] [n (%)]       | 3000-A8/A14 [45] [n (%)]       |
| TNL        | GLI + TNL                       | BG + TNL                       |
| N          | 363                             | 320 (88.2)                     |
| AE         | 80 (90.0)                       | 72 (90.0)                      |
| ADR        | 31 (8.5)                        | 10 (12.5)                      |
| SAE        | 20 (5.5)                        | 3 (3.8)                        |
| Discontinued because of AE | 11 (3.0) | 5 (6.3) | 5 (5.3) | 5 (6.7) | 9 (4.5) | 19 (6.8) |
| Hypoglycemia | 9 (2.5)             | 4 (5.0)                        | 1 (1.1)                         | 1 (1.3)                     | 3 (1.5)                  | 30 (10.7)                | 28 (20.0)               |

Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J), version 11.1, 13.0, 13.1, and 15.0
ADR adverse drug reaction, AE adverse event, αGI α-glucosidase inhibitor, BG biguanide, GLI glinide, n number of patients, PIO pioglitazone, SU sulfonylurea, SAE serious adverse event, TNL teneligliptin

*aPooled analysis using data from the 3000-A7 and A8 studies

△ Adis
from 20 to 40 mg at week 28 \((n = 204)\), no increasing trends in the incidences of AEs or hypoglycemia were observed (weeks 28–52 vs. weeks 0–28). Although the incidence of serious AEs was elevated with higher doses of teneligliptin, none of these AEs were related to the study drug. While the HbA1c reduction in the dose-increased population was low (approximately \(-0.1\%\)), 52.9% of patients showed a response to the teneligliptin dose increase (HbA1c change less than or equal to \(-0.1\%\)). Therefore, a dose increase to 40 mg may be an important therapeutic option for some patients [46].

In a subgroup analysis of a 52-week, pooled study (3000-A8/A14) stratified by age (<65 and ≥65 years), there were no differences in efficacy and safety profiles between subgroups. Moreover, no elevation in the incidence of hypoglycemia was observed in elderly patients treated with teneligliptin compared with non-elderly patients [45]. Similarly, when teneligliptin was used as an adjunct to insulin (3000-A15), there was no trend towards a higher incidence of hypoglycemia in patients aged <65 years versus those aged ≥65 years [44].

7 Data from Non-Japanese Studies

The 24-week efficacy of teneligliptin was assessed in Korean patients with T2DM inadequately controlled with diet and exercise (MP_C302) [47]. Patients were randomized to receive placebo or teneligliptin 20 mg once daily for 24 weeks. At week 24, the difference in change in HbA1c from baseline \([LS\ mean (95\%\ CI)]\) between the teneligliptin and placebo groups was \(-0.94\%\) \((-1.22, -0.65)\) \((p < 0.0001)\). In addition, two other studies assessed the efficacy and safety of teneligliptin plus metformin in the treatment of T2DM in Korean (MP_C301) and European patients (MP-513-E07) [48, 49]. This combination has complementary effects and the potential to provide better blood glucose control than metformin alone. Teneligliptin plus metformin was well tolerated and significantly reduced HbA1c and FPG versus placebo in both studies.

8 Development of a Fixed-Dose Combination Drug

The efficacy and safety of teneligliptin as add-on therapy to canagliflozin was evaluated in patients with T2DM who had inadequate glycemic control with canagliflozin monotherapy (MT2412-J02). Patients were randomized to receive teneligliptin 20 mg \((n = 77)\) or placebo \((n = 77)\) once daily. Teneligliptin as an add-on therapy to canagliflozin provided a greater HbA1c-lowering effect than placebo \([between-group\ difference\ = -0.94\%\ (-1.16, -0.72);\ p < 0.001]\) by week 24 [50]. Similar results were reported when canagliflozin was administered as an add-on therapy to teneligliptin over 24 weeks in a double-blind, placebo-controlled study \([difference\ versus\ placebo\ in\ the\ change\ from\ baseline\ \(-0.88\%\ (-1.15, -0.60);\ p < 0.001]\) [51] or 52 weeks in a long-term, open-label study \([difference\ versus\ baseline\ \(-0.99\%\ (-1.12, -0.85))\] [52]. No new safety concerns were identified during the studies. A drug–drug interaction was not observed, as described in Sect. 4.4. Results from these trials led the Japanese PMDA, from July 2017, to approve the dual therapy (teneligliptin/canagliflozin) as a FDC for clinical use in T2DM. This was the first approval of a DPP-4 inhibitor/SGLT-2 inhibitor FDC tablet in Japan.

