Report on the Deliberation Results

February 5, 2015

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

[Brand name]	Zafatek Tablets 50 mg
	Zafatek Tablets 100 mg
[Non-proprietary name]	Trelagliptin Succinate (JAN*)
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 7, 2014

[Results of deliberation]
In the meeting held on January 30, 2015, 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 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. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to prepare a risk management plan and implement it appropriately.

**Japanese Accepted Name (modified INN)*

Review Report

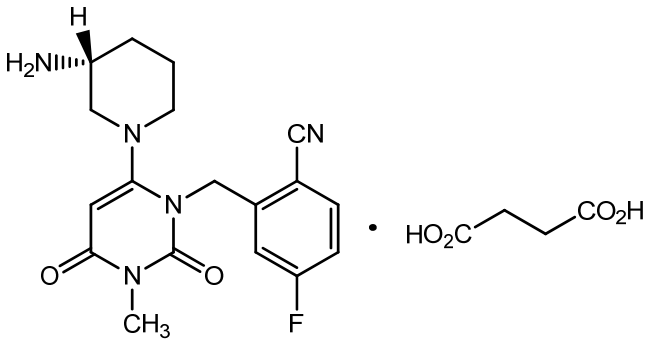
January 13, 2015

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 registration are as follows.

[Brand name]	Zafatek Tablets 50 mg Zafatek Tablets 100 mg
[Non-proprietary name]	Trelagliptin Succinate
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 7, 2014
[Dosage form/Strength]	Each tablet contains 50 or 100 mg of trelagliptin present as Trelagliptin Succinate.
[Application classification]	Prescription drug, (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{18}H_{20}FN_5O_2 \cdot C_4H_6O_4$
Molecular weight: 475.47
Chemical name: 2-({6-[(3*R*)-3-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl}methyl)-4-fluorobenzonitrile monosuccinate

[Items warranting special mention] None

[Reviewing office] Office of New Drug I

Review Results

January 13, 2015

[Brand name]	Zafatek Tablets 50 mg Zafatek Tablets 100 mg
[Non-proprietary name]	Trelagliptin Succinate
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 7, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of type 2 diabetes mellitus has been demonstrated and its safety is acceptable in view of its observed benefits. Safety issues such as hypoglycaemia, skin disorder-related adverse events and hypersensitivity, cardiovascular risk, proarrhythmic risk associated with QT/QTc interval prolongation, gastrointestinal disorder (including pancreatitis), tumor risk, immune system disorders, and infections as well as the safety profile in patients with renal or hepatic impairment and in the elderly, etc. need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication]	Type 2 diabetes mellitus
[Dosage and administration]	The usual adult dosage is 100 mg of trelagliptin orally administered once weekly.
[Conditions for approval]	The applicant is required to prepare a risk management plan and implement it appropriately.

Review Report (1)

November 10, 2014

I. Product Submitted for Registration

[Brand name]	Zafatek Tablets 50 mg Zafatek Tablets 100 mg
[Non-proprietary name]	Trelagliptin Succinate
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 7, 2014
[Dosage form/Strength]	Each tablet contains 50 or 100 mg of trelagliptin present as Trelagliptin Succinate.
[Proposed indication]	Type 2 diabetes mellitus
[Proposed dosage and administration]	The usual adult dosage is 100 mg of trelagliptin orally administered once weekly.

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

A summary of the submitted data and an outline of 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.

Zafatek Tablets 50 mg and 100 mg (hereinafter collectively referred to as "Zafatek") contain Trelagliptin Succinate (hereinafter referred to as "trelagliptin") as the active ingredient. Trelagliptin was a dipeptidyl peptidase (DPP)-4 inhibitor discovered by Takeda California, Inc., and Zafatek has been developed to allow for once-weekly administration.

The applicant has submitted a marketing application for Zafatek (trelagliptin), claiming that the efficacy and safety of trelagliptin have been confirmed in patients with type 2 diabetes mellitus.

[redacted].

In Japan, the following DPP-4 inhibitors have already been approved as daily-dose products: sitagliptin phosphate hydrate, vildagliptin, alogliptin benzoate, linagliptin, teneligliptin hydrobromide hydrate, anagliptin, and saxagliptin hydrate.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

[redacted].

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry (MS), ultraviolet-visible spectrophotometry (UV), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR), and X-ray crystallography.

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

[redacted].

[redacted].

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

[redacted].

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

The stability studies conducted on the drug substance are as shown in Table 1. Photostability data showed that the drug substance is photostable.

Table 1. Stability studies for drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	Pilot 3 batches	25°C	60%RH	Polyethylene bag (sealed)	24 months
Accelerated	Pilot 3 batches	40°C	75%RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when it is packaged in double polyethylene bags and the bags are then stored in a fiber drum at room temperature, in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003, ICH Q1E Guideline). The long-term study will be continued up to 36 months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of drug product and formulation development

The drug product is immediate release film-coated tablets, each containing 66.5 mg or 133 mg of the drug substance (50 mg or 100 mg of trelagliptin, respectively). It contains D-mannitol, microcrystalline cellulose, croscarmellose sodium, hydroxypropylcellulose, sodium stearyl fumarate, hypromellose, macrogol 6000, titanium oxide, yellow ferric oxide (for 50 mg Tablets only), and red ferric oxide as excipients.

