Report on the Deliberation Results

April 27, 2012

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

[Brand name]	Tenelia Tablets 20 mg
[Non-proprietary name]	Teneligliptin Hydrobromide Hydrate (JAN*)
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	August 26, 2011

[Results of deliberation]
In the meeting held on April 27, 2012, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

**Japanese Accepted Name (modified INN)*

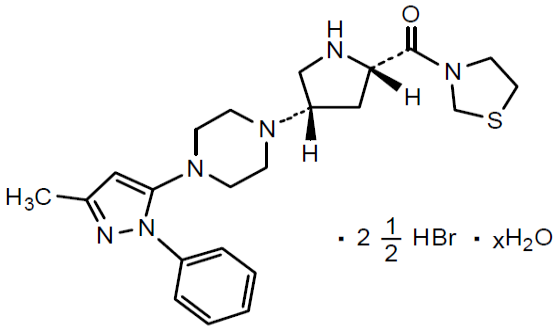
Review Report

April 5, 2012
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for approval are as follows.

[Brand name]	Tenelia Tablets 20 mg
[Non-proprietary name]	Teneligliptin Hydrobromide Hydrate
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	August 26, 2011
[Dosage form/Strength]	Each tablet contains Teneligliptin Hydrobromide Hydrate, equivalent to 20 mg of teneligliptin
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{22}H_{30}N_6OS \cdot 2\frac{1}{2}HBr \cdot xH_2O$

Molecular weight: 628.86

Chemical name:

{(2S,4S)-4-[4-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl) piperazin-1-yl] pyrrolidin-2-yl} (1,3-thiazolidin-3-yl) methanone hemipentahydrobromide hydrate

[Items warranting special mention] None

[Reviewing office] Office of New Drug I

Review Results

April 5, 2012

[Brand name]	Tenelia Tablets 20 mg
[Non-proprietary name]	Teneligliptin Hydrobromide Hydrate
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	August 26, 2011

[Results of review]

Based on the submitted data, it is concluded that the efficacy of the product in patients with type 2 diabetes mellitus has been demonstrated and its safety is acceptable in view of its observed benefits. Safety information on hypoglycemia, gastrointestinal disorder, pancreatitis, hepatic impairment, etc., as well as the safety and efficacy in patients with renal impairment, patients with hepatic impairment, and in the elderly patients need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration.

[Indication]	Type 2 diabetes mellitus; The drug product should be used only in patients who have not sufficiently responded to either of the following treatments. (a) Diet and/or exercise therapy alone (b) Use of sulfonylureas in addition to diet and/or exercise therapy (c) Use of thiazolidinediones in addition to diet and/or exercise therapy
[Dosage and administration]	The usual adult dosage is 20 mg of teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 40 mg once daily while closely monitoring the clinical course.

Review Report (1)

March 2, 2012

I. Product Submitted for Registration

[Brand name]	Tenelia Tablets 20 mg
[Non-proprietary name]	Teneligliptin Hydrobromide Hydrate
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	August 26, 2011
[Dosage form/Strength]	Each tablet contains Teneligliptin Hydrobromide Hydrate, equivalent to 20 mg of teneligliptin
[Proposed indication]	Type 2 diabetes mellitus; The drug product should be used only in patients who have not sufficiently responded to either of the following treatments. (a) Diet and/or exercise therapy alone (b) Use of sulfonylureas in addition to diet and/or exercise therapy (c) Use of thiazolidinediones in addition to diet and/or exercise therapy
[Proposed dosage and administration]	The usual adult dosage is 20 mg of teneligliptin orally administered once daily. If efficacy is insufficient, the dose may be increased up to 40 mg once daily while closely monitoring the clinical course.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The proposed product is a tablet that contains, as the active ingredient, teneligliptin hydrobromide hydrate (hereinafter referred to as teneligliptin), a dipeptidyl peptidase (DPP)-4 inhibitor developed by Mitsubishi Tanabe Pharma Corporation.

Glucagon-like peptide-1 (GLP-1), a peptide secreted from the gastrointestinal tract in response to food intake, enhances insulin secretion and suppresses glucagon secretion from the pancreas, thereby playing an important role in controlling postprandial blood glucose level. The peptide is rapidly inactivated by degradation by DPP-4, an enzyme widely distributed in the body, resulting in a short half-life of only approximately 2 minutes. A DPP-4 inhibitor suppresses GLP-1 degradation, increasing the concentration of active GLP-1 in the blood, which stimulates glucose-dependent insulin secretion and, at the same time, suppresses glucagon secretion, thereby exhibiting a glucose lowering effect.

A marketing application for this drug product was submitted by Mitsubishi Tanabe Pharma Corporation with the claim that the efficacy and safety of this product in patients with type 2 diabetes mellitus have been demonstrated.

As of February 2012, the drug product has not been approved in foreign countries, and it is under development in Korea.

In Japan, the following DPP-4 inhibitors have already been approved: sitagliptin phosphate hydrate, vildagliptin, alogliptin benzoate, and linagliptin.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is white powder. Its physicochemical properties have been determined regarding the following parameters: description, solubility, hygroscopicity, pH, melting point and thermal analysis, dissociation constant, distribution coefficient, optical rotation, and crystalline polymorphism (X-ray powder diffraction). The chemical structure of the drug substance has been elucidated by elementary analysis, ultraviolet-visible absorption spectrometry (UV), infrared spectrometry (IR), nuclear magnetic resonance spectrometry (^{1}H, ^{13}C), mass spectrometry (electrospray ionization), and single crystal X-ray diffraction.

2.A.(1).2) Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as the starting materials.

[redacted] process is defined as the critical process step. [redacted] is also controlled as the critical intermediate.

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance include content, description, identification (UV, IR, qualitative test), purity (heavy metals, related substances [liquid chromatography (HPLC)], enantiomers [HPLC], residual solvents [ethanol, 2-propanol (gas chromatography)]), water content, residues on ignition, and assay (HPLC).

2.A.(1).4) Stability of drug substance

Table 1 shows the results of stability tests of the drug substance. Results of the photostability testing showed that the drug substance was stable to light.

Table 1. Stability tests of drug substance

Test	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term stability testing	Commercial scale, 3 lots	25°C	60% RH	[redacted]	18 months
Accelerated testing	Commercial scale, 3 lots	40°C	75% RH		6 months

As shown in the above, the retest period of 30 months has been proposed for the drug substance when stored at room temperature in [redacted] under [redacted], according to the guideline "Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003, hereafter referred to as ICH Q1E guideline). The long-term stability testing is planned to continue up to 36 months.

2.A.(2) Drug product

2.A.(2).1) Drug product, formulation, and formulation development

The drug product is a tablet containing 31 mg of the drug substance (equivalent to 20 mg of teneligliptin). The drug product contains, as excipients, D-mannitol, corn starch, hydroxypropylcellulose, light anhydrous silicic acid, low substituted hydroxypropylcellulose, magnesium stearate, hypromellose, macrogol 400, titanium oxide, iron sesquioxide, and hydrogenated oil.

2.A.(2).2) Manufacturing process

The drug product is manufactured by a process comprising [redacted]. Process control items and control limits are defined for [redacted].

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include content, description, identification (UV), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.A.(2).4) Stability of drug product

Table 2 shows the results of the stability tests of the drug product. Results of the photostability test showed an increase in a related substance Deg-C[1] over time, but it is considered unnecessary to store the product under a light-protected conditions.

Table 2. Stability tests of drug product

Test	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term stability testing	Pilot scale, 3 lots	25°C	60% RH	PTP packaging or plastic bottle packaging	18 months
Accelerated testing	Pilot scale, 3 lots	40°C	75% RH		6 months

As shown in the above, the shelf life of 30 months has been proposed for the drug product when stored at room temperature in PTPs or in plastic bottles, according to the ICH Q1E guideline. The long-term stability testing is planned to continue up to 36 months.

2.B Outline of the review by PMDA

As a result of the following reviews, PMDA has concluded that the quality of the drug substance and the drug product is appropriately controlled based on the submitted data.

Stability tests of drug product

Regarding the change in water content of the drug product stored in plastic bottles in the long-term stability testing and in the accelerated testing, the applicant attributed it to [redacted]. PMDA asked the applicant to explain the reason for such an assumption by showing [redacted].

The applicant responded as follows:

The drug product was stored [redacted]. The drug product in PTP package was [redacted], and water content

[1] [redacted]

increased to [redacted] under the long-term conditions and to [redacted] under the accelerated conditions. With the drug product stored in the plastic bottle, in contrast, there was little or no increase in water content [redacted] either under the long-term or accelerated conditions, which suggested [redacted]. From these results, the applicant considers that, for the drug product in PTP package, [redacted] water [redacted] water content [redacted].

In light-exposed samples, the amount of the related substance Deg-C increased over time (yield approximately [redacted]% at providing an overall illumination of ≥1.2 million lux·h, net near ultraviolet energy of ≥200 W·h/m^2), suggesting the effect of light on the drug product. PMDA asked the applicant to explain the reason for determining that no light-protected storage was necessary.

The applicant responded as follows:
In the photostability testing of unpackaged drug product, purity test showed that the amount of the related substance Deg-C in the light-exposed sample increased over time. However, the yield was only [redacted]% under a storage condition of 1.2 million lux·h, which was far below [redacted] stipulated in ICH-Q3B (R2) Guideline "Impurities in New Drug Products" (PFSB/ELD Notification No. 0624001 dated June 24, 2003). In addition, light exposure had no effect on any other test parameters (description, identification, dissolution, assay, water content, hardness, and purity [enantiomers]). On the basis of the above results, the applicant has determined that it is not necessary to store the drug product under light-protected conditions.

PMDA accepted the above response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

In primary pharmacodynamic studies, the mechanism of action *in vitro* and glucose lowering effect *in vivo* in normal animals and animal models of diabetes mellitus were investigated. In addition, secondary pharmacodynamic studies were conducted to investigate the inhibitory effect of teneligliptin on various enzymes and receptors, and safety pharmacology studies were conducted to evaluate the effect on the central nervous, cardiovascular, respiratory, renal/urinary, and gastrointestinal systems. No pharmacodynamic drug interaction studies have been performed. The dose and concentration of each test substance were expressed in terms of the free base.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* studies

(a) DPP-4 inhibition (4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-4)

Inhibitory activity of teneligliptin and its metabolites[2] (M1, M2, M3, M4, M5) on human recombinant dipeptidyl peptidase (DPP) -4 was investigated by adding a synthetic fluorescent substrate to human recombinant DPP-4.[3] Teneligliptin and its metabolites M1, M2, M4, and M5 concentration-dependently inhibited human recombinant DPP-4, with the IC_{50} values and its 95% confidence interval (CI) being 0.889 nM [0.812, 0.973] for teneligliptin, 34.3 nM [30.9, 37.9] for M1, 35.7 nM [31.9, 39.9] for M2, 0.951 nM [0.865, 1.05] for M4, and 5.06 nM [4.56, 5.62] for M5. M3 up to 1000 nM did not inhibit DPP-4. Teneligliptin competitively inhibited DPP-4, with

[2] Thiazolidine 1-oxide (M1), thiazolidine 1,1-dioxide (M2), carboxyl form with thiazolidine released (M3), thiazolidine with hydroxymethylated pyrazole (M4), thiazolidine with hydroxylated phenyl group (M5)

[3] Metabolites were tested using the following salts: M1, trifluoroacetate; M2, trifluoroacetate hydrate; M3, trifluoroacetate hydrate; M4 maleate hydrate; and M5, trifluoroacetate.

Ki values and its 95% CI being 0.406 nM [0.330, 0.500].

Inhibitory effect of teneligliptin on DPP-4 in human plasma was investigated by adding a synthetic fluorescent substrate to human plasma. Teneligliptin concentration-dependently inhibited DPP-4, with IC_{50} values and its 95% CI being 1.75 nM [1.62, 1.89].

(b) Comparison of DPP-4-inhibiting effect with drugs of the same class (4.2.1.1-3, 4.2.1.1-5, 4.2.1.1-6)

The inhibitory effect of teneligliptin and other DPP-4 inhibitors (sitagliptin,[4] vildagliptin,[5] saxagliptin[6]) on human recombinant DPP-4 was investigated by adding a synthetic fluorescent substrate to human recombinant DPP-4. IC_{50} values and the 95% CI of each substance were 1.01 nM [0.940, 1.08] for teneligliptin, 6.74 nM [6.26, 7.25] for sitagliptin, 10.5 nM [9.76, 11.2] for vildagliptin, and 2.51 nM [2.35, 2.69] for saxagliptin.

The inhibitory effect of teneligliptin, sitagliptin,[4] and vildagliptin[5] on DPP-4 in human and rat plasma was investigated by adding a synthetic fluorescent substrate to human and rat plasma. IC_{50} values and the 95% CI of each substance for human plasma DPP-4 were 1.45 nM [1.10, 1.93] for teneligliptin, 4.88 nM [3.90, 6.10] for sitagliptin, and 7.67 nM [6.99, 8.42] for vildagliptin, and for rat plasma DPP-4, 1.14 nM [1.07, 1.21], 10.4 nM [9.50, 11.5], and 6.81 nM [6.12, 7.59], respectively.

(c) Suppression of the degradation of active GLP-1 in rat plasma (4.2.1.1-7)

The suppressive effect of teneligliptin and vildagliptin[5] on the degradation of glucagon-like peptide-1 (GLP-1) (7-36) was investigated by adding GLP-1 (7-36) amide to rat plasma and measuring the concentration of residual GLP-1 (7-36) amide by enzyme-linked immunosorbent assay (ELISA). Teneligliptin and vildagliptin concentration-dependently suppressed the degradation of GLP-1 (7-36) in rat plasma, with IC_{50} values and its 95% CI being 2.92 nM [2.21, 3.87] and 11.8 nM [9.98, 13.9], respectively.

3.(i).A.(1).2) *In vivo* studies

(a) Effect in normal animals

i) Plasma DPP-4 inhibition in single-dose administration (4.2.1.1-8, 4.2.1.1-9)

Teneligliptin (0.01, 0.1, 1, 10 mg/kg), sitagliptin,[4] (0.1, 1, 10, 100 mg/kg), vildagliptin[5] (0.1, 1, 10, 100 mg/kg), or vehicle[7] was administered to male rats (8 per group) in a single oral dose under non-fasting conditions, and plasma DPP-4 activity was measured over time up to 24 hours after administration. As a result, in each drug group, plasma DPP-4 activity[8] was dose-dependently inhibited, with ED_{50} values and its 95% CI being 0.41 mg/kg [0.32, 0.51], 27.28 mg/kg [22.35, 33.31], and 12.77 mg/kg [10.13, 16.10].

Teneligliptin (0.13, 0.43, 1.3 mg/kg), vildagliptin[5] (0.3 mg/kg), or vehicle[7] was administered to male monkeys (3 per group) in a single oral dose, and plasma DPP-4 activity, blood glucose, and plasma insulin concentration were measured over time up to 24 hours after administration. In animals treated with teneligliptin, plasma DPP-4 activity[8] was dose-dependently inhibited; the maximum rate of inhibition relatie to baseline was 65.53% ± 1.07% (mean ± standard error) in the 0.13 mg/kg group, 78.80% ± 1.85% in the 0.43 mg/kg group, and 93.07% ± 0.44% in the 1.3 mg/kg group, whereas in the vildagliptin group, the maximum rate of inhibition relative to baseline was 66.73% ± 2.85%. In teneligliptin groups, a significant DPP-4-inhibitory effect was

[4] Sitagliptin maleate hydrate

[5] Vildagliptin in free form

[6] Saxagliptin trifluoroacetate hydrate

[7] 0.5% hydroxypropylmethylcellulose solution

[8] Minimum value of DPP-4 in each animal

observed, even at 24 hours after administration (28.30% ± 1.35% in the 0.13 mg/kg group, 51.70% ± 2.14% in the 0.43 mg/kg group, 65.77% ± 0.59% in the 1.3 mg/kg group), compared with the control group. Neither teneligliptin nor vildagliptin affected blood glucose level or plasma insulin concentration measured simultaneously.

ii) Effect on fasting blood glucose level (4.2.1.1-14)

Teneligliptin (0.01, 0.1, 1, 10, 100 mg/kg) or vehicle[7] was administered to male rats (7-8 per group) in a single oral dose under fasting conditions, and blood glucose and plasma insulin concentration were measured over time up to 6 hours after administration. As a result, teneligliptin had little or no effect either on blood glucose or on plasma insulin concentration. Results of plasma DPP-4 activity at 0.5 and 6 hours after administration showed that the activity decreased significantly in the ≥1 mg/kg groups compared with the control group, with the activity being inhibited by ≥80% (at 0.5 hours after administration) and by ≥60% (at 6 hours after administration) from the baseline level.

(b) Effect in Zucker Fatty rats

i) Suppression of blood glucose increase in oral glucose tolerance test (4.2.1.1-10)

Teneligliptin (0.01, 0.03, 0.1, 0.3, 1, 3 mg/kg) or vehicle[7] was administered to male Zucker Fatty rats (13-week old, 10 per group) in a single oral dose under fasting conditions and, at 30 minutes after administration, glucose solution (1 g/kg) was administered orally (OGTT). Blood glucose, plasma insulin concentration, and plasma DPP-4 activity were measured over time up to 240 minutes after OGTT. As a result, $AUC_{0\text{-}60\ min}$ of glucose at 60 minutes after OGTT (changes from the time of OGTT) decreased significantly in the teneligliptin ≥0.03 mg/kg groups compared with the control group, whereas the maximum plasma insulin concentration (changes from the time of OGTT) increased significantly in the teneligliptin ≥0.1 mg/kg groups compared with the control group. Plasma DPP-4 activity was inhibited up to 240 minutes after OGTT by 13% to 20% in the control group, by 19% to 26% in the teneligliptin 0.01 mg/kg group, by 33% to 41% in the 0.03 mg/kg group, by 58% to 64% in the 0.1 mg/kg group, by 74% to 85% in the 0.3 mg/kg group, by 85% to 93% in the 1 mg/kg group, and by 92% to 94% in the 3 mg/kg group relative to the baseline level.

ii) Suppression of blood glucose increase in oral mixed carbohydrate tolerance test (4.2.1.1-11)

Teneligliptin (0.1, 0.3, 1 mg/kg) or vehicle[7] was administered to male Zucker Fatty rats (13-week old, 10 per group) in a single oral dose under fasting conditions, and mixed carbohydrate solution[9] (3.5 g/kg) was administered orally at 15 minutes after administration (first load) and at 12 hours and 15 minutes after administration (second load). Blood glucose, plasma insulin concentration, and plasma DPP-4 activity were measured over time up to 15 hours after the first load. $AUC_{0\text{-}120\ min}$ of glucose over 120 minutes after the first load and $AUC_{720\text{-}840\ min}$ of glucose over 120 minutes after the second load decreased significantly in the teneligliptin 0.1, 0.3, and 1 mg/kg groups compared with the control group. Maximum plasma insulin concentration increased significantly in the teneligliptin ≥0.1 mg/kg groups in the first load and in the teneligliptin ≥0.3 mg/kg groups in the second load, compared with the control group. Plasma DPP-4 activity was inhibited by -5% to 2% in the control group, by 41% to 53% in the teneligliptin 0.1 mg/kg group, by 59% to 80% in the 0.3 mg/kg group, and 72% to 91% in the 1 mg/kg group, up to 15 hours after the first load relative to the baseline level.

iii) Effect on active GLP-1 concentration in plasma (4.2.1.1-12)

Teneligliptin (0.01, 0.1, 1 mg/kg) or vehicle[7] was administered orally to male Zucker Fatty rats (13-week old, 12 per group) in a single dose under fasting conditions and, after 15 minutes,

[9] Starch:sucrose:lactose = 6:3:1

the mixed carbohydrate solution[9] (3.5 g/kg) was administered orally. Active GLP-1 concentration, blood glucose, plasma insulin concentration, and plasma DPP-4 activity were measured over time up to 240 minutes after mixed carbohydrate load. Maximum active GLP-1 concentration in plasma after mixed carbohydrate load (changes after carbohydrate load) increased significantly in the teneligliptin ≥0.1 mg/kg groups compared with the control group. $AUC_{0\text{-}120\ min}$ of glucose over 120 minutes after mixed carbohydrate load decreased significantly in the teneligliptin ≥0.1 mg/kg groups compared with the control group, and maximum plasma insulin concentration increased significantly in the teneligliptin ≥0.1 mg/kg groups compared with the control group. Plasma DPP-4 activity was inhibited by -6% to 4% in the control group, by 4% to 12% in the teneligliptin 0.01 mg/kg group, by 45% to 54% in the 0.1 mg/kg group, and by 84% to 91% in the 1 mg/kg group relative to the baseline level, up to 240 minutes after mixed carbohydrate load.

(c) Suppression of blood glucose increase in KK-A^y mice (4.2.1.1-13)

Teneligliptin (0.1, 0.3, 1, 3, 10 mg/kg) or vehicle[7] was administered to male KK-A^y mice (11-week old, 12 per group) in a single oral dose under fasting conditions, followed by OGTT after 30 minutes. Results of blood glucose over time up to 240 minutes after OGTT showed that $AUC_{0\text{-}60\ min}$ of glucose over 60 minutes after OGTT decreased significantly in the teneligliptin ≥0.3 mg/kg groups compared with the control group. Plasma DPP-4 activity at 240 minutes after OGTT decreased significantly in the teneligliptin ≥0.3 mg/kg groups compared with the control group; the inhibition rates were 5.58% ± 2.65% (mean ± standard error) in the control group, 9.92% ± 2.37% in the teneligliptin 0.1 mg/kg group, 16.58% ± 3.30% in the 0.3 mg/kg group, 32.05% ± 2.72% in the 1 mg/kg group, 52.88% ± 2.51% in the 3 mg/kg group, and 70.37% ± 1.22% in the 10 mg/kg group, relative to the baseline level.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Selectivity to DPP-4-related enzymes (4.2.1.2-1)

The inhibitory effect of teneligliptin and M1,[10] the major metabolite of teneligliptin, on DPP-4-related enzymes (DPP-8, DPP-9, fibroblast activation protein) was investigated. As a result, IC_{50} values against DPP-4-related enzymes and its 95% CI were 0.189 μM [0.134, 0.267], 0.150 μM [0.132, 0.170], and >10 μM, respectively, for teneligliptin and 6.96 μM [5.37, 9.01], 2.72 μM [2.44, 3.03] and >10 μM, respectively, for M1. The effect of teneligliptin on other DPP-4-related enzymes was not investigated.

3.(i).A.(2).2) Effect on various enzymes, receptors, etc (4.2.1.2-2, 4.2.1.2-3)

A total of 174 types of enzymes, 164 types of receptors, ion channels, and transporters were treated with 10 μM teneligliptin to investigate the inhibition effect of teneligliptin on enzyme activities and ligand-binding of receptors, etc. Teneligliptin inhibited the ligand-binding of histamine H_1 receptor and sigma-1 receptor by 90% and 67%, respectively, whereas it did not inhibit any other enzymes, receptors, etc., by more than 50%, except DPP-4. The effect of teneligliptin in ligand binding inhibition of histamine H_1 receptor and sigma-1 receptor was investigated in detail. Results showed that IC_{50} values of teneligliptin and its 95% CI were 0.775 μM [0.304, 1.98] (0.331 μg/mL) and 16.2 μM [6.88, 38.2], respectively. A similar investigation with M1[10] (10 μM), the major metabolite of teneligliptin, showed that M1 inhibited the ligand binding of histamine H_1 receptor by 59% with IC_{50} value and the 95% CI being 5.19 μM [1.80, 14.9] (2.297 μg/mL). IC_{50} value of teneligliptin and M1 against histamine H_1 receptor were 3.5 and 29 times, respectively, of the plasma C_{max} of unbound teneligliptin

[10] M1 was tested using trifluoroacetate hydrate.

(0.095 μg/mL)[11] and the total M1 (0.078 μg/mL)[12] observed in a clinical study in Japan, where maximum clinical dose in Japan (40 mg/day) was administered to the Japanese. On the basis of these results, the applicant considers that teneligliptin is unlikely to induce an effect associated with histamine H_1 receptor in clinical practice.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effect on the central nervous system (4.2.1.3-1–4.2.1.3-6)

Teneligliptin (1, 10, 100 mg/kg) or vehicle[13] was administered to male rats (6 per group) in a single oral dose, and they were monitored for general symptoms and behavior before administration and at 1, 2, 4, and 8 hours after administration by modified Irwin's method. Teneligliptin up to 100 mg/kg did not have any effect on general symptoms or behavior.

Teneligliptin (the same doses) or vehicle[13] was administered to male rats (16 per group) in a single oral dose, and spontaneous motor activity was measured up to 8 hours after administration. In a separate experiment, teneligliptin (the same doses) was administered to male rats (8 per group) in a single oral dose and, at 30 minutes after administration, the effect on electroshock-induced seizures and pentylenetetrazol-induced seizures was investigated. Also, teneligliptin (the same doses) was administered to male rats (8 per group) in a single oral dose, and the effect on motor coordination was investigated using a rotating rod method before administration and at 1, 2, 4, and 8 hours after administration. In still another study, teneligliptin (the same doses) was administered to male rats (8 per group) in a single oral dose, and rectal temperature was measured before administration and at 1, 2, 4, and 8 hours after administration. Results showed that teneligliptin up to 100 mg/kg had no effect on any of these parameters.

C_{max} of unbound teneligliptin in plasma following 100 mg/kg administration was 6.62 μg/mL,[14] which is 70 times the C_{max} (0.095 μg/mL)[11] of unbound teneligliptin in plasma following the administration to Japanese subjects of the maximum clinical dose in Japan (40 mg/day).

3.(i).A.(3).2) Cardiovascular effects

(a) *In vitro* studies (4.2.1.3-7–4.2.1.3-9)

Using HEK293 cells that stably express hERG channel, the effect of teneligliptin (1, 10, 100 μM) and M1[10] (30, 100 μM) on hERG potassium current was investigated. Teneligliptin concentration-dependently decreased hERG potassium current, with the inhibition being statistically significant at 10 and 100 μM compared with the control[15] (inhibition rate relative to control: 22.6% at teneligliptin 1 μM, 75.9% at teneligliptin 10 μM, and 95.9% at teneligliptin 100 μM) (IC_{50} value, 3.45 μM [1.47 μg/mL]). M1 at 30 and 100 μM inhibited hERG potassium current by 2.0% and 19.0%, respectively, compared with the control,[16] and showed a statistically significant inhibition at 100 μM (IC_{50} value: ≥100 μM).

Using the ventricular papillary muscle of guinea pigs, the effect of teneligliptin (1, 10, 100 μM) or vehicle[15] on action potential duration (APD) was investigated. Teneligliptin did not affect

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[11] C_{max} of total teneligliptin under steady state was estimated by simulation based on the plasma concentration data obtained by single oral administration of the maximum clinical dose in Japan (40 mg/day) to Japanese healthy adult male subjects (Study 3000-A1, 5.3.3.1-1), and the C_{max} (unbound form) was calculated from the *in vitro* plasma protein binding rate in human plasma (4.2.2.3-5).

[12] C_{max} of total M1 under steady state following administration of the maximum clinical dose in Japan (40 mg/day) to Japanese subjects was estimated from the ratio of plasma radioactivity concentration of M1 to that of teneligliptin in the mass balance study in single oral dose administration in Caucasian healthy adult male subjects (Study MP-513-E08, 5.3.3.1-5).

[13] 0.5% carboxymethylcellulose sodium solution

[14] Estimated from 13-week oral toxicity study in rats (4.2.3.2-3) and *in vitro* plasma protein binding rate (4.2.2.3-5).

[15] Distilled water

[16] 0.1% dimethyl sulfoxide

resting membrane potential, action potential amplitude, or maximum upstroke velocity, whereas teneligliptin at ≥10 μM concentrations significantly increased APD in a concentration-dependent manner compared with the control.

(b) *In vivo* studies (4.2.1.3-10, 4.2.1.3-11 [Reference data])

Teneligliptin (3, 10, 30 mg/kg) or vehicle[13] was administered to male monkeys (4 animals) in a single oral dose starting from the lowest dose for every 6 days, and the effect on blood pressure, heart rate, and electrocardiogram (ECG) (PR, QRS, QT, QTc) was investigated before administration and at 0.5, 1, 2, 4, and 6 hours after administration. As a result, teneligliptin up to 30 mg/kg had no effect on blood pressure or heart rate compared with the control, whereas significant prolongation in QT and QTc intervals[17] was observed at teneligliptin 30 mg/kg compared with the control group.

Teneligliptin (1, 2, 7 mg/kg) was administered intravenously to male dogs (3 animals) under anesthesia at 30-minute intervals starting from the lowest dose. As a result, a significant QTc interval prolongation[17] was observed at teneligliptin 7 mg/kg compared with the baseline value.

3.(i).A.(3).3 Effect on respiratory system (4.2.1.3-12)

Teneligliptin (1, 10, 100 mg/kg) or vehicle[13] was administered to male rats (8 per group) in a single oral dose, and the effect on respiratory rate, tidal volume, and minute ventilation was investigated before administration and at 1, 2, 4, and 8 hours after administration. Teneligliptin up to 100 mg/kg did not affect respiratory rate, tidal volume, or minute ventilation. C_{max} of unbound teneligliptin in plasma following 100 mg/kg administration was 6.62 μg/mL,[14] which was 70 times the C_{max} (0.095 μg/mL)[11] of unbound plasma teneligliptin following the administration to Japanese subjects of the maximum clinical dose in Japan (40 mg/day).

3.(i).A.(3).4 Effect on renal/urinary system (4.2.1.3-13)

Teneligliptin (1, 10, 100 mg/kg) or vehicle[13] was administered to male rats (8 per group) in a single oral dose, and the effect on urine volume and urinary electrolytes (Na, Ca, Cl ions) excretion was investigated every hour up to 4 hours after administration. Teneligliptin up to 100 mg/kg did not affect urine volume or urine electrolyte excretion. C_{max} of unbound teneligliptin in plasma following 100 mg/kg administration was 6.62 μg/mL,[14] which was 70 times the C_{max} (0.095 μg/mL)[11] of unbound plasma teneligliptin following the administration to Japanese subjects of the maximum clinical dose in Japan (40 mg/day).

3.(i).A.(3).5 Effect on gastrointestinal system (4.2.1.3-14)

Teneligliptin (1, 10, 100 mg/kg) or vehicle[13] was administered to male rats (10 per group) in a single oral dose, and the effect on gastric emptying rate was investigated. The gastric emptying rate decreased by 95% in the 100 mg/kg group compared with the control group. Plasma concentration of unbound teneligliptin following the administration of the drug at the no-observed-effect-level (NOEL) (10 mg/kg) was 0.990 μg/mL,[14] which was 10 times the C_{max} (0.095 μg/mL)[11] of unbound plasma teneligliptin following the administration to Japanese subjects of the maximum clinical dose in Japan (40 mg/day).

[17] Calculated by Bazett's correction formula

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Efficacy of teneligliptin

Taking into account the fact that efficacy of teneligliptin was evaluated only by single dose studies, PMDA asked the applicant to explain in detail the relationships among the DPP-4 inhibitory effect of teneligliptin, pharmacodynamic effects (e.g., blood glucose parameter), and plasma teneligliptin concentration and, based on these relationships, to explain the efficacy in repeated administration, including the appropriateness of the dosage regimen of teneligliptin in clinical use.

The applicant responded as follows:

A preliminary repeated dose study was conducted to evaluate the efficacy of teneligliptin administered once daily for 2 weeks. In this study, teneligliptin (0.3, 1 mg/kg) or vehicle[7] was administered orally to male Zucker Fatty rats (13-week old, 10 per group) under fasting conditions on Day 1 and Day 14 and, at 15 minutes (first load) and at 12 hours and 15 minutes (second load) after administration of teneligliptin, mixed carbohydrate solution[9] (3.5 g/kg) was administered orally. In animals loaded with mixed carbohydrate solution on Day 1, teneligliptin at both doses significantly increased the maximum plasma insulin concentration and significantly decreased $AUC_{0\text{-}120\ min}$ of glucose over 120 minutes both after the first and the second load with mixed carbohydrate solution. In animals loaded with mixed carbohydrate solution on Day 14, teneligliptin increased the maximum plasma insulin concentration, not significantly after the first load but significantly after the second load, and teneligliptin at both doses significantly decreased $AUC_{0\text{-}120\ min}$ of glucose over 120 minutes both after the first and the second load. These results demonstrated that repeated administration of teneligliptin suppressed blood glucose increase. Both on Day 1 and Day 14 of administration, teneligliptin inhibited plasma DPP-4 activity by ≥40% continuously up to 15 hours after the first load. In the primary pharmacodynamics studies (4.2.1.1-10–12), plasma DPP-4 activity was inhibited by approximately 40% at the lowest dose that had a significant effect compared with control group, from which it is expected that teneligliptin, if present at a concentration that inhibits plasma DPP-4 activity by ≥40%, will increase the concentration of active plasma GLP-1 and decreases blood glucose level. In Zucker Fatty rats, administration of teneligliptin at ≥0.1 mg/kg doses exhibited a lasting DPP-4-inhibitory activity (≥40% inhibition up to 15 hours after the first mixed carbohydrate load) and suppressed blood glucose increase (4.2.1.1-11). Plasma teneligliptin concentration at 12 hours after 0.1 mg/kg administration was 10.12 ng/mL (4.2.2.2-2) and, in the *in vitro* study (4.2.1.1-7) that investigated the suppression of active GLP-1 in rat plasma, maximum and similar activity to suppress GLP-1 degradation was achieved at ≥30 nM (12.8 ng/mL) concentrations of teneligliptin.

These results suggest that teneligliptin, if maintained at a plasma concentration of approximately ≥10 ng/mL, will effectively inhibit DPP-4 resulting in lasting suppression of GLP-1 degradation, leading to a glucose lowering effect.

Under steady state in repeated administration of teneligliptin 20 mg to humans, DPP-4 inhibition rate and plasma teneligliptin concentration at 24 hours after administration were 61.8% and 28.83 ng/mL, respectively (Study 3000-A12). The plasma teneligliptin concentration exceeds the concentration that has a glucose lowering effect as expected from the results of nonclinical studies. Also, the glucose lowering effect is observed after breakfast, lunch, and supper invariably. Thus, the proposed dosage regimen, 20 mg once daily, is consistent with the pharmacodynamic effect suggested from the results of nonclinical studies and is therefore considered appropriate.

PMDA considers as follows:

The discussion of the applicant on the relationship between the pharmacodynamic effect and plasma concentration of teneligliptin is understandable to a certain extent. However, since no nonclinical studies were conducted on the persistence of the glucose lowering effect up to 24 hours after teneligliptin administration and on the effect of teneligliptin in once daily

repeated administration using HbA1c as the index, PMDA will further discuss the effect of repeated administration in the clinical section, including the appropriateness of the dosage regimen of teneligliptin [for efficacy in humans, see "4.(iii).B.(2).1) Efficacy of monotherapy and 4.(iii).B.(5).1)Dosage regimen].

3.(i).B.(2) Cardiovascular effects

In vitro and *in vivo* studies on teneligliptin show effects suggestive of QTc interval prolongation. Therefore, PMDA asked the applicant to discuss the safety of teneligliptin in humans in this respect.

The applicant responded as follows:

IC_{50} value of teneligliptin in hERG current suppression was 3.45 μM (1.47 μg/mL). In the ventricular papillary muscle of guinea pigs, teneligliptin at 10 μM (4.27 μg/mL) prolonged action potential duration. In a telemetry study in monkeys, administration of teneligliptin at 30 mg/kg (estimated concentration of unbound teneligliptin in plasma: 4.50 μg/mL[18]) prolonged QTc interval. C_{max} of unbound teneligliptin in plasma following administration to Japanese subjects at the maximum clinical dose in Japan (40 mg/day) was estimated to be 0.095 μg/mL,[11] and the IC_{50} value of teneligliptin against hERG current was 15 times this unbound teneligliptin level, and NOEL of teneligliptin in the ventricular papillary muscle of guinea pigs (1 μM [0.427 μg/mL]) was 4 times this unbound teneligliptin level. Also, the concentration of unbound teneligliptin following the administration at 10 mg/kg, the NOEL at the telemetry study in monkeys, was estimated to be 1.67 μg/mL,[18] which was 17 times the unbound teneligliptin level in humans. In addition, the hERG current-suppressing effect of M1, the major metabolite in humans, is very weak compared with that of teneligliptin, being only 19.0% at 100 μM (44.26 μg/mL). Since C_{max} (total concentration) of M1 following administration of teneligliptin 40 mg is estimated to be 0.078 μg/mL,[12] the metabolite is very unlikely to prolong QTc interval.

In addition, in the Thorough QT/QTc study, QTc interval prolongation was observed only time points near t_{max} after administration of teneligliptin 160 mg, and no clinically significant QTc interval prolongation was observed at 40 mg [see "4.(ii).A.(6) Pharmacodynamic study"].

From these results, teneligliptin at the daily dose of up to 40 mg is unlikely to cause clinically significant QTc interval prolongation.

PMDA, taking into account the fact that effects suggestive of QTc interval prolongation were observed consistently throughout *in vitro* and *in vivo* nonclinical studies, will continuously examine the effect of teneligliptin on the cardiovascular system in the clinical section [see "4.(ii).B.(3) QTc interval-prolonging effect of teneligliptin" and "4.(iii).B.(3).6) Cardiovascular risks" and "4.(iii).B.(3).7) QTc interval-prolongation and proarrhythmic risk"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Pharmacokinetics of teneligliptin was investigated following the intravenous or oral administration of teneligliptin or ^{14}C-labeled teneligliptin to rats and monkeys. Pharmacokinetics in repeated administration was also investigated based on the toxicokinetics in toxicity studies. Plasma levels of unchanged teneligliptin, metabolites (M1, M2), and the stereoisomer were measured by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation in plasma was 0.5 or 10 ng/mL for unchanged teneligliptin, 10 and 5 ng/mL for metabolites M1 and M2, respectively, and 1 ng/mL for stereoisomers. Radioactivity in biological samples was measured by liquid scintillation counting

[18] Estimated from the data of the 52-week oral toxicity study in monkeys (4.2.3.2-8) and *in vitro* plasma protein binding rate (4.2.2.3-5)

(LSC) or by whole-body autoradiography. Metabolites were analyzed[19] using a high performance liquid chromatography equipped with a radioactivity detector (HPLC-RI). The results from the main studies are described below. In the pharmacokinetic studies, doses of teneligliptin, concentrations of unchanged teneligliptin and of metabolites in the test samples are all expressed in terms of the free base.

3.(ii).A.(1) Absorption (4.2.2.2-1–4.2.2.2-9)

Table 3 shows pharmacokinetic parameters of unchanged teneligliptin in plasma following a single intravenous dose or single oral dose of teneligliptin to male rats or male monkeys.

Table 3. Pharmacokinetic parameters of unchanged plasma teneligliptin following a single dose

Animal species (number of animals)	Route of administration	Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL_{tot} (mL/h/kg)	V_{ss} (L/kg)	BA (%)
Rats (n = 4)	i.v.	0.3	—	—	14.23 ± 6.30	320.76 ± 35.69	943.24 ± 95.45	8.906 ± 3.287	—
	p.o.	0.1	0.88 ± 0.25	5.48 ± 2.94	15.84 ± 2.32	91.81 ± 24.07	—	—	85.9
		0.3	0.75 ± 0.29	20.65 ± 6.58	8.97 ± 1.64	202.12 ± 29.59	—	—	63.0
		1	0.75 ± 0.29	152.41 ± 46.60	8.43 ± 1.75	672.94 ± 99.32	—	—	62.9
Monkeys (n = 4)	i.v.	0.3	—	—	23.12 ± 8.78	1074.91 ± 196.70	286.40 ± 53.57	4.802 ± 1.347	—
	p.o.	0.1	0.50 ± 0.00	28.27 ± 5.30	18.86 ± 2.46	295.44 ± 66.17	—	—	83.2 ± 16.7
		0.3	1.38 ± 1.11	85.13 ± 28.61	15.24 ± 4.59	613.16 ± 75.83	—	—	57.6 ± 5.3
		1	0.88 ± 0.25	273.54 ± 70.41	16.11 ± 1.77	1571.64 ± 250.84	—	—	44.1 ± 2.6

Mean ± standard deviation, -: Not calculated

t_{max}: Time to maximum plasma concentration, C_{max}: Maximum plasma concentration, $t_{1/2}$: Elimination half-life, $AUC_{0-\infty}$: Area under the plasma concentration-time curve (extrapolated to infinity), CL_{tot}: Total body clearance, V_{ss}: Volume of distribution under steady state, BA: Bioavailability (BA of rats was calculated from mean $AUC_{0-\infty}$ in the intravenous administration group and mean $AUC_{0-\infty}$ in the oral administration group at each dose.)

^{14}C-labeled teneligliptin was administered orally (1 mg/kg) or intravenously (1 mg/kg) in a single dose to male rats (4 animals) and male monkeys (4 animals). As a result, the absorption rate (mean ± standard deviation [SD]) calculated from the ratio of $AUC_{0-\infty}$ of total radioactivity was 79.0% ± 6.5% in rats and 71.0% ± 7.4% in monkeys.

Teneligliptin (0.1, 1 mg/kg) was administered in a single oral dose to male Zucker Fatty rats (4 per group). As a result, the C_{max} were 11.69 ± 2.86 and 307.55 ± 155.60 ng/mL, $AUC_{0-\infty}$were 312.26 ± 55.11 and 2523.21 ± 273.67 ng·h/mL, t_{max} were 9.00 ± 2.00 and 1.00 ± 0.00 hour, and $t_{1/2}$ were 13.96 ± 1.96 and 8.39 ± 0.92 hours, respectively.

^{14}C-labeled teneligliptin (1 mg/kg) was administered orally to male rats (4 animals) once daily for 14 days. On Day 1 and Day 14 of administration, the C_{max} were 67.5 ± 9.9 and 160.1 ± 65.2 ng

[19] Metabolites in *in vivo* and *in vitro* study samples were identified by comparison with reference standards using a quadrupole mass spectrometer, a quadrupole time-of-flight mass spectrometer, or an ion trap mass spectrometer.

eq./mL, $AUC_{0-\infty}$were 704.4 ± 22.4 and 1012.5 ± 119.8 ng eq.·h/mL, t_{max} were 1.9 ± 1.3 and 0.9 ± 0.3 hours, and $t_{1/2}$ were 7.9 ± 1.0 and 13.3 ± 1.4 hours, respectively. Radioactivity concentration in plasma reached a steady state on Day 5 of administration.

Pharmacokinetics of teneligliptin was investigated in repeated oral toxicity studies[20] in male and female rats (10-150 mg/kg/day) and in male and female monkeys (10-75/60 mg/kg/day). Accumulation ratio calculated from the $AUC_{0-24\,h}$ was 1.5 to 2.2 in rats (values in Week 13 or 26/ values in initial administration) and 0.6 to 1.6 in monkeys (values in Week 13, 26, or 52/ values in initial administration).