9 Postmarketing Surveillance

Although the efficacy and safety profiles of teneligliptin were characterized in clinical trials, these studies were relatively short-term (12–52 weeks). Therefore, to assess long-term safety and efficacy, the 3-year, postmarketing surveillance (PMS) RUBY (exploRing the long-term efficacy and safety including cardiovascular events in patients with type 2 diaBetes treated by teneligliptin in the real-world; Japi-cCTI-153047) is being performed in more than 10,000 Japanese patients. Interim results (data cut-off date 28 June 2017) are shown in Table 6 [53]. Safety data were available from 10,532 Japanese T2DM patients \(6338\ males/4194\ females\) with a median administration period of 731 days. Overall, ADRs and serious ADRs were reported in 364 \(3.46\%\) and 91 patients \(0.86\%\), respectively, and hypoglycemia, constipation, and hepatic function abnormal were the most common ADRs. Hypoglycemia \(0.32\%\) and constipation \(0.27\%\) were the most common ADRs reported in pooled data from clinical trials \(2.6\%\ and 0.9\%\, respectively\); however, hepatic function abnormal, albeit mild in severity, was reported more frequently in this survey \(0.24\%\) than in the pooled analysis \(0.1\%\) [53]. Teneligliptin, administered as monotherapy or as combination therapy for up to 2 years, reduced HbA1c from 3 months of treatment, with sustained glucose-lowering effects observed over 2 years. No change in mean bodyweight was observed. A subgroup analysis was also performed across three age groups \(<65\ years;\ 65–<75\ years;\ and\ ≥75\ years\);\ efficacy\ and\ safety\ profiles\ did\ not\ differ\ markedly\ among\ the\ three\ age\ groups\ (Table 6).

A further interim subgroup analysis was performed on data obtained from patient case reports in the RUBY surveillance to verify the long-term safety and efficacy of teneligliptin in Japanese patients with T2DM and impaired renal function [54]. At the start of teneligliptin treatment, patients were classified into G1–G5 stages of chronic kidney disease (CKD) according to estimated glomerular filtration rate.
The Unique Pharmacological and Pharmacokinetic Profile of Teneligliptin

10 Efficacy in Patients with Renal Impairment

Because teneligliptin can be used in T2DM patients with renal impairment, including those on hemodialysis, without the need for dose adjustment, the efficacy and safety of teneligliptin in T2DM patients with CKD requiring hemodialysis has been assessed in several small observational studies [55–59]. Otsuki et al. showed that administration of teneligliptin 20 mg (n = 14) significantly reduced glycated albumin (GA) compared with controls at week 28 (−3.1%, p < 0.05; baseline means of 21.9% in the control group and 21.1% in the teneligliptin group) [55]. Furthermore, Homma et al. showed that treatment with teneligliptin (n = 15) over 12 weeks markedly reduced FPG compared with controls (n = 10) [56]. Treatment with teneligliptin was well tolerated in both studies, with no episodes of hypoglycemia reported.

Wada et al. showed that 4-week teneligliptin treatment (n = 10; patients had a GA level ≥ 18.3%) improved blood glucose AUC as assessed by continuous glucose monitoring (CGM) on both hemodialysis and non-hemodialysis days (both p = 0.004) and significantly reduced GA and FPG values, without severe hypoglycemia [57]. In a randomized, crossover study in T2DM patients (n = 13) with CKD, Tanaka et al. showed that teneligliptin 20 mg/day or linagliptin 5 mg/day (administered once daily for 6 days and then switching for a further 6 days) had comparable beneficial effects on mean amplitude of glucose excursion, 24-h mean sensor glucose levels, and AUC for sensor glucose levels ≥ 180 mg/dL (AUC ≥ 180), with a comparable incidence of...

Table 6  Safety and efficacy profile of teneligliptin in the RUBY postmarketing surveillance program [53]