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

[redacted].

[redacted].

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

The proposed specifications for the drug product include content, description, identification (UV), uniformity of dosage units (Test Method A), dissolution (HPLC), and assay (HPLC).

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

The stability studies conducted on the drug product are as shown in Table 2. Photostability data showed that the drug product is photostable.

[redacted]

Table 2. Stability studies for drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	Pilot 3 batches	25°C	60%RH	PTP	24 months
Accelerated	Pilot 3 batches	40°C	75%RH		6 months

[redacted]. The long-term study will be continued up to 36 months.

2.B Outline of the review by PMDA

As a result of review of the submitted data and the following considerations, PMDA concluded that the quality of the drug substance and drug product is appropriately controlled.

2.B.(1) Control strategy for drug substance

PMDA asked the applicant to explain the justification for control of the starting materials and critical intermediates.

The applicant responded as follows:

The results of spiking experiments using related substances of the individual starting materials and critical intermediates and the residual solvents have demonstrated that the critical intermediates and drug substance (unmilled) meet their respective control values. In addition, impurities related to the starting materials have been found to be eliminated during the manufacturing process if the starting materials that meet their respective control values are used. [redacted]. Furthermore, related substances increased in the critical intermediates stored under the accelerated condition, and the storage temperature is therefore changed so that the critical intermediates will be stored in a cool place not at room temperature. Based on the above, the control of the starting materials and critical intermediates is considered adequate.

PMDA accepted the applicant's response.

2.B.(2) Control of uniformity of dosage units

[redacted]. PMDA asked the applicant to explain whether blend uniformity in the manufacturing process could be secured by employing Test Method A.

The applicant responded as follows:

[redacted].

In addition, the uniformity of dosage unit was evaluated by Test Methods A and B for [redacted] batches each of both 50 and 100 mg tablets, and the results were comparable between the two tests. Therefore, evaluation of uniformity of dosage units using Test Method A is considered acceptable.

PMDA accepted the applicant's response.

[redacted]

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

As primary pharmacodynamic studies, *in vitro* studies on the inhibitory effects of Trelagliptin Succinate ("trelagliptin") and its metabolites on dipeptidyl peptidase (DPP)-4 and its related enzymes were conducted. In addition, *in vivo* studies on mechanism of action and hypoglycemic activity in diabetic animal models were conducted. As secondary pharmacodynamic studies, *in vitro* studies on effects on various enzymes, receptors, ion channels, and transporters were conducted. As safety pharmacology studies, studies on effects on cardiovascular and respiratory systems were conducted. Effects on the central nervous system were evaluated in a 4-week repeated oral dose toxicity study in rats.[5] As pharmacodynamic drug interaction studies, studies on effects of trelagliptin in combination with various oral hypoglycemic agents were conducted. The dose of trelagliptin and similar drugs are expressed in terms of free base.

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

3.(i).A.(1).1) Enzyme inhibition

(a) Inhibitory effect on DPP-4 (4.2.1.1-1)

The inhibitory effect of trelagliptin on DPP-4 was evaluated by adding a synthetic substrate to DPP-4 derived from human colon adenocarcinoma-derived Caco-2 cells. The results showed a concentration-dependent inhibition of DPP-4, with the 50% inhibitory concentration (IC_{50}) [95% confidence interval (CI)] being 5.4 [5.2, 5.7] nmol/L.

The inhibitory effect of trelagliptin on DPP-4 was evaluated by adding a synthetic substrate to human, dog, and rat plasma. The results showed a concentration-dependent inhibition of DPP-4 in human, dog, and rat plasma, with IC_{50} [95% CI] being 4.2 [4.1, 4.3], 6.2 [6.0, 6.4], and 9.7 [8.0, 11.8] nmol/L, respectively.

(b) Mode of DPP-4 inhibition (4.2.1.1-10)

The mode of DPP-4 inhibition was studied by using recombinant human DPP-4. As a result, trelagliptin inhibited DPP-4 activity in a concentration- and time-dependent manner, with an inhibition constant (Ki) of 1.5 ± 0.1 nmol/L (mean ± standard deviation [SD]). Trelagliptin competitively and reversibly inhibited DPP-4, and the dissociation half-life of trelagliptin-DPP-4 complex was approximately 30 minutes.

(c) Inhibition of DPP-4-related enzymes (4.2.1.1-2)

The Inhibitory effect of trelagliptin on rat kidney-derived DPP-II, recombinant human DPP-8, DPP-9, and fibroblast activation protein α (FAPα), and rat brain-derived prolyl endopeptidase (PEP) was evaluated. The results showed that the IC_{50} value is >100 μmol/L for all these enzymes.

(d) Inhibitory effect of trelagliptin metabolite on DPP-4 and its related enzymes (4.2.1.1-9, Reference data)

The inhibitory effect of a trelagliptin metabolite (M-I)[6] on recombinant human DPP-4 and its related enzymes (DPP-II, DPP-8, DPP-9, FAPα, PEP) was evaluated. The results showed that the IC_{50} value was 6.9 nmol/L[7] against DPP-4 and >100 μmol/L against the individual related enzymes.