Teneligliptin (1 mg/kg) was administered to male rats (4 animals) in a single oral dose, and concentrations of unchanged teneligliptin (2S4S form) and stereoisomers (2R4R form, 2R4S form, or 2S4R form) in plasma were measured. Concentrations of the stereoisomers were below the lower limit of quantitation at all measuring time points

3.(ii).A.(2) Distribution (4.2.2.3-1–4.2.2.3-6)

^{14}C-labeled teneligliptin (1 mg/kg) was administered to male rats (4 animals for each time point) in a single oral dose. The maximum concentrations of radioactivity were noted in the large intestine at 12 hours after administration, in the testis, epididymis, and cecum at 5 hours after administration, and in other tissues at 0.5 hours after administration. Excluding the gastrointestinal tract, high radioactivity was detected in the kidney and in the liver, and $t_{1/2}$ was 68.3 hours in the kidney and 69.0 hours in the liver. After reaching the maximum level, radioactivity in most of the tissues decreased over time, whereas high radioactivity was detected even at 168 hours after administration in the following tissues, in the decreasing order of radioactivity: kidney, liver, small intestine, spleen, lung, epididymis, thymus, skin, mesenteric lymph node, large intestine, bone marrow, submandibular gland, adrenals, cecum, pancreas, brown fat, prostate gland, stomach, and femur. At that time point, radioactivity in the kidney was 13% of the maximum level and radioactivity in other tissue was ≤3% of the maximum level in each tissue. In the kidney, radioactivity was localized in the medulla at all time points. ^{14}C-labeled teneligliptin (1 mg/kg) was administered to pigmented male rats (1 animal for each time point) in a single oral dose. As a result, radioactivity concentration at 168 hours after administration was highest in the eyeballs, followed in descending order by the kidney, skin, liver, and radioactivity disappeared from the eyeballs and skin more gradually than from other tissues, with the $t_{1/2}$ being 290.3 and 269.6 hours, respectively. ^{14}C-labeled teneligliptin (1 mg/kg) was administered orally to male rats with DPP-4 activity (1 animal for each time point) and to male rats with DPP-4 activity deficiency (1 animal for each time point). Radioactivity was distributed in the outer zone of renal medulla in rats with DPP-4 activity, whereas no marked distribution in the zone was observed in rats with DPP-4 activity deficiency. ^{14}C-labeled teneligliptin (1 mg/kg) was administered orally to male rats (4 animals for each time point) once daily for 21 days. As a result, the tissue/plasma ratio of radioactivity at 0.5, 5, 12, and 24 hours after administration on Day 21 was 0.7 to 1.5 times the ratio observed on Day 14.

^{14}C-labeled teneligliptin (1 mg/kg) was administered to pregnant rats (Gestation day 18, 3 animals for each time point) in a single oral dose. Radioactivity concentrations in the blood, plasma, brain, heart, lung, liver, adrenals, kidney, mammary gland, ovary, and placenta of maternal animals reached the maximum level at 0.5 hours after administration, whereas radioactivity concentration in the uterus, amniotic fluid, and fetal membrane reached the maximum level at 5 hours after administration. At 0.5 and 5 hours after administration, radioactivity concentrations in the placenta, amniotic fluid, and fetal membrane were 1.7 and 4.1 times (placenta), <0.3 times (amniotic fluid), and 3.1 and 14.3 times (fetal membrane) the plasma radioactivity in maternal animals. Radioactivity concentration in the blood of fetuses at 0.5 and 5 hours after administration

[20] 26-week oral toxicity study in rats (4.2.3.2-4) and 52-week oral toxicity study in monkeys (4.2.3.2-8)

was 0.15 to 0.31 times the radioactivity in the blood of maternal animals.

The mean plasma protein binding rate of ^{14}C-labeled teneligliptin (20-500 ng/mL) (measured by ultrafiltration method) in mice, rats, rabbits, dogs, and monkeys were 72.1% to 75.5%, 62.5% to 68.2%, 87.1% to 88.5%, 63.8% to 68.7%, and 74.9% to 79.3%, respectively. The mean distribution rate in blood cells following the addition of ^{14}C-labeled teneligliptin (20-500 ng/mL) to blood in mice, rats, rabbits, dogs, and monkeys were 20.9% to 22.9%, 25.0% to 26.7%, 9.4% to 14.8%, 36.5% to 38.9%, and 25.5% to 27.2%, respectively. ^{14}C-labeled teneligliptin (1 mg/kg) was administered orally to male rats (4 animals for each time point) in a single dose or once daily for 21 days. As a result, the mean distribution rate in blood cells up to 24 hours after single-dose administration was 26.6% to 35.7% and, in the repeated administration, the distribution rate on Day 1, Day 14, and Day 21 were 19.2% to 21.0%, 7.8% to 57.3%, and 25.0% to 69.9%, respectively [for data in humans, see "4.(ii).A.(1) Studies using human biomaterials"].

3.(ii).A.(3) Metabolism (4.2.2.4-1–4.2.2.4-3)

After administration of ^{14}C-labeled teneligliptin, the metabolites (M1, M2, M3, M4, M5) were identified in biological samples of rats and monkeys or in the reaction solution of monkey liver microsomes.

^{14}C-labeled teneligliptin (1 mg/kg) was administered to male rats (4 animals) in a single oral dose. As a result, the percentages (mean ± SD) of unchanged teneligliptin to radioactivity in plasma at 0.5 and 5 hours after administration were 86.7% ± 6.4% and 63.2% ± 27.9%, respectively, and the percentage of M1 was 3.8% ± 0.9% at 0.5 hours after administration. The cumulative urinary excretion rate up to 48 hours after administration relative to the administered radioactivity for unchanged teneligliptin, M1, M2, M3, M4, and M5 were 5.6% ± 1.8%, 2.6% ± 0.4%, 0.2% ± 0.1%, 0.3% ± 0.1%, 1.5% ± 0.4%, and 0.4% ± 0.0%, respectively. The cumulative fecal excretion rate were 9.3% ± 1.0%, 1.9% ± 0.4%, 1.0% ± 0.2%, 1.0% ± 0.3%, 5.5% ± 1.0%, and 2.5% ± 0.6%, respectively, and cumulative biliary excretion rate were 0.7% ± 0.1%, 34.4% ± 0.6%, 1.2% ± 0.1%, 1.0% ± 0.2%, 2.9% ± 0.7%, and 2.6% ± 0.8%, respectively.

^{14}C-labeled teneligliptin (1 mg/kg) was administered to male monkeys (4 animals) in a single oral dose. The percentages of unchanged teneligliptin at 1 and 5 hours after administration to radioactivity in plasma were 45.5% ± 8.0% and 32.7% ± 9.6%, respectively, and the percentages of M1 were 13.3% ± 4.3% and 10.0% ± 4.4%, respectively. The percentages of M2, M3, M4, and M5 at 1 hour after administration were 1.1% ± 1.0%, 1.0% ± 0.4%, 2.1% ± 0.4%, and 3.6% ± 1.1%, respectively. The cumulative urinary excretion rate up to 48 hours after administration relative to the administered radioactivity for unchanged teneligliptin, M1, M2, M3, M4, and M5 were 2.7% ± 0.6%, 9.7% ± 2.0%, 1.2% ± 0.3%, 1.7% ± 0.3%, 2.1% ± 0.5%, and 1.9% ± 0.5%, respectively. The cumulative fecal excretion rate up to 72 hours after administration for unchanged teneligliptin, M2, M3, M4, and M5 were 4.6% ± 1.9%, 0.8% ± 0.1%, 7.8% ± 2.2%, 1.4% ± 0.4%, and 1.3% ± 0.6%, respectively [for data of humans, see "4.(ii).A.(2).3) Mass balance study"].

3.(ii).A.(4) Excretion (4.2.2.5-1–4.2.2.5-4)

^{14}C-labeled teneligliptin (1 mg/kg) was administered intravenously or orally to male rats (4 animals each) in a single dose. The cumulative urinary excretion rate (mean ± SD) up to 168 hours after administration relative to the administered radioactivity were 16.4% ± 0.6% and 16.2% ± 2.0%, respectively, and the cumulative fecal excretion rate were 77.9% ± 1.8% and 86.7% ± 2.1%, respectively. Radioactivity in the cadaver at 168 hours after administration were 1.6% ± 0.1% and 1.8% ± 0.2%, respectively, of the administered radioactivity, and the cumulative biliary excretion rate up to 48 hours after administration relative to the administered radioactivity was 69.1% ± 4.9% in a single dose oral administration.

^{14}C-labeled teneligliptin (1 mg/kg) was administered orally to bile duct-cannulated male rats (4 animals) in a single dose. The cumulative urinary, fecal, and biliary excretion rates up to 48 hours after administration relative to the administered radioactivity were 8.2% ± 1.4%, 21.7% ± 2.2%, and 69.1% ± 4.9%, respectively, and the radioactivity in the cadaver at 48 hours after administration was 4.0% ± 0.1% of the administered radioactivity.

Bile was collected up to 8 hours after oral administration of ^{14}C-teneligliptin (1 mg/kg) to bile duct-cannulated male rats (4 animals) and administered it into the duodenum of other rats. The cumulative urinary, fecal, and biliary excretion rate up to 48 hours after administration relative to the administered radioactivity were 3.4% ± 0.6%, 57.5% ± 17.1%, and 10.9% ± 3.2%, respectively, and the radioactivity in the cadaver at 48 hours after administration was 13.3% ± 4.7% of the administered radioactivity.

^{14}C-teneligliptin (1 mg/kg) was administered orally to male rats (4 animals) once daily for 14 days. The cumulative urinary and fecal excretion rate up to 168 hours from the administration on Day 14 relative to the administered radioactivity were 12.7% ± 1.5% and 85.7% ± 1.8%, respectively, and the radioactivity in the cadaver was 0.2% of the administered radioactivity.

^{14}C-teneligliptin (1 mg/kg) was administered intravenously or orally to male monkeys (4 animals each) in a single dose. The cumulative urinary excretion rate up to 168 hours after administration relative to the administered radioactivity were 31.1% ± 2.3% and 32.9% ± 3.9%, respectively, and the cumulative fecal excretion rate were 60.3% ± 2.9% and 66.5% ± 3.5%, respectively.

^{14}C-teneligliptin (1 mg/kg) was administered orally to lactating rats (Postpartum day 12, 3 animals) in a single dose. The ratio of radioactivity in milk to that in plasma from 0.5 to 24 hours after administration was 0.82 to 1.25, and the ratios of the C_{max} and $AUC_{0-\infty}$ of radioactivity in milk to that in plasma were 0.92 and 1.00, respectively.

3.(ii).B Outline of the review by PMDA

On the basis of the findings in the distribution study in pigmented male rats that teneligliptin was eliminated at a slower rate from the eyeballs and the skin than other tissues, indicating the high affinity of teneligliptin to melanin, PMDA asked the applicant to explain the safety of teneligliptin in humans (in particular, safety to the eyes and the skin in long-term administration in Japanese subjects).

The applicant responded as follows:
In the 26-week oral carcinogenicity study in CB6F1-Tg rasH2 mice, no histopathological findings possibly caused by teneligliptin were observed in the eyes or the skin in the 600 mg/kg/day group (exposure level was 118.6-126.8 times the $AUC_{0\text{-}24\ h}$[21] reached when the maximum clinical dose in Japan [40 mg/day] was administered to Japanese subjects). Also, in the 52-week oral toxicity study in monkeys, no abnormality was observed in ophthalmologic examination or in ocular histopathological examination in the 75 mg/kg/day group (dose reduced to 60 mg/kg/day from Day 46. The exposure level was 44.9-46.6 times the $AUC_{0\text{-}24\ h}$[21] reached when the maximum clinical dose in Japan [40 mg/day] was administered to Japanese subjects). As regards the skin, in contrast, necrotic skin lesion was observed at the terminal region of the body, as is the case with approved DPP-4 inhibitor drugs. The skin lesion of teneligliptin was speculated to be similar to that observed with drugs of the same class, but compared to the other drugs of the same class, the lesions occurred only at a higher exposure level. By that and from the results of clinical studies

[21] $AUC_{0\text{-}24\ h}$ under steady state (3628.1 ng·h/mL) was estimated by simulation based on the plasma concentration data obtained when the maximum clinical dose in Japan (40 mg) was administered in a single oral dose to Japanese healthy adult male subjects (Study 3000-A1, 5.3.3.1-1).

on teneligliptin and drugs of the same class, it is suggested that the skin toxicity is likely to be unique only to monkeys.

Regarding safety of teneligliptin to the eyes and the skin in Japanese subjects, adverse events classified as "eye disorders" and "skin and subcutaneous tissue disorders" were investigated based on the results of the integrated analysis of the Japanese clinical studies (double-blind comparative studies, 3000-A3 to A7; long-term treatment studies, 3000-A6 to A8).

In double-blind comparative studies, the incidence of adverse events classified as "eye disorders" in the placebo, 2.5 mg, 10 mg, 20 mg, and 40 mg groups were 1.9% (8 of 428 subjects), 2.0% (1 of 49 subjects), 4.7% (6 of 129 subjects), 2.1% (8 of 377 subjects), and 5.5% (7 of 128 subjects), respectively, and there were no adverse events for which causal relationship with the study drug could not be denied[22] (adverse drug reactions). Although the incidence of adverse events was slightly higher in the 10 mg and 40 mg groups compared with the placebo group, it did not have the tendency to increase dose-dependently. In long-term treatment studies, the incidence of adverse events classified as "eye disorders" in the monotherapy group, sulfonylurea concomitant therapy group, and thiazolidinedione concomitant therapy group were 7.9% (12 of 151 subjects), 11.8% (33 of 280 subjects), and 9.0% (18 of 201 subjects), respectively. No adverse drug reactions were observed. The incidence of adverse events classified as "eye disorders" by the time of occurrence was similar among "Day 0 to 84," "Day 85 to 168," "Day 169 to 252," and "Day 253 to 364." The time of the occurrence did not show any specific tendency, and the incidence did not increase with the treatment duration.

In double-blind comparative studies, the percentage incidence of adverse events classified as "skin and subcutaneous tissue disorders" in the placebo, 2.5 mg, 10 mg, 20 mg, and 40 mg groups were 3.3% (14 of 428 subjects), 4.1% (2 of 49 subjects), 7.8% (10 of 129 subjects), 6.4% (24 of 377 subjects), and 5.5% (7 of 128 subjects), respectively, and the incidence of adverse drug reactions were 0.5% (2 of 428 subjects), 0.0% (0 of 49 subjects), 0.8% (1 of 129 subjects), 1.3% (5 of 377 subjects), and 0.0% (0 of 128 subjects), respectively.
The incidence of adverse events was slightly higher in the teneligliptin groups compared with the placebo group, but did not have the tendency to increase dose-dependently. In long-term treatment studies, the incidence of adverse events classified as "skin and subcutaneous tissue disorders" in the monotherapy group, sulfonylurea concomitant therapy group, and thiazolidinedione concomitant therapy group were 19.9% (30 of 151 subjects), 16.8% (47 of 280 subjects), and 13.9% (28 of 201 subjects), respectively, and the incidence of adverse drug reactions were 2.0% (3 of 151 subjects), 0.7% (2 of 280 subjects), and 3.0% (6 of 201 subjects), respectively. The incidence, by the time of the occurrence, of adverse events classified as "skin and subcutaneous tissue disorders" was similar among "Day 0 to 84", "Day 85 to 168", "Day 169 to 252", and "Day 253 to 364." The time of the occurrence did not show any specific tendency, and the incidence did not increase with the treatment duration.

Thus, the results of non-clinical toxicity studies did not show any toxicity related to the eyes or the skin possibly caused by the high melanin affinity. Also, in Japanese clinical studies, the incidence of eye or skin-related adverse events did not tend to increase dose-dependently or with the increase in treatment duration. From these results, the applicant considered that teneligliptin is unlikely to pose any safety problems caused by the melanin affinity in Japanese patients with type 2 diabetes mellitus.

PMDA accepted the response that teneligliptin was unlikely to pose any safety problems caused

[22] Causal relationship with the investigational product was judged using a 4-grade rating scale: "not related", "unlikely related", "possibly related", and "related". Adverse events judged as "possibly related" or "related" were defined as adverse drug reactions.

by the melanin affinity, based on the results of nonclinical studies and Japanese clinical studies. However, in view of the fact that skin-related adverse drug reactions are reported with approved DPP-4 inhibitors, PMDA considers it necessary to collect safety information related to the skin, etc., after marketing.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Teneligliptin toxicology studies conducted include single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (antigenicity studies, immunotoxicity studies, toxicity studies on metabolites). All *in vivo* studies, except the micronucleus study of metabolites in mice, were conducted by oral administration using 0.5% carboxymethylcellulose sodium solution as vehicle. In the toxicology studies, doses of teneligliptin and concentrations of unchanged teneligliptin and of metabolites in test samples are all expressed in terms of the free base.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1-1, 4.2.3.1-2)

In the single-dose study in which teneligliptin (0 [vehicle], 1000, 2000 mg/kg) was administered orally to Wistar rats (5 each of males and females per group), 1 male in the 2000 mg/kg group showed a hunched position, decreased response, slowing of respiration, etc., and was sacrificed moribund and necropsied on Day 6 of administration. Therefore, the approximate lethal dose in rats was determined to be 2000 mg/kg (4.2.3.1-1). In the oral dose titration study in cynomolgus monkeys (1 each of male and female), vomiting, salivation, and eyelid closure (female only) were observed after 1000 mg/kg administration, and severe convulsion occurred in the male from 22 minutes after 2000 mg/kg administration, and the animal was sacrificed moribund at 30 minutes after administration and necropsied. From these results, the approximate lethal dose of teneligliptin in cynomolgus monkeys was determined to be 2000 mg/kg, and administration of teneligliptin 2000 mg/kg in the female was therefore cancelled (4.2.3.1-2).

3.(iii).A.(2) Repeat-dose toxicity

3.(iii).A.(2).1) Two-week oral toxicity study in rats (4.2.3.2-2, Reference data)

Teneligliptin (0 [vehicle], 100, 300, 1000 mg/kg/day) was administered orally to Wistar rats (3 each of males and females per group) for 2 weeks. In the 1000 mg/kg/day group, all animals died or sacrificed moribund and necropsied on Day 5 of administration. In the 300 mg/kg/day group, 2 males and all females were sacrificed moribund and necropsied from Day 7 to 14 of administration. These animals showed hyperplasia of esophageal and proventricular mucosal epithelium, hyperkeratosis, submucosal infiltration of inflammatory cells, disappearance, decrease, or swelling of parietal cells in the glandular stomach, erosion of intestinal mucosa, single-cell death in mucosal epithelium, single-cell death of hepatocytes in the liver, bile duct proliferation, basophilic change and hypertrophy of the tubular epithelium in the outer zone of renal medulla, decrease in lymphocytes in the periarterial lymphatic sheath (PALS) of the spleen, bone marrow congestion, and foamy alveolar macrophages.

3.(iii).A.(2).2) Thirteen-week oral toxicity study in rats (4.2.3.2-3)

Teneligliptin (0 [vehicle], 10, 30, 100, 200 mg/kg/day) was administered orally to Wistar rats (12 each of males and females per group in the main study; 3 each of males and females in the toxicokinetics study) for 13 weeks (main study). Also, a 4-week recovery study was conducted in the control, 100, and 200 mg/kg/day groups (6 each of males and females per group). Three males in the main study group and 1 male in the toxicokinetics study group, all treated with 200 mg/kg/day of teneligliptin, were sacrificed moribund and necropsied from Day 12 to 19 of administration. Changes in general conditions included unkept coat in females of the 100 mg/kg/day group, piloerection, loss of hair, emaciation, etc., in the 200 mg/kg/day group, and suppression of body weight increase in males of the 200 mg/kg/day group. Hematology test

showed shortened activated partial thromboplastin time (APTT) in males in the ≥30 mg/kg/day groups (only 200 mg/kg/day groups in females); platelet count low (males) in the 100 mg/kg/day group; and changes in red blood cell parameters (red blood cell count high [females], reticulocyte ratio high [males], haematocrit low [males], mean cell volume low, increase in the number of animals with red blood cell microcytes, etc.), and white blood cell count high (neutrophils, lymphocytes, basophils, large unstained cells) in the 200 mg/kg/day group. Clinical chemistry findings showed plasma aspartate aminotransferase (AST) high (≥100 mg/kg/day groups), alanine aminotransferase (ALT) high (males in 200 mg/kg/day group), and inorganic phosphorus concentration high (males in ≥100 mg/kg/day groups, females in ≥30 mg/kg/day groups), etc. Pathological examination showed increased weight of lung and adrenal gland and decreased weight of epididymis, prostate, and seminal vesicle in the 200 mg/kg/day group. Histopathological findings observed were accumulation of alveolar macrophages in the ≥100 mg/kg/day groups, infiltration of inflammatory cells and cell death in the adrenal cortex, thickening of the epidermis, decrease and swelling of parietal cells in the glandular stomach, hyperplasia of proventricular mucosal epithelium, thickening of duodenal villi, atrophy of seminiferous tubules in the testis, and decrease of colloid in the prostate and in the seminal vesicle in the 200 mg/kg/day group. All findings tended to recover during the 4-week recovery period. From these results, the no observed adverse effect level (NOAEL) in this study was determined to be 30 mg/kg/day. $AUC_{0\text{-}24\ h}$ in the 30 mg/kg/day group at Week 13 was 41,700 ng·h/mL in males and 41,400 ng·h/mL in females, which was 11.5 and 11.4 times, respectively, the clinical exposure level.[21]

3.(iii).A.(2).3) Twenty-six-week oral toxicity study in rats (4.2.3.2-4)

Teneligliptin (0 [vehicle], 10, 30, 150 mg/kg/day) was administered orally to Wistar rats (12 each of males and females per group) for 26 weeks. Animals in the ≥30 mg/kg/day groups showed white blood cell count high (neutrophils, lymphocytes, basophils, monocytes, large unstained cells) and plasma inorganic phosphorus high. Animals in the 150 mg/kg/day group showed unkept coat, piloerection, suppression of body weight increase, increased red blood cell count, increased reticulocyte ratio, increased number of animals with red blood cell microcytes, increased plasma ALT and AST concentrations, decreased total plasma protein, albumin, total cholesterol, and triglyceride concentrations, accumulation of alveolar macrophages, thickening of epidermis, delayed spermatid release from testis, etc. From these results, the NOAEL in this study was determined to be 10 mg/kg/day. $AUC_{0\text{-}24\ h}$ in the 10 mg/kg/day group at week 26 was 14,600 ng·h/mL in males and 13,600 ng·h/mL in females, which was 4.0 and 3.7 times, respectively, the clinical exposure level. [21]

3.(iii).A.(2).4) Four-week oral toxicity study in monkeys (4.2.3.2-6, Reference data)

Teneligliptin (0 [vehicle], 60, 100, 300 mg/kg/day) was administered orally to cynomolgus monkeys (1 each of male and female per group) for 4 weeks. Male and female in the 300 mg/kg/day group showed aggravation of general conditions (hunched position, tremor, enophthalmos, etc.) and were therefore sacrificed moribund and necropsied on Day 14 of administration. These animals showed loss of parietal cells in the stomach, single-cell death in mucosal epithelial, enlarged glandular cavity in the intestinal tract, increased cell division in the mucosal membrane, vacuolization of tubular epithelium in the renal cortex, vacuolization and single-cell death in the transitional epithelium of renal pelvis, urinary duct, and bladder. Animals in the 100 mg/kg/day group showed findings in stomach, kidney, renal pelvis, urinary tract, and bladder which were similar to those observed in animals of the 300 mg/kg/day group.

3.(iii).A.(2).5) Thirteen-week oral toxicity study in monkeys (4.2.3.2-7)

Teneligliptin (0 [vehicle], 10, 30, 100 mg/kg/day) was administered orally to cynomolgus monkeys (3 or 5 each of males and females per group) for 13 weeks. Two males in the 100 mg/kg/day group showed abrasion of the skin of the tail and of the auricular end, and one

was withdrawn from teneligliptin administration and the other was euthanized and necropsied. One female in the 100 mg/kg/day group died after showing severe salivation, gasping, and convulsion immediately after administration on Day 68 of administration. Since the animal did not show any acute symptom until 1 day before the death, it was considered that the death was not caused by the toxicity of teneligliptin. In the 100 mg/kg/day group, ECG showed QT and QTc interval prolongation, clinical chemistry showed total plasma cholesterol concentration low, and histopathological examination showed necrosis and ulcer of the wounded site of the skin in 2 males with cutaneous symptoms, and thymic involution/atrophy in other animals. From these results, the NOAEL in this study was determined to be 30 mg/kg/day. The $AUC_{0\text{-}24\ h}$ in the 30 mg/kg/day group at Week 13 was 51,544 ng·h/mL in males and 47,339 ng·h/mL in females, which was 14.2 and 13.0 times, respectively, the clinical exposure level.[21]

3.(iii).A.(2).6) Fifty-two-week oral toxicity study in monkeys (4.2.3.2-8)

Teneligliptin (0 [vehicle], 10, 30, 75 mg/kg/day) was administered orally to cynomolgus monkeys (4 each of males and females per group) for 52 weeks. Also, a 6-week recovery study was conducted in the control group and in the 75 mg/kg/day group (2 each of males and females per group). One male and 2 females in the 75 mg/kg/day showed necrotic dermatosis in the auricle, tail, etc., and in these animals, teneligliptin was withdrawn or administered in reduced dose from Day 40.[23] In other animals in the same group, teneligliptin dose was reduced to 60 mg/kg/day from Day 46. In animals in the 75 mg/kg/day group that showed cutaneous symptoms necessitating withdrawal of teneligliptin administration, clinical chemistry test showed plasma AST high, β and γ-globulin high, total plasma cholesterol low, inorganic phosphorus low, and albumin concentration low. Also, histopathological examination of these animals showed infiltration of inflammatory cells, ulcer, epithelial hyperplasia into the skin lesion, follicles in the lumbar lymph node, and increased cell density in the paracortex. Animals in the 75 mg/kg/day group showed QTc interval prolongation as well. From these results, the NOAEL in this study was determined to be 30 mg/kg/day. The $AUC_{0\text{-}24\ h}$ in the 30 mg/kg/day group at Week 52 was 89,500 ng·h/mL in males and 51,500 ng·h/mL in females, which was 24.7 and 14.2 times, respectively, the clinical exposure level. [21]

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1, 4.2.3.3.2-2)

In bacterial reverse mutation tests, in bone marrow micronucleus tests in rats after oral administration, and in unscheduled DNA synthesis test in liver cells, teneligliptin was negative for genotoxicity. In a chromosomal aberration test with cultured mammalian cells, the frequency of cells with abnormal structure increased after treatment with 2250 and 2500 μg/mL of teneligliptin for 6 hours in the absence of metabolic activation system. However, since the cell growth index at these concentrations was only 29% and 19%, respectively, from which the applicant considers that the changes were secondary to cytotoxicity. From these results, the applicant has determined that teneligliptin is not genotoxic.

3.(iii).A.(4) Carcinogenicity

3.(iii).A.(4).1) 104-week oral carcinogenicity study in rats (4.2.3.4.1-1)

Teneligliptin (0 [vehicle], 10, 25, 75 mg/kg/day in males and 0 [vehicle], 10, 30, 100 mg/kg/day in females) was administered to Wistar rats (55 each of males and females per group) for 104 weeks. Administration of teneligliptin did not cause any increase in neoplastic lesion. The number

[23] One male (animal No. 579) was given 75 mg/kg/day of teneligliptin up to Day 39, withdrawn from teneligliptin administration from Day 40 to 57, and given 60 mg/kg/day of teneligliptin from Day 58 when skin symptoms resolved. As regards 2 females, one (animal No. 580) was given 75 mg/kg/day of teneligliptin until Day 39, withdrawn from Day 40 to 66, given 60 mg/kg/day of teneligliptin from Day 67 when skin symptoms resolved up to Day 78, withdrawn from Day 79 to 224, and given 45 mg/kg/day from Day 225 to 254. The other (animal No. 582) was given 75 mg/kg/day of teneligliptin until Day 39, withdrawn from Day 40 to 62, given 60 mg/kg/day of teneligliptin from Day 63 when skin symptoms resolved up to Day 80, withdrawn from Day 81 to 210, given 45 mg/kg/day of teneligliptin from Day 211 to 254, and was euthanized on Day 254 and autopsied.

of animals with anterior pituitary adenoma or those with fibroadenoma of breast (females only) decreased in males of the 75 mg/kg/day group and in females of the 100 mg/kg/day group compared with the control group. Non-neoplastic lesions observed were mineralization of renal papilla and pelvis epithelium in males of the ≥25 mg/kg/day groups, hyperplasia of thymic epithelium in females of the ≥30 mg/kg/day groups, increased number of animals with foamy alveolar macrophages in males of the 75 mg/kg/day group and in females of the 100 mg/kg/day group, and increased frequency of renal tubular casts and chronic progressive nephropathy in females of the 100 mg/kg/day group. From these results, the NOAEL was determined to be 75 mg/kg/day in males and 100 mg/kg/day in females for neoplastic changes, and 10 mg/kg/day in both males and females for non-neoplastic changes. The $AUC_{0\text{-}24\ h}$ at Week 52 was 17,400 and 16,100 ng·h/mL, respectively, in males and females of the 10 mg/kg/day group, 237,000 ng·h/mL in the 75 mg/kg/day group, and 278,000 ng·h/mL in the 100 mg/kg/day group, which was 4.8, 4.4, 65.3, and 76.6 times, respectively, the clinical exposure level.[21]

3.(iii).A.(4).2) Four-week oral range-finding study in CB6F1-nonTg rasH2 mice (4.2.3.4.2-2)

Teneligliptin (0 [vehicle], 300, 600, 1000 mg/kg/day) was administered orally to CB6F1-nonTg rasH2 mice (10 each of males and females per group) for 4 weeks. Animals in the ≥600 mg/kg/day groups showed decreased food consumption, hyperplasia of proventriculus localized to squamous epithelium, diffuse hypertrophy of hepatocytes in the liver, etc. In the 1000 mg/kg/day group, one of each male and female died while other animals showed decreased locomotor activity, degeneration of the seminiferous tubular epithelium, etc. From these results, the maximum tolerated dose in this study was determined to be 600 mg/kg/day.

3.(iii).A.(4).3) Twenty-six-week oral carcinogenicity study in CB6F1-Tg rasH2 mice (4.2.3.4.2-3)

Teneligliptin (0 [vehicle], 20, 60, 200, 600 mg/kg/day) was administered orally to CB6F1-Tg rasH2 mice (25 each of males and females per group) for 26 weeks. Teneligliptin did not increase the mortality. Animals in the ≥200 mg/kg/day groups showed a slightly greater increase in body weight and a slight increase in food consumption. Teneligliptin did not increase neoplastic lesions. Non-neoplastic lesions observed were hyperplasia of the proventriculus localized to squamous epithelium in the ≥200 mg/kg/day groups, diffuse hyperplasia of mucosal epithelium of the bladder, diffuse hypertrophy of hepatocytes, enhanced extramedullary haemopoiesis of the spleen, diffuse vacuolization of adrenal fasciculate cells, and localized hyperplasia of mucosal epithelium of the gallbladder in the 600 mg/kg/day group. From these results, the NOAEL was determined to be 600 mg/kg/day for neoplastic changes and 60 mg/kg/day for non-neoplastic changes. The $AUC_{0\text{-}24\ h}$ at Week 26 was 20,299 and 16,025 ng·h/mL, respectively, in males and females of the 60 mg/kg/day group, and 430,295 and 460,010 ng·h/mL, respectively, in males and females of the 600 mg/kg/day group, which was 5.6 and 4.4 times, and 118.6 and 126.8 times, respectively, the clinical exposure level.[21]

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Studies of fertility and early embryonic development to implantation in rats (4.2.3.5.1-1, 4.2.3.5.1-2)

Teneligliptin (0 [vehicle], 30, 70, 150 mg/kg/day) was administered orally to male Wister rats (22 per group) for 4 weeks before mating, during mating period, and from mating up to 1 day before necropsy (66 days in total). Animals in the 150 mg/kg/day group showed suppressed body weight increase and decreased food consumption. The effects on reproductive function observed were low number of vaginal plugs, low number of implantation, low epididymal weight, and low number of sperms in the epididymal tail, and high percentage of abnormal sperms. Teneligliptin had no effect on the copulation rate, fertilization rate, weight and histology of male reproductive organ, or percentage of motile sperm. From these results, the NOAEL of teneligliptin

was determined to be 70 mg/kg/day for general condition, reproductive function, and early embryogenesis in male animals.

Teneligliptin (0 [vehicle], 30, 100, 200 mg/kg/day) was administered orally to female Wistar rats (22 per group) from 2 weeks before mating up to Gestation day 7. Animals in the 200 mg/kg/day group showed suppressed body weight increase (Gestation day 4-8), low number of implantation, high rate of early embryonic death, and low number of live fetuses. Teneligliptin had no effect on estrous cycle, copulation rate, conception rate, or days required for copulation. From these results, the NOAEL of teneligliptin was determined to be 100 mg/kg/day for the general condition, reproductive function, and early embryogenesis in female animals.

3.(iii).A.(5).2) Study on embryo-fetal development in rats (4.2.3.5.2-2)

Teneligliptin (0 [vehicle], 10, 30, 100 mg/kg/day) was administered orally to pregnant female Wistar rats (20 per group) from Gestation day 6 to 17. Rats were caesarean-sectioned on Gestation day 20 and subjected to evaluation of the effect of teneligliptin on fetuses. Findings observed in maternal animals were slight suppression of body weight increase in teneligliptin groups and decreased food consumption in the 100 mg/kg/day group. Findings related to embryonal-fetal development were increased incidence of cervical rib and decreased number of ossified sternebrae and metacarpal bones in the 100 mg/kg/day group. Teneligliptin had no teratogenic effect nor caused embryonal death. From these results, the NOAEL of teneligliptin was determined to be < 10 mg/kg/day for general condition in maternal animals and 30 mg/kg/day for embryo-fetal development. The $AUC_{0\text{-}24\ h}$ was 12,400 ng·h/mL in the 10 mg/kg/day group and 41,400 ng·h/mL in the 30 mg/kg/day group,[24] which was 3.4 and 11.4 times, respectively, the clinical exposure level.[21]

3.(iii).A.(5).3) Study on embryo-fetal development in rabbits (4.2.3.5.2-4)

Teneligliptin (0 [vehicle], 10, 30, 60 mg/kg/day) was administered orally to pregnant NZW rabbits (22 per group) from Gestation day 6 to 19. Rabbits were caesarean-sectioned on Gestation day 29 and subjected to evaluation of effects on fetuses. Maternal animals showed no changes attributable to teneligliptin administration. As a finding related to embryo-fetal development, incomplete ossification of the 5th sternebra was observed in the 60 mg/kg/day group, but no teratogenicity nor effect on embryonal death was observed. From these results, the NOAEL of teneligliptin was determined to be 60 mg/kg/day in maternal animals and 30 mg/kg/day for embryo-fetal development. The $AUC_{0\text{-}24\ h}$ on Gestation day 19 was 61,700 ng·h/mL in the 30 mg/kg/day group and 176,000 ng·h/mL in the 60 mg/kg/day group, which was 17.0 and 48.5 times, respectively, the clinical exposure level.[21]

[24] Data obtained at Week 13 of administration in the 13-week oral toxicity study in rats (4.2.3.2-3).

3.(iii).A.(5).4) Study for effects on pre- and postnatal development, including maternal function in rats (4.2.3.5.3-1)

Teneligliptin (0 [vehicle], 10, 30, 100 mg/kg/day) was administered orally to female Wistar rats (22 per group) from Gestation day 6 until Postpartum day 20. In maternal animals of the 100 mg/kg/day group, decreased food consumption was observed during the nursing period, whereas teneligliptin had no effect on the delivery, nursing conditions, or necropsy findings at weaning. In F_1 pups of the 100 mg/kg/day group, suppression of body weight increase was observed before weaning, whereas teneligliptin had no effect on survival, growth and differentiation, functional development, behavior and learning, reproductive capacity, or necropsy findings. From these results, the NOAEL of teneligliptin was determined to be 30 mg/kg/day both for general condition and function of maternal animals and for F_1 pups.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Antigenicity study (4.2.3.7.1-1)

Teneligliptin was negative for active systemic anaphylactic reaction in guinea pigs, passive cutaneous anaphylactic reaction in guinea pigs using the serum of sensitized guinea pigs, and passive cutaneous anaphylactic reaction in rats using the serum of sensitized mice. From these results, the applicant has considered that teneligliptin is not antigenic.

3.(iii).A.(6).2) Immunotoxicity studies (4.2.3.7.2-1, 4.2.3.7.2-2)

A CD3-induced T lymphocyte proliferation test and a mixed lymphocyte culture test were performed and, based on the results, teneligliptin was determined to have no effect on lymphocyte proliferation (4.2.3.7.2-1).

Teneligliptin (0 [vehicle], 10, 30, 100 mg/kg/day) was administered orally to Wistar rats (10 each of males and females per group) for 4 weeks. As a result, animals in the ≥30 mg/kg/day groups showed white blood cell count high (mainly caused by lymphocyte count high), high level of CD45RA-positive B-lymphocyte count and CD3-positive T-lymphocyte count, and low ratio of CD26-positive B lymphocytes. In the spleen, high ratio of CD45RA-positive B lymphocytes was observed in males of the ≥30 mg/kg/day groups and low ratio of CD3-positive T lymphocytes was observed in females of the 100 mg/kg/day group. Histopathological examination showed increased cell density in the paracortex of mesenteric, mandibular, and axillary lymph nodes in the ≥30 mg/kg/day groups. In a plaque-forming assay, teneligliptin had no effect on plaque formation. Although blood test and histopathological examination showed effects of teneligliptin, the effects were minimal and teneligliptin had no effect on plaque formation. On the basis of these results, the applicant has determined that teneligliptin has no immunotoxicity (4.2.3.7.2-2).

3.(iii).A.(6).3) Toxicity studies of metabolites (4.2.3.7.5-1–4.2.3.7.5-6)

Among the metabolites of teneligliptin in humans, M1 was detected in the mass balance study [see "4.(ii).A.(2).3) Mass balance study"] in an amount exceeding the lower limit requiring safety evaluation. Therefore, the safety of metabolite M1 was investigated.

The NOAEL of teneligliptin in the 52-week oral toxicity study in monkeys (4.2.3.2-8), 26-week oral carcinogenicity study in CB6F1-Tg rasH2 mice (4.2.3.4.2-3), and study on embryo-fetal development in rabbits (4.2.3.5.2-4), the $AUC_{0\text{-}24\ h}$ of M1 were 10.3 to 10.7, 5.8 to 6.6, and 8.0 μg·h/mL, respectively, which corresponds to 12 to 13, 7 to 8, and 10 times the exposure level of $AUC_{0\text{-}24\ h}$[25] of M1 when the maximum clinical dose in Japan (40 mg/day) is administered to Japanese subjects. Therefore, the metabolite was considered unlikely to pose any concerns

[25] The $AUC_{0\text{-}24\ h}$ and C_{max} of M1 and M2 under steady state (0.8 μg·h/mL and 0.078 μg/mL [M1], 0.073 μg·h/mL and 0.004 μg/mL [M2]) following the administration of the maximum clinical dose in Japan (40 mg/day) to Japanese subjects were estimated from the ratio of the radioactivity of M1 and M2 in plasma to that of teneligliptin in the single dose oral mass balance study in Caucasian healthy adult male subjects (Study MP-513-E08, 5.3.3.1-5).

about general toxicity or toxicity in embryo-fetal development.

Genotoxicity of metabolites M1 and M2 was investigated. In the bacterial reverse mutation test and in the bone marrow micronucleus test by intravenous administration in male mice (strain ICR, 5-6 animals per group), both M1 and M2 were considered negative for genotoxicity (4.2.3.7.5-1, 4.2.3.7.5-3, 4.2.3.7.5-4, 4.2.3.7.5-6). In the chromosomal aberration test using cultured mammalian cells, M1 and M2 increased the frequency of cells with structural chromosomal aberration at and above 3750 μg/mL and at 3500 μg/mL, respectively (4.2.3.7.5-2, 4.2.3.7.5-5). In the micronucleus test in mice, the plasma level of M1 and M2 immediately after administration was estimated to be 520.3 and 474.0 μg/mL, which is approximately 6700 and 118,500 times the C_{max}[25] observed following the administration of the maximum clinical dose in Japan (40 mg/day) to Japanese subjects. Also, the $AUC_{0\text{-}24\ h}$ of M1 and M2 in the carcinogenicity study in CB6F1-Tg rasH2 mice (4.2.3.4.2-3) was 86.4 to 110.4 and 2.2 to 2.6 μg·h/mL, which corresponds to 108 to 138 and 30 to 35 times the $AUC_{0\text{-}24\ h}$[25] observed following the administration of the maximum clinical dose in Japan (40 mg/day) to Japanese subjects. On the basis of these wide margins of differences in the exposure level, the applicant has determined that M1 and M2 pose little or no concerns about genotoxicity or carcinogenicity.

3.(iii).A.(6).4) Photosafety evaluation (4.2.3.7.7-1, Reference data)

Teneligliptin has no maximum absorption in the ultraviolet-visible range (290-700 nm) withlow molar extinction coefficient at 290 nm. Therefore, no phototoxicity test was performed.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Gastrointestinal toxicity

PMDA, taking account of toxicity findings in repeat-dose toxicity studies in rats and cynomolgus monkeys such as hyperplasia and hyperkeratosis of mucosal epithelium in the esophagus and proventriculus, and disappearance of parietal cells in the stomach, asked the applicant to explain the mechanism of the occurrences of these changes and their safety in humans.

The applicant responded as follows:

It is reported that hyperplasia of the mucosal epithelium in the esophagus and proventriculus and accompanying hyperkeratosis occur in response to various stimuli, particularly in erosion, ulcer, inflammation, etc. (Manabe S, et al. *Histopathology of Toxicologic Pathology*. Japanese Society of Toxicologic Pathology. 2000; 153-167). No clear injurious changes such as ulcer were observed in repeated oral dose toxicity studies of teneligliptin, whereas infiltration of inflammatory cells into the submucosal region of the proventriculus was observed in the 2-week oral toxicity study in rats and single-cell death in the gastric mucosal epithelium was observed in the 4-week oral dose toxicity study in monkeys, which suggest that teneligliptin has a direct injurious effect on the gastrointestinal mucosa when administered at high concentration. No pathological changes were observed in the gastrointestinal tract at the dose of 30 mg/kg/day in the 26-week oral dose toxicity study in rats or at the dose of 75/60 mg/kg/day in the 52-week oral dose toxicity study in monkeys. The concentrations of teneligliptin solution administered in these studies were 3 mg/mL and 15/12 mg/mL, respectively. When teneligliptin 40 mg is administered together with water 100 mL to humans, the concentration of the drug in the stomach is 0.4 mg/mL, which is below the concentration that did not cause any pathological change of gastrointestinal tract in the toxicity studies. These results suggest that the injury of the gastrointestinal mucosa observed in rats and monkeys is unlikely to pose safety problems in humans.

3.(iii).B.(2) Accumulation of alveolar macrophages

PMDA, taking account of the findings in the repeat-dose toxicity study and the carcinogenicity study in rats that teneligliptin increased the number of animals in which accumulation of

alveolar macrophages or foamy alveolar macrophages occured, asked the applicant to explain the mechanism of the occurrence of these findings and their safety in humans.