| Categories                                | All patients [n (%)] | <65 years [n (%)] | 65 to < 75 years [n (%)] | ≥ 75 years [n (%)] |
|-------------------------------------------|---------------------|------------------|-------------------------|-----------------|
| Safety (safety analysis set)              |                     |                  |                         |                 |
| ADRs (serious + non-serious)              |                     |                  |                         |                 |
| No. of patients                           | 10,532              | 4527             | 3320                    | 2685            |
| ADRs                                      | 364 (3.46)          | 135 (2.98)       | 133 (4.01)              | 96 (3.58)       |
| All hypoglycemiaa                         | 34 (0.32)           | 9 (0.20)         | 18 (0.54)               | 7 (0.26)        |
| Hypoglycemia                              | 25 (0.24)           | 5 (0.11)         | 15 (0.45)               | 5 (0.19)        |
| Blood glucose decreased                   | 8 (0.08)            | 4 (0.09)         | 3 (0.09)                | 1 (0.04)        |
| Hypoglycemic unconsciousness              | 1 (0.01)            | 0 (0.00)         | 0 (0.00)                | 1 (0.04)        |
| Constipation                              | 28 (0.27)           | 10 (0.22)        | 12 (0.36)               | 6 (0.22)        |
| Hepatic function abnormal                 | 25 (0.24)           | 15 (0.33)        | 4 (0.12)                | 6 (0.22)        |
| Serious ADRs                              | 91 (0.86)           | 22 (0.49)        | 34 (1.02)               | 35 (1.30)       |
| All hypoglycemiaa                         | 9 (0.09)            | 2 (0.04)         | 4 (0.12)                | 3 (0.11)        |
| Hypoglycemia                              | 7 (0.07)            | 2 (0.04)         | 3 (0.09)                | 2 (0.07)        |
| Blood glucose decreased                   | 1 (0.01)            | 0 (0.00)         | 1 (0.03)                | 0 (0.00)        |
| Hypoglycemic unconsciousness              | 1 (0.01)            | 0 (0.00)         | 0 (0.00)                | 1 (0.04)        |
| Efficacy (efficacy analysis set)          |                     |                  |                         |                 |
| HbA1c (%)                                 |                      |                  |                         |                 |
| No. of patients at the start              | 9296                | 3995             | 2977                    | 2324            |
| No. of patients at 2 years                | 4549                | 1966             | 1498                    | 1085            |
| Change from baseline to 2 years           | −0.75 (1.36)        | −0.72 (0.02)     | −0.76 (0.02)            | −0.77 (0.03)    |
| LS mean (SE)                              |                      |                  |                         |                 |

Medical Dictionary for Regulatory Activities/Japanese (MedDRA/J), version 20.0

ADRs adverse drug reactions, LS least square, SE standard error, SD standard deviation

a ‘All hypoglycemia’ included hypoglycemia, blood glucose decreased, and hypoglycemic unconsciousness
hypoglycemia [58]. Finally, Yajima et al. assessed the efficacy of once-daily teneligliptin 20 mg, when coadministered with insulin in 21 T2DM patients on hemodialysis, by CGM and found that coadministration of teneligliptin and insulin significantly reduced median (interquartile range) total daily insulin dose from 18 U (9–24) to 6 U (0–14) \( (p = 0.049) \) [59]. Collectively, these results suggest that teneligliptin is a valuable treatment option for glycemic control in patients with T2DM undergoing hemodialysis.

### 11 Effects of Teneligliptin on Oxidative Stress and Endothelial Function

Teneligliptin appears to have multifaceted effects on endothelial function, via its antioxidant capabilities, anti-inflammatory properties, antiplatelet activity, and hydroxyl-radical (-OH) scavenging properties. Oxidative stress induced by elevated glucose levels facilitates cardiovascular endothelial damage in T2DM [8, 9]. Two studies sought to verify the potential protective actions of teneligliptin or teneligliptin in combination with GLP-1, in endothelial cells exposed to high glucose (HG) [60, 61]. In both studies, human umbilical vein endothelial primary cells (HUVECs) were exposed to normal glucose (NG; 5 mmol/L) or HG (25 mmol/L) for 21 days, or to HG for 14 days followed by NG for 7 days to mimic a high-metabolic memory state (HM). The cells were continually treated with either teneligliptin (0.1, 1.0, and 3.0 μmol/L) or sitagliptin (0.5 μmol/L) [60], or with teneligliptin (3.0 μmol/L) [61]. Teneligliptin demonstrated antioxidant properties by reducing reactive oxygen species (ROS) levels and initiating the transcriptional cascade of antioxidant genes at the cellular level. Of note, the efficacy of teneligliptin 0.1 μmol/L at reducing ROS was similar to that observed with sitagliptin 0.5 μmol/L, suggesting that teneligliptin has more potent antioxidant properties. Moreover, it enhanced proliferation and endoplasmic reticulum homeostasis, reduced apoptosis in HG conditions, and overcame the metabolic memory effect [60, 61]. GLP-1 has a vascular protective effect, which enhances the antioxidative pathway; however, hyperglycemia reduces its positive effect, a phenomenon known as ‘GLP-1 endothelial resistance’ [62]. The combination of teneligliptin and GLP-1 enhanced the antioxidant response of teneligliptin in HG- and HM-exposed HUVECs, which suggests that the simultaneous administration of these two drugs can counter GLP-1 endothelial resistance [61].