3.(i).A.(1).2) Effects in various animal models

A single subcutaneous injection of streptozotocin 120 mg/kg was given to Wistar Kyoto rats (1-2 days of age) to generate non-obese type 2 diabetes mellitus model rats with impaired insulin secretion (N-STZ-1.5 rats). Effects of trelagliptin were evaluated using N-STZ-1.5 rats, obese type 2 diabetes animal models with insulin resistance (Wistar fatty rats), and *ob/ob* mice.

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5 Study for effects on hERG current was a non-GLP study (4.2.1.3-1).

6 Trifluoroacetate, *N*-demethylated trelagliptin, was used.

7 Mean (n = 2)

(a) Effects in animal model of non-obese type 2 diabetes mellitus

Single-dose study in N-STZ-1.5 rats (4.2.1.1-3)

A single oral dose of trelagliptin (0.01, 0.03, 0.1, 0.3 mg/kg) or vehicle[8] was administered to overnight-fasted male N-STZ-1.5 rats (26 weeks of age, n = 6/group) and, 1 hour later, 1 g/kg of glucose was orally loaded. As a result, the area under the plasma glucose concentration-time curve over 120 minutes after glucose load ($AUC_{0\text{-}120\ min}$) decreased in a dose-dependent manner, and a significant decrease in $AUC_{0\text{-}120\ min}$ was observed in the ≥0.1 mg/kg groups compared with the control group. In addition, the plasma insulin concentrations at 10 minutes after glucose load increased in a dose-dependent manner, and a significant increase in plasma insulin was observed in the ≥0.03 mg/kg groups compared with the control group. The plasma DPP-4 activity at 30 minutes after glucose load decreased in a dose-dependent manner, and a significant decrease in plasma DPP-4 activity was observed in the ≥0.03 mg/kg groups compared with the control group. The change in plasma active glucagon-like peptide-1 (GLP-1) concentrations from baseline to 10 minutes after glucose load increased in a dose-dependent manner, and a significant increase in the change was observed in the ≥0.1 mg/kg groups compared with the control group.

(b) Effects in obese type 2 diabetes animal model

i) Single-dose study in Wistar fatty rats (4.2.1.1-4)

A single oral dose of trelagliptin (0.01, 0.03, 0.1, 0.3 mg/kg) or vehicle[8] was administered to overnight-fasted female Wistar fatty rats (12 weeks of age, n = 6/group) and, 1 hour later, 1 g/kg of glucose was orally loaded. As a result, the area under the plasma glucose concentration-time curve over 60 minutes after glucose load ($AUC_{0\text{-}60\ min}$) decreased in a dose-dependent manner and a significant decrease in $AUC_{0\text{-}60\ min}$ was observed in the ≥0.03 mg/kg groups compared with the control group. In addition, the plasma insulin concentrations at 10 minutes after glucose load increased in a dose-dependent manner and a significant increase in plasma insulin was observed in the ≥0.1 mg/kg groups compared with the control group. The plasma DPP-4 activity at 40 minutes after administration of trelagliptin decreased in a dose-dependent manner.

ii) Inhibition of DPP-4 activity and elevation of active GLP-1 levels in *ob/ob* mice (dietary administration) (4.2.1.1-5, Reference data)

Trelagliptin (0.001%, 0.003%, 0.01%, 0.03% [w/w]) was administered in the diet for 3 days to male *ob/ob* mice (8 weeks of age, n = 5/group)[9] and the inhibition of DPP-4 activity and levels of active GLP-1 were evaluated after the end of administration. In the control group, male *ob/ob* mice (8 weeks of age, n = 5) were fed for 3 days with standard diet only. As a result, plasma DPP-4 activity decreased and plasma active GLP-1 concentrations increased both in a dose-dependent manner, and the decrease and increase were significant at all dose levels compared with the control group.

iii) Hypoglycemic effect in *ob/ob* mice (dietary administration) (4.2.1.1-6, Reference data)

Trelagliptin (0.003%, 0.03% [w/w]) was administered in the diet for 4 weeks to male *ob/ob* mice (7 weeks of age, n = 8/group)[10] and glycated hemoglobin levels and related parameters were evaluated after the end of administration. In addition, following an overnight fasting after the end of administration, fasting plasma glucose levels, triglyceride levels, and pancreatic insulin content were measured. In the control group, male *ob/ob* mice (7 weeks of age, n = 8) were fed for 4 weeks with standard diet only. As a result, the change in glycated hemoglobin levels from baseline significantly decreased in the 0.03% group compared with the control group (0.0% ± 0.4%, -0.6% ± 1.0%, and -0.9% ± 0.8% [mean ± SD] in the control, 0.003%, and 0.03% groups, respectively). The plasma insulin concentrations and pancreatic insulin content significantly increased in the 0.03% group compared with the control group. Moreover, casual plasma triglyceride levels significantly decreased in the 0.003% and 0.03% groups compared with the control group, but no effects of trelagliptin were observed on casual and fasting plasma levels of glucose and triglycerides, total plasma cholesterol, plasma free fatty acid, food consumption, or body weight.

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[8] 0.5% methylcellulose solution

[9] Dose levels of trelagliptin 0.001%, 0.003%, 0.01%, and 0.03% calculated from food consumption were 1.6, 4.8, 15.5, and 50.3 mg/kg/day, respectively.

[10] Dose levels of trelagliptin 0.003% and 0.03% calculated from food consumption were 5.7 and 51.9 mg/kg/day, respectively.