The applicant responded as follows:
Given that teneligliptin has an amphiphilic cationic chemical structure, a feature characteristic to compounds that induce phospholipidosis, alveolar macrophages and foamy alveolar macrophages observed in toxicity studies of teneligliptin appears to reflect phospholipidosis induced by teneligliptin. Since these changes may sometimes lead to organic or functional damages, toxicological significance of phospholipidosis should be discussed based upon the outcome of long-term repeated administration (Chatman LA, et al., *Toxicol Pathol*. 2009;37: 997-1005). Given that (1) teneligliptin-induced phospholipidosis was seen only in animals treated with ≥100 mg/kg/day of the drug in the 2-week oral dose toxicity study in rats, (2) prolonged treatment period did not cause a decrease in the threshold dose for inducing phospholipidosis or an increase in affected organ, (3) the changes were confirmed to be reversible, and (4) no findings indicating pulmonary tissue damage or changes in clinical signs such as abnormal respiration suggestive of functional damage of the lung were observed, these changes are not considered to be toxicologically serious. In the oral toxicity studies in monkeys and in CB6F1-Tg rasH2 mice, the exposure levels achieved were higher than $AUC_{0\text{-}24\ h}$ (130 μg·h/mL) achieved in rats that were treated with 100 mg/kg/day of teneligliptin and had foamy alveolar macrophages in the 2-week oral dose toxicity study. Nevertheless, the monkeys and mice showed no pathological changes suggestive of phospholipidosis in the lung, which suggests that rats were more sensitive to these changes than monkeys and mice. In addition, the NOEL of teneligliptin for these changes was 30 mg/kg/day in the 104-week oral carcinogenicity study in rats. The $AUC_{0\text{-}24\ h}$ (71.4 μg·h/mL) at this dose is approximately 20 times that of the clinical exposure level,[21] ensuring a sufficiently wide safety margin. Therefore, it is unlikely that administration of teneligliptin at the maximum clinical dose in Japan (40 mg/day) would cause pathological changes in the lung suggestive of phospholipidosis.

3.(iii).B.(3) Cutaneous toxicity in monkeys
PMDA asked the applicant to explain the mechanism of occurrence of skin toxicity observed in monkeys and its safety in humans.

The applicant responded as follows:
Among DPP-4 inhibitors currently marketed in Japan or in foreign countries, vildagliptin (marketed in Japan) and saxagliptin (yet to be marketed in Japan) are reported to induce necrotic cutaneous toxicity at the terminals of the body when administered repeatedly to cynomolgus monkeys. The teneligliptin-induced cutaneous toxicity was observed only in monkeys, toxicity was observed as necrotic lesions in the skin at the terminals of the body, and histopathologically, the lesions were observed as necrosis, ulcer, hyperplasia, and inflammation of the epidermis. Therefore, the cutaneous toxicity observed with teneligliptin resembles that caused by vildagliptin and saxagliptin. Although the mechanism of occurrence of cutaneous toxicity has yet to be clarified, it is reported to be caused by the inhibition of DPP-8 or DPP-9 (data submitted for marketing application for Januvia tablets 25 mg/50 mg/100 mg). In view of the facts that teneligliptin has a wider safety margin compared with vildagliptin and saxagliptin regarding the cutaneous toxicity in monkeys, that no clear increase was observed in the incidence of serious necrotic dermatosis or other skin-related adverse drug reactions in clinical studies of teneligliptin [see "4.(iii).B.(3).2) Skin and subcutaneous tissue disorders (including hypersensitivity reactions)"], and that there were no reports of cutaneous toxicity in clinical

studies of either vildagliptin or saxagliptin,[26,27,28,29] skin cutaneous toxicity is most likely to be unique only to monkeys.

PMDA accepted the applicant's response in 3.(iii).B.(1) to (3) above.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

In clinical development of teneligliptin, 5 formulations (2.5 mg tablets, 10 mg tablets [A and B with different component ratios], 20 mg tablets, 40 mg tablets) were used. The types of the drug product[30] used in Japanese clinical studies (evaluation data) are as shown in Table 4.

Table 4. Types of drug product used in Japanese clinical studies (evaluation data)

Drug product	Study name (Study No.)
2.5 mg tablets	Phase I single-dose study (3000-A1), Phase II exploratory study (3000-A3)
10 mg tablets (Formulation A)	Phase I multiple-dose study (3000-A2)
10 mg tablets (Formulation B)	Bioequivalence study (3000-A9) Clinical pharmacology study (3000-A12) Phase II exploratory study (3000-A3), Phase II confirmatory study (3000-A4)
20 mg tablets a)	Food effect study (3000-A13) Drug-drug interactions study with glimepiride (3000-A10) Drug-drug interactions study with pioglitazone (3000-A11) Bioequivalence study (3000-A9) Clinical pharmacology study (3000-A12) Phase III double-blind confirmatory study (3000-A5) Phase III sulfonylurea concomitant therapy study (3000-A6) Phase III thiazolidinedione concomitant therapy study (3000-A7) Phase III long-term treatment study (3000-A8)
40 mg tablets	Phase I single-dose study (3000-A1), Phase I multiple-dose study (3000-A2) Phase II exploratory study (3000-A3), Phase II confirmatory study (3000-A4)

a) Proposed commercial drug product

Unchanged teneligliptin, M1 and stereoisomers[31] in human biomaterials were measured by high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation was 1 ng/mL for all these compounds. Metabolites in human biomaterials were analyzed by accelerator mass spectroscopy (AMS) or by liquid scintillation counting (LSC).

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26 FDA review report for saxagliptin, 2009, Medical Review(s) (Application number: 22-350)

27 Ligueros-Saylan M, *Diabetes Obes Metab*, 2010;12: 495-509.

28 Deacon CF, *Diabetes Obes Metab*, 2011;13: 7-18.

29 Data submitted for marketing application for Equa tablets 50 mg

30 The types of the drug product used in the foreign thorough QT/QTc study (Study MP-513-A01, evaluation data) were 10 mg tablets (Formulation B) and 40 mg tablets.

31 In the measurement of concentrations of the stereoisomers (2R4R, 2R4S, 2S4R forms) of teneligliptin in Studies 3000-A1, MP-513-E01, 3000-A2, and MP-513-E02, the 2S4R's peak overlapped the bottom of teneligliptin's peak in some plasma samples because of the high teneligliptin concentration, resulting in inaccurate measurement of the concentration of the stereoisomer. Therefore, in order to detect 2S4R in plasma samples with high teneligliptin concentration, the samples were diluted 5 or 25 fold with blank plasma depending on the plasma teneligliptin concentration and again measured. In this case, the lower limit of quantitation was 5 or 25 ng/mL instead of 1 ng/mL achieved with undiluted samples.

The data of the Japanese clinical studies (Studies 3000-A1, 3000-A9, 3000-A13) were submitted as evaluation data on biopharmaceutics. The data of a foreign clinical study (Study MP-513-E01) were submitted as reference data. The results from the main studies are described below.

4.(i).A.(1) Food effect study (5.3.1.1-1, Study 3000-A13 [[redacted] to [redacted] 20[redacted]])

A randomized, open-label, 2-arm, 2-period, cross-over study was conducted in Japanese healthy adult male subjects (target sample size of 14) to evaluate the effect of food consumption on the pharmacokinetics of teneligliptin following a single dose oral administration.

In period I and period II, teneligliptin 20 mg was to be administered in a single oral dose after fasting for ≥10 hours (fasting administration) or at 10 minutes after breakfast (postprandial administration). A washout period of ≥14 days was required between the 2 periods.

All of 14 treated subjects were included in the populations for pharmacokinetic analysis and for safety analysis.

Regarding pharmacokinetics, the C_{max} (mean ± SD) of unchanged plasma teneligliptin following fasting and postprandial administration was 236.2 ± 43.8 and 187.5 ± 33.6 ng/mL, respectively, $AUC_{0\text{-}72\ h}$ was 1861.1 ± 148.1 and 1814.6 ± 183.3 ng·h/mL, t_{max} was 1.1 ± 0.4 and 2.6 ± 1.1 hours, and $t_{1/2}$ was 27.8 ± 9.3 and 28.3 ± 9.5 hours. The ratio of the geometric mean (postprandial/fasting) of C_{max} and $AUC_{0\text{-}72\ h}$ with their 2-sided 90% CI were 0.80 [0.72, 0.88] and 0.97 [0.93, 1.02], respectively.

Regarding safety, no adverse events were observed. There was no particularly relevant variability in vital signs or ECG.

4.(i).A.(2) Bioequivalence study (5.3.1.2-1, Study 3000-A9 [[redacted] to [redacted] 20[redacted]])

A randomized, open-label, 2-arm, 2-period, cross-over study was conducted in Japanese healthy adult male subjects (target sample size of 22) to evaluate the bioequivalence of teneligliptin 10 mg tablets (Formulation B) and 20 mg tablets.

Two 10 mg tablets (Formulation B) or one 20 mg tablet was to be administered in a single oral dose under fasted conditions in period I and in period II. A washout period of ≥13 days was required between the 2 periods.

All of 22 treated subjects were included in the safety analysis population. Of which, pharmacokinetic analysis was performed using the data obtained from 21 subjects. Excluded was 1 subject withdrawn from the study due to an adverse event.

Regarding pharmacokinetics, the ratio of the geometric mean (20 mg tablet/10 mg tablets [Formulation B]) of C_{max} and $AUC_{0\text{-}72\ h}$ of unchanged plasma teneligliptin with their two-sided 90% CI were 1.02 [0.97, 1.07] and 0.98 [0.96, 1.00], respectively, which were within the bioequivalence criteria stipulated by “Guidelines for Bioequivalence Testing of Generic Drugs” (PMSB/ELD Notification No. 487 dated December 22, 1997, partially revised by PFSB/ELD Notification No. 1124004 dated November 24, 2006).

Regarding safety, 2 adverse events (influenza, C-reactive protein increased) were observed in 2 subjects who received 10 mg tablets (Formulation B). Adverse events leading to treatment discontinuation occurred in 1 subject (1 event) (influenza). There were no adverse drug reactions. There was no particularly relevant variability in vital signs or in ECG.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

Results of 7 Japanese clinical studies (Studies 3000-A1 to A4, 3000-A10 to A12) and 1 foreign clinical study (Study MP-513-A01) were submitted as the evaluation data, and results of 9 foreign clinical studies (Studies MP-513-E01 to E03, MP-513-E05, MP-513-E06, MP-513-E08 to E11) were submitted as the reference data. In addition, data of studies using human biomaterials were submitted. The results from main studies are described below.

4.(ii).A.(1) Studies using human biomaterials (5.3.2.1-1, 5.3.2.2-1 to 8)

The mean binding ratio of ^{14}C-labeled teneligliptin (20-500 ng/mL) to human plasma protein, measured by ultrafiltration method, was 77.6% to 82.2%.

^{14}C-labeled teneligliptin was added to human serum albumin, human γ-globulin, or α1-acid glycoprotein solutions to create a solution with the concentration of 100 ng/mL. The binding rate (mean ± SD) measured by ultrafiltration method was 73.7% ± 0.7%, 7.8% ± 0.6%, and 61.2% ± 1.8%, respectively.

The mean distribution rate of ^{14}C-labeled teneligliptin (20-500 ng/mL) in blood cells in human blood was 22.8% to 25.6%.

Metabolism of ^{14}C-labeled teneligliptin was investigated using microsomes expressing human CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) and FMO isoforms (FMO1, FMO3, FMO5). As a result, CYP3A4 produced mainly M1 together with a slight amount of M3. CYP2D6 produced M1 and M4 in minute amounts, while FMO1 and FMO3 produced M1. Other CYP and FMO isoforms did not produce metabolites. Metabolism of teneligliptin (10 μmol/L) by human liver microsomes was inhibited by 47.0% by ketoconazole (0.5 μmol/L), a specific inhibitor of CYP3A4, and by 67.2% by methimazole (200 μmol/L), a specific inhibitor of FMO, but not by quinidine (1 μmol/L), a specific inhibitor of CYP2D6.

Metabolic clearance of ^{14}C-labeled teneligliptin to M1 was investigated using microsomes expressing human CYP isoform (CYP3A4) and FMO isoforms (FMO1 and FMO3). As a result, the metabolic clearance by CYP3A4, FMO1, and FMO3 was 0.889 μL/pmol P450/min, 0.260 μL/pmol FMO/min, and 0.413 μL/pmol FMO/min, respectively.

Inhibitory effect of teneligliptin (5-500 μmol/L) and M1 (5-500 μmol/L) on each CYP isoform (CYP1A2, 2A6, 2B6, 2C8, 2C8/9, 2C19, 2D6, 2E1, 3A4) and FMO was investigated using human liver microsomes. The IC_{50} of teneligliptin against CYP2D6, 3A4, and FMO activities was 489.4, 197.5, and 467.2 μmol/L, respectively, whereas teneligliptin did not inhibit other isoforms (IC_{50} > 500 μmol/L). M1 did not have an inhibitory effect on any of the isoforms (IC_{50} > 500 μmol/L).

CYP1A2- and 3A4-inducing activity of teneligliptin (0.1-10 μmol/L) was investigated using human primary cultured hepatocytes. The mRNA expression level of CYP1A2 and 3A4 and their metabolic activities were less than 2 times those observed with the vehicle control (0.1% purified water) and less than 10% of the induction rate achieved by positive controls omeprazole and rifampicin.

Transcellular transport of ^{14}C-labeled teneligliptin (1, 10 μmol/L) was investigated using human P-gp-expressing LLC-PK1 cells derived from porcine renal epithelial cells. The ratio of permeability coefficient B to A/A to B (A to B, from apicolateral membrane side to basement membrane side; B to A, from basement membrane side to apicolateral membrane side), adjusted by control cells, was 0.79 and 7.41, respectively, for control substances mannitol and digoxin, and 6.81 and 5.27, respectively, for teneligliptin at 1 and 10 μmol/L. The K_m of P-gp for

teneligliptin transport was 16.9 μmol/L. The inhibitory effect of teneligliptin (0, 1, 10, 99 μmol/L) on digoxin transport by human P-gp-expressing LLC-PK1 cells was investigated. The ratios of permeability coefficient adjusted by control cells were 10.25, 8.92, 11.22, and 4.36, respectively, showing a reduction in digoxin transporting activity to 42.5% by teneligliptin 99 μmol/L compared with the control.

Incorporation of teneligliptin (0.1-100 μmol/L) into cells expressing hOAT1, hOAT3, and hOCT2 was investigated. Teneligliptin inhibited the transport of estrone-3 sulfate by hOAT3 with IC_{50} of 99.2 μmol/L, but did not inhibit the transport of substrates mediated by other transporters (p-aminohippuric acid by hOAT1, metformin by hOCT2).

4.(ii).A.(2) Studies in healthy adult subjects

4.(ii).A.(2).1) Phase I single-dose study (5.3.3.1-1, Study 3000-A1 [to 20])

A placebo-controlled, randomized, double-blind comparative study was conducted in Japanese healthy adult male subjects (target sample size of 48) to investigate the safety, pharmacokinetics, food effect, and pharmacodynamics following a single oral dose of teneligliptin.

Placebo or teneligliptin (2.5, 10, 20, 40, 80, 160 mg) was administered in a single oral dose under fasting conditions in Steps 1, 2, 3, 4-1, 5, and 6. In Step 4-2, placebo or teneligliptin (40 mg) was administered in a single oral dose immediately before meal (at 1 minute before the start of breakfast). A washout period of 21 days was required between Step 4-1 and Step 4-2. Of 8 subjects in each step, 2 subjects were randomly assigned to the placebo group, and 6 subjects to the teneligliptin group.

All of 48 treated subjects were included in the populations for pharmacodynamic analysis and for safety analysis. Among them, all 36 subjects treated with teneligliptin were included in the pharmacokinetic analysis population.

The pharmacokinetic parameter values of unchanged teneligliptin and M1 following a single-dose administration were as shown in Table 5. The ratio of the geometric means (immediately before meal/fasting) of C_{max} and AUC_{0-t} of unchanged plasma teneligliptin following the administration of teneligliptin 40 mg under fasting conditions or immediately before meal, and their two-sided 90% CI, were 1.09 [0.87, 1.36] and 1.00 [0.91, 1.10], respectively, and the t_{max} (mean ± SD) was 1.3 ± 0.9 hours in administration under fasting conditions and 0.9 ± 0.5 hours in administration immediately before meal. The plasma concentrations of the stereoisomers (2R4R, 2R4S, 2S4R forms) of teneligliptin (2S4S form) following a single oral dose of teneligliptin 80 mg were below the lower limit of quantitation[32] at all measuring time points.

[32] 2R4R and 2R4S forms, 1 ng/mL; 2S4R form, 25 ng/mL

Table 5. Pharmacokinetic parameters of unchanged teneligliptin and M1 following a single-dose oral administration

Parameter	Analyte	2.5 mg (n = 6)	10 mg (n = 6)	20 mg (n = 6)	40 mg[a)] (n = 6)	40 mg[b)] (n = 6)	80 mg (n = 6)	160 mg (n = 6)
C_{max} (ng/mL)	Unchanged teneligliptin	13.90 ± 3.79	77.22 ± 19.84	187.20 ± 44.70	382.40 ± 89.83	420.67 ± 114.92	955.77 ± 207.45	2107.83 ± 450.30
	M1	3.17 ± 0.97	18.36 ± 4.99	49.72 ± 9.14	90.85 ± 19.48	85.49 ± 16.07	232.40 ± 69.33	532.17 ± 68.65
AUC_{0-t} (ng·h/mL)	Unchanged teneligliptin	230.7 ± 50.2	794.5 ± 136.9	1882.3 ± 408.9	3499.7 ± 763.7	3497.0 ± 734.8	7485.0 ± 1370.7	18,042.8 ± 5396.3
	M1	17.4 ± 6.8	162.3 ± 22.9	497.9 ± 113.3	971.7 ± 274.2	935.0 ± 260.0	1982.8 ± 229.4	5037.5 ± 1112.9
t_{max} (h)	Unchanged teneligliptin	1.5 (1.0, 2.0)	1.3 (0.5, 3.0)	1.8 (1.0, 2.0)	1.0 (0.5, 3.0)	0.8 (0.5, 1.5)	1.5 (0.5, 2.0)	1.3 (0.5, 1.5)
	M1	1.8 (1.0, 3.0)	1.5 (1.0, 3.0)	1.5 (1.0, 3.0)	1.5 (1.0, 4.0)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)	1.5 (1.0, 2.0)
$t_{1/2}$ (h)	Unchanged teneligliptin	31.4 ± 10.7	25.7 ± 2.1	24.2 ± 5.0	20.8 ± 3.2	27.5 ± 9.8	24.8 ± 8.2	23.5 ± 4.7
	M1	5.5 ± 1.2	14.7 ± 3.1	10.5 ± 3.1	16.4 ± 2.9	21.2 ± 13.4	18.6 ± 6.5	18.9 ± 3.3
CL/F (mL/h/kg)	Unchanged teneligliptin	151 ± 26	179 ± 29	169 ± 39	169 ± 27	176 ± 31	168 ± 22	141 ± 37
	M1	1675 ± 296	827 ± 158	651 ± 104	649 ± 198	665 ± 231	617 ± 82	470 ± 82
$fe_{0-72\,h}$ (%)	Unchanged teneligliptin	17.4 ± 1.2	17.2 ± 4.9	21.0 ± 4.8	22.1 ± 5.4	22.5 ± 8.9	22.9 ± 3.7	25.1 ± 3.3
	M1	19.2 ± 2.8	21.1 ± 3.5	23.5 ± 2.3	26.2 ± 7.6	21.8 ± 6.0	30.8 ± 5.0	35.4 ± 9.4
CL_r (mL/h/kg)	Unchanged teneligliptin	32 ± 2	33 ± 6	37 ± 4	39 ± 6	42 ± 14	41 ± 9	39 ± 12
	M1	448 ± 108	184 ± 29	151 ± 33	160 ± 33	—	189 ± 26	167 ± 51

Mean ± SD, t_{max} is expressed in median (minimum, maximum), -: Not calculated
C_{max}: Maximum plasma concentration, AUC_{0-t}: Area under plasma concentration-time curve up to the last point with the quantifiable level, t_{max}: Time to maximum plasma concentration, $t_{1/2}$: Elimination half-life, CL/F: Apparent total body clearance, $fe_{0-72\,h}$: Cumulative urinary excretion rate from 0 to 72 hours, CL_r: Renal clearance
a) Step 4-1 (administration under fasting conditions)
b) Step 4-2 (administration immediately before meal)

Regarding pharmacodynamics, the maximum inhibitory rate (E_{max}, mean ± SD) of dipeptidyl peptidase (DPP) -4 following fasted administration[33] in the placebo group, teneligliptin 2.5, 10, 20, 40, 80, and 160 mg groups were 8.98% ± 14.6%, 46.8% ± 3.84%, 73.2% ± 3.20%, 86.0% ± 2.00%, 90.7% ± 2.06%, 94.8% ± 0.73%, and 95.8% ± 0.89%, respectively. The DPP-4 inhibition rate at 24 hour after administration ($E_{24\,h}$) were -6.01% ± 3.94%, 22.3% ± 4.92%, 41.7% ± 2.78%, 53.9% ± 4.13%, 59.8% ± 5.06%, 73.2% ± 4.93%, and 83.6% ± 2.80%, respectively. The $AUC_{0-2\,h}$ of active glucagon-like peptide-1 (GLP-1) in plasma after lunch were 1.60 ± 1.69, 4.79 ± 4.77, 6.09 ± 1.24, 5.03 ± 2.31, 3.52 ± 3.00, 7.71 ± 4.46, and 4.14 ± 1.64 pmol·h/L, respectively.

Regarding safety, 4 adverse events occurred in 3 of 12 subjects in the placebo group and 16 adverse events in 10 of 36 subjects in the teneligliptin group. All events were mild in severity and resolved except remission of wound (10 mg group). Adverse drug reactions occurred in 3 of 12 subjects in the placebo group (3 events) (1 event each of diarrhoea, somnolence, and dizziness postural) and in 5 of 36 subjects in the teneligliptin group (6 events) (2 events of diarrhoea, 1

[33] The E_{max} and $E_{24\,h}$ (mean ± SD) of DPP-4 inhibition rate following administration of 40 mg teneligliptin immediately before meal were 91.5% ± 2.25% and 61.9% ± 6.42%, respectively.

event each of abdominal pain upper, and dizziness postural in the 10 mg group; 1 event each of headache and abdominal pain in the 40 mg group). There was no particularly relevant variability in vital signs or in ECG. There were no deaths, other serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(2).2) Phase I multiple-dose study
(5.3.3.1-2, Study 3000-A2 [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind comparative study was conducted in Japanese healthy male subjects (target sample size of 20) to investigate the safety, pharmacokinetics, and pharmacodynamics of teneligliptin in single and multiple oral dose of teneligliptin.

In Step 1, placebo or teneligliptin (20 mg) was administered in a single oral dose 30 minutes before breakfast and, from after 72 hours, the same dose was administered orally 30 minutes before breakfast once daily for 7 days. In Step 2, placebo or teneligliptin (80 mg) was administered in a single oral dose at 30 minutes before breakfast and, from after 72 hours, the same dose was administered orally at 30 minutes before breakfast once daily for 7 days. Of 10 subjects in each Step, 3 subjects were randomized to the placebo group and 7 subjects to the teneligliptin group.

All 20 treated subjects were included in the populations for pharmacodynamic analysis and for safety analysis, and all 14 subjects treated with teneligliptin were included in the pharmacokinetic analysis population.

Regarding pharmacokinetics, the C_{max} (mean ± SD) of unchanged plasma teneligliptin following a single-dose administration and 7-day multiple-dose administration were 160.6 ± 47.3 and 220.1 ± 59.9 ng/mL, respectively, in the 20 mg group and 926.7 ± 213.1 and 1180.9 ± 194.5 ng/mL, respectively, in the 80 mg group; the $AUC_{0\text{-}24\,h}$ was 1057.2 ± 283.9 and 1514.6 ± 370.5 ng·h/mL in the 20 mg group and 5257.7 ± 511.5 and 7292.2 ± 733.1 ng·h/mL in the 80 mg group; the $t_{1/2}$ was 25.8 ± 4.9 and 30.2 ± 6.9 hours in the 20 mg group and 17.6 ± 2.7 and 23.7 ± 4.7 hours in the 80 mg group; the CL/F was 191 ± 37 and 204 ± 34 mL/h/kg in the 20 mg group and 192 ± 7 and 186 ± 8 mL/h/kg in the 80 mg group; and the t_{max} (median) was 1 hour in both dose groups in single-dose administration as well as in 7-day multiple-dose administration. The cumulative urinary excretion rate from Day 1 to Day 13 ($fe_{D1\text{-}D13}$) was 21.3% ± 2.9% in the 20 mg group and 19.4% ± 2.9% in the 80 mg group. The cumulative coefficient (multiple dose/single dose) for C_{max} and $AUC_{0\text{-}24\,h}$ were 1.387 and 1.439, respectively, in the 20 mg group and 1.292 and 1.386, respectively, in the 80 mg group. The C_{max} of M1 following single-dose administration and following 7-day multiple-dose administration was 29.3 ± 6.8 and 41.9 ± 8.5 ng/mL, respectively, in the 20 mg group and 341.1 ± 175.4 and 336.8 ± 126.8 ng/mL, respectively, in the 80 mg group; the $AUC_{0\text{-}24\,h}$ was 218.0 ± 49.9 and 357.0 ± 94.0 ng·h/mL in the 20 mg group and 2463.7 ± 928.9 and 2975.0 ± 860.9 ng·h/mL in the 80 mg group; the $t_{1/2}$ was 22.6 ± 6.2 and 23.7 ± 5.9 hours in the 20 mg group and 17.2 ± 4.4 and 17.8 ± 4.5 hours in the 80 mg group; and the t_{max} (median) was 1.5 to 2.0 hours in both dose groups in single-dose administration as well as in 7-day multiple-dose administration. The $fe_{D1\text{-}D13}$ was 25.5% ± 3.7% in the 20 mg group and 35.0% ± 8.1% in the 80 mg group. The plasma concentrations of the stereoisomers (2R4R, 2R4S, 2S4R forms) following multiple-dose administration of teneligliptin (2S4S form, 20, 80 mg) were below the lower limit of quantitation[34] at all measured time points.

Regarding pharmacodynamics, the maximum inhibition rate of DPP-4 (E_{max}, mean ± SD) in the placebo group, teneligliptin 20 and 80 mg groups were 9.80% ± 8.11%, 83.5% ± 4.19%, and 94.9% ± 0.69%, respectively, after single-dose administration, and 9.65% ± 4.41%, 90.1% ± 3.21%, and 96.6% ± 0.33%, respectively, after 7-day multiple-dose administration; the $E_{24\,h}$ was

[34] 2R4R and 2R4S forms, 1 ng/mL; 2S4R form, 1 or 5 ng/mL (20 mg group), 5 ng/mL (80 mg group)

7.23% ± 10.3%, 53.7% ± 4.50%, and 77.8% ± 3.15%, respectively, after single-dose administration and -0.22% ± 15.4%, 66.9% ± 4.17%, and 85.0% ± 2.19%, respectively, after 7-day multiple-dose administration; the $AUC_{0\text{-}2\ h}$ of active plasma GLP-1 after breakfast was 3.42 ± 1.79, 9.95 ± 3.77, and 9.78 ± 2.94 pmol·h/L, respectively, after single-dose administration and 3.27 ± 1.47, 9.67 ± 4.57, and 11.52 ± 3.58 pmol·h/L, respectively, after 7-day multiple-dose administration; and the $AUC_{0\text{-}2\ h}$ after supper was 1.98 ± 0.94, 7.17 ± 1.76, and 8.77 ± 2.29 pmol·h/L, respectively, after single-dose administration and 1.46 ± 1.48, 8.27 ± 2.79, and 11.08 ± 4.31 pmol·h/L, respectively, after 7-day multiple-dose administration.

Regarding safety, 14 adverse events were observed in 6 of 6 subjects in the placebo group and 11 adverse events were observed in 7 of 14 subjects in the teneligliptin group. One of the 2 events of ventricular extrasystoles observed in the 20 mg group was moderate in severity, while all other adverse events were mild. Nasopharyngitis improved (20 mg group) and cheilitis persisted (placebo group), whereas all other adverse events resolved. Adverse drug reactions occurred in 3 of 6 subjects in the placebo group (9 events) (1 event each of diarrhoea, pain in jaw, anaemia, palpitations, malaise, somnolence, and inappetence, 2 events of abdominal pain) and in 4 of 14 subjects in the teneligliptin group (5 events) (2 events of ventricular extrasystoles, 1 event of somnolence in 20 mg group; 1 event each of ventricular extrasystoles and alanine aminotransferase [ALT] increased in 80 mg group). There were no deaths, other serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(2).3) Mass balance study (5.3.3.1-5, StudyMP-513-E08 [[redacted] to [redacted] 20[redacted]], Reference data)

An open-label, uncontrolled study was conducted in foreign healthy adult male subjects (target sample size of 6) to investigate the mass balance, metabolite profile, and pharmacokinetics following a single-dose administration of ^{14}C-labeled teneligliptin.

Approximately 20 mg (as free form) of ^{14}C-labeled teneligliptin was administered in a single oral dose after fasting for ≥10 hours.

All 6 treated subjects were included in the populations for pharmacokinetic analysis and for safety analysis.

Regarding pharmacokinetics, the percentages of $AUC_{0\text{-}\infty}$ of unchanged teneligliptin, M1, M2, M3, M4, and M5 to $AUC_{0\text{-}\infty}$ within the total plasma radioactivity were 71.1%, 14.7%, 1.3%, 1.3%, 0.3%, and 1.1%, respectively, and the mean $t_{1/2}$ of unchanged teneligliptin, M1, M2, M3, M4, and M5 in plasma were 24.5, 19.2, 19.9, 17.3, 30.3 and 25.6 hours, respectively. The cumulative urinary excretion rate[35] (mean ± SD) of unchanged teneligliptin, M1, M2, and M3 to the administered radioactivity up to 120 hours after administration were 14.8% ± 1.4%, 17.7% ± 3.5%, 1.4% ± 0.3%, and 1.9% ± 0.5%, respectively, and the cumulative fecal excretion rate[36] of unchanged teneligliptin, M1, M3, M4, and M5 were 26.1% ± 2.1%, 4.0% ± 2.6%, 1.6% ± 0.4%, 0.3% ± 0.3%, and 1.3% ± 0.5%, respectively.

Regarding safety, a total of 12 adverse events were observed in 5 of 6 subjects; all of them were mild in severity and resolved. There was 1 event of adverse drug reaction (headache) in 1 of 6 subjects. There was no particularly relevant variability in vital signs or ECG. Neither were there deaths, other serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(3) Studies in patients

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[35] M4 was not detected in the urine. M5 was detected in 3 of 6 subjects; the excretion rate was less than 1% in all of them.

[36] M2 was detected in feces in 2 of 6 subjects; the excretion rate was less than 1% in both of them.

4.(ii).A.(3).1) Clinical pharmacology study (5.3.4.2-1, Study 3000-A12 [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese patients with type 2 diabetes mellitus to investigate the effect of teneligliptin on blood glucose control and safety [for the details of the study design and the results of efficacy and safety studies, see "4.(iii).A.(2).1) Clinical pharmacology study"].

Regarding pharmacokinetics, the C_{max} (mean ± SD) of unchanged plasma teneligliptin after 4-week multiple-dose administration in the 10 mg and 20 mg groups (33 subjects per group) was 125.0 ± 25.2 and 274.5 ± 57.4 ng/mL, respectively, $AUC_{0\text{-}24\ h}$ was 830.9 ± 211.3 and 1625.1 ± 352.8 ng·h/mL, $t_{1/2}$ was 20.8 ± 9.5 and 18.9 ± 6.8 hours, and t_{max} (median) was 1 hour in both groups.

Regarding pharmacodynamics, the maximum DPP-4 inhibition rate (E_{max}, mean ± SD) after 4-week multiple-dose administration in the placebo group (32 subjects), 10 mg group (33 subjects), and 20 mg group (33 subjects) were 12.7% ± 6.6%, 81.3% ± 3.7%, and 89.7% ± 2.5%, and $E_{24\ h}$ were 0.8% ± 7.0%, 53.1% ± 7.1%, and 61.8% ± 6.3%, respectively. The change in $AUC_{0\text{-}2\ h}$ (least squares mean) of active plasma GLP-1 after 4-week multiple-dose administration from baseline (value at the end of the run-in period) were 0.27, 8.02, and 8.32 pmol·h/L after breakfast, 0.44, 8.36, and 7.92 pmol·h/L, after lunch, and 0.39, 7.82, and 8.61 pmol·h/L, after supper, respectively.

4.(ii).A.(3).2) Phase II exploratory study (5.3.5.1-1, Study 3000-A3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese patients with type 2 diabetes mellitus to investigate the efficacy and safety of teneligliptin [for the details of the study design and the results of efficacy and safety studies, see "4.(iii).A.(2).2) Phase II exploratory study"].

Regarding pharmacokinetics, the concentration (mean ± SD) of unchanged plasma teneligliptinbefore administration, and 0.5, 1, 1.5, and 2.5 hours after administration at Week 12 was 6.2 ± 2.7, 11.3 ± 6.9, 21.8 ± 7.3, 20.5 ± 5.5, and 19.0 ± 4.6 ng/mL, respectively, in the 2.5 mg group (47 subjects), 18.8 ± 15.9, 64.2 ± 47.2, 119.0 ± 41.7, 101.9 ± 29.9, and 83.5 ± 20.9 ng/mL, respectively, in the 10 mg group (38-39 subjects), and 60.2 ± 38.6, 334.5 ± 196.5, 553.3 ± 142.7, 440.8 ± 100.2, and 346.7 ± 77.3 ng/mL, respectively, in the 40 mg group (44-45 subjects).

Regarding pharmacodynamics, the mean plasma DPP-4 inhibition rate from before administration up to 2.5 hours after administration of teneligliptin at Week 12 in the placebo group (42 subjects), 2.5 mg group (47 subjects), 10 mg group (38-39 subjects), and 40 mg group (44-45 subjects) were -0.2% to 4.3%, 38.4% to 58.6%, 54.8% to 81.6%, and 69.9% to 93.9%, respectively. The change in $AUC_{0\text{-}2\ h}$ (least squares mean) of active plasma GLP-1 at 12-week administration from baseline (at the end of run-in period) in the placebo group (39 subjects), 2.5 mg group (46 subjects), 10 mg group (37 subjects), and 40 mg group (44 subjects) were 0.4, 10.8, 11.4, and 12.8 pmol·h/L, respectively.

4.(ii).A.(3).3) Phase II confirmatory study (5.3.5.1-2, Study 3000-A4 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese patients with type 2 diabetes mellitus to investigate the efficacy and safety of teneligliptin [for the details of the study design and the results of efficacy and safety studies, see "4.(iii).A.(2).3) Phase II confirmatory study"].

Regarding pharmacokinetics, the concentration of plasma teneligliptin (mean ± SD) before administration, and 0.5, 1, 1.5, and 2.5 hours after administration of teneligliptin at Week 12 were 15.7 ± 11.0, 51.6 ± 41.5, 107.5 ± 38.3, 92.5 ± 24.9, and 77.4 ± 17.6 ng/mL, respectively, in the 10 mg (80-83 subjects), 32.1 ± 22.4, 142.4 ± 109.3, 251.5 ± 89.6, 206.0 ± 60.2, and 168.7 ± 41.2 ng/mL, respectively, in the 20 mg group (75-76 subjects), and 59.5 ± 25.7, 270.5 ± 252.2, 529.4 ± 199.5, 425.1 ± 133.4, and 360.0 ± 91.9 ng/mL, respectively, in the 40 mg group (75 subjects).

Regarding pharmacodynamics, the mean plasma DPP-4 inhibition rate from before administration up to 2.5 hours after administration of teneligliptin at Week 12 in the placebo group (74-76 subjects), 10 mg group (80-83 subjects), 20 mg group (76 subjects), and 40 mg group (75 subjects) were 1.2% to 4.5%, 54.4% to 81.8%, 61.1% to 87.8%, and 73.3% to 94.1%, respectively. Change in $AUC_{0\text{-}2\,h}$ (least squares mean) of active plasma GLP-1 at 12-week administration from baseline (at the end of run-in period) in the placebo group (73 subjects), teneligliptin 10 mg group (77 subjects), 20 mg group (71 subjects), and 40 mg group (71 subjects) were 2.2, 15.8, 18.6, and 14.9 pmol·h/L, respectively.

4.(ii).A.(4) Studies on intrinsic factors

4.(ii).A.(4).1) Study on the effect of age and sex (5.3.3.3-1, Study MP-513-E05 [[redacted] to [redacted] 20[redacted]], Reference data)

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in foreign healthy adult subjects (19 males, 21 females) to investigate the effect of age and sex on the safety, pharmacokinetics and pharmacodynamics of teneligliptin in single oral dose administration.

A combination of placebo and teneligliptin 80 mg, teneligliptin 20 mg and 80 mg, or teneligliptin 20 mg and placebo was administered orally to non-elderly male and female subjects (aged ≥45 and <65 years) and to elderly male and female subjects (aged ≥65 and ≤75 years), each in a single dose at 30 minutes before breakfast, before and after a washout period of at least 2 weeks.

All 40 treated subjects (21 non-elderly subjects [9 males, 12 females] and 19 elderly subjects [10 males, 9 females]) were included in the safety analysis population. Excluding 4 subjects with protocol deviations, a total of 36 subjects were included in the populations for pharmacokinetic analysis and for pharmacodynamic analysis.

Regarding pharmacokinetics, the ratio (female/male; males, 12 subjects in each dose group; females, 12 subjects in each dose group) of geometric least squares mean of C_{max}, $AUC_{0\text{-}t}$ and $t_{1/2}$ of unchanged plasma teneligliptin and their two-sided 90% CI were 1.16 [1.00, 1.34], 1.13 [1.01, 1.27], and 1.30 [1.13, 1.51], respectively, in the 20 mg group, and 1.30 [1.07, 1.58], 1.08 [0.96, 1.22], and 1.15 [1.04, 1.27], respectively, in the 80 mg group, and C_{max}, $AUC_{0\text{-}t}$, and $t_{1/2}$ of M1 were 1.23 [0.96, 1.58], 1.19 [0.95, 1.49], and 1.14 [0.92, 1.42], respectively, in the 20 mg group and 1.43 [1.18, 1.72], 1.15 [0.99, 1.34], and 1.04 [0.88, 1.23], respectively, in the 80 mg group. The ratio (elderly/non-elderly) of geometric least squares mean of C_{max}, $AUC_{0\text{-}t}$, and $t_{1/2}$ of unchanged plasma teneligliptin and their two-sided 90% CI were 1.01 [0.87, 1.16], 1.09 [0.97, 1.23], and 1.05 [0.91, 1.22], respectively, in the 20 mg group and 0.98 [0.81, 1.19], 1.14 [1.02,

1.29], and 1.05 [0.95, 1.16], respectively, in the 80 mg group, and C_{max}, AUC_{0-t}, and $t_{1/2}$ of M1 were 0.87 [0.68, 1.11], 1.00 [0.80, 1.25], and 1.10 [0.88, 1.37], respectively, in the 20 mg group and 0.90 [0.75, 1.09], 0.92 [0.79, 1.07], and 0.94 [0.80, 1.11], respectively, in the 80 mg group.

Regarding pharmacodynamics, the maximum DPP-4 inhibition rate (E_{max}, mean ± SD) in the placebo group, the 20 mg group, and the 80 mg group was 16.1% ± 12.0%, 81.4% ± 2.9%, and 93.3% ± 1.5% in male subjects (6 subjects in each group) and 11.8% ± 5.3%, 83.2% ± 2.4%, and 94.8% ± 0.3% in female subjects (6 subjects in each group) in the non-elderly group; and 13.7% ± 10.7%, 83.5% ± 1.8%, and 93.7% ± 1.5% in male subjects and 13.6% ± 1.8%, 83.9% ± 3.0%, and 94.3% ± 0.4% in female subjects in the elderly group. The $E_{24\,h}$ were 2.7% ± 16.4%, 49.9% ± 3.0%, and 72.0% ± 3.1%, respectively, in male subjects and 5.1% ± 3.6%, 51.4% ± 7.1%, and 70.6% ± 3.1%, respectively, in female subjects in the non-elderly group; and -0.2% ± 7.3%, 57.2% ± 5.1%, and 74.3% ± 1.5%, respectively, in male subjects and 4.8% ± 5.2%, 56.4% ± 3.4%, and 75.6% ± 4.2% in female subjects in the elderly group. The $AUC_{0-2.5\,h}$ of active plasma GLP-1 were 6.4 ± 4.0, 13.1 ± 5.7, and 14.4 ± 7.2 pmol·h/L, respectively, in male subjects and 7.0 ± 2.3, 23.1 ± 7.8, and 20.3 ± 9.2 pmol·h/L, respectively, in female subjects in the non-elderly group; and 6.0 ± 2.2, 14.4 ± 4.2, and 16.0 ± 4.2 pmol·h/L, respectively, in male subjects and 9.1 ± 2.2, 32.2 ± 24.2, and 15.4 ± 6.6 pmol·h/L, respectively, in female subjects in the elderly group.

Regarding safety, adverse events were observed in the non-elderly group in 3 of 6 male subjects (6 events) and in 6 of 9 female subjects (10 events) in the placebo group, in 2 of 6 male subjects (2 events) and in 5 of 6 female subjects (10 events) in the 20 mg group, and in 2 of 6 male subjects (6 events) and in 6 of 8 female subjects (14events) in the 80 mg group. Adverse events were observed in the elderly group in 3 of 6 male subjects (12 events) and in 4 of 6 female subjects (6 events) in the placebo group, in 4 of 7 male subjects (9 events) and in 2 of 6 female subjects (2 events) in the 20 mg group, and in 0 of 6 male subjects (0 event) and in 1 of 6 female subjects (1 event) in the 80 mg group. Among these adverse events, adverse drug reactions were observed in the non-elderly group in 1 of 6 male subjects (2 events) (1 event each of diarrhoea and micturition urgency) and in 2 of 9 female subjects (3 events) (1 event each of headache, dizziness, and palpitations) in the placebo group, in 3 of 6 female subjects (4 events) (3 events of headache, 1 event of dizziness) in the 20 mg group, and in 4 of 8 female subjects (8 events) (4 events of headache, 1 event each of somnolence, pharynx dry, diarrhoea, and transaminases increased) in the 80 mg group. Adverse drug reactions were observed in the elderly group in 2 of 6 male subjects (5 events) (2 events of headache, 1 event each of dizziness, diarrhoea, and feeling hot) and in 2 of 6 female subjects (4 events) (1 event each of somnolence, headache, diarrhoea, and abdominal distension) in the placebo group, in 3 of 7 male subjects (4 events) (1 event each of syncope vasovagal, headache, hyperhidrosis, and myalgia) and in 1 of 6 female subjects (1 event) (diarrhoea) in the 20 mg group, and in 1 of 6 female subjects (1 event) (headache) in the 80 mg group. There was no particularly relevant variability in vital signs or ECG. There were no deaths, other serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(4).2) Pharmacokinetic study in subjects with renal impairment (5.3.3.3-2, Study MP-513-E09 [[redacted] to [redacted] 20[redacted]], Reference data)

An open-label, parallel-group study was conducted in foreign adult male and female subjects to investigate the pharmacokinetics, safety, and tolerability of teneligliptin in subjects with renal impairment.

Teneligliptin (20 mg) was administered to healthy adult subjects[37] (Ccr[38] > 80 mL/min, 16

[37] 8 subjects as the control for subjects with mild to severe renal impairment (Group 1) and 8 subjects as the control for patients with end-stage renal failure (Group 2)

[38] Creatinine clearance estimated by Cockcroft-Gault equation

subjects), subjects with mild renal impairment (50 ≤ Ccr ≤ 80 mL/min, 8 subjects), subjects with moderate renal impairment (30 ≤ Ccr < 50 mL/min, 8 subjects), subjects with severe renal impairment (Ccr < 30 mL/min, 8 subjects), and patients with end-stage renal failure requiring hemodialysis (8 subjects) in a single oral dose[39].

All 48 treated subjects were included in the populations for pharmacokinetic analysis and for safety analysis.

Pharmacokinetic parameters of unchanged plasma teneligliptin following a single-dose administration of 20 mg teneligliptin were as shown in Table 6 (subjects with mild to severe renal impairment) and in Table 7 (patients with end-stage renal failure).