In addition to inducing the transcriptional cascade of antioxidant genes, teneligliptin has -OH scavenging properties. While teneligliptin does not scavenge \( \cdot \)O\(_2\)\(^-\), it has been shown to scavenge \( \cdot \)OH. This was confirmed by X-band electron spin resonance spectroscopy using a spin trap agent to detect free radicals and estimate radical scavenging properties and, in vivo, by assessing the effect of oral teneligliptin on urinary excretion of 8-hydroxy-2\(^\prime\)-deoxyguanosine (8-OHdG) in DPP-4-deficient diabetic rats [63]. Teneligliptin scavenged -OH in a dose-dependent manner, changing its structure to form metabolite M1, which is also found in vivo. Teneligliptin was shown to have greater -OH scavenging activity than glutathione, and had direct -OH scavenging properties that are not attributable to DPP-4 inhibition because it was observed in DPP-4-deficient rats. The novel chemical structure of teneligliptin may be responsible for its -OH scavenging properties. In contrast, the DPP-4 inhibitors alogliptin and linagliptin do not exhibit \( \cdot \)O\(_2\)\(^-\) and -OH scavenging properties [63].

Oxidative stress in perivascular adipose tissue (PVAT) contributes to systemic inflammation and may promote endothelial dysfunction and atherosclerosis [64]. Oral administration of teneligliptin (60 mg/kg/day) to apolipoprotein-E-deficient (ApoE KO) mice for 20 weeks reduced the expression of inflammatory molecules in PVAT, and inhibited atherosclerosis compared with vehicle. Furthermore, the administration of teneligliptin for 8 weeks ameliorated endothelium-dependent vasodilation and reduced oxidative stress, as determined by urinary 8-OHdG excretion \( (p<0.05) \), compared with vehicle [64]. Moreover, in spontaneous hypertensive rats, SHR/Ndmcr-cp (cp/cp), long-term treatment with teneligliptin (10 mg/kg/day for 12 weeks) significantly attenuated endothelial dysfunction through the upregulation of endothelium-derived nitric oxide synthase mRNA [65].

A case-control study by Sagara et al. sought to elucidate the effect of teneligliptin on oxidative stress and endothelial function in Japanese patients with T2DM and CKD. Forty-five patients with T2DM and CKD who had received sitagliptin for at least 12 months were randomized to continue sitagliptin \( (n = 23) \) or switch to teneligliptin \( (n = 22) \) for 24 weeks. From baseline to 24 weeks, no significant between-group differences were noted regarding changes in HbA1c, eGFR, and urinary albumin excretion; however, the switch to teneligliptin was associated with significantly improved values for reactive hyperemia index (RHI), a measure of endothelial function. The antioxidant activity of teneligliptin was demonstrated by decreased levels of derivatives of reactive oxygen metabolites, a novel marker of oxidative stress; this antioxidant effect was strongly linked with the improved RHI values. The suppression by teneligliptin of glucose fluctuations that induce oxidative stress, together with its antioxidant effects, may have contributed to the improvement in vascular function [66].

In a clinical study involving 103 individuals with T2DM, 47 of whom were receiving hemodialysis, teneligliptin 20 mg administered once daily for 3 months significantly
reduced plasma levels of soluble P-selectin, platelet-derived microparticles, and plasminogen activator inhibitor 1 compared with baseline levels, particularly in those receiving hemodialysis, and significantly increased adiponectin levels [67]. Similarly, Hashikata et al. showed that the administration of teneligliptin in T2DM patients (n = 29) for 3 months resulted in improvements in left ventricular function (E/e ratio) and endothelial function (based on reactive hyperemia peripheral arterial tonometry [RH-PAT] value), and increased serum adiponectin levels compared with baseline levels, suggesting possible cardioprotective effects [68]. The mechanism by which teneligliptin increases circulating adiponectin remains to be determined.

12 Comparison with Other DPP-4 Inhibitors

DPP-4 inhibitors have differing pharmacokinetic and pharmacodynamic properties that may be clinically relevant in certain patient groups. The main pharmacokinetic differences between DPP-4 inhibitors marketed in Japan are summarized in Table 7 [69–82].