3.(i).A.(1).3) Comparison with existing DPP-4 inhibitors

(a) Comparison with alogliptin benzoate and sitagliptin phosphate (4.2.1.1-7)

The inhibitory effects of trelagliptin, alogliptin benzoate (alogliptin), and sitagliptin phosphate on DPP-4 activity was evaluated using recombinant human DPP-4. As a result, the IC_{50} values [95% CI] of trelagliptin, alogliptin, and sitagliptin phosphate against DPP-4 were 1.3 [1.1, 1.5], 5.3 [5.0, 5.7], and 16.0 [15.1, 16.9] nmol/L, respectively.

(b) Comparison of inhibition of plasma DPP-4 activity in N-STZ-1.5 rats (4.2.1.1-8)

A single oral dose of trelagliptin (0.03, 0.1, 0.3 mg/kg) or alogliptin (0.3, 1, 3 mg/kg) was administered to overnight-fasted male N-STZ-1.5 rats (20 weeks of age, n = 6/group), and plasma DPP-4 activity from 1 to 8 hours post-dose was measured. The results showed that both compounds decreased plasma DPP-4 activity in a dose-dependent manner. The inhibition peaked at 1 to 2 hours post-dose in all groups, and the plasma DPP-4 activity relative to baseline (mean ± SD) was 28.9% ± 6.9%, 11.5% ± 1.5%, and 6.5% ± 1.2% in animals receiving trelagliptin 0.03, 0.1, and 0.3 mg/kg, respectively; and 23.4% ± 3.9%, 11.7% ± 1.6%, and 6.7% ± 1.2% in animals receiving alogliptin 0.3, 1, and 3 mg/kg, respectively. The plasma DPP-4 activity at 8 hours post-dose relative to baseline was 42.1% ± 2.3%, 22.9% ± 3.9%, and 11.6% ± 1.8% in animals receiving trelagliptin 0.03, 0.1, and 0.3 mg/kg, respectively; and 33.9% ± 3.7%, 26.3% ± 2.0%, and 20.8% ± 3.0% in animals receiving alogliptin 0.3, 1, and 3 mg/kg, respectively.

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

Effects on enzymes, receptors, ion channels, and transporters (4.2.1.2-1, Reference data)

An evaluation on the inhibitory effect of trelagliptin on 126 types of enzymes, receptors, ion channels, and transporters showed no ≥50% inhibition by 10 μmol/L trelagliptin.

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

3.(i).A.(3).1) Effects on the central nervous system

Effects on general symptoms and behavior in rats (4.2.3.2-3)

In a toxicity study, trelagliptin (50, 250, 1000 mg/kg/day) or vehicle[8] was administered orally to male and female rats (n = 10-15/group) for 4 weeks. General symptoms and behavior were evaluated using the functional observational battery before dosing and 1 hour after the first dose. The results showed no effects of trelagliptin up to 1000 mg/kg.

The plasma concentration of unchanged trelagliptin at 1 hour after administration of trelagliptin 1000 mg/kg (21,550 ng/mL) was approximately 36-fold the maximum plasma concentration (C_{max}) of unchanged trelagliptin[11] observed in humans receiving the recommended clinical dose.

3.(i).A.(3).2) Effects on the cardiovascular system

(a) Effects on hERG current (4.2.1.3-1, Reference data)

Effects of trelagliptin[12] (3, 30 μmol/L) or cisapride (positive control, 0.1 μmol/L) on the hERG current were evaluated in CHO cells stably expressing hERG channels. The results showed that the percent inhibition of hERG currents relative to baseline was 6.5% and 17.4% at 3 and 30 μmol/L trelagliptin, respectively. The percent inhibition by cisapride was found to be 94%.

The concentration of trelagliptin 30 μmol/L (10,727 ng/mL) was equivalent to approximately 18-fold the C_{max}[11] of unchanged trelagliptin observed in humans receiving the recommended clinical dose.

(b) Effects on blood pressure, heart rate, and electrocardiogram in unanesthetized dogs (4.2.1.3-2)

Single escalating oral doses of trelagliptin (7.5, 15, 25 mg/kg) or vehicle[13] were administered to unanesthetized male and female dogs (n = 4/sex/group) at 7-day intervals, and body temperature, blood pressure (systolic, diastolic, and mean blood pressures), heart rate, and electrocardiographic parameters

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[11] The C_{max} (602.625 ng/mL) seen on Day 14 in healthy Japanese adult subjects in the multiple-dose study (Study CPH-002) in which the subjects received a single oral dose of trelagliptin100 mg on Day 1 followed by oral doses of trelagliptin100 mg once daily from Day 4 to Day 14 (for 11 days).

[12] Trifluoroacetate of trelagliptin was used.

[13] Deionized water

(PR, RR, QRS, QT, and QTc intervals[14]) were measured by telemetry from 2 hours before to 20 hours after each dosing. The results showed no apparent effects on any of the parameters. In animals receiving trelagliptin 25 mg/kg, troponin I and T levels were not affected within 2 hours after completion of the telemetry evaluation.

The C_{max} (4600 ng/mL)[15] of unchanged trelagliptin following a single dose of trelagliptin 25 mg/kg was approximately 7.6-fold the C_{max}[11] of unchanged trelagliptin observed in humans receiving the recommended clinical dose.