Table 6. Pharmacokinetic parameters of unchanged plasma teneligliptin following a single oral dose of teneligliptin 20 mg (subjects with mild to severe renal impairment)

Parameter	Group 1 (n = 8)	Subjects with mild renal impairment (n = 8)		Subjects with moderate renal impairment (n = 8)		Subjects with severe renal impairment (n = 8)	
	Mean (SD)	Mean (SD)	Geometric least squares mean ratio (%) [90% CI][a)]	Mean (SD)	Geometric least squares mean ratio (%) [90% CI][a)]	Mean (SD)	Geometric least squares mean ratio (%) [90% CI][a)]
C_{max} (ng/mL)	176.5 (38.4)	208.0 (53.3)	108.0 [86.2, 135.1]	203.6 (42.3)	111.5 [89.1, 139.6]	191.6 (49.1)	104.2 [82.1, 132.2]
$AUC_{0-\infty}$ (ng·h/mL)	1772.7 (657.3)	2234.2 (278.6)	124.6 [101.0, 153.8]	3090.3 (868.6)	167.6 [135.8, 206.9]	2833.3 (652.3)	148.9 [119.1, 186.1]
$t_{1/2}$ (h)	26.1 (5.0)	27.7 (7.9)	99.8 [75.9, 131.3]	36.0 (11.0)	136.2 [103.6, 179.1]	29.8 (11.0)	102.4 [76.6, 136.9]
t_{max}[b)] (h)	1.00	1.00	–	1.00	–	1.00	–
CL/F (L/h)	12.2 (3.0)	9.1 (1.2)	80.2 [65.0, 99.0]	6.9 (1.9)	59.7 [48.3, 73.7]	7.4 (1.7)	67.2 [53.7, 84.0]
V_Z/F (L)	459.3 (141.3)	356.4 (93.5)	80.1 [61.3, 104.8]	346.5 (107.6)	81.3 [62.2, 106.3]	303.9 (86.3)	68.8 [51.8, 91.4]

Group 1: Healthy adult subjects, V_Z/F: Apparent distribution volume calculated from the elimination phase, -: Not calculated
a) Geometric least squares mean ratio (subjects with renal impairment/Group 1), CI = confidence interval
b) Median

[39] Teneligliptin was to be administered to subjects in Group 1 and subjects with mild to severe renal impairment at 30 minutes before meal after fasting for 10 hours, and to subjects in Group 2 and patients with end-stage renal failure at 30 minutes before meal after fasting for at least 6 hours. Patients with end-stage renal failure were to take teneligliptin orally in a single dose in each study period after hemodialysis (breakfast at around 6:00, hemodialysis from 7:30 to approx. 11:30, teneligliptin 20 mg administration at 30 minute before taking standard meal [around 12:00]) and before hemodialysis (snack at around 23:00 one day before the day of administration, teneligliptin 20 mg administration at 30 minute before taking the standard meal [around 5:30], hemodialysis from 7:30 to approx. 11:30).

Table 7. Pharmacokinetic parameters of unchanged plasma teneligliptin following a single oral dose of teneligliptin 20 mg (patients with end-stage renal failure)

Parameter	Group 2 (n = 8)	Patients with end-stage renal failure (n = 8)			
		Administration before hemodialysis		Administration after hemodialysis	
	Mean (SD)	Mean (SD)	Geometric least squares mean ratio (%) [90% CI][a)]	Mean (SD)	Geometric least squares mean ratio (%) [90% CI][a)]
C_{max} (ng/mL)	195.8 (43.3)	164.5 (78.9)	84.7 [63.5, 112.8]	219.0 (118.9)	109.6 [82.3, 146.1]
AUC_{0-43h} (ng·h/mL)	1569.5 (345.5)	1520.4 (298.0)	97.8 [82.4, 116.0]	1820.9 (285.4)	116.4 [98.1, 138.2]
$AUC_{0-\infty}$ (ng·h/mL)	1843.1 (450.0)	2162.5 (488.1)	117.4 [94.0, 146.5]	2472.9 (599.7)	131.9 [105.7, 164.6]
$t_{1/2}$ (h)	18.3 (5.7)	22.7 (7.7)	119.0 [89.1, 158.9]	23.6 (5.8)	131.2 [98.3, 175.2]
t_{max}[b)] (h)	1.25	1.00	–	1.02	–
CL/F (L/h)	11.4 (2.7)	9.7 (2.3)	85.2 [68.3, 106.3]	8.5 (2.2)	75.8 [60.7, 94.6]
V_Z/F (L)	297.8 (110.6)	309.1 (98.9)	101.4 [77.8, 132.1]	280.2 (49.2)	99.5 [76.3, 129.6]

Group 2: Healthy adults, -: Not calculated
a) Geometric least squares mean ratio (subjects with renal impairment/Group 2), CI = confidence interval
b) Median

The mean fraction of teneligliptin unbound to plasma protein in subjects in Group 1 and subjects with mild, moderate, and severe renal impairment (8 subjects each) were 44.3%, 33.0%, 38.1%, and 32.6%, respectively, in blood samples collected at 1 hour after administration and 36.2%, 32.8%, 33.3%, and 31.8%, respectively, at 10 hours after administration. The mean fraction of teneligliptin unbound to plasma protein in subjects in Group 2 and in patients with end-stage renal failure treated with teneligliptin after hemodialysis and those treated before hemodialysis (8 subjects each) were 40.1%, 39.9%, and 54.2%, respectively, in blood samples collected at 1 hour after administration and 38.2%, 44.5%, and 43.5%, respectively, at 10 hours after administration.

Regarding safety, adverse events occurred in 2 of 16 healthy adult subjects (2 events) (1 event each in Group 1 and Group 2) and in 1 of 8 subjects with moderate renal impairment (5 events). Among these adverse events, adverse drug reactions occurred in 1 of 8 subjects (1 event) (headache) in Group 1, and in 1 of 8 subjects with moderate renal impairment (5 events) (1 event each of dyspepsia, aspartate aminotransferase [AST] increased, ALT increased, gamma-glutamyltransferase [γ-GTP] increased, blood alkaline phosphatase increased). AST increased and ALT increased were classified as serious adverse events. No other serious adverse events were observed. QTcB interval prolongation (501 msec) and QTcF interval prolongation (499 msec) were observed in the 12-lead ECG in 1 subject with severe renal impairment but not classified as adverse events. There were no deaths or adverse events leading to treatment discontinuation.

4.(ii).A.(4).3) Pharmacokinetic study in subjects with hepatic impairment (5.3.3.3-3, Study MP-513-E10 [[redacted] to [redacted] 20[redacted]], Reference data)

An open-label, parallel group study was conducted in foreign adult male and female subjects to investigate the pharmacokinetics, safety, and tolerability of teneligliptin in subjects with hepatic impairment.

Teneligliptin (20 mg) was administered orally 30 minutes before meal after fasting for ≥10 hours

to healthy adults (8 subjects), subjects with mild hepatic impairment (8 subjects), and subjects with moderate hepatic impairment (8 subjects) (classification of the severity of hepatic impairment by Child-Pugh score: score 5-6 [mild]; score 7-9 [moderate]).

All 24-treated subjects were included in the populations for pharmacokinetic analysis and for safety analysis.

Pharmacokinetic parameters of unchanged plasma teneligliptin following a single oral dose of teneligliptin 20 mg were as shown in Table 8.

Table 8. Pharmacokinetic parameters of unchanged plasma teneligliptin following a single oral dose of teneligliptin 20 mg

Parameter	Healthy adult subjects (n = 8)	Subjects with mild hepatic impairment (n = 8)		Subjects with moderate hepatic impairment (n = 8)	
	Mean (SD)	Mean (SD)	Geometric least squares mean ratio (%) [90% CI][a)]	Mean (SD)	Geometric least squares mean ratio (%) [90% CI][a)]
C_{max} (ng/mL)	185.9 (84.7)	229.3 (86.2)	125.5 [97.1, 162.1]	247.6 (113.0)	137.7 [106.6, 178.0]
AUC_{0-t} (ng·h/mL)	1438.0 (215.6)	2118.1 (781.0)	149.5 [124.4, 179.8]	2319.3 (475.4)	162.7 [135.3, 195.6]
$AUC_{0-\infty}$ (ng·h/mL)	1548.8 (209.1)	2207.9 (790.0)	145.9 [122.1, 174.2]	2418.9 (505.8)	159.4 [133.5, 190.4]
$t_{1/2}$ (h)	24.8 (6.4)	27.9 (7.1)	121.6 [94.1, 157.0]	30.9 (6.6)	137.6 [106.5, 177.7]
t_{max}[b)] (h)	1.00	0.75	–	0.50	–
CL/F (L/h)	13.1 (1.7)	9.8 (2.5)	68.6 [57.4, 81.9]	8.6 (1.7)	62.7 [52.5, 74.9]
V_Z/F (L)	469.8 (132.8)	384.6 (112.5)	83.4 [68.5, 101.5]	374.2 (77.3)	86.3 [70.9, 105.1]

-: Not calculated
a) Geometric least squares mean ratio (subjects with hepatic impairment/healthy adult subjects), CI = confidence interval
b) Median

The mean fraction of teneligliptin unbound to plasma protein in healthy adult subjects and in subjects with mild and moderate hepatic impairment were 34.5%, 39.8%, and 42.5%, respectively, in blood samples collected at 1 hour after administration and 32.5%, 36.9%, and 47.5%, respectively, at 12 hours after administration.

Regarding safety, adverse events occurred in 3 of 8 healthy adult subjects (3 events), in 1 of 8 subjects with mild hepatic impairment (1 event), and in 1 of 8 subjects with moderate hepatic impairment (2 events). Among these, 2 events of headache observed in 2 of 8 healthy adult subjects were classified as adverse drug reactions. QTcB interval prolongation in 12-lead ECG was observed in 1 subject with mild hepatic impairment and in 3 subjects with moderate hepatic impairment (subject with mild hepatic impairment [508 msec, at 2 hours after administration], subjects with moderate hepatic impairment [501 msec, at 2 hours after administration; 510 msec, at 4 hours after administration; and 503 msec, at 6 hours after administration]), but were not classified as adverse events. There were no deaths, other serious adverse events, or adverse events

leading to treatment discontinuation.

4.(ii).A.(5) Drug-drug interaction studies

4.(ii).A.(5).1) Drug-drug interactions study with glimepiride (5.3.3.4-1, Study 3000-A10 [[redacted] to [redacted]])

An open-label study was conducted in Japanese healthy adult male subjects (target sample size of 35) to investigate the drug-drug interactions when teneligliptin was administered in concomitant with glimepiride.

In Group 1 (16 subjects), teneligliptin (40 mg) was administered in a single oral dose before breakfast (at 30 minutes before breakfast) in Study period I, and in Study period II, glimepiride (1 mg) was administered orally before breakfast (at 30 minutes before breakfast) once daily from Day 1 to 4, and teneligliptin (40 mg) was administered in a single oral dose before breakfast (at 30 minutes before breakfast) on Day 2. In Group 2 (19 subjects), glimepiride (1 mg) was administered before breakfast (at 30 minutes before breakfast) in a single oral dose in Study period I, and in Study period II, teneligliptin (40 mg) was administered orally before breakfast (at 30 minutes before breakfast) once daily from Day 1 to 7, and glimepiride (1 mg) was administered before breakfast (at 30 minutes before breakfast) in a single oral dose on Day 7.[40]

All 35 treated subjects were included in the populations for pharmacokinetic analysis and for safety analysis.

Regarding pharmacokinetics, the ratio of the geometric mean (concomitant therapy/teneligliptin monotherapy) of C_{max} and $AUC_{0\text{-}72\ h}$ of unchanged plasma teneligliptin and their two-sided 90% CI in Group 1 were 0.97 [0.87, 1.09] and 0.92 [0.90, 0.95], respectively, and the ratio of the geometric mean (combined administration/glimepiride alone) of C_{max} and $AUC_{0\text{-}12\ h}$ of unchanged plasma glimepiride and their two-sided 90% CI in Group 2 were 1.02 [0.93, 1.11] and 1.01 [0.97, 1.06], respectively.

Regarding safety, 1 adverse event (tonsillitis [after concomitant therapy]) occurred in 1 of 16 subjects in Group 1, and 1 adverse event (C-reactive protein increased [before concomitant therapy]) in 1 of 19 subjects in Group 2. Both were mild in severity. There were no adverse drug reactions. There was no particularly relevant variability in vital signs or in ECG. There were no deaths, other serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(5).2) Drug-drug interaction study with pioglitazone (5.3.3.4-2, Study 3000-A11 [[redacted] to [redacted]])

An open-label study was conducted in Japanese healthy adult male subjects (target sample size of 40) to investigate the drug-drug interactions when teneligliptin was administered in concomitant with pioglitazone.

In Group 1 (16 subjects), teneligliptin (40 mg) was administered in a single oral dose before breakfast (at 30 minutes before breakfast) in Study period I; and in Study period II, pioglitazone (30 mg) was administered orally before breakfast (at 30 minutes before breakfast) once daily from Day 1 to 9, and teneligliptin (40 mg) was administered in a single oral dose before breakfast (at 30 minutes before breakfast) on Day 7. In Group 2 (24 subjects), pioglitazone (30 mg) was administered before breakfast (at 30 minutes before breakfast) in a single oral dose in Study period I; and in Study period II, teneligliptin (40 mg) was administered orally before breakfast (at 30 minutes before breakfast) once daily from Day 1 to 9, and pioglitazone (30 mg) was

[40] The interval of teneligliptin administration between Study period I and Study period II in Group 1 was to be at least 10 days, and the interval of glimepiride administration between Study period I and Study period II in Group 2 was to be at least 8 days.

administered before breakfast (at 30 minutes before breakfast) in a single oral dose on Day 7.[41]

All 40 treated subjects were included in the populations for pharmacokinetic analysis and for safety analysis.

Regarding pharmacokinetics, the ratio of the geometric mean (concomitant therapy/teneligliptin monotherapy) of C_{max} and $AUC_{0\text{-}72\ h}$ of unchanged plasma teneligliptin with their two-sided 90% CI in Group 1 were 1.12 [0.98, 1.27] and 1.02 [0.99, 1.06], respectively, and the ratio of the geometric mean (concomitant therapy/pioglitazone monotherapy) of C_{max} and $AUC_{0\text{-}72\ h}$ of unchanged plasma pioglitazone with their two-sided 90% CI in Group 2 were 1.00 [0.92, 1.10] and 1.13 [1.05, 1.21], respectively. The values observed for M-III, an active metabolite of plasma pioglitazone, were 1.04 [0.98, 1.11] and 1.11 [1.06, 1.17], respectively, and the values observed for M-IV, another active metabolite of plasma pioglitazone, were 1.03 [0.96, 1.10] and 1.05 [0.99, 1.10], respectively.

Regarding safety, 1 adverse event (C-reactive protein increased [after concomitant therapy]) occurred in 1 of 16 subjects in Group 1 and 1 adverse event (C-reactive protein increased [after concomitant therapy]) in 1 of 24 subjects in Group 2. Both were mild in severity. There were no adverse drug reactions. There was no particularly relevant variability in vital signs or in ECG. There were no deaths, other serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(5).3) Drug-drug interaction study with metformin
(5.3.3.4-3, Study MP-513-E06 [[redacted] to [redacted] 20[redacted]], Reference data)

A randomized, open-label, parallel-group comparative study was conducted in foreign healthy adult male and female subjects (target sample size of 40) to investigate the drug-drug interactions when teneligliptin was administered in concomitant with metformin.

In Group 1 (20 subjects), teneligliptin (40 mg) was administered orally before breakfast (at 30 minutes before breakfast) from Day 1 to 8, and metformin (850 mg) was administered orally twice daily after breakfast and after supper from Day 6 to 8. In Group 2 (20 subjects), metformin (850 mg) was administered twice daily after breakfast and after supper from Day 1 to 8 and teneligliptin (40 mg) was administered orally before breakfast (at 30 minutes before breakfast) from Day 4 to 8.

All 40 treated subjects were included in the safety analysis population. Among them, 38 subjects were included in the pharmacokinetic analysis population. Excluded were 2 subjects who discontinued the study due to an adverse event (vomiting).

Regarding pharmacokinetics, the geometric least squares mean ratio (concomitant therapy/teneligliptin monotherapy) of C_{max} and $AUC_{0\text{-}24\ h}$ of unchanged plasma teneligliptin with their two-sided 90% CI in Group 1 were 0.91 [0.85, 0.97] and 1.04 [1.00, 1.09], respectively, and the geometric least squares mean ratio (concomitant therapy/metformin monotherapy) of C_{max} and $AUC_{0\text{-}12\ h}$ of unchanged plasma metformin with their two-sided 90% CI in Group 2 were 1.06 [0.97, 1.15] and 1.21 [1.14, 1.28], respectively.

Regarding safety, 25 adverse events occurred in 9 of 20 subjects following the teneligliptin monotherapy and 15 adverse events in 10 of 19 subjects following the concomitant therapy in Group 1. Eleven adverse events occurred in 8 of 20 subjects following

[41] The interval of teneligliptin administration between Study period I and Study period II in Group 1 was to be at least 10 days, and the interval of pioglitazone administration between Study period I and Study period II in Group 2 was also to be at least 10 days.

the metformin monotherapy and 18 adverse events in 11 of 20 subjects following the concomitant therapy in Group 2. Two subjects discontinued the study because of adverse events (vomiting): 1 subject in Group 1 after receiving teneligliptin on Day 1 and 1 subject in Group 2 after receiving the concomitant therapy on Day 5. There were 22 adverse drug reactions in 9 of 20 subjects following the teneligliptin monotherapy and 12 adverse drug reactions in 8 of 19 subjects following the concomitant therapy in Group 1. Eleven adverse drug reactions occurred in 8 of 20 subjects following the metformin monotherapy and 13 adverse drug reactions in 10 of 20 subjects following the concomitant therapy in Group 2. There was no particularly relevant variability in vital signs or in ECG. There were no deaths or other serious adverse events.

4.(ii).A.(5).4) Drug-drug interaction study with ketoconazole
(5.3.3.4-4, Study MP-513-E11 [[redacted] to [redacted] 20[redacted]], Reference data)

An open-label study was conducted in foreign healthy adult male and female subjects (target sample size of 16) to investigate the effect of ketoconazole on the pharmacokinetics of teneligliptin.

Teneligliptin (20 mg) was administered in a single oral dose under fasting conditions on Day 1 and on Day 11, and ketoconazole (400 mg) was administered orally once daily at breakfast (under fasted conditions on Day 11) from Day 8 to 13.

All 16 treated subjects were included in the safety analysis population. Among them, 14 subjects were included in the pharmacokinetic analysis population. Excluded were 2 who discontinued the study because of adverse events (ventricular extrasystoles, vomiting).

Regarding pharmacokinetics, the geometric least squares mean ratio (concomitant therapy/teneligliptin monotherapy) of C_{max} and $AUC_{0\text{-}t}$ of unchanged plasma teneligliptin with their two-sided 90% CI were 1.37 [1.25, 1.50] and 1.49 [1.38, 1.60], respectively.

Regarding safety, 10 adverse events occurred in 6 of 16 subjects following the teneligliptin monotherapy, 10 adverse events in 8 of 14 subjects following the ketoconazole monotherapy, and 15 adverse events in 7 of 14 subjects following the concomitant therapy. Two subjects discontinued the study because of adverse events: one had ventricular extrasystoles after the teneligliptin monotherapy (approximately 12 hours after the initial administration) and the other had vomiting after the teneligliptin monotherapy (approximately 2.5 days after the initial administration). There were 2 adverse drug reactions (headache) in 2 of 16 subjects after the teneligliptin monotherapy and 4 adverse drug reactions (2 events of palpitations, 1 event each of headache and dizziness) in 3 of 14 subjects after the concomitant therapy. There was no particularly relevant variability in vital signs or in ECG. There were no deaths or other serious adverse events.

4.(ii).A.(6) Pharmacodynamic study
Thorough QT/QTc study (5.3.4.1-1, Study MP-513-A01 [[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, placebo and moxifloxacin-controlled, parallel-group comparative study was conducted in foreign healthy adult male and female subjects (target sample size of 240, 60 subjects per group) to investigate the effect of multiple-dose administration of teneligliptin (40, 160 mg) on QTc intervals.

Placebo, teneligliptin 40 mg, and 160 mg were administered orally once daily for 4 days (placebo group, 40 mg group, and 160 mg group). In the moxifloxacin group (positive control group), placebo was administered orally once daily for 3 days and moxifloxacin 400 mg on Day 4.

All 240 treated subjects (60 subjects in placebo group, 59 subjects in 40 mg group, 59 subjects in

160 mg group, 62 subjects in moxifloxacin group) were included in the safety analysis population. Among these, 236 subjects (58 subjects in placebo group, 59 subjects in 40 mg group, 58 subjects in 160 mg group, 61 subjects in moxifloxacin group), were included in the population for ECG analysis. Excluded were 4 subjects from whom ECG data could not be obtained.

Regarding pharmacokinetics, the C_{max} (mean ± SD) of unchanged plasma teneligliptin on Day 4 of administration were 499.7 ± 111.3 and 2259 ± 509 ng/mL, $AUC_{0\text{-}24\ h}$ were 3552 ± 697 and 16,340 ± 3394 ng·h/mL, respectively, in the 40 mg group and the 160 mg group, and t_{max} (median) was 1 hour in both groups. For M1, the C_{max} were 114.5 ± 29.7 and 532.4 ± 158.4 ng/mL, $AUC_{0\text{-}24\ h}$ were 925.5 ± 219.9 and 3890 ± 865 ng·h/mL, respectively, in the 40 mg group and the 160 mg group, and t_{max} (median) was 1.5 hours in both groups.

Regarding the difference in QTcI interval from baseline, the difference between the teneligliptin group and the placebo group (ddQTcI) with its two-sided 90% CI in the 40 mg group and 160 mg group were 3.9 [0.2, 7.6] and 9.3 [5.6, 13.0] msec, respectively, with the upper limit of the one-sided 95% CI exceeding 10 msec (Table 9). For the difference in QTcI interval from baseline, the difference between the moxifloxacin group and the placebo group with its two-sided 90% CI was 10.1 [6.5, 13.7] msec, with the lower limit of one-sided 95% CI exceeding 5 msec, from which it was concluded that analytical sensitivity was ensured.

Table 9. Difference between teneligliptin or moxifloxacin group versus placebo group in the difference in QTc interval from baseline, with two-sided 90% CI

Treatment group	Subjects analyzed (No. of subjects)	ddQTcI[a)]		ddQTcF[a)]	
		Time of measurement	Maximum ddQTcI [90% CI]	Time of measurement	Maximum ddQTcF [90% CI]
40 mg group	All (n = 59)	3 h post-dose	3.9 [0.2, 7.6]	24 h post-dose	4.9 [1.9, 8.0]
	Males (n = 27)	0.5 h post-dose	3.8 [-0.8, 8.4]	0.5 h post-dose	5.1 [0.9, 9.4]
	Females (n = 32)	4 h post-dose	5.3 [-0.4, 11.0]	0 h post-dose	5.6 [1.2, 9.9]
160 mg group	All (n = 58)	1.5 h post-dose	9.3 [5.6, 13.0]	1.5 h post-dose	11.2 [8.1, 14.3]
	Males (n = 30)	1.5 h post-dose	10.4 [6.0, 14.8]	1.5 h post-dose	11.5 [7.4, 15.5]
	Females (n = 28)	1.5 h post-dose	7.5 [1.6, 13.4]	1.5 h post-dose	10.5 [6.1, 14.9]
Moxifloxacin group	All (n = 61)	2 h post-dose	10.1 [6.5, 13.7]	1 h post-dose	12.1 [9.1, 15.2]
	Males (n = 28)	1 h post-dose	8.9 [4.4, 13.4]	1 h post-dose	11.7 [7.5, 15.8]
	Females (n = 33)	2 h post-dose	10.9 [5.3, 16.6]	4 h post-dose	12.0 [7.7, 16.3]

Unit: msec

a) Least squares mean of the difference between teneligliptin or moxifloxacin group versus placebo group in the difference in QTcI interval from baseline, calculated by each compensation formula.

Regarding safety, 22 adverse events occurred in 17 of 60 subjects in the placebo group, 34 adverse events in 19 of 59 subjects in the 40 mg group, 39 adverse events in 22 of 59 subjects in the 160 mg group, and 39 adverse events in 21 of 62 subjects in the moxifloxacin group (23 adverse events in 15 of 62 subjects during 3 days of placebo administration, 16 adverse events in 13 of 62 subjects after moxifloxacin administration). As for adverse drug reactions, 12 adverse drug reactions occurred in 10 of 60 subjects in the placebo group, 15 adverse drug reactions in 9 of 59 subjects in the 40 mg group, 16 adverse drug reactions in 10 of 59 subjects in the 160 mg group, and 21 adverse drug reactions in 14 of 62 subjects in the moxifloxacin group (8 adverse drug reactions in 6 of 62 subjects during 3 days of placebo administration, 13 adverse drug reactions in 10 of 62 subjects after moxifloxacin administration). Most of the adverse events were mild in severity. Adverse events with an incidence of more than 5% were headache, nausea, dizziness, and ventricular tachycardia.

No deaths were reported. Appendicitis (1 subject in 160 mg group) was classified as a serious adverse event, but its causal relationship with the study drug was denied. Appendicitis was the only adverse event leading to treatment discontinuation. As regards adverse events related to findings on Holter monitoring ("cardiac disorders" in the system organ class), 4 adverse events occurred in 4 of 60 subject in the placebo group, 11 adverse events in 7 of 59 subjects in the 40 mg group, 5 adverse events in 4 of 59 subjects in the 160 mg group, and 5 adverse events in 4 of 62 subjects in the moxifloxacin group. Of these, 1 case occurred after moxifloxacin administration and all others occurred during placebo administration period. None of them were classified as adverse drug reactions.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Safety in subjects with renal or hepatic impairment

PMDA asked the applicant to explain whether it is necessary or not to adjust the teneligliptin dose from the point of view of the pharmacokinetic characteristics of teneligliptin, based on the results of the pharmacokinetic studies in subjects with renal impairment and subjects in hepatic impairment (Studies MP-513-E09, MP-513-E10).

The applicant responded as follows:

In the foreign mass balance study (Study MP-513-E08), ^{14}C-labeled teneligliptin was administered in a single dose. As a result, the mean cumulative urinary accumulation rate up to 120 hours after administration relative to the administered radioactivity for unchanged teneligliptin, M1, M2, and M3 were 14.8%, 17.7%, 1.4%, and 1.9%, respectively; and the mean cumulative fecal excretion rate for unchanged teneligliptin, M1, M3, M4, and M5 were 26.1%, 4.0%, 1.6%, 0.3%, and 1.3%, respectively. These results suggested that teneligliptin, after absorption, was metabolized or eliminated from the body via excretion from the kidney, with the metabolism and renal excretion contributing to 65.6% and 34.4%, respectively, of the body clearance. If renal excretion of teneligliptin is completely lost due to renal impairment, then the total body clearance is speculated to be approximately two thirds of the normal value, resulting in an approximately 1.5-fold increase in AUC compared with the patients with normal renal function. The increase of this extent was comparable to the increase in $AUC_{0-\infty}$ in subjects with severe renal impairment or patients with end-stage renal failure observed in Study MP-513-E09. CYP3A4, FMO1, and FMO3 are considered to be involved mainly in the metabolism of teneligliptin. Results of Study MP-513-E10 showed that the geometric least squares mean of $AUC_{0-\infty}$ in subjects with mild and moderate hepatic impairment was approximately 1.46 and 1.59 times, respectively, of healthy adult subjects. Since patients with hepatic impairment generally have decreased metabolic enzyme activity and decreased hepatic blood flow, the exposure level of teneligliptin was likely to have increased in these patients because of decreased metabolic clearance of teneligliptin in the liver. There is a report that CYP3A activity is decreased by approximately 40% in patients with hepatic cirrhosis (Ohnishi A, *Tokyo Jikei-kai Ika Daigaku Zasshi 2011*;126: 71-8). Assuming that the metabolic activity is decreased by 50% in subjects with severe hepatic impairment, the total body clearance would be approximately two thirds that of the normal value, since approximately two thirds of the absorbed teneligliptin is considered to be eliminated by metabolism. As a result, the AUC would increase by approximately 1.5-fold compared with patients with normal hepatic function. However, in the phase II exploratory study (Study 3000-A3) and in the phase II confirmatory study (Study 3000-A4), when teneligliptin 40 mg was administered to patients with type 2 diabetes mellitus for 12 weeks, the plasma DPP-4 inhibition rate immediately before administration was 69.87% and 73.28%, respectively, and the plasma DPP-4 inhibition rate increased more slowly from approximately >70%, compared with the increase of plasma teneligliptin concentration. Therefore, acute hypoglycemia is unlikely to occur in these patients taking into account of the mechanism of action of teneligliptin. Although teneligliptin was not investigated at the dose of 40 mg in Studies MP-513-E09 and MP-513-E10, the exposure level of teneligliptin following the administration of teneligliptin 40 mg in patients

with renal impairment or hepatic impairment is unlikely to exceed the exposure level reached in patients with normal renal or hepatic function receiving teneligliptin 80 mg. Also, in the light of the observations that the exposure level did not exceed the level reached at the NOAEL in non-clinical toxicity studies and that teneligliptin was well tolerated up to 80 mg in the multiple-dose study in Japanese healthy adult male subjects (Study 3000-A2), teneligliptin is unlikely to pose any significant safety problem. However, since subjects with severe hepatic impairment were not investigated in clinical studies and have therefore never been treated with teneligliptin, caution will be advised in the package insert (draft) that teneligliptin has not been used in patients with severe hepatic impairment and the safety in these patients has not been established.

PMDA considers as follows:
PMDA understands the applicant's response that the extent of increase in the exposure level in patients with renal or hepatic impairment will not pose any significant safety problem, as determined from the pharmacokinetic characteristics of teneligliptin that it is eliminated via 2 different pathways, metabolism mainly by CYP3A4, FMO1, and FMO3 and renal excretion, as well as from the results of Studies MP-513-E09 and MP-513-E10. However, PMDA will continue to examine, in the clinical section, the appropriateness of administering teneligliptin in patients with renal or hepatic impairment, including the evaluation of its safety [see "4.(iii).B.(6).1) Patients with renal impairment" and "4.(iii).B.(6).2) Patients with hepatic impairment"].

4.(ii).B.(2) Drug-drug interaction studies
PMDA asked the applicant to explain the safety for concomitant use of drugs that may affect teneligliptin by drug-drug interactions (CYP3A4 inhibitors, FMO inhibitors, P-gp inhibitors), based on the results of clinical studies.

The applicant responded as follows:
Since teneligliptin is metabolized by CYP3A4 and by FMO, and serves as a substrate for P-gp, the applicant considered that concomitant use with a CYP3A4 inhibitor, an FMO inhibitor, or a P-gp inhibitor may affect the pharmacokinetics of teneligliptin, resulting in an increase in plasma teneligliptin concentration. Taking account of the above consideration, safety of teneligliptin was investigated based on the results of Japanese clinical studies (double-blind comparative studies, 3000-A3 to A7; long-term treatment studies, 3000-A6 to A8).[42] Results of the integrated analysis of the double-blind comparative studies showed that the incidence of adverse events was slightly higher in subjects receiving concomitantly with the inhibitor; a similar tendency was observed in the placebo group as well. However, the incidence did not show a tendency of dose-dependent increase. Adverse events that occurred with a particularly high incidence in subjects administered concomitantly with the inhibitor were "infections and infestations" and "gastrointestinal disorders," and a similar tendency was observed in the placebo group as well. The incidence of adverse drug reactions was slightly higher in subjects in the 10 mg and 20 mg groups who were administered concomitantly with the inhibitor. However, the tendency was similar to that observed in the placebo group; and in the 40 mg group, there was no difference in the incidence between subjects administered concomitantly with the inhibitor and those not concomitantly administered. There were no serious adverse events or adverse events leading to study drug discontinuation in subjects in the 2.5 mg group, 10 mg group, or 40 mg group who were administered concomitantly with the inhibitor. In the 20 mg group, there was no significant difference in the incidence of serious adverse events or adverse events leading to study drug discontinuation, regardless of whether the inhibitor was concomitantly administered or not. Results of the integrated analysis of the long-term treatment studies were similar to those of the

[42] The CYP3A4 inhibitors and P-gp inhibitors were selected by referring to FDA draft guidance "Guidance for Industry Drug Interaction Studies - Study Design, Data Analysis, and Implications for Dosing and Labeling (Table 2, p.19)," a textbook "*Mechanisms of Drug interactions, 8th edition*, Ishiyaku Publishers, Inc.," and a drug-drug interaction database (Metabolism & Transport Drug Interaction Database: DIDB). The FMO inhibitors were selected from the results of DIDB search.

integrated analysis of the double-blind comparative studies, showing no difference in the overall tendency even after a long-term treatment of teneligliptin. On the basis of these results, the applicant considered that concomitant use with CYP3A4 inhibitors, FMO inhibitors, and P-gp inhibitors has little or no effect on the safety of teneligliptin. Regarding efficacy, results of the integrated analysis of the double-blind comparative studies showed that the differences between the teneligliptin group and the placebo group in the changes in HbA1c, fasting blood glucose, and 2-hour postprandial blood glucose level at the end of the treatment period were not significantly different regardless of whether a CYP3A4 inhibitor, an FMO inhibitor, or a P-gp inhibitor was concomitantly administered or not. Similarly, results of the integrated analysis of the long-term treatment studies did not show any significant difference in the observed values at each measuring time point or changes at the end of the treatment period regardless of the use or non-use of concomitant drugs. These results suggest that concomitant use with these inhibitors has little or no effect on the efficacy of teneligliptin.

PMDA concluded that the applicant's response is acceptable based on the information currently available. At the same time, PMDA considers that it is necessary to appropriately provide the information to the clinical practice when new findings on drug-drug interactions become available.

4.(ii).B.(3) QTc interval-prolonging effect of teneligliptin

PMDA, by pointing out that QTc interval prolongation was observed following the administration of teneligliptin 160 mg in the Thorough QT/QTc study, asked the applicant to explain the extent of possible increase in the exposure level in Japanese patients with type 2 diabetes mellitus who are predisposed to increase in the exposure level, following the administration of 20 or 40 mg of teneligliptin, including the explanation of the relationship between the exposure level and QTc interval prolongation in the Thorough QT/QTc study.

The applicant responded as follows:

Results of Studies MP-513-E09, MP-513-E10, MP-513-E11, and MP-513-E05 suggest that factors that increase the C_{max} of teneligliptin may include renal impairment, hepatic impairment, concomitant use with a CYP3A4/P-gp inhibitor, and sex (female). The results of these studies suggested that C_{max} of teneligliptin would increase approximately 1.04 to 1.12 fold in subjects with renal impairment, 1.25 to 1.38 fold in subjects in hepatic impairment, 1.37 fold in subjects administered concomitantly with a CYP3A4/P-gp inhibitor, and 1.16 to 1.30 fold in female subjects. Regarding the sex among these factors, both male and female subjects were enrolled in the Thorough QT/QTc study in a ratio of approximately 1:1, and the difference in C_{max} between male and female subjects can be largely explained by the difference in body weight. Therefore, the sex was not regarded as a noteworthy factor in the present discussion. Teneligliptin is metabolized by CYP3A4 and the metabolic activity was decreased by 47.0% by ketoconazole, a specific inhibitor of CYP3A4. On the other hand, there is a report that CYP3A activity is decreased by approximately 40% in patients with hepatic cirrhosis (Ohnishi A, *Tokyo Jikei-kai Ika Daigaku Zasshi* 2011;126: 71-8). These results suggest that the extent of the decrease in the activity of CYP3A4, the CYP isoform with the highest expression level and the highest enzymatic activity in the liver, is similar between patients with hepatic cirrhosis and subjects administered concomitantly with ketoconazole. In fact, C_{max} of teneligliptin increased to a similar extent in subjects with moderate hepatic impairment (1.38 fold) and in subjects administered concomitantly with ketoconazole (1.37 fold). These results suggest that decreased CYP3A4 activity is the major factor causing the increase in C_{max} of teneligliptin in subjects with hepatic impairment. Therefore, among the factors that increase the C_{max} of teneligliptin, hepatic impairment and concomitant use of CYP3A4/P-gp inhibitors can be regarded as overlapping factors.

On the basis of the above, the ratio of increase in C_{max} caused by each of the factors, moderate renal impairment, moderate hepatic impairment, and concomitant use with CYP3A4/P-gp inhibitors, was calculated, and effects caused by combinations of the factors were estimated. As

a result, the ratio of C_{max} increase was estimated to be 1.98 times at the maximum (moderate renal impairment plus concomitant use of CYP3A4/P-gp inhibitor). In the presence of these factors in combination, the C_{max} in Japanese patients was 435.88 ng/mL at teneligliptin 20 mg and 857.54 ng/mL at teneligliptin 40 mg, and 5.2 times of the value at 20 mg and 2.6 times of the value at 40 mg were estimated to be comparable to the C_{max} reached after administration of teneligliptin 160 mg in the Thorough QT/QTc study. Similarly, when C_{max} at 20 mg and 40 mg in the presence of the combinations of factors was estimated using the 95% upper limit of the CI of the geometric mean of C_{max}, the values were estimated to be 530.88 ng/mL and 1075.73 ng/mL, respectively, and the C_{max} reached at 160 mg in the Thorough QT/QTc study were estimated to be 4.3 and 2.1 times, respectively.

On the basis of the above results, the C_{max} reached at teneligliptin 160 mg in the Thorough QT/QTc study is estimated to be within 4.3 to 5.2 times and 2.1 to 2.6 times the C_{max} reached following the administration of teneligliptin at 20 mg and 40 mg in the presence of multiple factors, respectively, even if the upper limit of the CI is taken into account.

PMDA understands the applicant's response that, even in the presence of multiple factors (moderate renal impairment plus concomitant use of CYP3A4/P-gp inhibitor), plasma teneligliptin concentration does not reach the level that showed QTc interval prolongation in the Thorough QT/QTc study. However, given that patients with type 2 diabetes mellitus often have impairment in renal or hepatic function etc., i.e., in drug metabolism or clearance, and are therefore treated concominantly with other drugs, and that body weight is one of the factors for the increase in the exposure level, the possibility cannot be excluded that the exposure level may be greater than that caused by the multiple factors as estimated by the applicant. In addition, a QTc interval-prolonging effect was observed in Thorough QT/QTc study. Therefore, PMDA will continuously examine, in the clinical section, QTc interval prolongation and proarrhythmic risk [see "4.(iii).B.(3).7) QTc interval prolongation and proarrhythmic risk"].

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

Results of the following studies were submitted as evaluation data: 6 studies in Japanese healthy adult subjects (Studies 3000-A1, 3000-A2, 3000-A9 to A11, 3000-A13), a clinical pharmacology study in Japanese patients with type 2 diabetes mellitus (Study 3000-A12), 2 phase II studies (Studies 3000-A3, 3000-A4), 4 phase III studies (Studies 3000-A5 to A8), and Thorough QT/QTc study in foreign healthy adult male and female subjects (Study MP-513-A01). Also, results of 9 clinical studies, including the following studies, were submitted as reference data: a late phase II metformin concomitant therapy study in foreign patients with type 2 diabetes mellitus (Study MP-513-E07), a pharmacokinetic study in foreign patients with renal impairment (Study MP-513-E09), and a pharmacokinetic study in foreign patients with hepatic impairment (Study MP-513-E10). The results from the main studies are described below. HbA1c is expressed in JDS value in the following description.

4.(iii).A.(1) Clinical pharmacology studies

For the outline and the safety results of the 6 studies in Japanese healthy adult subjects (Studies 3000-A1, 3000-A2, 3000-A9 to A11, 3000-A13), the Thorough QT/QTc study in foreign healthy adult male and female subjects (Study MP-513-A01), the pharmacokinetic study in foreign subjects with renal impairment (Study MP-513-E09), and the pharmacokinetic study in foreign subjects with hepatic impairment (Study MP-513-E10), see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies." For the clinical pharmacology study in Japanese patients with type 2 diabetes mellitus (Study 3000-A12), see "4.(iii).A.(2) Phase II studies."

4.(iii).A.(2) Phase II studies

4.(iii).A.(2).1) Clinical pharmacology study (5.3.4.2-1, Study 3000-A12 [[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese patients with type 2 diabetes mellitus[43] (target sample size of 90; 30 subjects per group) to investigate the effect of teneligliptin on blood glucose control and safety [for pharmacokinetics and pharmacodynamics, see "4.(ii).A.(3).1) Clinical pharmacology study"].

Placebo was administered orally once daily before breakfast during the 4-week run-in period, then placebo or teneligliptin (10 mg or 20 mg) was administered orally once daily before breakfast (30 minutes before breakfast) for 4 weeks.

All 99 treated subjects (32 subjects in placebo group, 34 subjects in 10 mg group, 33 subjects in 20 mg group) were included in the populations for safety analysis and for efficacy analysis. None of the subjects discontinued the study prematurely.

Regarding efficacy, changes in blood glucose-related endpoints (2-hour postprandial blood glucoselevel, $AUC_{0\text{-}2\ h}$ of postprandial blood glucose level, fasting blood glucose level, and mean blood glucose level over a 24 hour period) from baseline at Week 4 of treatment period were as shown in Tables 10, 11, and 12. In the 10 mg group and in the 20 mg group, all endpoint values significantly decreased compared with the placebo group, but there was no significant difference between the 10 mg group and the 20 mg group.

[43] Patients with type 2 diabetes mellitus who were receiving diet and exercise therapy, did not take any oral hypoglycemic agent from ≥8 weeks before the start of the run-in period (if subjects had been taking an oral hypoglycemic agent, a wash-out period of ≥8 weeks was required after informed consent), in whom HbA1c level was ≥6.5% to <10.0% and fasting blood glucose level was ≤270 mg/dL at the start of the run-in period, HbA1c level was ≥6.5% to <10.0% and fasting blood glucose level was 126 mg/dL to 270 mg/dL at 2 weeks after the start of the run-in period, and the difference in HbA1c between at 2 weeks after the start of the run-in period and at the start of the run-in period was ≤0.5%.