The elimination half-lives of DPP-4 inhibitors are widely variable, with half-lives ranging from approximately 2 h to more than 100 h (Table 7). DPP-4 inhibitors vary in dosing regimens (once-daily, twice-daily, or once-weekly administration) according to their half-lives.

A key difference in the pharmacokinetic properties of DPP-4 inhibitors is their varied elimination routes, and this difference is related to the need for dose adjustments in T2DM patients with renal dysfunction. Whereas most DPP-4 inhibitors predominantly undergo renal excretion, linagliptin is excreted mostly unchanged in feces via biliary action [81], and teneligliptin is eliminated by hepatic metabolism mediated by CYP3A4 or FMO3, or excreted from the kidney in an unchanged form; thus, linagliptin and teneligliptin can be administered without dose adjustments in T2DM patients with renal impairment.

Teneligliptin appears to be less affected by CYP3A4 and P-glycoprotein inhibitors, because, even if such inhibition occurs, teneligliptin is still excreted via the kidneys and metabolized by FMO3. Conversely, the AUC from time zero to 24 h (AUC_{24}) of linagliptin used in combination with ritonavir, a CYP3A4 and P-glycoprotein inhibitor, increased twofold compared with the AUC_{24} for linagliptin monotherapy, while the AUC during the dosing interval at steady-state (AUC_{T,ss}) of linagliptin used in combination with rifampicin, a CYP3A4 and P-glycoprotein inducer, decreased by 40% [81]. These effects may be the result of the inhibition/induction of gastrointestinal P-glycoprotein [81, 83] and the partial inhibition/induction of CYP3A4. Therefore, linagliptin needs to be used with caution in combination with CYP inhibitors or inducers owing to possible safety risks and the potential for reduced efficacy [14, 72, 84]. Similarly, metabolism of saxagliptin is mediated via CYP3A4/5; thus, concomitant use of CYP3A4/5 inhibitors and inducers can alter its pharmacokinetics, and dose reductions should be considered when saxagliptin is used in combination with CYP3A4 inhibitors [14, 74, 85]. Consideration of potential drug–drug interactions is particularly relevant for elderly patients in whom polypharmacy is common, raising the potential for diminishing treatment efficacy or increasing the risk of AEs [86].

13 Clinical Implications

Teneligliptin has unique pharmacokinetic and pharmacological properties. From a pharmacokinetic perspective, teneligliptin is metabolized by CYP3A4 and FMO3, or excreted from the kidney in an unchanged form. Because of its multiple elimination pathways, dose adjustment is not needed in patients with hepatic or renal impairment, and it is considered to have a low potential for drug–drug interactions. Elderly T2DM patients, especially those aged ≥ 80 years, frequently have reduced renal function [87]. Moreover, elderly T2DM patients commonly have many medications prescribed [88]. As for FMO, a few drugs are metabolized by FMO (approximately 2%) [89, 90] and the enzyme activity of FMO3 does not differ between non-elderly (30–59 years) and elderly (60–79 years) populations [91]. Therefore, FMO is an important back-up mechanism. The involvement of multiple metabolic enzymes, together with multiple elimination pathways, may make teneligliptin less susceptible to age-related pharmacokinetic changes and drug–drug interactions. In accordance with these characteristics, the pharmacokinetic profile of teneligliptin does not differ between non-elderly (45–64 years) and elderly (65–75 years) populations. Actually, the safety and efficacy profile of teneligliptin appears to be unaffected by age in clinical studies or real-world clinical data (PMS). The pharmacokinetic profile in broader populations, such as individuals aged ≥ 75 years, has not yet been evaluated, and further research is needed to investigate the pharmacokinetic profile of teneligliptin in very elderly patients.

In addition to its DPP-4 inhibitory effect, teneligliptin has antioxidative properties, which induce the antioxidant cascade, as well as -OH scavenging properties. Furthermore, teneligliptin has shown endothelial protective effects in several non-clinical and clinical studies. Because teneligliptin has been shown to overcome the metabolic memory effect in endothelial cells [60, 61], early treatment with teneligliptin may be useful for preventing diabetic complications, in addition to its glucose-lowering effect. Collectively, these unique pharmacokinetic and pharmacological properties of...
## Table 7 Pharmacokinetic differences among dipeptidyl-peptidase-4 inhibitors