3.(i).A.(3).3) Effects on the respiratory system

Effects on the respiratory system in rats (4.2.1.3-3)

A single oral dose of trelagliptin (10, 30, 100 mg/kg) or vehicle[13] was administered to male rats (n = 8/group). Respiratory rate, tidal volume, and minute ventilation were measured from approximately 1 hour pre-dose to 4 hours post-dose using whole-body plethysmography. The results showed no effects on any of the parameters.

The C_{max} (6260 ng/mL)[16] of unchanged trelagliptin following a single dose of trelagliptin 100 mg/kg was approximately 10-fold the C_{max}[11] of unchanged trelagliptin observed in humans receiving the recommended clinical dose.

3.(i).A.(4) Pharmacodynamic drug interactions

3.(i).A.(4).1) Effect of trelagliptin in combination with a biguanide (4.2.1.4-1)

Overnight-fasted male Wistar fatty rats (20 weeks of age, n = 6/group) were treated with a single oral dose of trelagliptin (0.1 mg/kg) alone, metformin hydrochloride (50 mg/kg of metformin) alone, or trelagliptin in combination with metformin, followed 1 hour later by the oral glucose load (1 g/kg). As a result, no interaction was found between the 2 compounds in terms of $AUC_{0\text{-}120\ min}$ of glucose (two-way analysis of variance [ANOVA]). $AUC_{0\text{-}120\ min}$ of glucose in the trelagliptin plus metformin hydrochloride group significantly decreased compared with that in the trelagliptin alone group, but not significantly different from that in the metformin hydrochloride alone group. In the combination therapy group, a synergistic increase was observed in $AUC_{0\text{-}120\ min}$ of active GLP-1, but no combination effect was observed on $AUC_{0\text{-}120\ min}$ of insulin (two-way ANOVA).

3.(i).A.(4).2) Effect of trelagliptin in combination with a thiazolidine (4.2.1.4-2, 4.2.1.4-3)

Pioglitazone hydrochloride (3 mg/kg/day) or vehicle[8] was administered orally once daily for 1 week to male Wistar fatty rats (18 weeks of age, n = 6/group). After the 1-week treatment, the rats underwent an overnight fast, followed by a single oral dose of trelagliptin (0.1 mg/kg) or vehicle.[8] One hour later, 1 g/kg of glucose was orally loaded. As a result, no interaction was found between the 2 compounds in terms of $AUC_{0\text{-}120\ min}$ of glucose (two-way ANOVA). $AUC_{0\text{-}120\ min}$ of glucose significantly decreased in the trelagliptin plus pioglitazone hydrochloride group compared with that in each of the monotherapy groups.

Male *db/db* mice (6 weeks of age, n = 7/group) were treated with trelagliptin (0.03% [w/w]) alone, pioglitazone hydrochloride (0.0075% [w/w]) alone, or trelagliptin in combination with pioglitazone hydrochloride (in the diet) for 3 to 4 weeks.[17] As a result, no interaction was found between the 2 compounds in terms of glycated hemoglobin levels (two-way ANOVA). Glycated hemoglobin levels significantly decreased in the trelagliptin plus pioglitazone hydrochloride group compared with that in

[14] Calculated using Bazett's and Spence's correction formulae

[15] Calculated assuming linearity from C_{max} following the initial dose in male and female dogs receiving 25 mg/kg of trelagliptin in the 4-week repeated oral dose toxicity study in dogs (4.2.3.2-7)

[16] Calculated assuming linearity from C_{max} following the initial dose in male rats receiving 80 mg/kg of trelagliptin in the 13-week repeated oral dose toxicity study in rats (4.2.3.2-4)

[17] Dose level calculated from food consumption was 74.7 mg/kg/day in the trelagliptin alone group, 17.7 mg/kg/day in the pioglitazone hydrochloride alone group, and 63.1 mg/kg/day for trelagliptin and 15.8 mg/kg/day for pioglitazone hydrochloride in the combination therapy group.

each of the monotherapy groups. In addition, a synergistic increase was observed in the plasma insulin concentration and pancreatic insulin content in the combination therapy group (two-way ANOVA).[18]

3.(i).A.(4).3) Effect of trelagliptin in combination with a sulfonylurea (4.2.1.4-4)

Overnight-fasted male N-STZ-1.5 rats (33 weeks of age, n = 6/group) were treated with a single oral dose of trelagliptin (0.1 mg/kg) alone, glimepiride (10 mg/kg) alone, or trelagliptin in combination with glimepiride, followed 1 hour later by the oral glucose load (1.5 g/kg). As a result, no interaction was found between the 2 compounds in terms of $AUC_{0\text{-}120\ min}$ of glucose (two-way ANOVA). $AUC_{0\text{-}120\ min}$ of glucose significantly decreased in the trelagliptin plus glimepiride group compared with that in each of the monotherapy groups.

3.(i).A.(4).4) Effect of trelagliptin in combination with a short-acting insulin secretagogue (4.2.1.4-5)

Overnight-fasted male N-STZ-1.5 rats (35 weeks of age, n = 6/group) were treated with a single oral dose of trelagliptin (0.1 mg/kg) alone, nateglinide (50 mg/kg) alone, or trelagliptin in combination with nateglinide. At 1 hour after dosing of trelagliptin (or at 30 minutes after dosing of nateglinide), 1.5 g/kg of glucose was orally loaded. As a result, no interaction was found between the 2 compounds in terms of $AUC_{0\text{-}120\ min}$ of glucose (two-way ANOVA). $AUC_{0\text{-}120\ min}$ of glucose in the trelagliptin plus nateglinide group was not significantly different from that in each of the monotherapy groups.