Table 10. Changes from baseline in 2-hour postprandial blood glucose at week 4 of treatment

Parameter	Treatment group	No. of subjects	Changes from baseline	Difference from placebo group [95% CI][a)]	Difference between 10 mg group and 20 mg group [95% CI][a)]
Blood glucose at 2 h after breakfast	Placebo group	n = 32	-8.3 ± 32.8	—	—
	10 mg group	n = 34	-59.1 ± 30.1	-50.7 [-66.2, -35.2]	—
	20 mg group	n = 33	-43.0 ± 43.0	-38.1 [-53.7, -22.6]	12.5 [-2.9, 27.9]
Blood glucose at 2 h after lunch	Placebo group	n = 32	-5.9 ± 39.7	—	—
	10 mg group	n = 34	-43.0 ± 38.8	-34.8 [-53.1, -16.5]	—
	20 mg group	n = 33	-34.8 ± 44.5	-28.6 [-46.8, -10.3]	6.2 [-11.9, 24.4]
Blood glucose at 2 h after supper	Placebo group	n = 32	-1.9 ± 31.8	—	—
	10 mg group	n = 34	-42.6 ± 32.4	-37.5 [-52.4, -22.5]	—
	20 mg group	n = 33	-37.4 ± 39.5	-36.1 [-51.1, -21.2]	1.3 [-13.5, 16.2]

Unit: mg/dL, mean ± SD, -: Not applicable

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable, fasting blood glucose at 2 weeks after the start of run-in period as the factor, and 2-hour postprandial blood glucose level at baseline as the covariate, and its 95% CI

Table 11. Changes from baseline in $AUC_{0\text{-}2\ h}$ of postprandial blood glucose at week 4 of treatment

Parameter	Treatment group	No. of subjects	Changes from baseline	Difference from placebo group [95% CI][a)]	Difference between 10 mg group and 20 mg group [95% CI][a)]
$AUC_{0\text{-}2\ h}$ of blood glucose after breakfast	Placebo group	n = 32	-4.5 ± 46.4	—	—
	10 mg group	n = 34	-86.2 ± 43.8	-73.2 [-95.2, -51.2]	—
	20 mg group	n = 33	-73.4 ± 54.7	-66.5 [-88.4, -44.6]	6.7 [-15.0, 28.4]
$AUC_{0\text{-}2\ h}$ of blood glucose after lunch	Placebo group	n = 32	-0.2 ± 62.8	—	—
	10 mg group	n = 34	-93.1 ± 67.5	-86.1 [-115.4, -56.7]	—
	20 mg group	n = 33	-83.2 ± 67.5	-80.0 [-109.4, -50.5]	6.1 [-23.1, 35.3]
$AUC_{0\text{-}2\ h}$ of blood glucose after supper	Placebo group	n = 32	-5.2 ± 55.3	—	—
	10 mg group	n = 34	-76.2 ± 62.4	-63.9 [-90.5, -37.4]	—
	20 mg group	n = 33	-79.3 ± 67.9	-73.9 [-100.5, -47.4]	-10.0 [-36.3, 16.4]

Unit: mg·h/dL, mean ± SD, -: Not applicable

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable, fasting blood glucose at 2 weeks after the start of run-in period as the factor, and $AUC_{0\text{-}2h}$ of postprandial blood glucose at baseline as the covariate, and its 95% CI

Table 12. Changes from baseline in fasting blood glucose and mean blood glucose over 24 hours at Week 4 of treatment

Parameter	Treatment group	No. of subjects	Changes from baseline	Difference from placebo group [95% CI][a)]	Difference between 10 mg group and 20 mg group [95% CI][a)]
Fasting blood glucose	Placebo group	n = 32	-3.9 ± 19.2	–	–
	10 mg group	n = 34	-23.2 ± 20.9	-13.8 [-21.7, -5.9]	–
	20 mg group	n = 33	-20.8 ± 19.3	-13.6 [-21.5, -5.7]	0.2 [-7.6, 7.9]
Mean blood glucose over 24 hours	Placebo group	n = 32	-3.7 ± 21.5	–	–
	10 mg group	n = 34	-36.3 ± 25.3	-29.3 [-39.8, -18.8]	–
	20 mg group	n = 33	-29.1 ± 25.1	-25.5 [-36.0, -15.1]	3.8 [-6.6, 14.2]

Unit: mg/dL, mean ± SD, -: Not applicable

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable, fasting blood glucose at 2 weeks after the start of run-in period as the factor, and baseline fasting blood glucose or mean blood glucose level over 24 hours as the covariate, and its 95% CI

Regarding safety, the incidence of adverse events was 28.1% (9 of 32 subjects) in the placebo group, 23.5% (8 of 34 subjects) in the 10 mg group, and 18.2% (6 of 33 subjects) in the 20 mg group. Only ATL increased and γ-GTP increased observed in 1 subject in the 10 mg group was classified as adverse drug reactions. Adverse events reported by ≥3% in any of the treatment groups were as shown in Table 13.

Table 13. Adverse events reported by ≥3% in any of the treatment groups (safety analysis population)

Adverse event name	Placebo group (n = 32)	10 mg group (n = 34)	20 mg group (n = 33)
All adverse events	28.1 (9)	23.5 (8)	18.2 (6)
Nasopharyngitis	0.0 (0)	5.9 (2)	6.1 (2)
Upper respiratory tract inflammation	0.0 (0)	8.8 (3)	0.0 (0)
Diarrhoea	0.0 (0)	0.0 (0)	3.0 (1)
Colonic polyp	3.1 (1)	0.0 (0)	0.0 (0)
Glucose urine present	9.4 (3)	2.9 (1)	0.0 (0)
Protein urine present	6.3 (2)	0.0 (0)	3.0 (1)
Contusion	3.1 (1)	0.0 (0)	0.0 (0)
Excoriation	3.1 (1)	0.0 (0)	3.0 (1)
Tooth abscess	3.1 (1)	0.0 (0)	0.0 (0)

Incidence % (No. of subjects with event), MedDRA/J (ver.13.1)

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation. There were no adverse events caused by hypoglycemia or QTc interval prolongation. There was no particularly relevant variability in resting 12-lead ECG or vital signs.

4.(iii).A.(2).2) Phase II exploratory study (5.3.5.1.1, Study 3000-A3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese patients with type 2 diabetes mellitus[44] (target sample size of 200, 50 subjects per group) to investigate the efficacy and safety of teneligliptin [for pharmacokinetics and pharmacodynamics, see "4.(ii).A.(3).2) Phase II exploratory study"].

Placebo was administered orally before breakfast (at 30 minute before breakfast) once daily during the 4-week run-in period, then placebo or teneligliptin (2.5, 10, or 40 mg) was administered orally before breakfast (at 30 minute before breakfast) once daily for 12 weeks.

From a total of 187 treated subjects (45 subjects in placebo group, 49 subjects in 2.5 mg group, 46 subjects in 10 mg group, 47 subject in 40 mg group), 186 subjects, excluding 1 subject in the 10 mg group who received the study drug of another subject by mistake, were included in the safety analysis population and in the full analysis set (FAS) for efficacy. After excluding 12 subjects from the FAS, a population of 174 subjects (43 subjects in placebo group, 47 subjects in 2.5 mg group, 39 subjects in 10 mg group, 45 subjects in 40 mg group) was included in the per protocol set (PPS) and handled as the primary efficacy analysis set. The study was terminated prematurely in 9 subjects, including 2 subjects in the placebo group (1 subject due to adverse event, 1 subject due to the subject's request), 2 subjects in 2.5 mg group (1 subject due to the subject's request, 1 subject due to meeting exclusion criteria), 3 subjects in the 10 mg group (1 subject each due to adverse event, meeting exclusion criteria, and at the discretion of the investigator), and 2 subjects in the 40 mg group (meeting exclusion criteria).

Regarding efficacy, the changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of administration) in PPS, the primary endpoint, was as shown in Table 14. A significant decrease in HbA1c was observed in all teneligliptin groups compared with the placebo group. Dose-response relationship was examined by a contrast test as the secondary analysis. As a result, the pattern of saturating at 10 mg was best fit by the observed results. Results of analysis in FAS were similar to those obtained with PPS.

Table 14. Changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of administration) (PPS)

Treatment group	No. of subjects	End of run-in period (baseline)	Changes up to the end of treatment period (Week 12) (LOCF)	Difference from placebo group [95% CI][a)]
Placebo group	n = 43	7.83 ± 0.83	0.32 ± 0.64	–
2.5 mg group	n = 47	7.42 ± 0.72	-0.24 ± 0.46	-0.65 [-0.89, -0.42]
10 mg group	n = 39	7.83 ± 0.77	-0.67 ± 0.73	-0.99 [-1.23, -0.75]
40 mg group	n = 45	7.68 ± 0.91	-0.75 ± 0.48	-1.11 [-1.34, -0.87]

Unit: %, mean ± SD, LOCF: Imputation of missing values by Last Observation Carried Forward method,
-: Not applicable

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

[44] Patients with type 2 diabetes mellitus who were receiving diet and exercise therapy, did not take any oral hypoglycemic agent from ≥8 weeks before the start of the run-in period (if subjects had been taking an oral hypoglycemic agent, a wash-out period of 8 weeks was required after informed consent), in whom HbA1c level was ≥6.5% to < 9.5% at the start of the run-in period and at 2 weeks after the run-in period, fasting blood glucose level was 126 mg/dL to 240 mg/dL at the start of the run-in period, and the difference in HbA1c between at 2 weeks after the start of the run-in period and at the start of the run-in period was ≤0.5%.

Table 15 shows the results of the analysis of main secondary endpoints.

Table 15. Results of the analysis of main secondary endpoints (PPS)

Endpoint	Treatment group	End of run-in period (baseline)	Changes up to the end of treatment period (Week 12)	Difference from placebo group [95% CI][b)]
Fasting blood glucose[a)] (mg/dL)	Placebo group (n = 43)	161.2 ± 24.7	6.2 ± 24.0	–
	2.5 mg group (n = 47)	156.4 ± 26.2	-11.3 ± 19.8	-19.5 [-27.8, -11.2]
	10 mg group (n = 39)	159.6 ± 24.0	-19.9 ± 27.6	-26.7 [-35.4, -18.0]
	40 mg group (n = 45)	158.3 ± 28.6	-18.9 ± 18.6	-26.3 [-34.7, -17.9]
2-h postprandial blood glucose (mg/dL)	Placebo group	272.4 ± 58.8 (n = 43)	1.6 ± 48.3 (n = 42)	–
	2.5 mg group	245.8 ± 61.3 (n = 47)	-27.0 ± 39.1 (n = 47)	-35.1 [-51.7, -18.4]
	10 mg group	275.3 ± 47.7 (n = 39)	-65.6 ± 48.1 (n = 38)	-65.0 [-82.4, -47.6]
	40 mg group	253.3 ± 65.4 (n = 45)	-50.6 ± 33.8 (n = 45)	-56.7 [-73.4, -39.9]
$AUC_{0\text{-}2\ h}$ of postprandial blood glucose (mg·h/dL)	Placebo group	504.2 ± 84.1 (n = 43)	17.5 ± 72.3 (n = 42)	–
	2.5 mg group	465.1 ± 78.7 (n = 47)	-42.3 ± 51.0 (n = 47)	-69.6 [-95.2, -43.9]
	10 mg group	516.3 ± 70.0 (n = 39)	-101.7 ± 79.1 (n = 38)	-114.0 [-140.8, -87.2]
	40 mg group	489.3 ± 88.1 (n = 45)	-78.0 ± 55.5 (n = 45)	-98.2 [-123.8, -72.5]
Percentage of subjects achieving HbA1c level of <6.5%[c)] (%)	Placebo group	2.5 mg group	10 mg group	40 mg group
	2.3 (1/43 subjects)	8.5 (4/47 subjects)	12.8 (5/39 subjects)	26.7 (12/45 subjects)

Mean ± SD, -: Not applicable

a) Missing values were imputed by LOCF.

b) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

c) Percentage of subjects achieving the target level (number of subjects achieving the target level/total number of subjects evaluated)

Regarding safety, the incidence of adverse events in the placebo, 2.5 mg, 10 mg, and 40 mg groups were 51.1% (23 of 45 subjects), 55.1% (27 of 49 subjects), 62.2% (28 of 45 subjects), and 53.2% (25 of 47 subjects), respectively. The incidence of adverse drug reactions were 2.2% (1 of 45 subjects; eczema), 0.0% (0 of 49 subjects), 4.4% (2 of 45 subjects; rash, blood triglycerides increased), and 2.1% (1 of 47 subjects; nausea), respectively.
Adverse events reported by ≥3% in any of the treatment groups were as shown in Table 16.

Table 16. Adverse events reported by ≥3% in any of the treatment groups (population for safety analysis)

Adverse event name	Placebo group (n = 45)	2.5 mg group (n = 49)	10 mg group (n = 45)	40 mg group (n = 47)
All adverse events	51.1 (23)	55.1 (27)	62.2 (28)	53.2 (25)
Nasopharyngitis	15.6 (7)	16.3 (8)	8.9 (4)	10.6 (5)
Gastroenteritis	6.7 (3)	0.0 (0)	4.4 (2)	0.0 (0)
Pharyngitis	2.2 (1)	6.1 (3)	0.0 (0)	0.0 (0)
Dry eye	0.0 (0)	0.0 (0)	4.4 (2)	0.0 (0)
Periarthritis	0.0 (0)	0.0 (0)	0.0 (0)	4.3 (2)
Arthralgia	4.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Lumbar spinal stenosis	0.0 (0)	0.0 (0)	4.4 (2)	0.0 (0)
Back pain	2.2 (1)	2.0 (1)	0.0 (0)	6.4 (3)
Upper respiratory tract inflammation	8.9 (4)	12.2 (6)	13.3 (6)	2.1 (1)
Cervicobrachial syndrome	2.2 (1)	4.1 (2)	0.0 (0)	0.0 (0)
Headache	0.0 (0)	2.0 (1)	0.0 (0)	4.3 (2)

Incidence % (No. of subjects with event), MedDRA/J (Ver 10.0)

No deaths were reported. Only 1 serious adverse event (pharyngeal cyst) was reported in 1 subject in the placebo group. Adverse events leading to study drug discontinuation occurred in 1 subject (pharyngeal cyst) in the placebo group and 1 subject (diabetic retinopathy) in the 10 mg group. There were no adverse events caused by hypoglycemia or QTc interval prolongation. Resting 12-lead ECG showed moderate sinoatrial block in 1 subject in the 40 mg group, but its causal relationship with the study drug was denied. There was no particularly relevant variability in vital signs.

4.(iii).A(2).3) Phase II confirmatory study (5.3.5.1-2, Study 3000-A4 [20 to 20])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese patients with type 2 diabetes mellitus[45] (target sample size of 300, 75 subjects per group) to investigate the efficacy and safety of teneligliptin [for pharmacokinetics and pharmacodynamics, see "4.(ii).A.(3).3) Phase II confirmatory study"].

Placebo was administered orally before breakfast once daily during the 4-week run-in period, then placebo or teneligliptin (10, 20, or 40 mg) was administered orally before breakfast (at 30 minutes before breakfast) once daily for 12 weeks.

All 324 treated subjects (80 subjects in placebo group, 84 subjects in 10 mg group, 79 subjects in 20 mg group, 81 subjects in 40 mg group) were included in the safety analysis population and in the FAS. The study was terminated prematurely in 12 subjects, including 3 subjects in the placebo group (2 subject due to adverse event, 1 subject at the discretion of the investigator), 1 subject in the 10 mg group (at the discretion of the investigator), 3 subjects in the 20 mg group (2 subjects at the discretion of the investigator, 1 subject due to adverse event), and 5 subjects in the 40 mg group (3 subjects at the discretion of the investigator, 2 subjects due to adverse events).

[45] Patients with type 2 diabetes mellitus who were receiving diet and exercise therapy, did not take any oral hypoglycemic agent from ≥8 weeks before the start of the run-in period (if subjects had been taking an oral hypoglycemic agent, a wash-out period of ≥8 weeks was required after informed consent), in whom HbA1c level was ≥6.5% to <9.5% at the start of the run-in period and at 2 weeks after the start of the run-in period, fasting blood glucose level was ≤240 mg/dL at the start of the run-in period, and the difference in HbA1c between at 2 weeks after the start of the run-in period and at the start of the run-in period was ≤0.5%.

Regarding efficacy, changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of administration) in FAS, the primary endpoint, was as shown in Table 17. In order to determine the recommended dose of teneligliptin, a contrast test was performed on the change in HbA1c using the contrast coefficient (-3, 1, 1, 1) for each treatment group (placebo group, 10 mg group, 20 mg group, 40 mg group). The test showed significant results, and all teneligliptin groups showed a significant decrease in HbA1c compared with the placebo group as well.

Table 17. Changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of administration) (FAS)

Treatment group	No. of subjects	End of run-in period (baseline)	Changes up to the end of treatment period (Week 12) (LOCF)	Difference from placebo group [95% CI][a)]
Placebo group	n = 80	7.66 ± 0.73	0.07 ± 0.63	—
10 mg group	n = 84	7.60 ± 0.73	-0.79 ± 0.48	-0.88 [-1.03, -0.73]
20 mg group	n = 79	7.48 ± 0.73	-0.78 ± 0.53	-0.90 [-1.06, -0.75]
40 mg group	n = 81	7.43 ± 0.67	-0.87 ± 0.48	-1.01 [-1.16, -0.86]

Unit: %, mean ± SD, -: Not applicable

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

Table 18 shows the results of the analysis of main secondary endpoints.

Table 18. Results of the analysis of main secondary endpoints (FAS)

Endpoint	Treatment group	End of run-in period (baseline)	Changes up to the end of treatment period (Week 12)	Difference from placebo group [95% CI][a)]
Fasting blood glucose[a)] (mg/dL)	Placebo group (n = 80)	150.0 ± 30.3	1.2 ± 23.5	–
	10 mg group (n = 84)	148.0 ± 22.4	-15.7 ± 17.5	-17.8 [-23.4, -12.1]
	20 mg group (n = 79)	143.0 ± 26.8	-13.2 ± 19.8	-16.9 [-22.6, -11.2]
	40 mg group (n = 81)	141.9 ± 28.3	-15.8 ± 22.4	-20.0 [-25.7, -14.3]
2-h postprandial blood glucose (mg/dL)	Placebo group	242.0 ± 46.7 (n = 80)	5.3 ± 43.9 (n = 76)	–
	10 mg group	240.0 ± 55.5 (n = 84)	-46.0 ± 42.1 (n = 83)	-50.6 [-62.8, -38.4]
	20 mg group	231.9 ± 53.6 (n = 79)	-48.8 ± 42.9 (n = 76)	-56.8 [-69.2, -44.3]
	40 mg group	224.2 ± 54.8 (n = 81)	-47.0 ± 48.7 (n = 76)	-58.6 [-71.1, -46.1]
$AUC_{0\text{-}2\ h}$ of postprandial blood glucose (mg·h/dL)	Placebo group	461.2 ± 59.0 (n = 80)	4.4 ± 69.8 (n = 76)	–
	10 mg group	460.2 ± 67.2 (n = 84)	-68.4 ± 55.1 (n = 83)	-71.3 [-88.8, -53.9]
	20 mg group	450.3 ± 75.5 (n = 79)	-72.4 ± 57.0 (n = 76)	-79.1 [-96.9, -61.3]
	40 mg group	444.8 ± 73.5 (n = 81)	-71.4 ± 69.7 (n = 76)	-81.2 [-99.1, -63.4]
Percentage of subjects achieving HbA1c level of less than 6.5%[c)]	Placebo group	10 mg group	20 mg group	40 mg group
	2.6 (2/78 subjects)	32.5 (27/83 subjects)	40.5 (32/79 subjects)	51.3 (41/80 subjects)

Mean ± SD, -: Not applicable

a) Missing values were imputed by LOCF (in 1 subject each in 10 mg group and 20 mg group, all values after the administration of the study drug were missing and excluded from the analysis of changes).

b) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

c) Percentage of subjects achieving the target level (number of subjects achieving the target level/total number of subjects evaluated)

Regarding safety, the incidence of adverse events was 55.0% (44 of 80 subjects) in the placebo group, 59.5% (50 of 84 subjects) in the 10 mg group, 50.6% (40 of 79 subjects) in the 20 mg group, and 56.8% (46 of 81 subjects) in the 40 mg group. The incidence of adverse drug reactions was 7.5% in the placebo group (6 of 80 subjects; hypoglycemia [2 subjects], headache, flatulence, dyshidrosis, protein urine present), 4.8% in the 10 mg group (4 of 84 subjects; constipation [2 subjects], abdominal pain, blood uric acid increased/protein urine present), 2.5% in the 20 mg group (2 of 79 subjects; eczema, blood creatine phosphokinase increased), and 13.6% in the 40 mg group (11 of 81 subjects; hypoglycemia, hyperlipidaemia, vertigo, duodenal ulcer, gastrointestinal motility disorder, abdominal pain, abdominal distension/hypoglycemia, constipation/hypoglycemia, calculus ureteric, blood potassium increased, protein urine present). Adverse events reported by ≥3% in any of the treatment groups were as shown in Table 19.

Table 19. Adverse events reported by ≥3% in any of the treatment groups (population for safety analysis)

Adverse event name	Placebo group (n = 80)	10 mg group (n = 84)	20 mg group (n = 79)	40 mg group (n = 81)
All adverse events	55.0 (44)	59.5 (50)	50.6 (40)	56.8 (46)
Nasopharyngitis	13.8 (11)	19.0 (16)	11.4 (9)	17.3 (14)
Upper respiratory tract inflammation	0.0 (0)	3.6 (3)	1.3 (1)	2.5 (2)
Hypoglycaemia	3.8 (3)	0.0 (0)	1.3 (1)	3.7 (3)
Back pain	0.0 (0)	3.6 (3)	1.3 (1)	1.2 (1)
Constipation	0.0 (0)	3.6 (3)	2.5 (2)	1.2 (1)
Blood creatine phosphokinase increased	1.3 (1)	4.8 (4)	1.3 (1)	0.0 (0)
Urine ketone body present	1.3 (1)	3.6 (3)	5.1 (4)	2.5 (2)
Glucose urine present	7.5 (6)	1.2 (1)	5.1 (4)	3.7 (3)
Blood urine present	1.3 (1)	4.8 (4)	2.5 (2)	1.2 (1)
Protein urine present	5.0 (4)	4.8 (4)	2.5 (2)	2.5 (2)
Arthropod sting	0.0 (0)	0.0 (0)	0.0 (0)	3.7 (3)

Incidence % (No. of subjects with event), MedDRA/J (Ver 11.1)

One subject in the placebo group died of metastatic neoplasm, but this death was considered as not causally related to the study drug. There were no serious adverse events other than the death. Adverse events leading to study drug discontinuation were observed in 5 subjects, including 2 subjects in the placebo group (metastatic neoplasm [the death case], hyperglycaemia), 1 subject in the 20 mg group (diabetic retinopathy), and 2 subjects in the 40 mg group (vertigo, myalgia). Hypoglycemia was observed in 3 subjects in the placebo group (4 events), in 1 subject in the 20 mg group (1 event), and in 3 subjects in the 40 mg group (3 events). Among them, 2 events in 2 subjects in the placebo group and 3 events in 3 subjects in the 40 mg group were classified as adverse drug reactions, but all of them were mild in severity. There were no adverse events caused by QTc interval prolongation. There was no particularly relevant variability in the resting 12-lead ECG or vital signs.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Phase III double-blind confirmatory study (5.3.5.1-3, Study 3000-A5 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese patients with type 2 diabetes mellitus[46] (target sample size of 200, 100 subjects per group) to confirm the efficacy and safety of teneligliptin 20 mg.

Placebo was administered orally before breakfast once daily during the 4-week run-in period,. Then, placebo or teneligliptin (20 mg) was administered orally before breakfast (at 30 minutes before breakfast) once daily for 12 weeks.

All 203 treated subjects (104 subjects in placebo group, 99 subjects in 20 mg group) were included in the safety analysis population and in the FAS. The study was terminated prematurely in 10 subjects, including 8 subjects in the placebo group (3 subjects at the discretion of the investigator,

[46] Patients with type 2 diabetes mellitus who were receiving diet and exercise therapy, did not take any oral hypoglycemic agent from ≥8 weeks before the start of the run-in period (if subjects had been taking an oral hypoglycemic agent, a wash-out period of ≥8 weeks was required after informed consent), in whom HbA1c level was ≥6.5% to <10.0% at the start of the run-in period and at 2 weeks after the start of the run-in period, fasting blood glucose level was ≤270 mg/dL at the start of the run-in period, and the difference in HbA1c between at 2 weeks after the start of the run-in period and at the start of the run-in period was ≤0.5%.

2 subjects due to adverse events, 1 subject each due to subject's request, subject's personal reason, and HbA1c increased) and 2 subjects in the 20 mg group (adverse event).

Regarding efficacy, the changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of administration) in FAS, the primary endpoint, was as shown in Table 20. The difference (least squares mean) in the change between the 20 mg group and the placebo group, with its 95% CI, was -0.79% [-0.94%, -0.64%], demonstrating the superiority of the 20 mg group to the placebo group.

Table 20. Changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of administration) (FAS)

Treatment group	End of run-in period (baseline)	End of treatment period (Week 12)	Changes from baseline (LOCF)	Between-group difference [95% CI][a)]
Placebo group	7.58 ± 0.85 (n = 104)	7.63 ± 0.93 (n = 96)	0.18 ± 0.52	-0.79 [-0.94, -0.64]
20 mg group	7.53 ± 0.78 (n = 99)	6.91 ± 0.85 (n = 97)	-0.62 ± 0.53	

Unit: %, mean ± SD

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

Table 21 shows the results of the analysis of main secondary endpoints and the percentage of subjects achieving a decrease in HbA1c to <6.5%.

Table 21. Results of the analysis of main secondary endpoints and percentage of subjects achieving a decrease in HbA1c to <6.5% (FAS)

Endpoint	Treatment group	End of run-in period (baseline)	Changes up to the end of treatment period (Week 12)	Difference from placebo group [95% CI][b)]
Fasting blood glucose[a)] (mg/dL)	Placebo group (n = 104)	155.2 ± 31.6	-0.2 ± 20.5	–
	20 mg group (n = 99)	155.0 ± 30.3	-19.2 ± 18.2	-19.0 [-24.0, -13.9]
2-h postprandial blood glucose (mg/dL)	Placebo group	238.0 ± 59.1 (n = 104)	-2.3 ± 38.2 (n = 96)	–
	20 mg group	241.3 ± 55.3 (n = 99)	-48.8 ± 35.5 (n = 97)	-44.7 [-54.6, -34.8]
$AUC_{0\text{-}2\ h}$ of postprandial blood glucose (mg·h/dL)	Placebo group	458.5 ± 85.3 (n = 104)	1.4 ± 48.4 (n = 96)	–
	20 mg group	460.9 ± 78.3 (n = 99)	-74.3 ± 52.7 (n = 97)	-73.3 [-86.9, -59.8]
Percentage of subjects achieving HbA1c level of less than 6.5%[c)]	Placebo group		20 mg group	
	1.0 (1/102 subjects)		30.3 (30/99 subjects)	

Mean ± SD; 2-h postprandial blood glucose, $AUC_{0\text{-}2\ h}$ of postprandial blood glucose, mean ± SD (number of subjects at Week 12 of treatment period); -: Not applicable

a) Fasting blood glucose: missing values were imputed by LOCF (in 2 subject in the placebo group, all values after the administration of the study drug were missing and excluded from the analysis of changes).

b) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

c) Percentage of subjects achieving the target level (%) (number of subjects achieving the target level/total number of subjects evaluated)

Regarding safety, the incidence of adverse event was 63.5% (66 of 104 subjects) in the placebo group and 62.6% (62 of 99 subjects) in the 20 mg group. The incidence of adverse drug reactions was 4.8% in the placebo group (5 of 104 subjects; hypoglycemia, hypertension, duodenitis, constipation, protein urine present in 1 subject each) and 1.0% in the 20 mg group (1 of 99 subjects; constipation). Adverse events reported by ≥3% in any of the treatment groups were as shown in Table 22.

Table 22. Adverse events reported by ≥3% in any of the treatment groups (safety analysis population)

Adverse event name	Placebo group (n = 104)	20 mg group (n = 99)
All adverse events	63.5 (66)	62.6 (62)
Nasopharyngitis	6.7 (7)	12.1 (12)
Bronchitis	3.8 (4)	3.0 (3)
Upper respiratory tract inflammation	3.8 (4)	4.0 (4)
Colonic polyp	1.9 (2)	3.0 (3)
Periodontitis	3.8 (4)	1.0 (1)
Back pain	3.8 (4)	0.0 (0)
ALT increased	3.8 (4)	1.0 (1)
Blood creatine phosphokinase increased	3.8 (4)	2.0 (2)
Blood triglycerides increased	3.8 (4)	0.0 (0)
Glucose urine present	6.7 (7)	4.0 (4)

Incidence in percentage (No. of subjects with event), MedDRA/J (Ver 13.0)

No deaths were reported. Serious adverse events were observed in 4 subjects in the placebo group (vestibular neuronitis, gastric cancer, breast cancer, contusion in 1 subject each), but not in the 20 mg group. Adverse events leading to study drug discontinuation were observed in 2 subjects in the placebo group (hyperglycaemia, gastric cancer in 1 subject each) and in 2 subjects in the 20 mg group (eosinophilia, myasthenia gravis in 1 subject each). An adverse event of hypoglycemia was observed in 1 subject in the placebo group (1 event) and in 1 subject in the 20 mg group (2 events). The event observed in the subject in the placebo group was classified as an adverse drug reaction, but all hypoglycemia were mild in severity. There were no adverse events caused by QTc interval prolongation. There was no particularly relevant variability in the resting 12-lead ECG or vital signs.

4.(iii).A.(3).2) Phase III sulfonylurea concomitant therapy study (5.3.5.1-4, Study 3000-A6 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese subjects with type 2 diabetes mellitus who insufficiently responded to sulfonylureas (glimepiride)[47] (target sample size of 200 subjects, 100 subjects per group) to investigate the efficacy and safety of the concomitant use of teneligliptin with sulfonylureas.

Placebo was administered orally before breakfast once daily during the 4-week run-in period. Then, placebo or teneligliptin (20 mg) was administered at 30 minutes before breakfast once daily during period I (12-week double-blind period), followed by the administration of teneligliptin

[47] Patients with type 2 diabetes mellitus who were continuously receiving glimepiride at a fixed dosage regimen (1, 2, 3, or 4 mg/day) for ≥8 weeks before the start of the run-in period without taking any other oral hypoglycemic agent (if subjects had been taking other oral hypoglycemic agents, a wash-out period of ≥8 weeks was required after informed consent), in whom HbA1c level was 7.0% to <10.0% at the start of the run-in period and at 2 weeks after the start of the run-in period, fasting blood glucose level was ≤270 mg/dL at the start of the run-in period, and the difference in HbA1c between at 2 weeks after the start of the run-in period and at the start of the run-in period was ≤0.5%.

(20 mg) at 30 minutes before breakfast once daily during period II (40-week open-label period). If HbA1c was ≥7.0% after the Week 24 of the treatment period and no safety problem was observed, teneligliptin dose was to be increased from 20 mg to 40 mg from the next scheduled visit. For glimepiride, the dose used ≥12 weeks before the start of the double blind period was to be maintained throughout the treatment period. If hypoglycemia occurred next day and onwards after the visit at the end of the 12-week treatment period, or if fasting blood glucose tested at the clinical laboratory was ≤70 mg/dL, the dose could be decreased by 1 mg/day at a time, at the discretion of the investigator. Increasing the once-reduced dose was not allowed.

All 194 treated subjects (98 subjects in placebo group, 96 subjects in 20 mg group) were included in the safety analysis population and in the FAS. A total of 190 subjects (95 subjects in placebo group, 95 subjects in 20 mg group) completed the double-blind period (12 weeks) and proceeded to the open-label period (40 weeks). Of those who completed the double blind period, 87 subjects in the placebo group also completed the open-label period (P/T group), and 85 in the 20 mg group completed the open-label period (T/T group). The study was terminated prematurely in 4 subjects during the double-blind period (3 subjects in placebo group [2 subjects due to adverse events, 1 subject at the discretion of the investigator]; 1 subject in 20 mg group [adverse event]), and in 18 subjects during the open-label period (8 subjects in P/T group [4 subjects due to adverse events, 2 subjects due to fasting blood glucose increased, 1 subjects due to HbA1c increased, 1 subject due to the subject's request]; 10 subjects in T/T group [5 subjects due to adverse events, 3 subjects at the discretion of the investigator, 1 subject due to fasting blood glucose increased, 1 subject due to arrhythmia requiring immediate treatment during the treatment period]). Teneligliptin dose was increased to 40 mg in 129 subjects (64 subjects in P/T group, 65 subjects in T/T group).

Regarding efficacy, the change in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of the double-blind period) in FAS, the primary endpoint, was as shown in Table 23. The difference (least squares mean) in the change between the 20 mg group and the placebo group, with its 95% CI, was -1.00% [-1.16, -0.84], demonstrating the superiority of the 20 mg group to the placebo group.

Table 23. Changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (Week 12 of double-blind period) (FAS)

Treatment group	End of run-in period (baseline)	End of treatment period (Week 12)	Changes from baseline (LOCF)	Between-group difference [95% CI][a)]
Placebo group	8.08 ± 0.77 (n = 98)	8.40 ± 0.91 (n = 95)	0.29 ± 0.56	-1.00 [-1.16, -0.84]
20 mg group	8.10 ± 0.76 (n = 96)	7.39 ± 0.75 (n = 95)	-0.71 ± 0.60	

Unit: %, Mean ± SD

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

Table 24 shows the results of the analysis of main secondary endpoints and the percentage of subjects achieving a decrease in HbA1c to <6.5%.

Table 24. Results of the analysis of main secondary endpoints and percentage of subjects achieving a decrease in HbA1c to <6.5% (FAS)

Endpoint	Treatment group	End of run-in period (baseline)	Changes up to the end of treatment period (Week 12)	Difference from placebo group [95% CI][a)]
Fasting blood glucose[a)] (mg/dL)	Placebo group (n = 98)	163.4 ± 31.3	10.1 ± 24.0	–
	20 mg group (n = 96)	165.1 ± 24.5	-17.6 ± 23.4	-27.1 [-33.2, -21.0]
2-h postprandial blood glucose (mg/dL)	Placebo group	256.1 ± 50.5 (n = 95)	6.4 ± 46.6 (n = 92)	–
	20 mg group	258.6 ± 42.7 (n = 94)	-43.5 ± 42.7 (n = 93)	-49.1 [-61.4, -36.7]
$AUC_{0\text{-}2\,h}$ of postprandial blood glucose (mg·h/dL)	Placebo group	481.4 ± 70.9 (n = 95)	16.3 ± 63.7 (n = 92)	–
	20 mg group	488.6 ± 57.8 (n = 93)	-66.3 ± 56.4 (n = 92)	-81.1 [-98.0, -64.1]
Percentage of subjects achieving HbA1c level of less than 6.5%[c)]	Placebo group		20 mg group	
	0 (0/98 subjects)		8.3 (8/96 subjects)	

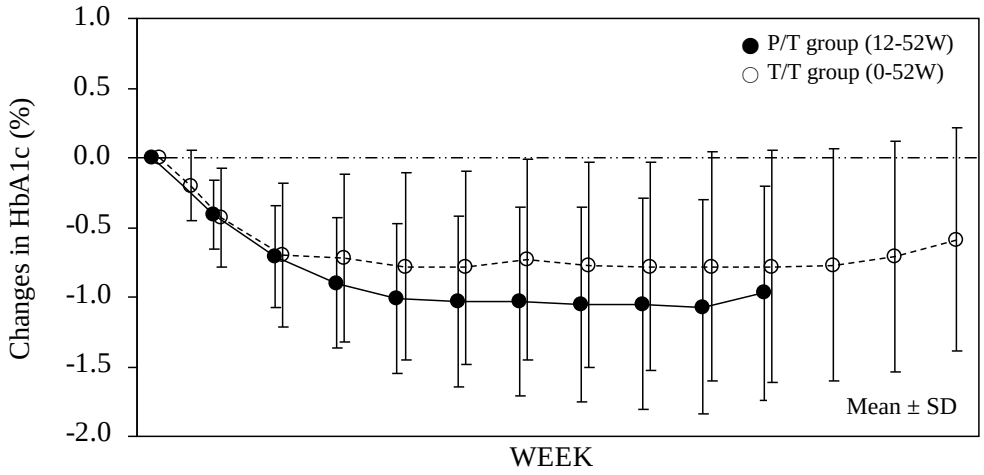
Mean ± SD, -: Not applicable

a) Missing values were imputed by LOCF

b) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

c) Percentage of subjects achieving the target level (%) (number of subjects achieving the target level/total number of subjects evaluated)

The changes in HbA1c (mean ± SD) from baseline (P/T group, Week 12 of treatment period; T/T group, Week 0 of treatment period [end of run-in period]) to Week 52 of the treatment period was -0.93% ± 0.76% [-1.09, -0.78] in the P/T group and -0.56% ± 0.87% [-0.74, 0.38] in the T/T group. Figure 1 shows the time course of the changes in HbA1c, which decreased from the baseline in both treatment groups. Among the subjects in whom teneligliptin dose was increased from 20 mg to 40 mg (64 subjects in P/T group, 65 subjects in T/T group), the percentage of those who achieved a decrease in HbA1c at 12 weeks after the dose increase was 51.6% (32 of 62 subjects) in the P/T group and 52.4% (33 of 63 subjects) in the T/T group. HbA1c decreased to <7.0% at 12 weeks after the dose increase in 11.1% (6 of 54 subjects) in the P/T group and in 9.6% (5 of 52 subjects) in the T/T group.



Number of subjects	2W	4W	8W	12W	16W	20W	24W	28W	32W	36W	40W	44W	48W	52W
P/T group (12-52W)	—	93	93	92	91	90	90	88	87	87	86			
T/T group (0-52W)	96	96	95	95	95	94	93	93	91	91	90	88	86	85

Figure 1. Time-course of changes in HbA1c (%) (mean ± SD)

Regarding safety, the incidence of adverse events during the double-blind period was 62.2% (61 of 98 subjects) in the placebo group and 64.6% (62 of 96 subjects) in the 20 mg group, and the incidence of adverse drug reactions was 6.1% (6 of 98 subjects) in the placebo group and 8.3% (8 of 96 subjects) in the 20 mg group. Adverse events reported by ≥3% in any of the treatment groups were as shown in Table 25. The only adverse event reported by at least 2 subjects in any of the groups was hypoglycemia, which occurred with the incidence of 2.0% (2 of 98 subjects) in the placebo group and 1.0% (1 of 96 subjects) in the 20 mg group.

Table 25. Adverse events reported by ≥3% in any of the treatment groups (double-blind period) (safety analysis population)

Adverse event name	Placebo group (n = 98)	20 mg group (n = 96)
All adverse events	62.2 (61)	64.6 (62)
Nasopharyngitis	16.3 (16)	19.8 (19)
Pharyngitis	3.1 (3)	4.2 (4)
Upper respiratory tract inflammation	3.1 (3)	5.2 (5)
Hypoglycaemia	3.1 (3)	2.1 (2)
Diarrhoea	1.0 (1)	3.1 (3)
Periarthritis	0.0 (0)	3.1 (3)
ALT increased	0.0 (0)	4.2 (4)
Blood triglycerides increased	2.0 (2)	3.1 (3)
Glucose urine present	21.4 (21)	2.1 (2)
Blood urine present	3.1 (3)	1.0 (1)
Protein urine present	5.1 (5)	4.2 (4)

Incidence % (No. of subjects with event), MedDRA/J Ver 13.0

During the 52-week treatment period, the incidence of adverse events was 94.7% (90 of 95 subjects) in the P/T and 94.8% (91 of 96 subjects) in the T/T group, and the incidence of adverse drug reactions was 21.1% (20 of 95 subjects) in the P/T group and 17.7% (17 of 96 subjects) in the T/T group. Adverse events reported by ≥5% in any of the treatment groups were as shown in Table 26. Adverse drug reactions reported by at least 2 subjects in any of the groups were

hypoglycemia (10.5% [10 of 95 subjects] in P/T group, 7.3% [7 of 96 subjects] in T/T group), constipation (0.0% [0 of 95 subjects] in P/T group, 2.1% [2 of 96 subjects] in T/T group), and aspartate aminotransferase increased (0.0% [0 of 95 subjects] in P/T group, 2.1% [2 of 96 subjects] in T/T group).

Table 26. Adverse events reported by ≥5% in any of the treatment groups (during the 52-week treatment period) (population for safety analysis)

Adverse event name	P/T group[a)] (n = 95)	T/T group (n = 96)
All adverse events	94.7 (90)	94.8 (91)
Nasopharyngitis	27.4 (26)	33.3 (32)
Pharyngitis	11.6 (11)	5.2 (5)
Bronchitis	3.2 (3)	8.3 (8)
Upper respiratory tract inflammation	7.4 (7)	9.4 (9)
Hypoglycaemia	12.6 (12)	9.4 (9)
Constipation	3.2 (3)	6.3 (6)
Gastroenteritis	5.3 (5)	2.1 (2)
Arthralgia	1.1 (1)	10.4 (10)
Eczema	4.2 (4)	6.3 (6)
Diabetic retinopathy	3.2 (3)	8.3 (8)
Contusion	3.2 (3)	6.3 (6)
Arthropod sting	5.3 (5)	5.2 (5)
ALT increased	3.2 (3)	6.3 (6)
Blood creatine phosphokinase increased	3.2 (3)	8.3 (8)
Blood triglycerides increased	4.2 (4)	5.2 (5)
Glucose urine present	17.9 (17)	11.5 (11)
Blood urine present	7.4 (7)	6.3 (6)
Protein urine present	13.7 (13)	16.7 (16)
Urine ketone body present	2.1 (2)	6.3 (6)

Incidence % (No. of subjects with event), MedDRA/J Ver. 13.1

a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period)

No deaths were reported. During the double-blind period, serious adverse events occurred in 2 subjects in the placebo group (sudden hearing loss, pneumonia in 1 subject each) but not in the 20 mg group. Adverse events leading to study drug discontinuation occurred in 2 subjects in the placebo group (sudden hearing loss, pneumonia/jaundice/hepatic function abnormal in 1 subject each) and in 1 subject in the 20 mg (white blood cell count decreased). The incidence of hypoglycemia was 3.1% (3 of 98 subjects, 5 events) in the placebo group and 2.1% (2 of 96 subjects, 2 events) in the 20 mg group. Hypoglycemia in 2 subjects in the placebo group (3 events) and in 1 subject in the 20 mg group (1 event) was classified as adverse drug reactions, but all were mild in severity. There were no subjects in whom glimepiride dose was decreased or administration of the study drug was discontinued. During the 52-week treatment period, 3 serious adverse events occurred in 2 subjects in the P/T group (maculopathy/cataract, retinal vein occlusion in 1 subject each) and 10 serious adverse events in 7 subjects in the T/T group (gastric cancer [2 subjects], large intestine carcinoma, colonic polyp, bile duct stone/cholangitis, large intestine carcinoma/ovarian enlargement, meniscus lesion/loose body in joint in 1 subject each). The treatment discontinuation due to adverse events that newly occurred from Week 12 to 52 of the treatment period were observed in 4 subjects in the P/T group (hypoglycemia, retinal vein occlusion, palpitations, haemoptysis in 1 subject each) and in 6 subjects in the T/T group (gastric cancer [2 subjects], atrial fibrillation, photosensitivity reaction, bile duct stone/cholangitis, large intestine carcinoma/ovarian enlargement in 1 subject each). The incidence of hypoglycemia was

12.6% (12 of 95 subjects, 29 events) in the P/T group and 9.4% (9 of 96 subjects, 17 events) in the T/T group. Except for 3 events in 2 subjects of the P/T group and 2 events in 2 subjects of the T/T group, all other cases of hypoglycemia were classified as adverse drug reactions. There were no adverse events caused by QTc interval prolongation. There was no particularly relevant variability in the resting 12-lead ECG or in vital signs.

4.(iii).A.(3).3) Phase III thiazolidinedione concomitant therapy study (5.3.5.1-5, Study 3000-A7 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group comparative study was conducted in Japanese subjects with type 2 diabetes mellitus who insufficiently responded to treatment with a thiazolidine agent (pioglitazone hydrochloride [hereafter referred to as "pioglitazone"])[48] (target sample size of 200, 100 subjects per group) to investigate the efficacy and safety of concomitant use of teneligliptin with pioglitazone.

Placebo was administered orally before breakfast once daily during the 4-week run-in period. Then, placebo or teneligliptin (20 mg) was administered at 30 minutes before breakfast once daily during the period I (12-week double-blind period), followed by the oral administration of teneligliptin (20 mg) at 30 minutes before breakfast once daily during the period II (40-week open-label period). If HbA1c was ≥7.0% at and after week 24 of the treatment period and there was no safety problem as judged by the investigator, teneligliptin dose was to be increased from 20 mg to 40 mg from the next scheduled visit. For pioglitazone, the dose used ≥16 weeks before the start of the double blind period was to be maintained throughout the treatment period.