|                  | Teneligliptin | Sitagliptin [69] | Vildagliptin [70] | Alogliptin [71] | Linagliptin [72] | Anagliptin [73] | Saxagliptin [74] | Trelagliptin [75] | Omarigliptin [76] |
|------------------|---------------|------------------|-------------------|-----------------|-----------------|-----------------|----------------|----------------|-----------------|
| **Standard dose** | Once daily 20 mg | Once daily 50 mg | Twice daily 50 mg | Once daily 25 mg | Once daily 5 mg  | Twice daily 100 mg | Once daily 5 mg  | Once weekly 100 mg | Once weekly 25 mg |
| **Dose increasing** | Yes (40 mg)   | Yes (100 mg)    | No                | No              | No              | Yes (200 mg)    | No             | No             | No              |
| **Dose adjustment** | No            | Yes (12.5, 25 mg) | Yes (50 mg, once daily) | Yes (6.25, 12.5 mg) | No             | Yes (once daily, 100 mg) | Yes (2.5 mg) | Yes (50 mg) | Yes (12.5 mg) |
| **t₁/₂, h** | 24.2 (5.0) | 11.4 (2.4) | 1.77 (0.23) | 17.1 (2.0) | 105 (8.26)       | 2.02 (0.208) | 6.20 (3.11) | 6.47 (0.98) | 54.3 (7.9) | 38.89 (25.78) |
| **Excretion** | Metabolism/renal excretion | Renal excretion | Metabolism | Renal excretion | Bile excretion | Metabolism/renal excretion | Renal excretion | Renal excretion | Renal excretion |
| **Metabolic enzyme** | CYP3A4 FMO3 | Minor | Non-CYP | Minor | Minor | Minor | Minor | Minor | No |
| **Renal impairment (AUC)** | 1.17- to 1.68-fold | 1.61- to 4.50-fold | 1.31- to 2.33-fold | 1.7- to 3.8-fold | 1.22- to 1.56-fold | 1.65- to 3.22-fold | 1.16- to 2.08-fold | 1.56- to 3.68-fold | 0.94- to 1.97-fold |
| **Drug–drug interactions (AUC)** | 1.49-fold (ketoconazole) | 1.29-fold (cyclosporine) | 2.01-fold (ritonavir) [81] | 1.81-fold (probenecid) | 2.45-fold (ketoconazole) [82] |

AUC area under the plasma concentration time-curve, CYP cytochrome P450, FMO3 flavin-containing monooxygenase 3, SD standard deviation, t₁/₂, elimination half-life

a Approval dose in Japan

b Geometric mean
Teneligliptin make it a valuable drug option for the treatment of a broad range of T2DM patients in clinical practice.

An FDC tablet of teneligliptin/canagliflozin was also approved in Japan. Owing to the differences in their mechanisms of action, teneligliptin and canagliflozin act in a complementary manner. Body weight management is important for maintaining good long-term glycemic control with DPP-4 inhibitors [92, 93], and the SGLT2 inhibitor canagliflozin reduces not only blood glucose but also body weight [94]; thus, the FDC of teneligliptin/canagliflozin also represents a useful therapeutic option for T2DM patients, with additional benefits such as adherence.

14 Conclusions

Teneligliptin demonstrates potent and sustained effects on glycemic control in patients with T2DM, both as a monotherapy and in combination with other antidiabetic drugs. Unlike many other DPP-4 inhibitors, the multiple elimination pathways of teneligliptin enable treatment to be administered to patients with renal or hepatic impairment without dose adjustment. Moreover, teneligliptin has pleiotropic effects, independent of glycemic control, which may lead to improved endothelial function and reduced vascular oxidative stress. These unique characteristics make teneligliptin a particularly viable consideration for a diverse range of T2DM patients, including those with renal impairment or elderly subjects.

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Author Contributions HI, TM, and MG conducted the literature search, discussed contribution points, and reviewed the manuscript. AC and VDN contributed discussion points relating to clinical implications, and reviewed the manuscript.

Compliance with Ethical Standards

Conflict of interest Antonio Ceriello has received research grants from Mitsubishi Tanabe Pharma Co., AstraZeneca, Eli Lilly, and Novartis; consulting fees or honorarium from AstraZeneca, Boehringer Ingelheim, DOC Generici, Eli Lilly, Janssen, Novo Nordisk, and OM Pharma; and payment for lectures, including service on speakers bureaus, from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Sanofi, and Takeda. Valeria De Nigris has no conflicts of interest to declare. Hiroaki Iijima, Takahiro Matsui, and Maki Gouda are employees of Mitsubishi Tanabe Pharma Corporation.

Ethical approval For this review, consent was not required.

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