3.(i).A.(4).5) Effect of trelagliptin in combination with an α-glucosidase inhibitor (4.2.1.4-6)

Overnight-fasted male N-STZ-1.5 rats (16 weeks of age, n = 6/group) were treated with a single oral dose of trelagliptin (0.1 mg/kg) alone, voglibose (0.03 mg/kg) alone, or trelagliptin in combination with voglibose. At 1 hour after dosing of trelagliptin (or at 30 seconds after dosing of voglibose), 2.5 g/kg of sucrose was orally loaded. As a result, no interaction was found between the 2 compounds in terms of $AUC_{0\text{-}180\ min}$ of glucose (two-way ANOVA). $AUC_{0\text{-}180\ min}$ of glucose in the trelagliptin plus voglibose group significantly decreased compared with that in the trelagliptin alone group, but was not significantly different from that in the voglibose alone group.

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

Persistence of activity

PMDA asked the applicant to discuss the persistence of pharmacological activity of trelagliptin in comparison with alogliptin, a drug with a similar structure[19] to trelagliptin, as well as the relationship between exposures and pharmacodynamic effects such as the inhibition of DPP-4 activity seen in non-clinical and clinical studies.

The applicant responded as follows:

The IC_{50} of trelagliptin and alogliptin against recombinant human DPP-4 was 1.3 and 5.3 nmol/L, respectively (4.2.1.1-7). The IC_{50} of trelagliptin against human and rat plasma DPP-4 was 4.2 and 9.7 nmol/L, respectively (4.2.1.1-1), and IC_{50} of alogliptin was 10 and 18 nmol/L, respectively.[20] No substantial differences in protein binding in human and rat plasma were found between these 2 compounds.[21] These findings suggests that inhibition of human and rat plasma DPP-4 activity by trelagliptin is approximately 2 to 4 times greater than that by alogliptin. An evaluation of inhibition of DPP-4 activity up to 8 hours post-dose in N-STZ-1.5 rats receiving a single oral dose of trelagliptin (0.03-0.3 mg/kg) or alogliptin (0.3-3 mg/kg) demonstrated that trelagliptin produces an inhibition comparable to that achieved by alogliptin, at a lower dose level (4.2.1.1-8). Based on the above, DPP-4 activity is considered to be inhibited at a lower plasma concentration of trelagliptin than that of alogliptin.

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[18] *db/db* mice have been known to present exhaustion of pancreatic β cells with increasing age, resulting in decreases in plasma insulin concentrations and pancreatic insulin content (Berglund O, et al., *Acta Endocrinol.* 1978;87:543-51). The applicant explained that the impact of excessive increase in plasma insulin concentration on the safety is limited because in mice receiving trelagliptin in combination with pioglitazone hydrochloride, plasma insulin concentrations remained at the baseline levels that were similar to those in the normal control mice as a result of inhibition of decrease in plasma insulin concentrations over time.

[19] Molecular weight (free base equivalent) is 357.3 and 339.39 for trelagliptin and alogliptin, respectively.

[20] According to the summary of the initial application for Nesina Tablets 6.25 mg, 12.5 mg, and 25 mg (date of approval for marketing application, April 16, 2010)

[21] For trelagliptin, 24.1% to 54.7% in rats and 22.1% to 27.6% in humans; for alogliptin, 25.2% to 52.0% in rats and 28.2% to 38.4% in humans

An evaluation of persistence of activity showed that the elimination half-life ($T_{1/2}$) of unchanged trelagliptin in plasma following a single oral dose of trelagliptin 3 mg/kg in rats was 3.6 hours (4.2.2.2-1), and time course of the inhibition of DPP-4 activity up to 8 hours after administration of trelagliptin was evaluated (4.2.1.1-8). The plasma concentration of unchanged trelagliptin at 1 to 2 hours after administration of the lowest dose (0.1 mg/kg), which produced a significant decrease in $AUC_{0\text{-}120\ min}$ of glucose in a single-dose study in N-STZ-1.5 rats (4.2.1.1-3), was estimated to be 2.92 to 3.05 ng/mL.[22] Since the percent inhibition of plasma DPP-4 activity at 1.5 hours post-dose was found to be 69% (4.2.1.1-3). Approximately 70% inhibition of DPP-4 activity and significant effects can be expected if a higher plasma concentration of unchanged trelagliptin than the above value is achieved. The exposure (C_{max}, 11.8 ng/mL) at the maximum dose (0.3 mg/kg) investigated in the primary pharmacodynamic studies in rats was considerably different from that (C_{max}, 602.625 ng/mL)[11] observed on Day 11 following once-daily administration for 11 days at the recommended clinical dose (100 mg). On the other hand, in patients who received trelagliptin once a week for 12 weeks at the recommended clinical dose (Study CCT-001), the plasma concentration of unchanged trelagliptin was 6.062 ng/mL at 7 days after the last dose and the percent inhibition of plasma DPP-4 activity was 78.15%, and the change in 2-hour postprandial blood glucose from baseline was significantly decreased compared with the placebo group. Based on the above evaluation of rat versus human data, the plasma concentration of unchanged trelagliptin and the inhibition of DPP-4 activity observed at 7 days after trelagliptin treatment at the recommended clinical dose were comparable to the exposure and inhibition of DPP-4 activity observed in rats receiving trelagliptin 0.1 to 0.3 mg/kg in the non-clinical studies; therefore, the hypoglycemic activity would be sustained even at 7 days after trelagliptin treatment at the recommended clinical dose.