All 204 treated subjects (101 subjects in placebo group, 103 subjects in 20 mg group) were included in the safety analysis population and in the FAS. A total of 196 subjects (98 subjects in placebo group, 98 subjects in 20 mg group) completed the double-blind period (12 weeks) and proceeded to the open-label period (40 weeks). Of those who completed the double blind period, 91 subjects in the placebo group also completed the open-label period (P/T group), and 88 subjects in the 20 mg group completed the open-label period (T/T group). The study was terminated prematurely in 8 subjects during the double-blind period (3 subjects in placebo group — 2 subjects due to adverse events, 1 subject due to meeting discontinuation criteria; 5 subjects in 20 mg group — 4 subjects at the discretion of the investigator, 1 subject due to adverse event), and in 17 subjects during the open-label period (7 subjects in P/T group — 4 subjects due to adverse events, 3 subjects at the discretion of the investigator; 10 subjects in T/T group — 5 subjects due to adverse events, 4 subjects due to subjects' request, 1 subject at the discretion of the investigator). Teneligliptin dose was increased to 40 mg in 58 subjects (27 subjects in P/T group, 31subjects in T/T group).

Regarding efficacy, the change in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (week 12 of the double-blind period) in FAS, the primary endpoint, was as shown in Table 27. The difference (least squares mean) in the change between the 20 mg group and the placebo group, with its 95% CI, was -0.74% [-0.87, -0.62], demonstrating the superiority of the 20 mg group to the placebo group.

[48] Patients with type 2 diabetes mellitus who were continuously receiving pioglitazone at a fixed dosage regimen (15 or 30 mg/day) for ≥12 weeks before the start of the run-in period, did not take any other oral hypoglycemic agent for ≥8 weeks before the start of the run-in period (if subjects had been taking other oral hypoglycemic agent, a wash-out period of ≥8 weeks was required after informed consent), in whom HbA1c level was ≥6.5% to <10.0% at the start of the run-in period and at 2 weeks after the start of the run-in period, fasting blood glucose level was ≤270 mg/dL at the start of the run-in period, and the difference in HbA1c between at 2 weeks after the start of the run-in period and at the start of the run-in period was ≤0.5%.

Table 27. Changes in HbA1c from the end of the run-in period (baseline) to the end of the treatment period (week 12 of administration in double-blind period) (FAS)

Treatment group	End of run-in period (baseline)	End of treatment period (Week 12)	Changes from baseline (LOCF)	Between-group difference [95% CI][a)]
Placebo group (n = 101)	7.60 ± 0.79 (n = 101)	7.45 ± 0.81 (n = 98)	-0.17 ± 0.47	-0.74 [-0.87, -0.62]
20 mg group (n = 103)	7.80 ± 0.91 (n = 103)	6.81 ± 0.66 (n = 98)	-0.97 ± 0.56	

Unit: %, mean ± SD

a) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

Table 28 shows the results of the analysis of main secondary endpoints and the percentage of subjects achieving a decrease in HbA1c to <6.5%.

Table 28. Results of the analysis of main secondary endpoints and percentage of subjects achieving a decrease in HbA1c to <6.5% (FAS)

Endpoint	Treatment group	End of run-in period (baseline)	Changes up to the end of treatment period (Week 12)	Difference from placebo group [95% CI][b)]
Fasting blood glucose[a)] (mg/dL)	Placebo group (n = 101)	145.7 ± 26.5	-3.5 ± 23.4	–
	20 mg group (n = 103)	150.7 ± 28.1	-22.0 ± 21.5	-16.4 [-21.9, -11.0]
2-h postprandial blood glucose (mg/dL)	Placebo group	221.5 ± 55.3 (n = 101)	-3.9 ± 38.3 (n = 98)	–
	20 mg group	230.9 ± 57.9 (n = 103)	-58.7 ± 47.2 (n = 98)	-51.3 [-61.4, -41.1]
$AUC_{0\text{-}2\,h}$ of postprandial blood glucose (mg·h/dL)	Placebo group	427.2 ± 75.3 (n = 101)	-11.4 ± 54.1 (n = 98)	–
	20 mg group	441.0 ± 81.0 (n = 103)	-87.4 ± 61.4 (n = 98)	-71.3 [-85.7, -57.0]
Percentage of subjects achieving HbA1c level of <6.5%[c)]	Placebo group		20 mg group	
	6.1 (6/98 subjects)		32.4 (33/102 subjects)	

Mean ± SD, -: Not applicable

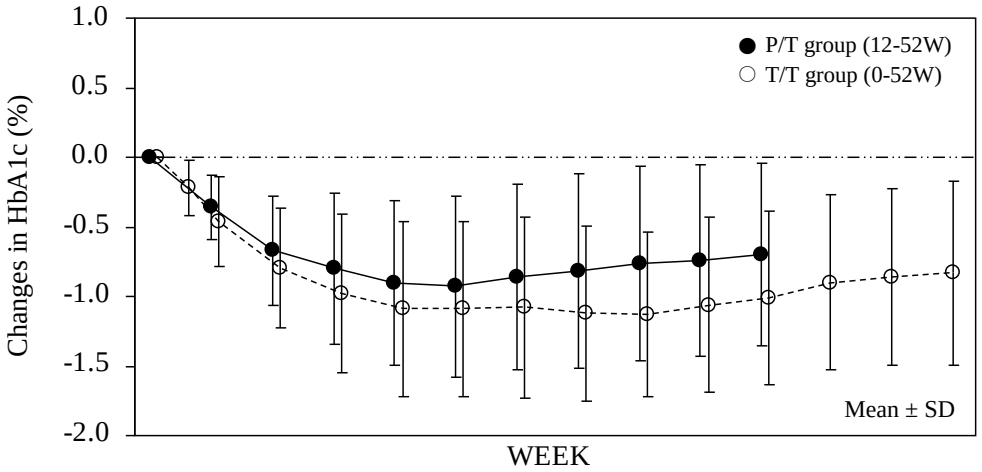
a) Missing values were imputed by LOCF

b) Least squares mean calculated by ANCOVA using treatment group as the explanatory variable and baseline HbA1c as the covariate, and its 95% CI

c) Percentage of subjects achieving the target level (%) (number of subjects achieving the target level/total number of subjects evaluated)

The changes in HbA1c (mean ± SD) from baseline (P/T group, Week 12 of treatment period; T/T group, Week 0 of treatment period [end of run-in period]) to Week 52 of the treatment period was -0.72% ± 0.67% [-0.85, -0.58] in the P/T group and -0.86% ± 0.66% [-0.98, -0.73] in the T/T group. Figure 2 shows the time course of the change in HbA1c, which decreased from baseline in both treatment groups. Among subjects in whom teneligliptin dose was increased from 20 mg to 40 mg (27 subjects in P/T group, 31 subjects in T/T group), the percentage of those who achieved a decrease in HbA1c at 12 weeks after the dose increase was 34.8% (8 of 23 subjects) in the P/T group and 17.2% (5 of 29 subjects) in the T/T group. HbA1c decreased to <7.0% at 12 weeks after the dose increase in 21.4% (3 of 14 subjects) in the P/T group and in 4.3% (1 of 23

subjects) in the T/T group.



Number of subjects	2W	4W	8W	12W	16W	20W	24W	28W	32W	36W	40W	44W	48W	52W
P/T group (12-52W)	—	98	97	96	96	96	95	93	90	91	91			
T/T group (0-52W)	102	102	98	98	96	96	96	95	94	93	92	89	88	88

Figure 2. Time-course of changes in HbA1c (%) (FAS) (mean ± SD)

Regarding safety, the incidence of adverse events during the double-blind period was 46.5% (47 of 101 subjects) in the placebo group and 61.2% (63 of 103 subjects) in the 20 mg group, and the incidence of adverse drug reactions was 2.0% (2 of 101 subjects) in the placebo group and 11.7% (12 of 103 subjects) in the 20 mg group. Table 29 shows adverse events reported by ≥3% in any of the treatment groups. The only adverse event reported by at least 2 subjects in any of the groups was dermatitis allergic, which occurred with an incidence of 0.0% (0 of 101 subjects) in the placebo group and 1.9% (2 of 103 subjects) in the 20 mg group.

Table 29. Adverse events reported by ≥3% in any of the treatment groups (double-blind period) (population for safety analysis)

Adverse event name	Placebo group (n = 101)	20 mg group (n = 103)
All adverse events	46.5 (47)	61.2 (63)
Nasopharyngitis	7.9 (8)	11.7 (12)
Cystitis	3.0 (3)	1.0 (1)
Upper respiratory tract inflammation	1.0 (1)	3.9 (4)
Oedema peripheral	5.9 (6)	1.9 (2)
Glucose urine present	7.9 (8)	2.9 (3)
Protein urine present	1.0 (1)	3.9 (4)
Blood urine present	2.0 (2)	2.9 (3)
Blood creatine phosphokinase increased	2.0 (2)	2.9 (3)

Incidence % (No. of subjects with event), MedDRA/J ver .13.1

During the 52-week treatment period, the incidence of adverse events was 90.8% (89 of 98 subjects) in the P/T group and 86.4% (89 of 103 subjects) in the T/T group; and the incidence of adverse drug reactions was 8.2% (8 of 98 subjects) in the P/T group and 14.6% (15 of 103 subjects) in the T/T group. Adverse events reported by ≥5% in any of the treatment groups were as shown in Table 30.

Table 30. Adverse events reported by ≥5% in any of the treatment groups (52-week treatment period) (population for safety analysis)

Adverse event name	P/T group[a)] (n = 98)	T/T group (n = 103)
All adverse events	90.8 (89)	86.4 (89)
Nasopharyngitis	33.7 (33)	32.0 (33)
Upper respiratory tract inflammation	10.2 (10)	11.7 (12)
Gastritis	4.1 (4)	5.8 (6)
Eczema	4.1 (4)	5.8 (6)
Back pain	6.1 (6)	6.8 (7)
Blood creatine phosphokinase increased	4.1 (4)	8.7 (9)
Urine ketone body present	6.1 (6)	1.9 (2)
Glucose urine present	6.1 (6)	6.8 (7)
Blood urine present	5.1 (5)	11.7 (12)
Protein urine present	3.1 (3)	8.7 (9)

Incidence % (No. of subjects with event), MedDRA/J ver. 13.1
a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period)

Adverse drug reactions reported by ≥2 subjects in any of the groups were hypoglycemia (1.0% [1 of 98 subjects] in P/T group, 1.9% [2 of 103 subjects] in T/T group), abdominal distension (0.0% [0 of 98 subjects] in P/T group, 1.9% [2 of 103 subjects] in T/T group), constipation (1.0% [1 of 98 subjects] in P/T group, 1.9% [2 of 103 subjects] in T/T group), dermatitis allergic (0.0% [0 of 98 subjects] in P/T group, 1.9% [2 of 103 subjects] in T/T group), eczema (0.0% [0 of 98 subjects] in P/T group, 1.9% [2 of 103 subjects] in T/T group), and rash (0.0% [0 of 98 subjects] in P/T group, 1.9% [2 of 103 subjects] in T/T group).

No deaths were reported. During the double-blind period, serious adverse events occurred in 1 subject in the placebo group (gastric cancer/colonic polyp) and in 4 subjects in the 20 mg group (haemorrhoids, loss of consciousness, gastric polyps, cataract in 1 subject each). Adverse events leading to study drug discontinuation occurred in 2 subjects in the placebo group (gastric cancer, skin exfoliation) and in 1 subject in the 20 mg group (spinocerebellar disorder). Hypoglycemia was observed in 2 subjects in the 20 mg group (2 events). One of the events in 1 subject was classified as an adverse drug reaction, but both cases of hypoglycemia were mild in severity. No hypoglycemia was observed in the placebo group. During the 52-week treatment period, serious adverse events occurred in 3 subjects in the P/T group (gastric cancer/oesophageal carcinoma, acute myocardial infarction, ovarian cancer in 1 subject each) and in 11 subjects in the T/T group (colonic polyp [2 subjects], prostate cancer/metastases to bone, myelopathy, upper respiratory tract inflammation, large intestine carcinoma, carotid artery stenosis, haemorrhoids, loss of consciousness, gastric polyps, cataract in 1 subject each). The treatment discontinuation due to adverse events that newly occurred from Week 12 to 52 of the treatment period occurred in 4 subjects in the P/T group (gastric cancer/oesophageal carcinoma, acute myocardial infarction, ovarian cancer, VIIth nerve paralysis in 1 subject each) and in 5 subjects in the T/T group (prostate cancer/metastases to bone, myelopathy, cardiomegaly/bundle branch block left, carotid artery stenosis, large intestine carcinoma in 1 subject each). The incidence of hypoglycemia was 1.0% (1 of 98 subjects, 1 event) in the P/T group and 1.9% (2 of 103 subjects, 4 events) in the T/T group. Except 1 event in 1 subject of the T/T group, all other cases of hypoglycemia were classified as adverse drug reactions. There were no adverse events caused by QTc interval prolongation. Resting 12-lead ECG showed inferior infarction in 1 subject in the placebo group, complete left bundle branch block in 1 subject in the 20 mg group, and atrial fibrillation in 1 subject in the T/T group, a causal relationship to the study drug was denied for any of the event. There was no particularly relevant variability in vital signs.

4.(iii).A.(3).4 Phase III long-term treatment study
(5.3.5.2-1, Study 3000-A8 [[redacted] to [redacted]])

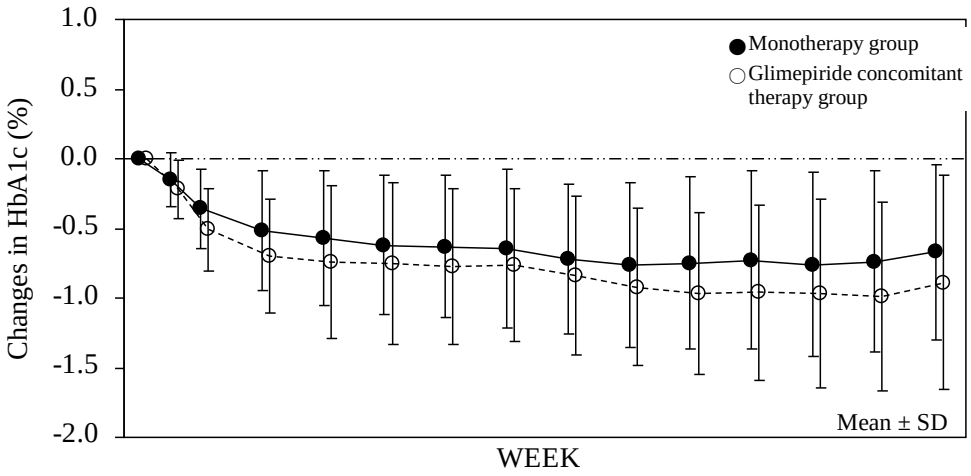
An open-label, long-term treatment study was conducted in Japanese patients with type 2 diabetes mellitus who insufficiently responded to diet and exercise therapy or to diet and exercise therapy plus sulfonylurea agent (glimepiride)[49] (target sample size of 230, 150 subjects in monotherapy group, 80 subjects in glimepiride concomitant therapy group) to investigate the safety and efficacy of teneligliptin.

After placebo was administered orally before breakfast once daily during the 4-week run-in period, teneligliptin (20 mg) was administered orally at 30 minutes before breakfast once daily for 52 weeks. If HbA1c was ≥7.0% at and after week 24 of the treatment period and there was no safety problem as judged by the investigator, teneligliptin dose was to be increased from 20 mg to 40 mg from the next scheduled visit. In the glimepiride concomitant therapy group, if hypoglycemia occurred or if fasting blood glucose tested at the clinical laboratory was ≤70 mg/dL, the dose could be decreased by 1 mg/day at a time, at the discretion of the investigator. Increasing the once-reduced dose was not allowed.

All 240 treated subjects (151 subjects in monotherapy group, 89 subjects in glimepiride concomitant therapy group) were included in the safety analysis populationand in the FAS. The study was terminated prematurely in 30 subjects, including 16 subjects in the monotherapy group (5 subjects due to subjects' request, 5 subjects at the discretion of the investigator, 4 subjects due to adverse events, 1 subject each due to aggravation of primary disease and due to ECG findings during the treatment period) and 14 subjects in the glimepiride concomitant therapy group (8 subjects due to adverse events, 4 subjects due to subjects' request, 2 subjects at the discretion of the investigator). Teneligliptin dose was increased to 40 mg before Week 52 of the treatment period in 36.4% (55 of 151 subjects) in the monotherapy group and in 53.9% (48 of 89 subjects) in the glimepiride concomitant therapy group.

Regarding efficacy, the time course of the change in HbA1c from baseline to each measuring time point in the FAS was as shown in Figure 3. The change in HbA1c (mean ± SD) from baseline to Week 52 of the treatment period, with its 95% CI, was -0.63% ± 0.67% [-0.74, -0.53] in the monotherapy group and -0.81% ± 0.76% [-0.98, -0.65] in the glimepiride concomitant therapy group, demonstrating a significant decrease from baseline in both groups ($p < 0.0001$, paired t-test).

[49] Patients with type 2 diabetes mellitus who were continuously receiving glimepiride at a fixed dosage regimen (1, 2, 3, or 4 mg/day) for ≥8 weeks before the start of the run-in period (for subjects treated with concomitant use with sulfonylurea agent) without taking any other oral hypoglycemic drug (if subjects had been taking other oral hypoglycemic agent, a wash-out period of ≥8 weeks was required after informed consent), in whom HbA1c level was ≥6.5% to <10.0% in the monotherapy group (≥7.0% to <10.0% in the glimepiride concomitant therapy group) at the start of the run-in period and at 2 weeks after the run-in period, fasting blood glucose level was ≤270 mg/dL at the start of the run-in period, and the difference in HbA1c between at 2 weeks after the start of the run-in period and at the start of the run-in period was ≤0.5%.



Number of subjects	2W	4W	8W	12W	16W	20W	24W	28W	32W	36W	40W	44W	48W	52W
Monotherapy group	151	151	151	150	149	147	144	142	140	138	138	137	135	135
Glimepiride concomitant	88	87	87	85	85	83	82	81	79	78	78	78	76	75

Figure 3. Time-course of changes in HbA1c (%) (FAS) (mean ± SD)

Of the subjects in whom teneligliptin dose was increased from 20 mg to 40 mg, the percentage of those who achieved a decrease in HbA1c at 12 weeks after the dose increase was 59.6% (31 of 52 subjects) in the monotherapy group and 56.5% (26 of 46 subjects) in the glimepiride concomitant therapy group, and HbA1c decreased to <7.0% at 12 weeks after the dose increase in 32.5% (13 of 40 subjects) in the monotherapy group and in 17.1% (7 of 41 subjects) in the glimepiride concomitant therapy group.

Regarding safety, the incidence of adverse events was 90.1% (136 of 151 subjects) in the monotherapy group and 95.5% (85 of 89 subjects) in the glimepiride concomitant therapy group, and the incidence of adverse drug reactions was 9.9% (15 of 151 subjects) in the monotherapy group and 18.0% (16 of 89 subjects) in the glimepiride concomitant therapy group. Adverse events reported by ≥5% in any of the treatment groups were as shown in Table 31. Adverse drug reactions reported by at least 2 subjects in any of the groups were cases of hypoglycemia (2.6% [4 of 151 subjects] in monotherapy group, 9.0% [8 of 89 subjects] in glimepiride concomitant therapy group).

Table 31. Adverse events reported by ≥5% in any of the treatment groups (safety analysis population)

Adverse event name	Monotherapy group (n = 151)	Glimepiride concomitant therapy group (n = 89)
All adverse events	90.1 (136)	95.5 (85)
Nasopharyngitis	37.1 (56)	32.6 (29)
Pharyngitis	5.3 (8)	4.5 (4)
Bronchitis	6.0 (9)	9.0 (8)
Hypoglycaemia	3.3 (5)	10.1 (9)
Insomnia	4.0 (6)	10.1 (9)
Hypertension	5.3 (8)	0.0 (0)
Upper respiratory tract inflammation	6.0 (9)	11.2 (10)
Gastric polyps	3.3 (5)	5.6 (5)
Gastritis	4.0 (6)	6.7 (6)
Eczema	5.3 (8)	3.4 (3)
Arthralgia	7.3 (11)	3.4 (3)
Osteoarthritis	0.7 (1)	6.7 (6)
Blood creatine phosphokinase increased	9.3 (14)	7.9 (7)
Urine ketone body present	1.3 (2)	5.6 (5)
Glucose urine present	6.0 (9)	18.0 (16)
Blood urine present	7.3 (11)	5.6 (5)
Protein urine present	9.3 (14)	14.6 (13)
Contusion	6.0 (9)	6.7 (6)

Incidence % (No. of subjects with event), MedDRA/J ver. 13.1

No deaths were reported. Serious adverse events occurred in 6 subjects in the monotherapy group (intestinal obstruction, sudden hearing loss, intervertebral disc protrusion, large intestine carcinoma, gastritis, diverticulitis in 1 subject each) and in 7 subjects in the glimepiride concomitant therapy group (cholecystitis/cholelithiasis, myelopathy, contusion/joint sprain, testicular neoplasm, gastric cancer, spinal compression fracture, intervertebral disc protrusion in 1 subject each). Among them, only testicular neoplasm observed in 1 subject in the glimepiride concomitant therapy group was classified as an adverse drug reaction. Adverse events leading to study drug discontinuation were observed in 4 subjects in the monotherapy group (intestinal obstruction, sudden hearing loss, malaise/decreased appetite/anxiety, large intestine carcinoma in 1 subject each) and in 8 subjects in the glimepiride concomitant therapy group (myelopathy, angina pectoris, joint sprain, testicular neoplasm, osteoarthritis, spinal compression fracture, gastric cancer, intervertebral disc protrusion in 1 subject each). The incidence of hypoglycemia was 3.3% (5 of 151 subjects, 6 events) in the monotherapy group and 10.1% (9 of 89 subjects, 19 events) in the glimepiride concomitant therapy group. Except 1 event in 1 subject of the monotherapy group and 1 event in 1 subject of the glimepiride concomitant therapy group, all other cases of hypoglycemia were classified as adverse drug reactions. There were no adverse events caused by QT interval prolongation. There was no particularly relevant variability in resting 12-lead ECG or in vital signs.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning

The applicant explained as follows:

In Japan, the following DPP-4 inhibitors have been approved; sitagliptin phosphate hydrate (sitagliptin), vildagliptin, alogliptin benzoate (alogliptin), and linagliptin. Sitagliptin and alogliptin are allowed to be administered once daily, but the dose should be reduced in subjects

with moderate renal impairment. In addition, sitagliptin is contraindicated in subjects with severe renal impairment. Vildagliptin is to be administered twice daily usually, and dose reduction is not required in subjects with renal impairment. Linagliptin is allowed to be administered once daily and it is not required to reduce the dose according to the severity of renal or hepatic impairment, but linagliptin is permitted only for monotherapy. Thus, the currently approved DPP-4 inhibitors have both merits and demerits. In contrast, teneligliptin may be administered once daily, does not have to be administered at a reduced dose even in subjects with renal or hepatic impairment, and may be used not only for monotherapy but also for concomitant therapy with sulfonylurea (SU) or thiazolidinedione (TZD). Teneligliptin is thus considered to be a highly useful drug. Currently, a Japanese clinical study on the concomitant therapy with oral hypoglycemic agents other than SU and TZD is being conducted, in accordance with "On release of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents" (PFSB/ELD Notification No. 0709-1 dated July 9, 2010).

PMDA considers as follows:
Results of the 3 phase III studies (Studies 3000-A5 to A7) have demonstrated the efficacy of teneligliptin in monotherapy, concomitant therapy with SU, and concomitant therapy with TZD [see "4.(iii).B.(2) Efficacy"] and that the treatments were well tolerated [see "4.(iii).B.(3) Safety"]. Therefore, teneligliptin can be a new treatment option of type 2 diabetes mellitus.

4.(iii).B.(2) Efficacy

4.(iii).B.(2).1) Efficacy of monotherapy

PMDA considers as follows:
The difference between the placebo group and the 20 mg group in the changes in HbA1c (least squares mean) from baseline to the end of the treatment period (Week 12 of administration), the primary endpoint in the phase III double-blind confirmatory study (Study 3000-A5), with its 95% CI, was -0.79% [-0.94, -0.64], demonstrating the superiority of the 20 mg group to the placebo group [see Table 20]. Also, results of the phase III long-term treatment study (Study 3000-A8) showed that the effect of teneligliptin administration (20-40 mg/day) lasted up to Week 52 of the treatment period [see Figure 3]. On the basis of these results, PMDA concludes that the efficacy of the monotherapy has been demonstrated. The use of a placebo as the comparator in Study 3000-A5 presents no major problems, since drugs with the same mechanism of action (DPP-4 inhibitors) had not been approved when Study 3000-A5 was initiated, although they are now widely used in clinical practice.

4.(iii).B.(2).2) Efficacy of concomitant therapy with SU

PMDA considers as follows:
The difference between the placebo group and the 20 mg group in the changes in HbA1c (least squares mean) from baseline to the end of the treatment period (Week 12 of administration), the primary endpoint in the phase III sulfonylurea concomitant therapy study (Study 3000-A6), with its 95% CI, was -1.00% [-1.16, -0.84], demonstrating the superiority of the 20 mg group to the placebo group [see Table 23]. Also, in 52-week administration in Study 3000-A6 and in the phase III long-term treatment study (Study 3000-A8), administration of teneligliptin (20-40 mg/day) in combination with glimepiride showed efficacy up to Week 52 of the treatment period [see Figures 1, 3]. On the basis of these results, PMDA concludes that the efficacy of SU concomitant therapy has been demonstrated. Regarding the effect of the dose of concomitant glimepiride on the efficacy endpoint, the change in HbA1c (least squares mean ± SD) from baseline to the end of the treatment period (Week 12 of administration) in Study 3000-A6 was 0.30% ± 0.06% in the placebo group (n = 75) and -0.75% ± 0.07% in the 20 mg group (n = 69) when glimepiride dose during the run-in period was ≤2 mg/day, and 0.26% ± 0.12% in the placebo group (n = 23) and -0.63% ± 0.11% in the 20 mg group (n = 27) when glimepiride >2 mg/day, demonstrating that teneligliptin was effective in reducing HbA1c level regardless of the dose of glimepiride used during the run-in period.

4.(iii).B.(2).3) Efficacy of concomitant therapy with TZD

PMDA considers as follows:

The difference between the placebo group and the 20 mg group in the changes in HbA1c (least squares mean) from baseline to the end of the treatment period (Week 12 of administration), the primary endpoint in the phase III thiazolidinedione concomitant therapy study (Study 3000-A7), with its 95% CI, was -0.74% [-0.87, -0.62], demonstrating the superiority of the 20 mg group to the placebo group [see Table 27]. Also, results of Study 3000-A7 showed that the effect of teneligliptin (20-40 mg/day) administered in combination with pioglitazone lasted up to Week 52 of the treatment period [see Figure 2]. On the basis of these results, PMDA concludes that the efficacy of TZD concomitant therapy has been demonstrated. Regarding the effect of the dose of concomitant pioglitazone on the efficacy endpoint, the change in HbA1c (least squares mean ± SD) from baseline to the end of the treatment period (Week 12 of administration) in Study 3000-A7 was -0.26% ± 0.06% in the placebo group (n = 59) and -0.96% ± 0.06% in the 20 mg group (n = 58) when pioglitazone dose during the run-in period was 15 mg/day, and -0.11% ± 0.07% in the placebo group (n = 42) and -0.92% ± 0.07% in the 20 mg group (n = 45) when pioglitazone dose was 30 mg/day, demonstrating that teneligliptin was effective in reducing HbA1c level regardless of the dose of pioglitazone used during the run-in period.

4.(iii).B.(3) Safety

Based on the occurrence of adverse events and adverse drug reactions in the placebo group and the teneligliptin groups in Japanese phase III studies [see Tables 22, 25, 29] and on the occurrence of adverse events in long-term administration [see Tables 26, 30, 31], PMDA considers that teneligliptin monotherapy, SU concomitant therapy, and TZD concomitant therapy are well tolerated. However, PMDA examined individual matters in further detail.

4.(iii).B.(3).1) Hypoglycemia

The applicant explained as follows:

In the integrated analysis of Japanese 12-week double-blinded studies (results of Studies 3000-A3 to A5 and of treatment period I in Studies 3000-A6 and 3000-A7; hereafter referred to as “integrated analysis of Japanese double-blind studies”), the incidence of hypoglycemia regarded as an adverse event was low in all of these studies, showed no significant difference compared with the placebo group, nor did it tend to increase dose-dependently [Table 32]. As regards severity, 1 incident of hypoglycemia in 1 subject of the placebo group in Study 3000-A4 was moderate in severity, while all other cases of hypoglycemia were mild. There were no serious adverse events or adverse events leading to study drug discontinuation.

Table 32. Occurrence of hypoglycemia (integrated analysis of Japanese double-blind studies)

Type of study	Study No.	Placebo group	Teneligliptin groups			
			2.5 mg group	10 mg group	20 mg group	40 mg group
Monotherapy	3000-A3	n = 45	n = 49	n = 45	—	n = 47
		0.0 (0) 0	0.0 (0) 0	0.0 (0) 0	—	0.0 (0) 0
	3000-A4	n = 80	—	n = 84	n = 79	n = 81
		3.8 (3) 4	—	0.0 (0) 0	1.3 (1) 1	3.7 (3) 3
	3000-A5	n = 104	—	—	n = 99	—
		1.0 (1) 1	—	—	1.0 (1) 2	—
SU concomitant therapy	3000-A6	n = 98	—	—	n = 96	—
		3.1 (3) 5	—	—	2.1 (2) 2	—
TZD concomitant therapy	3000-A7	n = 101	—	—	n = 103	—
		0.0 (0) 0	—	—	1.9 (2) 2	—

Incidence % (No. of subjects with event) No. of events, -: Not applicable

The integrated analysis of the results of the Japanese long-term treatment studies (Studies 3000-A6 to A8) (hereafter referred to as "integrated analysis of the Japanese long-term studies") showed that all cases of hypoglycemia were mild in severity, with none of them being serious. In Study 3000-A6, hypoglycemia reported as an adverse event leading to study drug discontinuation (1 event) occurred in 1 subject of the P/T group, and was classified as an adverse drug reaction. In this subject, hypoglycemia occurred 96 days after the start of treatment with teneligliptin 20 mg, which resolved after glucose and lunch intake. In Study 3000-A8, glimepiride dose was reduced from 2 mg/day to 1 mg/day in 1 subject who developed hypoglycemia (1 event). Both the incidence and the number of events for hypoglycemia were slightly higher in subjects treated with SU concomitant therapy compared with those treated with teneligliptin monotherapy or TZD concomitant therapy, but the incidence immediately after the start of treatment with teneligliptin (Day 0-14) was similar to that observed during other treatment periods, showing no tendency of increase with treatment duration [Table 33].

Table 33. Occurrence of hypoglycemia by treatment period (integrated analysis of Japanese long-term treatment studies)

Treatment period	Study 3000-A6 (SU concomitant)		Study 3000-A7 (TZD concomitant)		Study 3000-A8	
	P/T group[a)]	T/T group	P/T group[a)]	T/T group	Monotherapy group	Glimepiride concomitant therapy
Entire treatment period	n = 95	n = 96	n = 98	n = 103	n = 151	n = 89
	12.6 (12) 29	9.4 (9) 17	1.0 (1) 1	1.9 (2) 4	3.3 (5) 6	10.1 (9) 19
Day 0-14	n = 95	n = 96	n = 98	n = 103	n = 151	n = 89
	2.1 (2) 3	1.0 (1) 1	0.0 (0) 0	1.0 (1) 1	0.0 (0) 0	0.0 (0) 0
Day 15-28	n = 95	n = 96	n = 98	n = 103	n = 151	n = 89
	0.0 (0) 0	0.0 (0) 0	0.0 (0) 0	1.0 (1) 1	1.3 (2) 2	0.0 (0) 0
Day 29-84	n = 93	n = 96	n = 98	n = 103	n = 151	n = 88
	5.4 (5) 10	1.0 (1) 1	1.0 (1) 1	0.0 (0) 0	0.7 (1) 1	3.4 (3) 4
Day 85-168	n = 93	n = 95	n = 97	n = 98	n = 151	n = 86
	4.3 (4) 8	4.2 (4) 9	0.0 (0) 0	1.0 (1) 1	1.3 (2) 2	7.0 (6) 8
Day 169-252	n = 90	n = 93	n = 96	n = 96	n = 146	n = 83
	3.3 (3) 4	2.2 (2) 2	0.0 (0) 0	0.0 (0) 0	0.7 (1) 1	3.6 (3) 4
Day 253-364	n = 87	n = 91	n = 91	n = 94	n = 138	n = 79
	2.3 (2) 4	2.2 (2) 3	0.0 (0) 0	1.1 (1) 1	0.0 (0) 0	2.5 (2) 3
Day 365-	–	n = 86	–	n = 89	n = 135	n = 76
	–	1.2 (1) 1	–	0.0 (0) 0	0.0 (0) 0	0.0 (0) 0

Incidence % (No. of subjects with event) No. of events, -: Not applicable

a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period). Each of the events that continued from the placebo treatment period in the double-blind period was counted as 1 case.

In SU concomitant therapy (Studies 3000-A6, 3000-A8), the incidence of hypoglycemia did not show any tendency of increase with glimepiride dose [Table 34].

Table 34. Occurrence of hypoglycemia by glimepiride dose at the end of the run-in period (SU concomitant studies: Studies 3000-A6, 3000-A8)

Glimepiride dose	Study 3000-A6				Study 3000-A8
	Double-blind period		Long-term administration period		
	Placebo group	20 mg group	P/T group[a)]	T/T group	SU concomitant therapy group
All doses	n = 98	n = 96	n = 95	n = 96	n = 89
	3.1 (3) 5	2.1 (2) 2	12.6 (12) 29	9.4 (9) 17	10.1 (9) 19
1 mg/day	n = 45	n = 36	n = 44	n = 36	n = 36
	2.2 (1) 1	2.8 (1) 1	4.5 (2) 8	13.9 (5) 10	5.6 (2) 2
2 mg/day	n = 30	n = 33	n = 29	n = 33	n = 25
	6.7 (2) 4	0.0 (0) 0	27.6 (8) 19	6.1 (2) 5	20.0 (5) 9
3 mg/day	n = 17	n = 16	n = 16	n = 16	n = 19
	0.0 (0) 0	6.3 (1) 1	6.3 (1) 1	6.3 (1) 1	5.3 (1) 1
4 mg/day	n = 6	n = 11	n = 6	n = 11	n = 9
	0.0 (0) 0	0.0 (0) 0	16.7 (1) 1	9.1 (1) 1	11.1 (1) 7
≤ 2 mg/day	n = 75	n = 69	n = 73	n = 69	n = 61
	4.0 (3) 5	1.4 (1) 1	13.7 (10) 27	10.1 (7) 15	11.5 (7) 11
> 2 mg/day	n = 23	n = 27	n = 22	n = 27	n = 28
	0.0 (0) 0	3.7 (1) 1	9.1 (2) 2	7.4 (2) 2	7.1 (2) 8

Incidence % (No. of subjects with event) No. of events

a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period). Each of the events that continued from the placebo treatment period in the double-blind period was counted as 1 case.

As shown in the above, the incidence of hypoglycemia was low in the subjects treated with teneligliptin, and did not show any tendency of increase at a specific time. No severe or serious hypoglycemia was observed. In each concomitant therapy group, the incidence of hypoglycemia was low, but the SU concomitant therapy group experiencecd slightly higher incidence and the number of events compared with the monotherapy group or the TZD concomitant therapy group. On the basis of the above findings, and in compliance with the recommendation on the "Proper use of incretins and SU agents" issued by the committee for the proper use of incretins (GLP-1 receptor agonists and DPP-4 inhibitors) in 2010 and with the "Revision of 'Precaution' on the concomitant use of incretins and SU agents" (PFSB/SD Notification No. 0427-1, dated April 27, 2010), caution will be provided in Precautions section of the package insert that, if teneligliptin is concomitantly used with an SU, a reduction in the SU should be considered.

PMDA considers as follows:

In the Japanese double-blind studies, the incidence of hypoglycemia was comparable between the teneligliptin group and the placebo group. The incidence was low in all dose groups, and there were no cases of severe hypoglycemia. In the long-term treatment studies, the incidence of hypoglycemia did not show tendency of sizeable increase with the increase in the treatment duration either in the monotherapy group or in the TZD concomitant therapy group, whereas the incidence in the SU concomitant therapy group was slightly higher compared with the monotherapy group or the TZD concomitant therapy group, and hypoglycemia leading to study drug discontinuation has been reported in the group. Although the incidence of hypoglycemia did not show any tendency of increase with the dose of the SU (glimepiride) in clinical studies, it is appropriate to provide caution in the package insert that, if teneligliptin is concomitantly used with an SU, a reduction in the SU should be considered. Since hypoglycemia is an important adverse drug reaction related to the long-term prognosis of patients, it is necessary

to continue to collect information on hypoglycemia via post-marketing surveillance.

4.(iii).B.(3).2) Skin and subcutaneous tissue disorders (including hypersensitivity reactions)

The applicant explained as follows:

In the integrated analysis of Japanese double-blind studies, the incidence of adverse events classified as "skin and subcutaneous tissue disorders" in the system organ class was slightly higher in teneligliptin group (4.1%-7.8%) compared with the placebo group (3.3%), but did not show any tendency of dose-dependent increase [Table 35]. As regards severity, erythema nodosum observed in 1 subject of the 40 mg group in Study 3000-A was moderate, whereas all other events were mild. There were no serious adverse events related to the skin. The only skin-related adverse event leading to study drug discontinuation was skin exfoliation observed in 1 subject of the placebo group in Study 3000-A7. The most commonly reported events in teneligliptin groups were cases of eczema, all of which were mild in severity.

Table 35. Occurrence of adverse events classified as "skin and subcutaneous tissue disorders" in the system organ class (integrated analysis of Japanese double-blind studies)

Type of study	Study No.	Placebo group	Teneligliptin			
			2.5 mg group	10 mg group	20 mg group	40 mg group
Monotherapy	3000-A3	n = 45	n = 49	n = 45	–	n = 47
		2.2 (1)	4.1 (2)	8.9 (4)	–	4.3 (2)
	3000-A4	n = 80	–	n = 84	n = 79	n = 81
		5.0 (4)	–	7.1 (6)	7.6 (6)	6.2 (5)
	3000-A5	n = 104	–	–	n = 99	–
		2.9 (3)	–	–	5.1 (5)	–
SU concomitant therapy	3000-A6	n = 98	–	–	n = 96	–
		3.1 (3)	–	–	2.1 (2)	–
TZD concomitant therapy	3000-A7	n = 101	–	–	n = 103	–
		3.0 (3)	–	–	10.7 (11)	–
Total		n = 428	n = 49	n = 129	n = 377	n = 128
		3.3 (14)	4.1 (2)	7.8 (10)	6.4 (24)	5.5 (7)

Incidence % (No. of subjects with event), -: Not applicable

In the integrated analysis of Japanese long-term treatment studies, the incidence of adverse events classified as "skin and subcutaneous tissue disorders" in the system organ class was not significantly different among monotherapy, SU concomitant therapy, and TZD concomitant therapy groups [Table 36]. Most of the adverse events were mild in severity. Only dermatitis atopic, papule, and contact dermatitis observed in 1 subject each in the monotherapy group were determined as moderate. There were no severe or serious adverse events. Adverse event leading to study drug discontinuation was photosensitivity reaction observed in 1 subject of the SU concomitant therapy group in Study 3000-A6, and was classified as an adverse drug reaction. Necrotic dermatosis observed in the oral toxicity study in monkeys and serious hypersensitivity reactions observed with drugs of the same class were not observed in any of the clinical studies.

Table 36. Occurrence of adverse events classified as “skin and subcutaneous tissue disorders” in the system organ class (integrated analysis of Japanese long-term treatment studies)

Treatment group	Monotherapy	SU concomitant therapy		TZD concomitant therapy	Total
	3000-A8 (monotherapy group)	3000-A8 (glimepiride concomitant therapy group)	3000-A6	3000-A7	
P/T group[a)]	—	—	n = 95	n = 98	n = 193
	—	—	21.1 (20)	10.2 (10)	15.5 (30)
T/T group	n = 151	n = 89	n = 96	n = 103	n = 439
	19.9 (30)	10.1 (9)	18.8 (18)	17.5 (18)	17.1 (75)

Incidence % (No. of subjects with event), -: Not applicable

a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period). Each of the events that continued from the placebo treatment period through the double-blind period was counted as 1 case.

In the foreign late phase II metformin concomitant study (Study MP-513-E07, hereafter referred to as “foreign metformin concomitant therapy study”), the incidence of adverse events classified as “skin and subcutaneous tissue disorders” in the system organ class during the 24-week double-blind period (period I), in the placebo group, 5 mg group, 10 mg group, 20 mg group, and 40 mg group were 5.7% (5 of 88 subjects), 2.3% (2 of 87 subjects), 8.6% (8 of 93 subjects), 7.7% (7 of 91 subjects), and 2.3% (2 of 88 subjects), respectively, showing no tendency of dose-dependent increase. Most of the adverse events were mild or moderate in severity. There were no severe events, serious adverse events, or adverse events leading to study drug discontinuation. Similarly, during the open-label period (period II) from Week 24 to 52 (28 weeks) of administration, there were no severe or serious adverse events in any of the treatment groups.

As described above, necrotising dermatosis observed in the oral toxicity study in monkeys and serious hypersensitivity reactions observed with drugs of the same class were not observed in any of the Japanese or foreign clinical studies, which suggests that necrotising dermatosis observed in monkeys is unlikely to occur in humans. However, caution will be provided in the package insert that necrotising dermatosis was observed in monkeys.

PMDA considers as follows:
PMDA accepts the applicant’s response that serious skin disorders such as those observed in non-clinical studies were not observed either in Japanese or foreign clinical studies, and are therefore unlikely to occur in humans. However, in the integrated analysis of the Japanese double-blind studies, the incidence of adverse events classified as “skin and subcutaneous tissue disorders” in the system organ class tended to be higher in the 20 mg group than in the placebo group. In addition, an adverse drug reaction leading to study drug discontinuation (photosensitivity reaction) has been reported. Therefore, it is necessary to continue to collect information on skin disorders in the post-marketing surveillance.

4.(iii).B.(3).3) Gastrointestinal disorders (including pancreatitis)

The applicant explained as follows:
In the integrated analysis of Japanese double-blind studies, the incidence of adverse events classified as “gastrointestinal disorders” in the system organ class was as shown in Table 37. The incidence was slightly higher in the 40 mg group in the monotherapy (Study 3000-A3), and comparison with the placebo group showed that the incidence was slightly higher in the 20 mg group in the TZD concomitant therapy (Study 3000-A7). However, the results of the integrated analysis showed that the incidence was similar between any of the dose groups and the placebo group, showing no tendency of dose-dependent increase.