PMDA asked the applicant to explain the impact of persistent inhibition of DPP-4 activity on safety.

The applicant responded as follows:
Incretin hormones (GLP-1 and glucose-dependent insulinotropic polypeptide [GIP]) are involved in promotion of insulin secretion, and other known physiological substrates for DPP-4 and their major activities include stromal cell-derived factor 1 alpha (SDF-1α) with immunological and hematological activities, macrophage-derived chemokine (MDC) with immunological activity, gastrin-releasing peptide (GRP) with gastrointestinal activity, β-casomorphin with cardiovascular and neurological activities, peptide YY (PYY) with anorexigenic activity, and neuropeptide Y (NPY) with orexigenic activity.[23] Because evaluation of incidence of immunological, hematological, gastrointestinal, cardiovascular, and neurological adverse events and body weight in clinical studies showed no major safety issues, the persistent inhibition of DPP-4 activity by trelagliptin is unlikely to have a long-term impact on safety.

Based on the submitted data, PMDA considers that the mechanism of action and hypoglycemic activity of trelagliptin have been generally elucidated. However, evaluation was performed on the inhibition of DPP-4 activity only up to 8 hours post-dose in the primary pharmacodynamic studies, and thus the persistence of activity of trelagliptin has not been sufficiently supported by non-clinical study data. The marked increase in plasma trelagliptin concentrations following high-dose intermittent administration (i.e., once-weekly trelagliptin 100mg) and impacts of persistent or long-term inhibition of DPP-4 activity will be reviewed also in clinical sections [see "4.(ii).B.(1) Pharmacokinetic characteristics of trelagliptin," "4.(iii).B.(3) Safety," and "4.(iii).B.(6) Dosage and administration"].

3.(ii) Summary of pharmacokinetic studies

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

Trelagliptin or ^{14}C-trelagliptin was administered to rats and dogs intravenously or orally to evaluate pharmacokinetics. In addition, pharmacokinetics following repeat-dose administration was evaluated based on toxicokinetics in toxicity studies. Concentrations of unchanged trelagliptin and its metabolite (M-I) in plasma were measured by high performance liquid chromatography/tandem mass spectrometry

[22] Calculated assuming linearity from the plasma concentration of unchanged trelagliptin at 1 and 2 hours after a single oral dose of trelagliptin at 3 mg/kg in male rats (4.2.2.2-1).

[23] Yutaka Seino, *DPP-4 inhibitors*, Sentan Igaku-Sha Ltd., Tokyo, 2010; Brandt I, *et al., Advances in Experimental Medicine and Biology*. 2006;575:3-18; Shinpei Kasakura, *Cytokines and chemokines*, Nihon-Igakukan Co., ltd., Tokyo, 2004; Kaminski S, *et al.*, *J Appl Genet*. 2007;48(3):189-98; Masato Kasuga, *Encyclopedia of Molecular Targets and Therapeutic Agents for Diabetes*, Yodosha Company Limited., Tokyo, 2013.

(LC/MS/MS) with a lower limit of quantitation of 1.0 and 0.5 ng/mL, respectively, both in rats and dogs. Radioactivity in biological samples was measured using liquid scintillation counting (LSC), HPLC equipped with an on-line flow scintillation analyzer, and whole-body autoradiography. Dose levels and concentrations of trelagliptin in pharmacokinetic studies are expressed in terms of free base. Results of main studies are shown below.

3.(ii).A.(1) Absorption (4.2.2.2-1 to 4.2.2.2-9, 4.2.2.2-12)

Pharmacokinetic parameters of unchanged trelagliptin and its metabolite (M-I) in plasma following a single oral dose of and a single intravenous dose of trelagliptin in male rats and dogs were as shown in Table 3.

Table 3. Pharmacokinetic parameters of unchanged trelagliptin and its metabolite (M-I) following single-dose administration

Species (No. of animals)	Route of administration	Dose (mg/kg)	Analyte	C_{max} (ng/mL)	$AUC_{0\text{-}24\ h}$ (ng·h/mL)	T_{max} (h)	$T_{1/2}$ (h)	BA (%)
Rat (n = 3)	p.o.	3	Unchanged trelagliptin	118 ± 36	891 ± 107	2.3 ± 1.2	3.6 ± 0.6	50.3 ± 8.2
			M-I	12.5 ± 5.7	114 ± 29	4.7 ± 1.2	3.7 ± 1.0	-
	i.v.	1	Unchanged trelagliptin	430 ± 43	591 ± 65	0.08 ± 0.00	1.1 ± 0.0	-
			M-I	5.01 ± 0.52	29.4 ± 2.1	1.7 ± 0.6	2.7 ± 0.1	-
Dog (n = 4)	p.o.	3	Unchanged trelagliptin	439 ± 196	2410 ± 635	1.0 ± 0.0	3.5 ± 0.6	129.8 ± 37.6
			M-I	186 ± 52	2441 ± 413	2.8 ± 1.5	7.7 ± 1.4	-
	i.v.	1	Unchanged trelagliptin	-	619 ± 74	-	1.7 ± 0.1	-
			M-I	77.1 ± 12.0	878 ± 92	2.0 ± 0.0	7.0 ± 0.7	-