Table 37. Occurrence of adverse events classified as “gastrointestinal disorders” in the system organ class (integrated analysis of Japanese double-blind studies)

Type of study	Study No.	Placebo group	Teneligliptin groups			
			2.5 mg group	10 mg group	20 mg group	40 mg group
Monotherapy	3000-A3	n = 45	n = 49	n = 45	–	n = 47
		13.3 (6)	8.2 (4)	13.3 (6)	–	17.0 (8)
	3000-A4	n = 80	–	n = 84	n = 79	n = 81
		10.0 (8)	–	8.3 (7)	10.1 (8)	11.1 (9)
	3000-A5	n = 104	–	–	n = 99	–
		12.5 (13)	–	–	12.1 (12)	–
SU concomitant therapy	3000-A6	n = 98	–	–	n = 96	–
		8.2 (8)	–	–	12.5 (12)	–
TZD concomitant therapy	3000-A7	n = 101	–	–	n = 103	–
		5.0 (5)	–	–	12.6 (13)	–
Total		n = 428	n = 49	n = 129	n = 377	n = 128
		9.3 (40)	8.2 (4)	10.1 (13)	11.9 (45)	13.3 (17)

Incidence % (No. of subjects with event), -: Not applicable

In the integrated analysis of Japanese long-term treatment studies, the incidence of adverse events classified as “gastrointestinal disorders” in the system organ class was as shown in Table 38. The incidence was slightly higher in the TZD concomitant therapy group (Study 3000-A7), but most of the events were mild in severity; there were no adverse events that were classified as severe. Serious adverse events observed were gastritis and intestinal obstruction (1 subject each) in the monotherapy (Study 3000-A8), colonic polyp (1 subject) in the SU concomitant therapy (Study 3000-A6), and colonic polyp (2 subjects), gastric polyps (1 subject), and haemorrhoids (1 subject) in the TZD concomitant therapy (Study 3000-A7). As regards causal relationship with the study drug, the intestinal obstruction in the monotherapy group was judged as “unlikely related” while all other adverse events were judged as “not related”. Intestinal obstruction in 1 subject in the monotherapy group (Study 3000-A8) was the only adverse event leading to study drug discontinuation.

Table 38. Occurrence of adverse events classified as “gastrointestinal disorders” in the system organ class (integrated analysis of Japanese long-term treatment studies)

Treatment group	Monotherapy	SU concomitant therapy		TZD concomitant therapy	Total
	3000-A8 (monotherapy group)	3000-A8 (glimepiride concomitant group)	3000-A6	3000-A7	
P/T group[a)]	–	–	n = 95	n = 98	n = 193
	–	–	20.0 (19)	23.5 (23)	21.8 (42)
T/T group	n = 151	n = 89	n = 96	n = 103	n = 439
	29.8 (45)	33.7 (30)	29.2 (28)	35.0 (36)	31.7 (139)

Incidence % (No. of subjects with event), -: Not applicable

a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period). Each of the events that continued from the placebo treatment period through the double-blind period was counted as 1 case.

In the foreign metformin concomitant therapy study, the incidence of adverse events classified as "gastrointestinal disorders" in the system organ class during the double-blind period (period I) in the placebo group, 5 mg group, 10 mg group, 20 mg group, and 40 mg group were 6.8% (6 of 88 subjects), 10.3% (9 of 87 subjects), 9.7% (9 of 93 subjects), 12.1% (11 of 91 subjects), and 6.8% (6 of 88 subjects), respectively, showing no tendency of dose-dependent increase. Most of the events were mild or moderate in severity. Mallory-Weiss syndrome in 1 subject in the 10 mg group was the only adverse event judged as severe. Serious adverse events observed were umbilical hernia (1 subject) in the placebo group, Mallory-Weiss syndrome (1 subject) in the 10 mg group, and abdominal pain (1 subject) in the 40 mg group, which were judged as "not related," "unlikely related," and "not related," respectively, to the study drug. Adverse events leading to study drug discontinuation were abdominal pain upper (1 subject) in the 10 mg group and abdominal pain (1 subject) in the 40 mg group. Most of the adverse events observed during the open-label period (period II) were mild or moderate in severity. Pancreatitis acute (1 subject) in the 10 mg group was the only adverse event classified as severe that occurred during the open-label period (period II). Serious adverse events were pancreatitis acute (1 subject) in the 10 mg group and haemorrhoids (1 subject) in the 20 mg group, of which pancreatitis acute was classified as an adverse drug reaction.

Pancreatitis was not observed in Japanese clinical studies, whereas in the foreign metformin concomitant therapy study, pancreatitis acute (1 subject [1 event]) was observed at Day 360 after start of treatment, and was classified as a serious adverse drug reaction. Teneligliptin was withdrawn temporarily in this subject, but administration was resumed after the symptom resolved on Day 367, and the subject completed the study. In the case of sitagliptin, a drug of the same class, haemorrhagic pancreatitis and necrotising pancreatitis were reported in foreign countries after the market launch, and there were multiple reports of acute pancreatitis in Japan. Therefore, in the package insert of sitagliptin, a caution is raised against the illness as a clinically significant adverse reaction. In the package inserts of other drugs of the same class, pancreatitis is listed in the Other Adverse Reactions section as an adverse drug reaction of unknown frequency.

Thus, although pancreatitis was not observed in the Japanese clinical studies on teneligliptin, an adverse drug reaction of pancreatitis acute was observed in the foreign clinical study. Therefore, caution should be exercised against the occurrence of pancreatitis.

PMDA considers as follows:
In the integrated analysis of Japanese double-blind studies, the incidence of adverse events classified as "gastrointestinal disorders" in the system organ class tends to be slightly higher in the 20 mg group and in the 40 mg group than in the placebo group. As regards pancreatitis, although occurrence of pancreatitis acute was reported in subjects treated with teneligliptin in foreign clinical studies, there were no reports in Japanese clinical studies. It is sufficient to list pancreatitis acute in the Other Adverse Reactions section in the package insert to raise caution. However, with consideration given to the occurrence of pancreatitis with drugs of the same class, it will be necessary to continue to collect information on gastrointestinal disorders (including pancreatitis) via post-marketing surveillance.

4.(iii).B.(3).4) Musculoskeletal and connective tissue disorders

Based on the findings in the integrated analysis of Japanese double-blind studies that the incidence of adverse events classified as "musculoskeletal and connective tissue disorders" in the system organ class tended to be higher in the 20 mg group and in the 40 mg group than in other treatment groups, PMDA asked the applicant to explain the risk of musculoskeletal and connective tissue disorders in patients treated with teneligliptin.

The applicant responded as follows:
In the integrated analysis of Japanese double-blind studies, the incidence of adverse events classified as “musculoskeletal and connective tissue disorders” in the system organ class tended to be higher in the 20 mg group and in the 40 mg group than in other treatment groups, as shown in Table 39. Adverse events that occurred in the 20 mg group and in the 40 mg group were considered to be due to physical activities such as exercise, aging, complications, or medical history, and were judged as “not related” or “unlikely related” to the study drug. Most of the adverse events observed in Japanese double-blind studies were mild or moderate in severity. There were no severe or serious adverse events. Mild myalgia observed in 1 subject of the 40 mg group in Study 3000-A4 was the only adverse event leading to study drug discontinuation.

Table 39. Occurrence of adverse events classified as “musculoskeletal and connective tissue disorders” in the system organ class (integrated analysis of Japanese double-blind studies)

Type of study	Study No.	Placebo group	Teneligliptin groups			
			2.5 mg group	10 mg group	20 mg group	40 mg group
Monotherapy	3000-A3	n = 45	n = 49	n = 45	—	n = 47
		8.9 (4)	4.1 (2)	4.4 (2)	—	19.1 (9)
	3000-A4	n = 80	—	n = 84	n = 79	n = 81
		5.0 (4)	—	7.1 (6)	11.4 (9)	9.9 (8)
	3000-A5	n = 104	—	—	n = 99	—
		7.7 (8)	—	—	8.1 (8)	—
SU concomitant therapy	3000-A6	n = 98	—	—	n = 96	—
		6.1 (6)	—	—	13.5 (13)	—
TZD concomitant therapy	3000-A7	n = 101	—	—	n = 103	—
		5.9 (6)	—	—	11.7 (12)	—
Total		n = 428	n = 49	n = 129	n = 377	n = 128
		6.5 (28)	4.1 (2)	6.2 (8)	11.1 (42)	13.3 (17)

Incidence % (No. of subjects with event), -: Not applicable

In the integrated analysis of Japanese long-term treatment studies (Table 40), most of the adverse events were mild in severity. Serious adverse events were intervertebral disc protrusion in 1 subject in the monotherapy group, loose body in joint in 1 subject of the SU concomitant therapy group in Study3000-A6, and intervertebral disc protrusion in 1 subject of the glimepiride concomitant group in Study 3000-A8. Adverse events leading to study drug discontinuation were intervertebral disc protrusion in 1 subject of the SU concomitant therapy group and osteoarthritis in 1 subjects of the glimepiride concomitant group (Study 3000-A8). Thus, there was no tendency of marked increase in the incidence of serious adverse events or adverse events leading to study drug discontinuation in the long-term treatment. The incidence of adverse events in the SU concomitant therapy and in the TZD concomitant therapy was similar to that in the monotherapy.

Table 40. Occurrence of adverse events classified as “musculoskeletal and connective tissue disorders” in the system organ class (integrated analysis of Japanese long-term treatment studies)

Treatment group	Monotherapy	SU concomitant therapy		TZD concomitant therapy	Total
	3000-A8 (monotherapy)	3000-A8 (glimepiride concomitant group)	3000-A6	3000-A7	
P/T group[a)]	–	–	n = 95	n = 98	n = 193
	–	–	13.7 (13)	21.4 (21)	17.6 (34)
T/T group	n = 151	n = 89	n = 96	n = 103	n = 439
	21.9 (33)	25.8 (23)	30.2 (29)	23.3 (24)	24.8 (109)

Incidence % (No. of subjects with event), -: Not applicable

a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period). Each of the events that continued from the placebo treatment period through the double-blind period was counted as 1 case.

The incidence of adverse events classified as “musculoskeletal and connective tissue disorders” during the double-blind period (period I) in the foreign metformin concomitant therapy study in the placebo group, 5 mg group, 10 mg group, 20 mg group, and 40 mg group were 6.8% (6 of 88 subjects), 4.6% (4 of 87 subjects), 7.5% (7 of 93 subjects), 4.4% (4 of 91 subjects), and 3.4% (3 of 88 subjects), respectively, showing no tendency of increase in the 20 mg group or in the 40 mg group. Most of the adverse events observed during the double-blind period (period I) or during the open-label period (period II) were mild or moderate in severity. The only adverse events classified as severe were arthritis and arthralgia (1 subject each) in the 10 mg group, pain in extremity (1 subject) in the 20 mg group, and spinal osteoarthritis (1 subject) in the 40 mg group. Serious adverse events were spinal osteoarthritis (1 subject) in the 40 mg group that occurred during period I and musculoskeletal chest pain (1 subject) in the placebo group that occurred during period II, both of which were judged as “not related” to the study drug. There were no adverse events leading to study drug discontinuation.

Since there were no findings related to the musculoskeletal system in nonclinical studies of teneligliptin, the higher tendency of the incidence in the 20 mg group and in the 40 mg group than in other treatment groups observed in the integrated analysis of the Japanese double-blind studies is considered to be accidental. Therefore, the applicant considers that teneligliptin administration is unlikely to cause adverse events related to the musculoskeletal system.

PMDA considers as follows:
In light of the facts that the integrated analysis of the Japanese double-blind studies shows that the incidence of adverse events classified as “musculoskeletal and connective tissue disorders” in the system organ class is higher in the 20 mg group and in the 40 mg group than in the placebo group, and that the effect of DPP-4 inhibition on the musculoskeletal system over a long-term period is unknown, it is necessary to continue to collect information on musculoskeletal and connective tissue disorders via post-marketing surveillance.

4.(iii).B.(3).5) Hepatic impairment

PMDA, by pointing out the fact that hepatic impairment is reported as a clinically significant adverse reaction with other drugs in the same class, asked the applicant to explain the risk of teneligliptin causing hepatic impairment.

The applicant responded as follows:
To evaluate the risk of hepatic impairment caused by teneligliptin administration, the occurrence

of adverse events classified as “hepatobiliary disorders” in the system organ class and those related to changes in liver function test values as “investigations” were investigated. The incidence of adverse events classified as “hepatobiliary disorders” in the system organ class in the integrated analysis of the Japanese double-blind studies was 0.2% (1 of 428 subjects) in the placebo group, 0.0% (0 of 49 subjects) in the 2.5 mg group, 0.8% (1 of 129 subjects) in the 10 mg group, 1.1% (4 of 377 subjects) in the 20 mg group, and 0.8% (1 of 128 subjects) in the 40 mg, showing similar results between teneligliptin groups and the placebo group. The most commonly reported adverse event was hepatic steatosis, which did not show any tendency of dose-dependent increase in the incidence. All adverse events were mild in severity. In teneligliptin groups, there were no serious adverse events or adverse events leading to study drug discontinuation. The incidence of adverse events related to liver function test values in “investigations” classified in the system organ class was similar between all of teneligliptin groups and the placebo group. All adverse events were mild in severity, and there were no serious adverse events or adverse events leading to study drug discontinuation.

The incidence of adverse events classified as “hepatobiliary disorders” in the system organ class in the integrated analysis of the Japanese long-term treatment studies was 4.0% (6 of 151 subjects) in the monotherapy group, 3.2% (9 of 280 subjects) in the SU concomitant therapy group, and 3.5% (7 of 201 subjects) in the TZD concomitant therapy group, showing similar results in all treatment groups. Serious adverse events were observed in 1 subject in the SU concomitant therapy in Study 3000-A6 (2 events) (cholangitis, bile duct stone) and in 1 subject in the SU concomitant therapy in Study 3000-A8 (2 events) (cholelithiasis, cholecystitis). One subject in Study 3000-A6 discontinued the administration of the study drug. However, none of these events were judged as causally related to the study drug. The incidence of adverse events related to liver function test values in “investigations” classified in the system organ class was 4.6% (7 of 151 subjects) in the monotherapy, 5.7% (16 of 280 subjects) in the SU concomitant therapy, and 0.5% (1 of 201 subjects) in the TZD concomitant therapy, showing a higher tendency in the monotherapy group and in the SU concomitant therapy group compared with the TZD concomitant therapy group. All adverse events were mild in severity, and there were no serious adverse events or adverse events leading to study drug discontinuation.

The incidence of adverse events classified as “hepatobiliary disorders” in the system organ class during the double-blind period (period I) in the foreign metformin concomitant therapy study was 3.4% (3 of 88 subjects) in the placebo group, 2.3% (2 of 87 subjects) in the 5 mg group, 2.2% (2 of 93 subjects) in the 10 mg group, 1.1% (1 of 91 subjects) in the 20 mg group, and 0.0% (0 of 88 subjects) in the 40 mg group; thus the incidence was similar between teneligliptin groups and the placebo group and did not show any tendency of dose-dependent increase. The incidence of adverse events related to liver function test values in “investigations” classified in the system organ class was also similar between teneligliptin groups and the placebo group.

These results suggest that teneligliptin does not have any tendency to cause change in the occurrence of hepatic impairment.

PMDA considers as follows:
Results of the Japanese and foreign clinical studies showed that there was no significant difference in the incidence of adverse events related to hepatic impairment between teneligliptin group and the placebo group, and that there was no serious adverse drug reaction. However, given that hepatic impairment and jaundice were reported after marketing of drugs of the same class and that cautions are raised in the package insert of the drugs of same class against these disorders as clinically significant adverse reactions, it is necessary to continue to collect information on hepatic impairment in via post-marketing surveillance.

4.(iii).B.(3).6) Cardiovascular risks

The applicant explained as follows:

In the integrated analysis of the Japanese double-blind studies, the incidence of cardiovascular adverse events[50] was 2.8% (12 of 428 subjects) in the placebo group, 0.0% (0 of 49 subjects) in the 2.5 mg group, 3.1% (4 of 129 subjects) in the 10 mg group, 2.1% (8 of 377 subjects) in the 20 mg group, and 0.0% (0 of 128 subjects) in the 40 mg group. The most commonly reported adverse event was blood creatine phosphokinase increased, with the incidence being 2.1% (9 of 428 subjects) in the placebo group, 0.0% (0 of 49 subjects) in the 2.5 mg group, 3.1% (4 of 129 subjects) in the 10 mg group, 2.1% (8 of 377 subjects) in the 20 mg group, and 0.0% (0 of 128 subjects) in the 40 mg group. Blood creatine phosphokinase increased was the only adverse event that occurred in teneligliptin groups. In the integrated analysis of the Japanese long-term treatment studies, the incidence of cardiovascular adverse events was 8.7% (55 of 632 subjects), including blood creatine phosphokinase increased (45 subjects), carotid atherosclerosis (5 subjects), lacunar infarction (2 subjects), carotid artery stenosis (2 subjects), cerebrovascular stenosis, acute myocardial infarction, and cerebral infarction (1 subject each). Most of the adverse events were mild in severity, with none of them classified severe. Serious adverse events observed were acute myocardial infarction and carotid artery stenosis (1 subject each), which were judged as "unlikely related" and "not related", respectively, to the study drug. Administration of the study drug was discontinued in subjects with these serious adverse events. The incidence stratified by background medication was as follows: (i) monotherapy (10.6% [16 of 151 subjects] in monotherapy group in Study 3000-A8); (ii) SU concomitant therapy (7.9% [7 of 89 subjects] in SU concomitant therapy group in Study 3000-A8, 4.2% [4 of 95 subjects] in P/T group and 9.4% [9 of 96 subjects] in T/T group in Study 3000-A6; and (iii) TZD concomitant therapy (8.2% [8 of 98 subjects] in P/T group, 10.7% [11 of 103 subjects] in T/T group in Study 3000-A7). Thus, there was no significant difference in the incidence among the monotherapy group, SU concomitant therapy group, and TZD concomitant therapy group.

The incidence of cardiovascular adverse events during the double-blind period (period I) and during the open-label period (period II) in the foreign metformin concomitant therapy study was 0.0% (0 of 70 subjects) in the placebo group (period I, 24-week administration of placebo; period II, 28-week administration of teneligliptin 20 mg), 2.3% (2 of 87 subjects) in the 5 mg group, 0.0% (0 of 93 subjects) in the 10 mg group, 3.3% (3 of 91 subjects) in the 20 mg group, and 0.0% (0 of 88 subjects) in the 40 mg group. Adverse events classified as adverse drug reactions were cerebellar infarction and vertebrobasilar insufficiency (1 subject each) in the 20 mg group. Serious adverse events observed were transient ischaemic attack and ischaemic stroke (1 subject each) in the 5 mg group, and transient ischaemic attack and cerebellar infarction (1 subject each) in the 20 mg group. Adverse events leading to study drug discontinuation were ischaemic stroke (1 subject) in the 5 mg group and cerebellar infarction (1 subject) in the 20 mg group.

As regards vital signs (blood pressure systolic, blood pressure diastolic, pulse rate), results of the integrated analysis of the Japanese double-blind studies showed that changes from baseline values in all teneligliptin groups were small for all parameters and comparable to those in the placebo group [Table 41]. The most commonly reported adverse event related to vital signs was hypertension, with the incidence being 0.9% (4 of 428 subjects) in the placebo group, 2.0% (1 of 49 subjects) in the 2.5 mg group, 0.8% (1 of 129 subjects) in the 10 mg group, 0.5% (2 of 377 subjects) in the 20 mg group, and 0.8% (1 of 128 subjects) in the 40 mg group. Except for moderate hypotension and loss of consciousness observed in 1 subject of the 20 mg group, all other adverse events were mild in severity. There were no adverse events leading to study drug discontinuation.

As regards effects on lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), changes from baseline were small for all parameters in all teneligliptin groups in

[50] Events that correspond to "myocardial infarction" and to "central nervous system haemorrhages and cerebrovascular accidents" in broad search in Standardised MedDRA Queries (SMQ)

the integrated analysis of the Japanese double-blind studies; changes were not significantly different within teneligliptin groups, and were similar to those in the placebo group [Table 41]. The incidence of adverse events related to lipid parameters were 0.2% (1 of 428 subjects) for hyperlipidaemia and 1.6% (7 of 428 subjects) for blood triglycerides increased in the placebo group, 1.6% (2 of 129 subjects) for blood triglycerides increased in the 10 mg group, 1.6% (6 of 377 subjects) for blood triglycerides increased in the 20 mg group, and 0.8% (1 of 128 subjects) for hyperlipidaemia and 0.8% (1 of 128 subjects) for blood triglycerides increased in the 40 mg group. All events were mild in severity, and there were no serious adverse events or adverse events leading to study drug discontinuation.

As regards body weight, there was a tendency of increase from baseline in all teneligliptin groups compared with the placebo group in the integrated analysis of the Japanese double-blind studies, but the extent of the increase was small and not considered to be clinically significant [Table 41]. In the long-term treatment studies, the change in body weight (mean ± SD, LOCF) from baseline to the end of the administration was as follows: (i) monotherapy (0.19 ± 2.12 kg in monotherapy group in Study 3000-A8); (ii) SU concomitant therapy (0.52 ± 1.69 kg in SU concomitant therapy group in Study 3000-A8, 0.74 ± 1.85 kg in P/T group and 0.54 ± 1.77 kg in T/T group in Study 3000-A6; and (iii) TZD concomitant therapy (1.16 ± 2.15 kg in P/T group and 1.47 ± 2.93 kg in T/T group in Study 3000-A7). Although the extent of the increase tended to be greater in concomitant therapies compared with the monotherapy, the increase was small and not considered to be clinically significant.

Table 41. Changes in vital signs, lipid parameters, and body weight at Week 12 of treatment period from baseline (integrated analysis of Japanese double-blind studies)

Parameter	Placebo group (n = 409)	2.5 mg group (n = 47)	10 mg group (n = 125)	20 mg group (n = 366)	40 mg group (n = 121)
Blood pressure Systolic (mmHg)	0.2 ± 12.2	0.4 ± 13.3	0.0 ± 12.1	-1.3 ± 14.0	-1.1 ± 10.7
Blood pressure Diastolic (mmHg)	0.0 ± 7.8	-0.4 ± 8.3	-0.2 ± 8.5	-0.5 ± 8.7	-0.2 ± 7.3
Pulse rate (beats/min)	0.8 ± 8.8	0.0 ± 8.9	0.0 ± 7.5	1.4 ± 7.7	1.1 ± 8.0
Cholesterol total (mg/dL)	-2.4 ± 21.1	-4.1 ± 25.9	-3.3 ± 22.7	-7.6 ± 22.8	-4.3 ± 21.7
LDL cholesterol (mg/dL)	-1.5 ± 18.7	-6.6 ± 22.9	-0.9 ± 20.4	-5.6 ± 20.8	-1.7 ± 18.6
HDL cholesterol (mg/dL)	-0.2 ± 7.2	-1.1 ± 7.4	-0.9 ± 7.3	-1.1 ± 8.5	-0.8 ± 7.6
Triglycerides (mg/dL)	-1.9 ± 55.7	21.8 ± 102.5	-3.4 ± 113.2	-5.5 ± 70.3	-6.6 ± 70.8
Body weight (kg)	-0.15 ± 1.20	0.21 ± 1.16	0.34 ± 1.27	0.24 ± 1.48	0.24 ± 1.22

Mean ± SD

As regards ECG, results of the integrated analysis of the Japanese double-blind studies did not show significant difference in the occurrence of abnormal ECG findings among treatment groups. Adverse events that occurred after administration of the study drug that were classified as “clinically significant abnormalities” were observed in 1 subject in the 20 mg group (TZD concomitant therapy in Study 3000-A7) and in 1 subject in the 40 mg group (monotherapy in Study 3000-A3). They were reported as left bundle branch block and sinoatrial block, respectively, and both were judged as “unlikely related” to the study drug. As regards severity, the left bundle branch block was mild and the sinoatrial block was moderate.

During the double-blind period (period I) of the foreign metformin concomitant therapy study, there was no significant difference in the occurrence of ECG abnormalities among treatment groups. Adverse events that occurred after administration of the study drug and were classified as “clinically significant abnormalities” were atrial fibrillation and sinus bradycardia (1 subject each) in the 10 mg group, atrioventricular block first degree (1 subject) in the 20 mg group,

and atrial fibrillation (1 subject) in the 40 mg group. Only the atrioventricular block first degree (1 subject) in the 20 mg group was classified as an adverse drug reaction. The atrial fibrillation in the 10 mg group was reported as a serious adverse event and the causal relationship with the study drug was denied.

Thus, the results of Japanese and foreign clinical studies showed that teneligliptin administration did not cause change in vital signs, ECG, lipid parameters, or body weight, suggestive of any increase in cardiovascular risk. In addition, the incidences of adverse events and adverse drug reactions associated with cardiovascular system were low. On the basis of these results, the applicant considers that administration of teneligliptin is unlikely to increase the risk of cardiovascular events. However, cardiovascular risk caused by teneligliptin will be investigated in further detail by checking the occurrence of cardiovascular events via post-marketing surveillance.

PMDA considers as follows:
In Japanese clinical studies, teneligliptin did not cause detectable increase in cardiovascular risk; teneligliptin had no clear effect on the occurrence of cardiovascular adverse events, vital signs, ECG, or lipid parameters. However, given the limited number of subjects investigated in clinical studies and the limited treatment duration, it is considered necessary to continue to collect information on cardiovascular risk via post-marketing surveillance [see "4.(iii).B.(7) Post-marketing surveillance plan"].

4.(iii).B.(3).7) QTc interval prolongation and proarrhythmic risk
PMDA, by pointing out the finding in foreign Thorough QT/QTc study in which QTc interval prolongation was observed at 160 mg teneligliptin, asked the applicant to explain the relationship between the timing of ECG measurement in Japanese clinical studies and the time elapsed after administration of study drug and, based on that relationship, explain the data of ECG obtained in Japanese clinical studies.

The applicant responded as follows:
The phase III clinical study of teneligliptin was started before the publication of "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (PFSB/ELD Notification No. 1023-1 dated October 23, 2009; hereafter referred to as "ICH E14 guideline"). Therefore, ECG evaluation based on ICH E14 guideline was not performed. As a result, in the phase III study, the timing of ECG measurement was not specified and information on the timing of ECG measurement and on the timing of the administration of study drug was not collected, precluding the identification of the time elapsed between the administration and ECG measurement. In the categorical analysis of QTc measurements[51] (mean values) in the integrated analysis of the Japanese double-blind clinical studies, among patients with baseline QTc interval of ≤450 msec, 1 subject in the 40 mg group showed QTc interval exceeding 500 msec after administration of study drug, and 2 subjects in the 40 mg group showed a change in QTc interval exceeding 60 msec. Both appeared to be due to noises in the ECG waves resulting in high values recorded automatically, and were judged as not due to QTc interval prolongation associated with teneligliptin. In the categorical analysis in the integrated analysis of the Japanese long-term treatment studies, among patients with baseline QTc interval of ≤450 msec, 1 patient (monotherapy group) showed a QTc interval exceeding 500 msec with change from baseline exceeding 60 msec. These values were caused by errors in detecting the limb-lead terminal T wave in electrocardiography at Week 24 of the treatment period and judged as not findings indicating QTc interval prolongation. In the

[51] In Japanese and foreign clinical studies involving patients with type 2 diabetes mellitus, QTc interval was evaluated by 12-lead electrocardiography, and ECG parameters (heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) were evaluated centrally by heart specialists.

categorical analysis of QTcF measurements at Week 24 of the treatment period or at discontinuation in the double-blind period (period I) in the foreign metformin concomitant therapy study, QTcF did not exceed 480 msec in any of patients with baseline value of <450 msec, whereas change from baseline exceeded 60 msec in 1 patient in the 40 mg group. Results of ECG measurement at the study site or the results of the central evaluation of ECG by heart specialists fell under the criteria for study discontinuation and accordingly the study was terminated in 1 subject in the 5 mg group and 1 subject in the 10 mg group during the double-blind period (period I) and, during the open-label period (period II), in 3 subjects in the 5 mg/20 mg group (dose during period I/dose during period II), 3 subjects in the 10 mg/20 mg group, 1 subject in the 20 mg/20 mg group, and 3 subjects in the 40 mg/20 mg group.

PMDA asked the applicant to explain the safety in the patient group[52] with additional risk factors for adverse events suggestive of proarrhythmic[53] and torsades de pointes (TdP) described in ICH E14 guideline.

The applicant responded as follows:
The only adverse event with symptoms related to QT interval prolongation[54] observed in Japanese clinical studies was loss of consciousness (1 subject) in the 20 mg group during the double-blind period (period I) in Study 3000-A7. The loss of consciousness[55] was judged to be due to decreased blood pressure and not causally related to the study drug. Patients in the risk group described in ICH E14 guideline did not show any tendency of QTc interval prolongation after increase in teneligliptin dose to 40 mg. In the foreign metformin concomitant therapy study, adverse events were observed only in 1 subject each in the 5 mg group (syncope) and in the 10 mg group (ECG QT interval prolongation) during the open-label period (period II). The syncope was moderate in severity and judged as not causally related to the study drug. In the subject with ECG QT interval prolongation, the results of ECG measurement at the study center fell under the criteria for study discontinuation, and the study was therefore terminated. However, the adverse event was judged as "unlikely related" to the study drug, and the centralized evaluation of QTc in this subject did not show any findings indicative of QTc interval prolongation. As regards the patient group with an additional risk factor for TdP, patients with congestive heart failure had been excluded from the study according to the exclusion criteria. Therefore, patients with other risk factors were investigated for their safety. Of patients enrolled in the long-term treatment studies, approximately 6.1% to 14.6% had electrolyte abnormality, 25.2% to 37.9% had renal or hepatic impairment, 25.5% to 37.1% were female patients, and 27.0% to 39.8% were elderly patients. Of patients in whom teneligliptin dose was increased to 40 mg, 3.7% to 16.4% had electrolyte abnormality, 16.1% to 40.6% had renal or hepatic impairment, 11.1% to 43.6% were female patients, and 16.7% to 39.1% were elderly patients. The only adverse event related to QT interval prolongation symptom observed in these patients

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[52] Patients with electrolyte abnormality, patients with congestive heart failure, patients with impaired drug metabolism or clearance, female patients, patients younger than 16 years or older than 65 years of age

[53] Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, syncope, and epileptic seizure

[54] Events corresponding to "QT prolongation" in SMQ (cardiac arrest, cardio-respiratory arrest, ECG QT interval prolongation, Long QT syndrome, loss of consciousness, sudden death, syncope, torsade de pointes, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachycardia, sudden cardiac death, cardiac death, ECG repolarisation abnormality, ECG U-wave abnormality, ECG biphasic U waves, long QT syndrome congenital, cardiac fibrillation, ECG QT interval abnormal,ventricular tachyarrhythmia)

[55] The 61-year old male patient showed electrolyte abnormality (K, 3.4 mEq/L) in baseline laboratory test but did not have renal or hepatic impairment. Systemic blood pressure remained around 80 mmHg, from which the loss of consciousness was judged to be due to decreased blood pressure and was reported as a serious adverse event. The adverse event was considered to be a transient decrease in blood pressure caused by Selara tablets and Preminent tablets, drugs administered concomitantly, and judged as not causally related to the study drug.

was loss of consciousness (1 subject) in Study 3000-A7 described above. Measured QTc value of ECG did not show any tendency of prolongation after teneligliptin dose increase to 40 mg.

PMDA, by pointing out the fact that, in the phase III clinical study of teneligliptin, patients being treated for arrhythmia, patients with a past history of ventricular tachycardia, patients with abnormality in resting standard 12-lead ECG at the start and end of the run-in period, etc., were excluded[56] from the study, asked the applicant about the necessity of providing caution for these patients.

The applicant responded as follows:
The phase III studies of teneligliptin was conducted with consideration based on the effect on ECG evaluation, safety for patients, and ethics. Therefore, safety of teneligliptin administration in those patients as pointed out by PMDA was not investigated. On the other hand, the number of patients with atrial fibrillation, a particularly common type of arrhythmia, is in steady increase in Japan (Ohsawa M, et al., *J Epidemiol*, 2005;15: 194-6). It has been reported that the prevalence rate of atrial fibrillation is high in patients with hypertension, diabetes mellitus, or cardiac disease complications (Inoue H, et al., *Int J Cardiol*, 2009;137: 102-7). It is thus considered important that type 2 diabetic patients with arrhythmia be treated with hypoglycemic agents. Therefore, taking account of the current situation in Japan that the number of type 2 diabetic patients with arrhythmia has been increasing, it is deemed necessary that teneligliptin 40 mg be included in the treatment option at clinical practice for the treatment of patients who fall under the heart-related exclusion criteria of the phase III studies. As regarding the necessity for raising caution, teneligliptin is unlikely to increase cardiovascular risk, for the following reasons: (i) in non-clinical studies of teneligliptin, no heart-related findings were observed except QTc interval prolongation, (ii) evaluation of cardiovascular risk in Japanese and foreign clinical studies did not show any change suggestive of teneligliptin-induced increase in cardiovascular risk regarding vital signs, lipid parameters, body weight, or ECG, and (iii) the incidence of cardiovascular adverse events was low in these clinical studies. The results of nonclinical safety pharmacology studies suggested that the QTc interval prolongation observed with teneligliptin administration was due to the inhibition of hERG by the unchanged drug, and that prolongation is caused when blood teneligliptin concentration shows marked increase. The results of the foreign Thorough QT/QTc study showed that QTc interval prolongation was observed at around t_{max} following teneligliptin 160 mg administration, i.e., within the time window with high drug concentration, but the C_{max} reached at 160 mg is estimated to be 2.1 to 2.6 times that reached at 40 mg, even in the presence of multiple factors causing an increase in exposure level [see "4.(ii).B.(3) QTc intervalprolonging effect of teneligliptin"]. Risk of QTc interval prolongation following teneligliptin dose increase to 40 mg was investigated in the patient subpopulations with additional risk factors for TdP, such as those listed in ICH E14 guideline. The results suggested that there was no clinically significant safety problem related to QTc interval prolongation in any of the subgroups. Thus, teneligliptin is unlikely to induce cardiac disease other than QTc interval prolongation, and teneligliptin is unlikely to pose any significant safety problem related to QTc interval prolongation, as even when judged by the results of the study on the risk of QTc interval prolongation at 40 mg conducted with a focus on the increase in the C_{max} of teneligliptin, which is the primary cause of QTc interval prolongation, and on patients with additional risk factors for TdP listed in ICH E14 guideline.

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[56] The exclusion criteria included the following: arrhythmia (patients undergoing treatment for arrhythmia), cardiac failure (patients with symptoms of cardiac failure corresponding to NYHA class III or IV [patient with current, or past history of, cardiac failure in Study 3000-A7]), medical history (patient with a past history of ventricular tachycardia or ventricular fibrillation, occurrence of acute myocardial infarction, congestive heart failure, or unstable angina within 6 months before the start of the run-in period), ECG (patients with any of the following findings in resting standard 12-lead ECG at the start and end of the run-in-period; paroxysmal [supraventricular, ventricular, ectopic atrial] tachycardia, atrioventricular block [grade II or III], sick sinus syndrome [sinoatrial block, sinus arrest], ventricular fibrillation, QTc interval prolongation [$\geq$ 0.50 sec]).

As discussed above, although teneligliptin has not been used in patients who fall under the heart-related exclusion set in the phase III study, teneligliptin is unlikely to affect concurrent cardiac disease, and it is unlikely to pose any safety problem related to QTc interval prolongation at 40 mg administrations. Therefore, the applicant does not think it necessary to raise any particular caution in teneligliptin dose increase to 40 mg, other than close monitoring of the patient condition over time. However, as a precautionary measure, information will be provided in the package insert (draft) that QTc interval prolongation was observed following teneligliptin 160 mg administration in foreign Thorough QT/QTc study.

PMDA considers as follows:
In the phase III studies of teneligliptin, patients being treated for arrhythmia, patients with a history of ventricular tachycardia, and patients with abnormality in resting standard 12-lead ECG at the start and end of the run-in period were excluded. Therefore, the risks of QTc interval prolongation and arrhythmia in these patients have not been investigated. Also, since the timing for ECG measurement was not specified in the phase III studies, the possibility cannot be excluded that the effect of teneligliptin on QTc interval prolongation was not thoroughly investigated. In addition, taking into account that there are diabetic patients who have concurrent disease such as arrhythmia and ischemia, and that teneligliptin may be administered to such patients for a long period of time, it is deemed necessary to raise caution in administering teneligliptin to these patients and to collect information on proarrhythmic risk via post-marketing surveillance. The above conclusion will be finalized, also taking account of comments raised in the Expert Discussion.

4.(iii).B.(3).8) Relationship with the occurrence of tumors

The applicant explained as follows:
The incidence of adverse events classified as “neoplasms benign, malignant and unspecified (incl cysts and polyps)” in the system organ class was low in all treatment groups in the integrated analysis of the Japanese double-blind studies: 4 subjects in the placebo group (4 events) (gastric cancer [2 events in 2 subjects], metastatic neoplasm [1 event in 1 subject], breast cancer [1 event in 1 subject]), 2 subjects in the 10 mg group (2 events) (seborrhoeic keratosis, lung neoplasm), and 1 subject in the 20 mg group (1 event) (neoplasm skin). There were 4 serious adverse events in 4 subjects of the placebo group (gastric cancer [2 events in 2 subjects], metastatic neoplasm [1 event in 1 subject], breast cancer [1 event in 1 subject]), while there was no serious adverse event in the teneligliptin group. Also, adverse events observed in the teneligliptin group were all mild in severity.

In the integrated analysis of the Japanese long-term treatment studies, the incidence of the adverse events was as follows: 3.9% in the 52-week teneligliptin administration groups, i.e., T/T group in Studies 3000-A8, 3000-A6, and 3000-A7 (17 of 439 subjects [18 events]; large intestine carcinoma [4 subjects], gastric cancer [3 subjects], gastrointestinal neoplasm [2 subjects], uterine leiomyoma, prostate cancer/metastases to bone, thyroid neoplasm, acrochordon, testicular neoplasm, skin papilloma, lipoma, and seborrhoeic keratosis [1 subject each]) and 1.6% in P/T group (40-week administration) in Studies 3000-A6 and 3000-A7 (3 of 193 subjects [4 events]; gastric cancer/oesophageal carcinoma, ovarian cancer, ovarian neoplasm). There were 13 serious adverse events in 11 subjects (large intestine carcinoma [4 subjects], gastric cancer [3 subjects], gastric cancer/oesophageal carcinoma, testicular neoplasm, ovarian cancer, prostate cancer/metastases to bone). Among the above adverse events, those classified as adverse drug reactions were large intestine carcinoma in 1 subject of T/T group in Study 3000-A6, ovarian cancer in 1 subject of P/T group in Study 3000-A7, and testicular neoplasm in 1 subject of SU concomitant therapy group in Study 3000-A8.

During the double-blind period (period I) and the open-label period (period II) of the

foreign metformin concomitant therapy study, the incidence of adverse events classified as "neoplasms benign, malignant and unspecified (incl cysts and polyps)" in the system organ class was 0.0% (0 of 70 subjects) in the placebo group (teneligliptin 20 mg administered for 28 weeks), 0.0% (0 of 87 subjects) in the 5 mg group, 1.1% (1 of 93 subjects) in the 10 mg group, 3.3% (3 of 91 subjects) in the 20 mg group, and 2.3% (2 of 88 subjects) in the 40 mg group, showing no tendency of marked increase in teneligliptin groups during the long-term administration. Adverse events that newly occurred during the open-label period (period II) were skin papilloma in 1 subject of the 20 mg group and uterine leiomyoma in 1 subject of the 40 mg group. Uterine leiomyoma in the 40 mg group was classified as a serious adverse event.

PMDA considers as follows:
Results of the Japanese and foreign clinical studies do not suggest teneligliptin-induced increase in the risk of malignant tumors. However, since teneligliptin may be administered over a long period of time, teneligliptin was administered to only a limited number of subjects for a limited period in clinical studies, and the long-term systemic effect of DPP-4 inhibition is currently unknown, it is considered necessary to continue to collect information on the occurrence of tumors via post-marketing surveillance.

4.(iii).B.(4) Indications
PMDA considers as follows:
Results of Japanese clinical studies have demonstrated the efficacy of teneligliptin monotherapy, SU concomitant therapy, and TZD concomitant therapy [see "4.(iii).B.(2) Efficacy"] and the safety of teneligliptin is acceptable [see "4.(iii).B.(3) Safety"]. Therefore, there is no problem with the indications of teneligliptin monotherapy, SU concomitant therapy, and TZD concomitant therapy.

4.(iii).B.(5) Dosage and administration
4.(iii).B.(5).1) Dosage regimen
Although teneligliptin was always administered before breakfast in Japanese clinical studies, the dosing frequency of teneligliptin specifies once daily administration without specifying the time of day of the administration. PMDA asked the applicant to explain the appropriateness of this dosage regimen.

The applicant responded as follows:
In the clinical pharmacology study in patients with type 2 diabetes mellitus (Study 3000-A12), the concentration of active plasma GLP-1 in the 20 mg group increased significantly compared with the placebo group, regardless of whether teneligliptin was administered after breakfast, after lunch, or after supper, and blood glucose level after breakfast, after lunch, and after supper as well as fasting blood glucose level decreased significantly compared with the placebo group, demonstrating that once daily administration was sufficient for achieving improved blood glucose control. In the above study, when teneligliptin 20 mg was administered orally once daily before breakfast for 4 weeks, DPP-4 inhibition rate at 24 hours after administration (14.5 hours after supper) was 61.8%, which was similar to the rate in the 10 mg group before supper in the same study (61.7%). After supper, the blood glucose lowering effect in the 10 mg group was similar to that in the 20 mg group. These results suggested that the blood glucose lowering effect was expected to remain even at 24 hours after 20 mg administration, i.e., after breakfast on the next day, without decrease in the effect. As regards the effect of food intake, delayed absorption of teneligliptin was suggested in Study 3000-A13 which investigated the effect of food intake using the proposed formulation. However, when the concentration of unchanged plasma teneligliptin under steady state after fasting administration or postprandial administration was simulated from this study, the results suggested that food intake did not significantly affect the AUC of teneligliptin over 24 hours and the trough concentration under the steady state. From these results, the applicant considered that food intake affects are minimal in the pharmacokinetics of

teneligliptin.

On the basis of the above results, the applicant considers that teneligliptin, administered at any time in a day, is expected to be equally effective as once daily administration before breakfast.

PMDA considers as follows:
Based on the results of Study 3000-A12 and the results of the studies on the efficacy of monotherapy, SU concomitant therapy, and TZD concomitant therapy (phase III studies) in which teneligliptin was administered once daily [see Tables 20, 23, 27], it is appropriate to administer teneligliptin once daily. As regards the timing of administration, teneligliptin was administered only before breakfast in the 3 Japanese phase III studies described above, but there are no major problems in the applicant's explanation that a glucose lowering effect is expected regardless of the time of day of the administration, since the relationship between DPP-4 inhibition rate and the glucose lowering effect demonstrated in Study 3000-A12 suggests that the efficacy does not decrease even at 24 hours after administration. However, whether or not the timing of administration affects the control of blood glucose level was not investigated in clinical studies, and therefore PMDA considers it necessary to collect information on the relationship between the time of day of administration and efficacy via post-marketing surveillance.

4.(iii).B.(5).2) Dose
PMDA considers as follows:
Results of the phase II confirmatory study (Study 3000-A4), which was conducted in placebo group, 10 mg group, 20 mg group, and 40 mg group, showed that there was a significant dose-response relationship in the change in HbA1c at Week 12 of treatment period from baseline [see Table 17]; 2-hour postprandial blood glucose and the percentage of patients achieving HbA1c level of <6.5% tended to improve in the 20 mg group and 40 mg group compared with the 10 mg group [see Table 18]; the incidence of adverse drug reactions was 7.5% in the placebo group, 4.8% in the 10 mg group, 2.5% in the 20 mg group, and 13.6% in the 40 mg group, and hypoglycemia, albeit mild, was observed in 3 subjects (4 events) in the placebo group (2 events in 2 subjects were classified as adverse drug reactions), no subject in the 10 mg group, 1 subject (1 event) in the 20 mg group, and 3 subjects (3 events) in the 40 mg group (all events were classified as adverse drug reactions); and teneligliptin 20 mg was effective in all dosage regimens: the monotherapy, SU concomitant therapy, and TZD concomitant therapy [see Tables 20, 23, 27]. On the basis of these results, it is appropriate to select 20 mg as the usual dose.

The applicant explained the efficacy and safety when teneligliptin dose is increased to 40 mg in patients with insufficient response to 20 mg, as follows:
In the phase III studies (Study 3000-A6, A7) and the long-term treatment study (Study 3000-A8), teneligliptin dose was to be increased to 40 mg if HbA1c met the criteria for dose increase during 20 mg administration, to investigate the efficacy of teneligliptin 40 mg. In these 3 studies, the dose was increased to 40 mg in 45.9% (290 of 632 patients) of patients. Of 275 patients with HbA1c data available at 12 weeks after the dose increase, 49.1% (135 of 275 patients) showed a decrease in HbA1c from the level before dose increase and 30.9% (85 of 275 patients) showed a ≥0.3% decrease in HbA1c from the level before dose increase. HbA1c level decreased to <7.0% at 12 weeks after dose increase in 15.6% (35 of 224 patients) of patients. Fasting blood glucose decreased from the level observed before dose increase in 50.5% (139 of 275 patients) of patients. Regarding safety after dose increase, comparison of the incidence of adverse events for 12 weeks before and after teneligliptin dose increase to 40 mg in the integrated analysis of the Japanese long-term treatment studies [Table 42] showed that the incidence was 63.4% (184 of 290 patients) before dose increase and 73.8% (214 of 290 patients) after dose increase, the latter being slightly higher, although not markedly. Adverse events, classified by system organ class, that tended to show a higher incidence after the dose increase than before were "eye disorders", "gastrointestinal disorders", and "musculoskeletal and connective tissue disorders," but the incidence of any

specific events in each system organ class did not show tendency of increase after the dose increase. There was no tendency of marked increase in the incidence of hypoglycemia, either. Regarding severity, the incidence of mild adverse events was higher after the dose increase than before the dose increase, whereas the incidences of moderate and severe adverse events were not different between before and after the dose increase. There was no difference between before and after dose increase in the incidence of serious adverse events or adverse events leading to study drug discontinuation.

Table 42. Occurrence of adverse events before and after dose increase[a)]
(integrated analysis of Japanese long-term treatment studies)

		Before dose increase (n = 290)	After dose increase (n = 290)
All adverse events		63.4 (184)	73.8 (214)
Severity	Mild	60.0 (174)	70.0 (203)
	Moderate	3.1 (9)	2.8 (8)
	Severe	0.3 (1)	1.0 (3)
Serious adverse events		1.4 (4)	2.4 (7)
Adverse events leading to treatment discontinuation		0.7 (2)	2.8 (8)
Hypoglycaemia		1.4 (4)	1.7 (5)
SOC “gastrointestinal disorders”		9.3 (27)	12.4 (36)
SOC “skin and subcutaneous tissue disorders”		9.7 (28)	8.6 (25)
SOC “musculoskeletal and connective tissue disorders”		11.4 (33)	15.2 (44)
SOC “eye disorders”		3.4 (10)	6.2 (18)
SOC “investigations”		26.2 (76)	26.9 (78)
SOC “hepatobiliary disorders”		1.4 (4)	2.1 (6)

Incidence % (No. of subjects with event), MedDRA/J ver.13.1

a) Each of the events that continued in the study from 12 weeks before dose increase or at the time of dose increase was counted as 1 case.

The above results showed that, in patients with insufficient response to 20 mg, dose increase to 40 mg resulted in an improvement in blood glucose control and that there was no significant change in safety between before and after dose increase. Therefore, the applicant considers that dose increase to 40 mg has a clinical significance. Cautions are provided in the package insert (draft) that the dose increase to 40 mg should be done only if 20 mg is not sufficiently effective and that patient condition should be closely monitored over time after the dose increase.

PMDA considers as follows:
Taking account of the results of the 3 phase III studies (Study 3000-A6 to A8), there are no major problems in increasing the dose to 40 mg as appropriate, provided that the necessity of the dose increase is judged carefully based on thorough observation of the blood glucose control and safety of the patient receiving teneligliptin 20 mg. For the safety of dose increase to 40 mg in patients with renal or hepatic impairment, see “4.(iii).B.(6).1) Patients with renal impairment” and “4.(iii).B.(6).2) Patients with hepatic impairment.”

4.(iii).B.(6) Special populations

4.(iii).B.(6).1) Patients with renal impairment

PMDA asked the applicant about the safety in patients with renal impairment.

The applicant responded as follows:
Occurrence of adverse events in Japanese clinical studies was investigated in subjects with different severities of renal impairment (normal, Ccr ≥ 80 mL/min; mild, 50 ≤ Ccr <

80 mL/min; moderate, 30 ≤ Ccr < 50 mL/min; severe, Ccr < 30 mL/min). Subjects with severe renal impairment (Ccr < 30 mL/min) were not enrolled in Japanese clinical studies. Results of the integrated analysis of the Japanese double-blind studies (placebo group, 20 mg group, 40 mg group) showed that there were no major differences, among subject groups with different severity of renal impairment, in the incidence of adverse events, serious adverse events, adverse events leading to treatment discontinuation, adverse events by system organ class, or in the incidence of hypoglycemia [Table 43].

Table 43. Occurrence of adverse events by baseline renal function[a)] (Integrated analysis of Japanese double-blind studies: 12-week administration in placebo group, 20 mg group, and 40 mg group)

	Normal			Mild impairment			Moderate impairment	
	Placebo group (n = 327)	20 mg group (n = 293)	40 mg group (n = 95)	Placebo group (n = 96)	20 mg group (n = 81)	40 mg group (n = 33)	Placebo group (n = 5)	20 mg group (n = 3)
All adverse events	56.6 (185)	60.8 (178)	54.7 (52)	56.3 (54)	59.3 (48)	57.6 (19)	40.0 (2)	33.3 (1)
Serious adverse events	2.4 (8)	0.7 (2)	0.0 (0)	0.0 (0)	2.5 (2)	0.0 (0)	20.0 (1)	0.0 (0)
Adverse events leading to treatment discontinuation	2.4 (8)	1.7 (5)	2.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)	20.0 (1)	0.0 (0)
Hypoglycaemia	1.5 (5)	1.7 (5)	1.1 (1)	2.1 (2)	1.2 (1)	6.1 (2)	0.0 (0)	0.0 (0)
SOC “gastrointestinal disorders”	8.0 (26)	11.6 (34)	12.6 (12)	13.5 (13)	13.6 (11)	15.2 (5)	20.0 (1)	0.0 (0)
SOC “skin and subcutaneous tissue disorders”	1.5 (5)	5.5 (16)	5.3 (5)	7.3 (7)	9.9 (8)	6.1 (2)	40.0 (2)	0.0 (0)
SOC “musculoskeletal and connective tissue disorders”	5.5 (18)	10.2 (30)	13.7 (13)	10.4 (10)	13.6 (11)	12.1 (4)	0.0 (0)	33.3 (1)
SOC “investigations”	20.2 (66)	16.0 (47)	8.4 (8)	13.5 (13)	16.0 (13)	9.1 (3)	40.0 (2)	0.0 (0)
SOC “hepatobiliary disorders”	0.3 (1)	0.7 (2)	1.1 (1)	0.0 (0)	2.5 (2)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence % (No. of subjects with event), MedDRA/J ver.13.1

a) Grading of renal impairment by Cockcroft-Gault equation: normal, Ccr ≥ 80 mL/min; mild impairment, 50 ≤ Ccr < 80 mL/min; moderate impairment, 30 ≤ Ccr < 50 mL/min

Similarly, the integrated analysis of the Japanese long-term treatment studies did not show significant difference in the incidence of adverse events among subject groups with different severity of renal impairment [Table 44]. Investigation of the occurrence of hypoglycemia in SU concomitant therapy (integrated analysis of SU concomitant group in Studies 3000-A6 and 3000-A8 combined) showed that the incidence was 9.7% (21 of 216 subjects) in subjects with normal renal function, 14.5% (9 of 62 subjects) in subjects with mild renal impairment, and 0.0% (0 of 2 subjects) in subjects with moderate renal impairment, showing no tendency of increase in subjects with renal impairment.

Table 44. Occurrence of adverse events by baseline renal function[a)]
(integrated analysis of Japanese long-term treatment studies)

	Normal		Mild impairment		Moderate impairment	
	P/T group (n = 143)	T/T group (n = 346)	P/T group (n = 49)	T/T group (n = 89)	P/T group (n = 1)	T/T group (n = 4)
All adverse events	92.3 (132)	91.3 (316)	93.9 (46)	91.0 (81)	100.0 (1)	100.0 (4)
Serious adverse events	2.8 (4)	6.4 (22)	2.0 (1)	10.1 (9)	0.0 (0)	0.0 (0)
Adverse events leading to treatment discontinuation	4.9 (7)	5.2 (18)	2.0 (1)	6.7 (89)	0.0 (0)	0.0 (0)
Hypoglycaemia	5.6 (8)	5.8 (20)	10.2 (5)	5.6 (5)	0.0 (0)	0.0 (0)
SOC “gastrointestinal disorders”	21.7 (31)	30.1 (104)	22.4 (11)	38.2 (34)	0.0 (0)	25.0 (1)
SOC “skin and subcutaneous tissue disorders”	16.1 (23)	17.9 (62)	14.3 (7)	14.6 (13)	0.0 (0)	0.0 (0)
SOC “musculoskeletal and connective tissue disorders”	17.5 (25)	24.0 (83)	18.4 (9)	29.2 (26)	0.0 (0)	0.0 (0)
SOC “investigations”	30.8 (44)	40.8 (141)	40.8 (20)	46.1 (41)	0.0 (0)	25.0 (1)
SOC “hepatobiliary disorders”	4.2 (6)	3.5 (12)	2.0 (1)	3.4 (3)	0.0 (0)	0.0 (0)

Incidence % (No. of subjects with event), MedDRA/J ver.13.1

a) Grading of renal impairment by Cockcroft-Gault equation: normal, Ccr ≥ 80 mL/min; mild impairment, 50 ≤ Ccr < 80 mL/min; moderate impairment, 30 ≤ Ccr < 50 mL/min

PMDA asked the applicant to explain the safety for the case of teneligliptin dose increase to 40 mg in patients with renal impairment.

The applicant responded as follows:
In the long-term treatment study, teneligliptin dose was increased to 40 mg in 241 patients with normal renal function, 47 patients with mild renal impairment, and 2 patients with moderate renal impairment. The occurrence of adverse events after teneligliptin dose increase to 40 mg did not show any significant difference between patients with mild renal impairment and patients with normal function in each treatment group [Table 45]. In patients with mild renal impairment, gastritis (1 patient) was reported as a serious adverse event, which was judged as “not related” to the study drug. Two patients with moderate renal impairment developed adverse events after teneligliptin dose was increased to 40 mg: 1 patient (glimepiride concomitant group in Study 3000-A8) developed cheilitis and the 1 patient (T/T group of Study 3000-A7) developed blood urine present/protein urine present. Both events were classified as mild in severity and as “not related” to the study drug.

Table 45. Occurrence of adverse events by baseline renal function[a)]
(long-term treatment study: patients with dose increase to 40 mg)

	Renal function	3000-A6 (SU concomitant)		3000-A7 (TZD concomitant)		3000-A8	
		P/T group[b)]	T/T group	P/T group[b)]	T/T group	Monotherapy group	Glimepiride concomitant group
		n = 64	n = 65	n = 27	n = 30[c)]	n = 55	n = 47[c)]
All adverse events	Normal	92.2 (47/51)	87.8 (43/49)	90.9 (20/22)	74.1 (20/27)	75.0 (36/48)	84.1 (37/44)
	Mild impairment	84.6 (11/13)	81.3 (13/16)	80.0 (4/5)	66.7 (2/3)	85.7 (6/7)	100.0 (3/3)
Serious adverse events	Normal	0.0 (0/51)	4.1 (2/49)	4.5 (1/22)	7.4 (2/27)	2.1 (1/48)	4.5 (2/44)
	Mild impairment	0.0 (0/13)	0.0 (0/16)	0.0 (0/5)	0.0 (0/3)	14.3 (1/7)	0.0 (0/3)
Adverse events leading to treatment discontinuation	Normal	3.9 (2/51)	4.1 (2/49)	4.5 (1/22)	7.4 (2/27)	0.0 (0/48)	4.5 (2/44)
	Mild impairment	0.0 (0/13)	6.3 (1/16)	0.0 (0/5)	0.0 (0/3)	0.0 (0/7)	0.0 (0/3)
Hypoglycaemia	Normal	5.9 (3/51)	4.1 (2/49)	0.0 (0/22)	0.0 (0/27)	0.0 (0/48)	4.5 (2/44)
	Mild impairment	7.7 (1/13)	0.0 (0/16)	0.0 (0/5)	0.0 (0/3)	14.3 (1/7)	0.0 (0/3)
SOC “gastrointestinal disorders”	Normal	15.7 (8/51)	8.2 (4/49)	18.2 (4/22)	25.9 (7/27)	16.7 (8/48)	18.2 (8/44)
	Mild impairment	7.7 (1/13)	18.8 (3/16)	40.0 (2/5)	0.0 (0/3)	28.6 (2/7)	33.3 (1/3)
SOC “skin and subcutaneous tissue disorders”	Normal	21.6 (11/51)	18.4 (9/49)	0.0 (0/22)	14.8 (4/27)	12.5 (6/48)	9.1 (4/44)
	Mild impairment	7.7 (1/13)	6.3 (1/16)	0.0 (0/5)	0.0 (0/3)	14.3 (1/7)	0.0 (0/3)
SOC “musculoskeletal and connective tissue disorders”	Normal	15.7 (8/51)	20.4 (10/49)	22.7 (5/22)	7.4 (2/27)	16.7 (8/48)	15.9 (7/44)
	Mild impairment	7.7 (1/13)	43.8 (7/16)	20.0 (1/5)	33.3 (1/3)	28.6 (2/7)	33.3 (1/3)
SOC “investigations”	Normal	35.3 (18/51)	32.7 (16/49)	18.2 (4/22)	40.7 (11/27)	33.3 (16/48)	45.5 (20/44)
	Mild impairment	46.2 (6/13)	43.8 (7/16)	0.0 (0/5)	0.0 (0/3)	42.9 (3/7)	33.3 (1/3)
SOC “hepatobiliary disorders”	Normal	2.0 (1/51)	4.1 (2/49)	13.6 (3/22)	0.0 (0/27)	2.1 (1/48)	2.3 (1/44)
	Mild impairment	0.0 (0/13)	0.0 (0/16)	0.0 (0/5)	0.0 (0/3)	14.3 (1/7)	0.0 (0/3)

Incidence % (No. of subjects with event/No. of subjects in subgroup), MedDRA/J ver.13.1

a) Grading of renal impairment by Cockcroft-Gault equation: normal, Ccr ≥ 80 mL/min; mild impairment, 50 ≤ Ccr < 80 mL/min; moderate impairment, 30 ≤ Ccr < 50 mL/min

b) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period). Each of the events that continued from the placebo treatment period through the double-blind period was counted as 1 case.

c) Except 1 patient with moderate renal impairment

Thus, although the number of patients studied was limited, there was no significant difference in the occurrence of adverse events after dose increase to 40 mg among patients with different levels of renal impairment severity, suggesting that there is no significant safety problem in

administering teneligliptin 40 mg to patients with renal impairment.

PMDA considers as follows:
Results of the Japanese clinical studies have demonstrated that there are no major differences in the occurrence of adverse events among subjects with different levels of renal impairment severity. Also, results of the long-term treatment studies have shown that there is no major difference in the occurrence of adverse events after teneligliptin dose increase to 40 mg among subjects with different levels of renal impairment severity. However, in the Japanese clinical studies, only a limited number of patients with moderate renal impairment were available, and none of patients with severe renal impairment were studied. In addition, the long-term safety in these patients after dose increase to 40 mg was not evaluated. Therefore, it is considered necessary to continue to collect information on the safety in patients with renal impairment via post-marketing surveillance.

4.(iii).B.(6).2) Patients with hepatic impairment

PMDA asked the applicant to explain the safety of teneligliptin in patients with hepatic impairment.

The applicant responded as follows:
Results of the integrated analysis of the Japanese double-blind studies (placebo group, 20 mg group, 40 mg group) showed that there was no marked difference in the occurrence of adverse events between subjects with and without concurrent disease classified as "hepatobiliary disorders" in the system organ class at screening, and the incidence of adverse events did not show any dose-dependent increase in patients with hepatic impairment [Table 46]. Similarly, results of the integrated analysis of the Japanese long-term treatment studies did not show major differences in any treatment group in the incidence of all adverse events, serious adverse events, adverse events classified by system organ class, or hypoglycemia between subjects with and without concurrent hepatobiliary disorders [Table 47].

Table 46. Occurrence of adverse events by presence or absence of "hepatobiliary disorders" (system organ class) at screening (integrated analysis of Japanese double-blind studies)

	Without concurrent hepatobiliary disorders			With concurrent hepatobiliary disorders		
	Placebo group (n = 269)	20 mg group (n = 242)	40 mg group (n = 101)	Placebo group (n = 159)	20 mg group (n = 135)	40 mg group (n = 27)
All adverse events	55.0 (148)	59.1 (143)	56.4 (57)	58.5 (93)	62.2 (84)	51.9 (14)
Serious adverse events	1.9 (5)	0.4 (1)	0.0 (0)	2.5 (4)	2.2 (3)	0.0 (0)
Adverse events leading to treatment discontinuation	2.2 (6)	1.2 (3)	1.0 (1)	1.9 (3)	1.5 (2)	3.7 (1)
Hypoglycaemia	1.5 (4)	2.1 (5)	2.0 (2)	1.9 (3)	0.7 (1)	3.7 (1)
SOC "gastrointestinal disorders"	8.9 (24)	12.4 (30)	14.9 (15)	10.1 (16)	11.1 (15)	7.4 (2)
SOC "skin and subcutaneous tissue disorders"	2.2 (6)	6.2 (15)	6.9 (7)	5.0 (8)	6.7 (9)	0.0 (0)
SOC "musculoskeletal and connective tissue disorders"	7.1 (19)	9.9 (24)	11.9 (12)	5.7 (9)	13.3 (18)	18.5 (5)
SOC "investigations"	16.0 (43)	15.3 (37)	7.9 (8)	23.9 (38)	17.0 (23)	11.1 (3)
SOC "hepatobiliary disorders"	0.4 (1)	1.7 (4)	1.0 (1)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence % (No. of subjects with event), MedDRA/J ver.13.1

In the integrated analysis of the Japanese long-term treatment studies, the incidence of adverse events leading to study drug discontinuation in the T/T group of the monotherapy was 7.1% (4 of

56 subjects) in subject who had concurrent hepatobiliary disorders and 0.0% (0 of 95 subjects) in subjects who did not, showing a tendency of a higher incidence in subjects with concurrent hepatobiliary disorders, but there was no tendency of occurrence of any specific events.

Table 47. Occurrence of adverse events by presence or absence of "hepatobiliary disorders" (system organ class) at screening (integrated analysis of Japanese long-term treatment studies)

	Without concurrent hepatobiliary disorders		With concurrent hepatobiliary disorders	
	P/T group (n = 120)	T/T group (n = 276)	P/T group (n = 73)	T/T group (n = 163)
All adverse events	91.7 (110)	90.9 (251)	94.5 (69)	92.0 (150)
Serious adverse events	3.3 (4)	6.5 (18)	1.4 (1)	8.0 (13)
Adverse events leading to treatment discontinuation	5.0 (6)	5.8 (16)	2.7 (2)	4.9 (8)
Hypoglycaemia	5.0 (6)	6.2 (17)	9.6 (7)	4.9 (8)
SOC "gastrointestinal disorders"	18.3 (22)	29.3 (81)	27.4 (20)	35.6 (58)
SOC "skin and subcutaneous tissue disorders"	12.5 (15)	16.7 (46)	20.5 (15)	17.8 (29)
SOC "musculoskeletal and connective tissue disorders"	16.7 (20)	22.8 (63)	19.2 (14)	28.2 (46)
SOC "investigations"	28.3 (34)	40.2 (111)	41.1 (30)	44.2 (72)
SOC "hepatobiliary disorders"	4.2 (5)	4.0 (11)	2.7 (2)	2.5 (4)

Incidence in % (No. of subjects with event), MedDRA/J ver.13.1

PMDA asked the applicant to explain the safety of teneligliptin dose increase to 40 mg in patients with hepatic impairment.

The applicant responded as follows:
Among patients in whom teneligliptin dose was increased to 40 mg in the long-term treatment studies, 109 patients had concurrent hepatobiliary disorders. In the long-term treatment studies, there was no tendency of marked difference in the occurrence of adverse events after dose increase to 40 mg between patients with or without concurrent hepatobiliary disorders [Table 48].

Table 48. Occurrence of adverse events by presence or absence of “hepatobiliary disorders” (system organ class) at screening (long-term treatment studies: patients with dose increase to 40 mg)

	Concurrent hepatobiliary disorders	3000-A6 (SU concomitant)		3000-A7 (TZD concomitant)		3000-A8	
		P/T group[a)]	T/T group	P/T group[a)]	T/T group	Mono-therapy group	Glimepiride concomitant group
		n = 64	n = 65	n = 27	n = 31	n = 55	n = 48
All adverse events	No	88.2 (30/34)	82.5 (33/40)	84.2 (16/19)	76.0 (19/25)	78.9 (30/38)	84.0 (21/25)
	Yes	93.3 (28/30)	92.0 (23/25)	100.0 (8/8)	66.7 (4/6)	70.6 (12/17)	87.0 (20/23)
Serious adverse events	No	0.0 (0/34)	2.5 (1/40)	5.3 (1/19)	4.0 (1/25)	5.3 (2/38)	4.0 (1/25)
	Yes	0.0 (0/30)	4.0 (1/25)	0.0 (0/8)	16.7 (1/6)	0.0 (0/17)	4.3 (1/23)
Adverse events leading to treatment discontinuation	No	5.9 (2/34)	5.0 (2/40)	5.3 (1/19)	4.0 (1/25)	0.0 (0/38)	4.0 (1/25)
	Yes	0.0 (0/30)	4.0 (1/25)	0.0 (0/8)	16.7 (1/6)	0.0 (0/17)	4.3 (1/23)
Hypoglycaemia	No	5.9 (2/34)	5.0 (2/40)	0.0 (0/19)	0.0 (0/25)	2.6 (1/38)	8.0 (2/25)
	Yes	6.7 (2/30)	0.0 (0/25)	0.0 (0/8)	0.0 (0/6)	0.0 (0/17)	0.0 (0/23)
SOC “gastrointestinal disorders”	No	8.8 (3/34)	10.0 (4/40)	15.8 (3/19)	24.0 (6/25)	21.1 (8/38)	20.0 (5/25)
	Yes	20.0 (6/30)	12.0 (3/25)	37.5 (3/8)	16.7 (1/6)	11.8 (2/17)	21.7 (5/23)
SOC “skin and subcutaneous tissue disorders”	No	17.6 (6/34)	17.5 (7/40)	0.0 (0/19)	12.0 (3/25)	15.8 (6/38)	8.0 (2/25)
	Yes	20.0 (6/30)	12.0 (3/25)	0.0 (0/8)	16.7 (1/6)	5.9 (1/17)	8.7 (2/23)
SOC “musculoskeletal and connective tissue disorders”	No	14.7 (5/34)	22.5 (9/40)	21.1 (4/19)	8.0 (2/25)	18.4 (7/38)	16.0 (4/25)
	Yes	13.3 (4/30)	32.0 (8/25)	25.0 (2/8)	16.7 (1/6)	17.6 (3/17)	17.4 (4/23)
SOC “investigations”	No	35.3 (12/34)	30.0 (12/40)	15.8 (3/19)	40.0 (10/25)	34.2 (13/38)	52.0 (13/25)
	Yes	40.0 (12/30)	44.0 (11/25)	12.5 (1/8)	33.3 (2/6)	35.3 (6/17)	34.8 (8/23)
SOC “hepatobiliary disorders”	No	2.9 (1/34)	5.0 (2/40)	15.8 (3/19)	0.0 (0/25)	5.3 (2/38)	0.0 (0/25)
	Yes	0.0 (0/30)	0.0 (0/25)	0.0 (0/8)	0.0 (0/6)	0.0 (0/17)	4.3 (1/23)

Incidence % (No. of subjects with event/No. of subjects in subgroup), MedDRA/J ver.13.1

a) Data obtained during the teneligliptin administration period over 40 weeks (Week 12 to 52 in treatment period). Each of the events that continued from the placebo treatment period in the double-blind period was counted as 1 case.

On the basis of these results, the applicant considers it unnecessary to decrease teneligliptin dose, or provide any particular caution, in patients with mild or moderate hepatic impairment. However, since safety in patients with severe hepatic impairment was not investigated in clinical studies, cautions will be provided in the Careful Administration section in the Precautions and in the

Patients with Hepatic Impairment section in the Pharmacokinetics of the package insert (draft).

PMDA considers as follows:
Results of the Japanese clinical studies have demonstrated that there are no major differences in the occurrence of adverse events between patients with and without diseases classified as "hepatobiliary disorders" in the system organ class at screening. Also, results of the long-term treatment studies have shown that there is no major difference in the occurrence of adverse events after teneligliptin dose increase to 40 mg between patients with and without concurrent hepatobiliary disorders. However, in the Japanese clinical studies, patients were excluded if transaminase level at the start of the run-in period exceeded 2.5 times the upper limit of the reference range. Thus, only a limited number of patients with hepatic impairment were studied and especially, none of the patients with severe hepatic impairment were investigated in the Japanese clinical studies and, in addition, long-term safety after dose increase to 40 mg was not studied. Therefore, PMDA considers it necessary to continue to collect information in patients with hepatic impairment via post-marketing surveillance.

4.(iii).B.(6).3) Elderly patients
The applicant explained as follows:
In the integrated analysis of the Japanese double-blind studies (placebo group, 20 mg group, 40 mg group), the occurrence of adverse events by age group (<65 years, ≥65 years) was as shown in Table 49. There was no significant difference in the occurrence of adverse events between subjects aged <65 years and subjects aged ≥65 years, regardless of the treatment group (placebo group, 20 mg group, 40 mg group), suggesting that age of patients does not affect the safety of teneligliptin.

Table 49. Occurrence of adverse events by age group (<65 years, ≥65 years) (integrated analysis of Japanese double-blind studies)

	< 65 years			≥ 65 years		
	Placebo group (n = 281)	20 mg group (n = 262)	40 mg group (n = 92)	Placebo group (n = 147)	20 mg group (n = 115)	40 mg group (n = 36)
All adverse events	55.5 (156)	61.1 (160)	50.0 (46)	57.8 (85)	58.3 (67)	69.4 (25)
All adverse drug reactions	3.9 (11)	6.9 (18)	10.9 (10)	6.1 (9)	4.3 (5)	5.6 (2)
Serious adverse events	1.8 (5)	1.1 (3)	0.0 (0)	2.7 (4)	0.9 (1)	0.0 (0)
Adverse events leading to study drug discontinuation	2.1 (6)	1.9 (5)	1.1 (1)	2.0 (3)	0.0 (0)	2.8 (1)
Hypoglycaemia	1.8 (5)	1.9 (5)	2.2 (2)	1.4 (2)	0.9 (1)	2.8 (1)
SOC "gastrointestinal disorders"	8.5 (24)	12.6 (33)	13.0 (12)	10.9 (16)	10.4 (12)	13.9 (5)
SOC "skin and subcutaneous tissue disorders"	1.8 (5)	6.5 (17)	4.3 (4)	6.1 (9)	6.1 (7)	8.3 (3)
SOC "musculoskeletal and connective tissue disorders"	6.4 (18)	9.9 (26)	14.1 (13)	6.8 (10)	13.9 (16)	11.1 (4)
SOC "investigations"	19.9 (56)	17.9 (47)	5.4 (5)	17.0 (25)	11.3 (13)	16.7 (6)
SOC "hepatobiliary disorders"	0.4 (1)	0.4 (1)	0.0 (0)	0.0 (0)	2.6 (3)	2.8 (1)

Incidence % (No. of subjects with event), MedDRA/J ver.13.1

In the long-term treatment studies, the incidence of adverse events in T/T group was similar between subjects aged <65 years and subjects aged ≥65 years, while the incidences of serious adverse events and adverse events leading to treatment discontinuation in T/T group tended to be

higher in subjects aged ≥65 years compared with subjects aged <65 years. In P/T group, no significant differences were observed in the incidence between subjects aged <65 years and subjects aged ≥65 years. Examination of the incidence of hypoglycemia in SU concomitant therapy (integrated analysis of SU concomitant therapy group in Studies 3000-A6 and 3000-A8) showed that the incidence was 11.2% (22 of 196 subjects) in subjects aged <65 years and 9.5% (8 of 84 subjects) in subjects aged ≥65 years, showing no tendency of increase in the older age group.

Table 50. Occurrence of adverse events by age group (<65 years, ≥65 years) (integrated analysis of Japanese long-term treatment studies)

	< 65 years		≥ 65 years	
	P/T group (n = 121)	T/T group (n = 311)	P/T group (n = 72)	T/T group (n = 128)
All adverse events	94.2 (114)	90.7 (282)	90.3 (65)	93.0 (119)
Serious adverse events	2.5 (3)	5.1 (16)	2.8 (2)	11.7 (15)
Adverse events leading to treatment discontinuation	4.1 (5)	4.5 (14)	4.2 (3)	7.8 (10)
Hypoglycaemia	5.8 (7)	7.1 (22)	8.3 (6)	2.3 (3)
SOC “gastrointestinal disorders”	23.1 (28)	29.9 (93)	19.4 (14)	35.9 (46)
SOC “skin and subcutaneous tissue disorders”	14.9 (18)	17.7 (55)	16.7 (12)	15.6 (20)
SOC “musculoskeletal and connective tissue disorders”	19.8 (24)	22.5 (70)	13.9 (10)	30.5 (39)
SOC “investigations”	35.5 (43)	43.1 (134)	29.2 (21)	38.3 (49)
SOC “hepatobiliary disorders”	4.1 (5)	4.2 (13)	2.8 (2)	1.6 (2)

Incidence % (No. of subjects with event), MedDRA/J ver.13.1

PMDA considers as follows:
Although no specific tendency was observed in the relationship between age and the occurrence of adverse events in long-term administration in Japanese studies, since elderly patients often have reduced physiological functions, PMDA considered appropriate to provide caution in Use in the Elderly section of the package insert that teneligliptin should be administered while closely monitoring the patient condition. In addition, it will be necessary to continue to collect information on safety in elderly patients via post-marketing surveillance.

4.(iii).B.(7) Post-marketing surveillance plan
The applicant explained the post-marketing surveillance plan as follows:
The applicant plans to conduct a specified use-results survey on long-term use (observation period, [redacted] years; survey period, [redacted] years; target sample size of [redacted]) to collect information on the safety and efficacy under the routine use of teneligliptin. The sample size has to be 3000 or more in order to detect at least 1 case with an unknown adverse drug reaction with an incidence of 0.1%, at a probability of at least 95%. Assuming that [redacted]-year treatment duration rate is [redacted]%, [redacted]-year treatment duration rate is [redacted]%, and [redacted]-year treatment duration rate is [redacted]%, the samples size is set at [redacted] so that approximately [redacted] patients continue treatment with teneligliptin for [redacted] years. The applicant plans to evaluate the safety and efficacy in elderly patients, patients with renal impairment, and patients with hepatic impairment, by extracting pertinent cases from the above survey. As regards the survey period, the “Guideline for Clinical Evaluation of Oral Hypoglycemic Agents” (PFSB/ELD Notification No. 0709-1 dated July 9, 2010) cites a published report that investigated the frequency of cardiovascular diseases during the observation period of 2.5 years or longer, which states that “the estimated annual incidence of cardiovascular diseases in Japanese patients with type 2 diabetes mellitus is about 1% to 1.5%.” Therefore, the observation period in this survey is set at [redacted] years at the maximum for each patient to allow comparison between the incidence of cardiovascular adverse events in this survey and the above report.

PMDA considers as follows:
In this survey, it is necessary to collect safety information on hypoglycemia, gastrointestinal disorder, pancreatitis, hepatic impairment etc., as well as safety and efficacy information in patients with renal impairment, patients with hepatic impairment, and elderly patients. It is also necessary to collect information on cardiovascular risks and proarrhythmic risks. PMDA is currently requesting the applicant to further refine the details of the post-marketing surveillance plan. The details of the content of the plan will be finalized, taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

To be reported later.

2. PMDA's conclusion on the results of GCP on-site inspection

To be reported later.

IV. Overall Evaluation

Based on the submitted data, PMDA concludes that the efficacy of the proposed product in patients with type 2 diabetes mellitus has been demonstrated. Also, the safety is considered acceptable, but PMDA considers it necessary to continue to collect, via post-marketing surveillance, safety information on hypoglycemia, gastrointestinal disorder, pancreatitis, hepatic impairment, etc., as well as safety and efficacy information in patients with renal impairment or with hepatic impairment and in the elderly patients.

PMDA considers that the proposed product may be approved for the indication of type 2 diabetes mellitus, if it can be concluded that there are no particular problems based on comments from the Expert Discussion.

Review Report (2)

April 5, 2012

I. Product Submitted for Registration

[Brand name]	Tenelia Tablets 20 mg
[Non-proprietary name]	Teneligliptin Hydrobromide Hydrate
[Applicant]	Mitsubishi Tanabe Pharma Corporation
[Date of application]	August 26, 2011

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

The expert advisers supported PMDA's conclusions that the efficacy of the monotherapy, SU concomitant therapy, and TZD concomitant therapy has been demonstrated.

(2) Safety

1) Hypoglycemia

PMDA considered as follows:

In the Japanese double-blind studies, the incidence of hypoglycemia was comparable between the teneligliptin group and the placebo group. The incidence was low in all dose groups, and there were no cases of severe hypoglycemia. In the long-term treatment study, the incidence of hypoglycemia did not show any tendency of increase with the increase in the treatment duration either in the monotherapy group or in the TZD concomitant therapy group, whereas the incidence in the SU concomitant therapy group was slightly higher compared with the monotherapy group and the TZD concomitant therapy group, and there was a report of hypoglycemia that resulted in the study drug discontinuation. Although the incidence of hypoglycemia did not show any tendency of increase with the dose of the SU (glimepiride) in clinical studies, PMDA considers, as with the approved DDP-4 inhibitors, it is appropriate to provide caution in the package insert that, if teneligliptin is used in concomitant with an SU, reduction of the dose of SU should be considered. Since hypoglycemia is animportant adverse drug reaction related to the long-term prognosis of patients, it is considered necessary to continue to collect information on hypoglycemia via post-marketing surveillance.

The above conclusions of PMDA were supported by the expert advisers [for post-marketing surveillance, see "(6) Post-marketing surveillance plan"].

2) QTc interval prolongation and proarrhythmic risk

PMDA considered as follows:

In the phase III study of teneligliptin, patients being treated for arrhythmia, patients with a history of ventricular tachycardia, and patients with abnormality in resting standard 12-lead ECG at the start and end of the run-in period were excluded. Therefore, QTc interval prolongation and proarrhythmic risk in these patients have not been investigated. Also, since the phase III study was started before the publication of ICH E14 guideline and, as a result, ECG evaluation was not performed according to the guideline and the timing for ECG measurement was not specified in

the phase III study, the possibility cannot be excluded that the effect of teneligliptin on QTc interval prolongation was not thoroughly investigated. In addition, taking into account that there are diabetic patients who have complications such as arrhythmia and ischemia, and that teneligliptin may be administered to such patients for a long time of period, it is deemed necessary to raise caution in administering teneligliptin to these patients and to collect information on proarrhythmic risk via post-marketing surveillance [for post-marketing surveillance, see "(6) Post-marketing surveillance plan"]. The above conclusions of PMDA were largely supported by the expert advisors.

On the basis of the above, PMDA asked the applicant to appropriately provide caution in administering teneligliptin to patients prone to QT interval prolongation and to continue to collect information on proarrhythmic risk via post-marketing surveillance.

The applicant responded as follows:
Cautions will be provided by including the descriptions of patients prone to QT interval prolongation (e.g., patients with current or past arrhythmia such as severe bradycardia, patients with cardiac disease such as congestive cardiac failure, patients with hypokalaemia) in the Careful Administration section. And it will be stated in the Important Precautions section that teneligliptin administration should preferably be avoided in patients with current or past QT interval prolongation (e.g., long QT syndrome congenital) or with a past history of Torsades de pointes because adverse drug reactions such as QT interval prolongation may occur; in the Drug-drug Interactions section that caution should be exercised in concomitant use with a drug known to induce QT interval prolongation; and in Other Precautions section that QT interval prolongation is reported in patients treated with once-daily administration of teneligliptin 160 mg. Also, the applicant plans to check for occurrence of adverse events suggestive of proarrhythmic risk via post-marketing surveillance.

PMDA accepted the response.

(3) Indications
PMDA considers that results of the Japanese clinical studies have demonstrated the efficacy of teneligliptin monotherapy, SU concomitant therapy, and TZD concomitant therapy and that the safety of teneligliptin is acceptable. Therefore, PMDA concluded that there is no problem with the indications of teneligliptin monotherapy, SU concomitant therapy, and TZD concomitant therapy.

The above conclusions of PMDA were supported by the expert advisers.

(4) Dosage and administration
PMDA considered as follows:
Taking account of the results of Study 3000-A12 and the results of the studies on the efficacy of monotherapy, SU concomitant therapy, and TZD concomitant therapy (phase III studies) where teneligliptin was administered once daily, it is considered appropriate to administer the product once daily. As regards the timing of administration, teneligliptin was administered only before breakfast in the 3 Japanese phase III studies describe above, but there are no major problems in the applicant's explanation that a glucose lowering effect is expected, since the relationship between DPP-4 inhibition rate and the glucose lowering effect demonstrated in Study 3000-A12 suggests that the efficacy does not decrease even after 24 hours of administration. However, since whether or not the timing of administration affects the control of blood glucose level was not investigated in clinical studies, it is considered necessary to collect information on the relationship between the time of day of administration and efficacy in the post-marketing surveillance.

Regarding the dose, based on the results of the 3 phase III studies (3000-A6 to A8), there

are no major problems in increasing the dose to 40 mg as appropriate, provided that the necessity of the dose increase is judged carefully based on the thorough observation of the blood glucose control and safety of the patient receiving teneligliptin 20 mg.

The above conclusions of PMDA were supported by the expert advisers [for post-marketing surveillance, see "(6) Post-marketing surveillance plan"].

(5) Special populations

1) Patients with renal impairment

PMDA considered as follows:

Results of the Japanese clinical studies have demonstrated that there are no major differences in the occurrence of adverse events among patients with different levels of renal impairment severity, and results of the long-term treatment studies have shown that there is no major difference in the occurrence of adverse events after the teneligliptin dose increase to 40 mg among patients with different levels of renal impairment severity. However, in the Japanese clinical studies, only a limited number of patients with moderate renal impairment, and none of patients with severe renal impairment, were investigated. In addition, the long-term safety in these patients after dose increase to 40 mg was not studied. From reasons such as mentioned above, it is necessary to continue to collect information on the safety in patients with renal impairment via post-marketing surveillance.

The above conclusions of PMDA were supported by the expert advisers [for post-marketing surveillance, see "(6) Post-marketing surveillance plan"].

2) Patients with hepatic impairment

PMDA considers as follows:

Results of the Japanese clinical studies have demonstrated that there are no major differences in the occurrence of adverse events between patients with or without diseases classified as "hepatobiliary disorders" in the system organ class at screening. Also, results of the long-term treatment studies have shown that there is no major difference in the occurrence of adverse events after teneligliptin dose increase to 40 mg between these patient groups. However, in the Japanese clinical studies, patients with transaminase level exceeding 2.5 times the upper limit of the reference range at the start of the run-in period were excluded. Thus, only a limited number of patients were studied and none of patients with severe hepatic impairment were investigated in the Japanese clinical studies and, in addition, long-term safety after dose increase to 40 mg was not investigated. Therefore, it is necessary to continue to collect information in patients with hepatic impairment via post-marketing surveillance.

The above conclusions of PMDA were supported by the expert advisers [for post-marketing surveillance, see "(6) Post-marketing surveillance plan"].

3) Elderly patients

PMDA considered as follows:

Although no specific tendency was observed in the relationship between age and the occurrence of adverse events in long-term administration in Japanese studies, since elderly patients often have reduced physiological functions, it is appropriate to provide caution in the Use in the Elderly section of the package insert that teneligliptin should be administered while closely monitoring the patient condition. In addition, it is necessary to continue to collect information on safety in elderly patients via post-marketing surveillance.

The above conclusions of PMDA were supported by the expert advisers [for post-marketing surveillance, see "(6) Post-marketing surveillance plan"].

(6) Post-marketing surveillance plan

There are no major problems at the current moment in conducting a specified use-results survey on long-term use (observation period, [redacted] years; survey period, [redacted] years; planned sample size of [redacted]) to collect information on the safety and efficacy under the routine use of teneligliptin. However, it is also necessary to collect safety information on hypoglycemia, gastrointestinal disorder, pancreatitis, hepatic impairment, etc., as well as safety and efficacy information in patients with renal impairment, patients with hepatic impairment, and elderly patients. It is also necessary to collect information on cardiovascular risks and proarrhythmic risks, as well as information on the relationship between the timing of administration and efficacy.

The above conclusions of PMDA were supported by the expert advisers. On the basis of the above, PMDA instructed the applicant to present a post-marketing surveillance plan (draft).

The applicant responded as follows:

Information on the following events will be collected as noteworthy adverse drug reactions/adverse events: hypoglycemia, skin and subcutaneous tissue disorders, gastrointestinal disorders, musculoskeletal and connective tissue disorders, hepatic impairment, renal impairment, cardiovascular events, proarrhythmic risk, and tumor. Safety in patients with renal or hepatic impairment and elderly patients will be evaluated by analysis of subgroups in the specified use-results survey on the long-term use. As regards cardiovascular and proarrhythmic risks, information on lipid level, blood pressure, pulse rate, body weight, and ECG will be collected, and patients who had the incidence of adverse events will be subjected to re-investigation, and their detailed information will be collected for evaluation. Also, time of day of administration will be included in the survey items to collect information on the relationship between the timing of administration and efficacy.

PMDA accepted the response.

(7) Re-test period of a drug substance

The applicant proposed the following change:

In the accelerated testing (40°C, 75% RH) of the drug substance of a process validation lot, related substances showed a tendency of increase in the content to an extent not observed before. Therefore, the re-test period of the drug substance will be changed to 18 months, the period for which data in the long-term testing have been obtained.

PMDA instructed the applicant to thoroughly investigate the cause of the newly observed tendency and accepted the proposal, taking account of the fact that the related substances that showed an increasing tendency are controlled by the specifications for the drug substance.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, flaws were detected in the description of the contract between the sponsor and the laboratory test contractor. Notwithstanding these flaws requiring improvement, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA’s conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.1-1, 5.3.3.1-2, 5.3.5.1-2, 5.3.5.1-3,

5.3.5.1-4, 5.3.5.1-5). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the following indications and dosage and administration. The re-examination period is 8 years, neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug and the product is not classified as a biological product or a specified biological product.

[Indication]	Type 2 diabetes mellitus: The drug product should be used only in patients who have not sufficiently responded to either of the following treatments. (a) Diet and/or exercise therapy alone (b) Use of sulfonylureas in addition to diet and/or exercise therapy (c) Use of thiazolidinediones in addition to diet and/or exercise therapy
[Dosage and administration]	The usual adult dosage is 20 mg of teneligliptin administered orally once daily. If efficacy is insufficient, the dose may be increased up to 40 mg once daily while closely monitoring the clinical course.