Mean ± SD; -, Not calculated

C_{max}, Maximum plasma concentration; T_{max}, Time to reach the maximum plasma concentration; $AUC_{0\text{-}24\ h}$, Area under the plasma concentration-time curve from 0 to 24 hours; $T_{1/2}$, Half-life; BA, Bioavailability (calculated from $AUC_{0\text{-}24\ h}$ following an oral or intravenous dose)

The absorption rate (mean ± SD) calculated from the ratio of $AUC_{0\text{-}24\ h}$ of total radioactivity following a single oral dose of ^{14}C-trelagliptin (3 mg/kg) to that following a single intravenous dose of ^{14}C-trelagliptin (1 mg/kg) was 67.1% ± 7.5% in male rats (n = 3) and 96.1% ± 16.1% in male dogs (n = 4).

Following an injection of ^{14}C-trelagliptin 3 mg/kg into a jejunal loop created in a male rat (n = 1), radioactivity levels in portal vein plasma peaked within the first 0.5 hours post-dose, and approximately 3.1% of the administered radioactivity was absorbed from the jejunum by 2 hours post-dose. The major radiolabeled compound in both portal vein plasma and jejunum homogenate was unchanged trelagliptin.

A single oral dose of ^{14}C-trelagliptin 3 mg/kg was administered to male rats with thoracic duct fistula (n = 4). Within the first 24 hours post-dose, 51.7% ± 3.5% and 42.1% ± 3.6% (mean ± SD) of the administered radioactivity were recovered in urine and feces, respectively, and 0.6% ± 0.1% of the administered radioactivity was recovered in lymph fluid.

A single oral dose of trelagliptin 3, 10, or 30 mg/kg was administered to male rats (n = 3/group) and male dogs (n = 4/group). The pharmacokinetic parameters of unchanged trelagliptin and its metabolite (M-I) in plasma were as shown in Table 4. The plasma concentrations of unchanged trelagliptin and M-I in rats increased almost linearly with the increasing dose, while plasma concentrations of them in dogs showed slightly more than dose-proportional increases.

Table 4. Pharmacokinetic parameters of unchanged trelagliptin and its metabolite (M-I) following a single oral dose

Species (No. of animals)	Route of administration	Dose (mg/kg)	Analyte	T_{max} (h)	C_{max} (ng/mL)	$T_{1/2}$ (h)	$AUC_{0\text{-}24\ h}$ (ng·h/mL)
Rat (n = 3)	p.o.	3	Unchanged trelagliptin	1.0 ± 0.0	108 ± 29	4.2 ± 0.4	746 ± 87
			M-I	2.0 ± 1.7	9.55 ± 4.04	7.7 ± 5.2	85.1 ± 6.4
		10	Unchanged trelagliptin	1.5 ± 1.3	419 ± 38	3.3 ± 0.2	2601 ± 99
			M-I	2.7 ± 1.5	41.5 ± 1.0	3.8 ± 0.3	327 ± 19
		30	Unchanged trelagliptin	1.7 ± 1.2	1977 ± 261	5.2 ± 1.2	10,578 ± 563
			M-I	2.3 ± 1.2	139 ± 24	4.8 ± 1.4	977 ± 32
Dog (n = 4)	p.o.	3	Unchanged trelagliptin	4.3 ± 3.3	255 ± 144	4.4 ± 1.2	2511 ± 586
			M-I	6.5 ± 3.0	122 ± 15	10.0 ± 0.6	2338 ± 114
		10	Unchanged trelagliptin	3.5 ± 1.7	1141 ± 314	6.0 ± 0.6	11,503 ± 1370
			M-I	4.8 ± 1.5	341 ± 50	9.7 ± 0.4	6178 ± 754
		30	Unchanged trelagliptin	6.5 ± 3.0	3965 ± 1287	6.2 ± 0.2	52,762 ± 5716
			M-I	7.0 ± 1.2	601 ± 113	10.1 ± 0.6	14,230 ± 2150

Mean ± SD

T_{max}, Time to reach the maximum plasma concentration; C_{max}, Maximum plasma concentration; $T_{1/2}$, Half-life; $AUC_{0\text{-}24\ h}$, Area under the plasma concentration-time curve from 0 to 24 hours

The pharmacokinetic parameters of unchanged trelagliptin and its metabolite (M-I) following once-daily oral administration of trelagliptin 3 mg/kg for 14 days in male rats (n = 3) were as shown in Table 5.

Table 5. Pharmacokinetic parameters of unchanged trelagliptin and its metabolite (M-I) in rats following repeated oral dose

Analyte	Unchanged trelagliptin			M-I		
	Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
T_{max} (h)	2.3 ± 1.5	1.7 ± 2.0	0.42 ± 0.14	3.3 ± 1.2	3.0 ± 1.7	3.3 ± 1.2
C_{max} (ng/mL)	94.7 ± 21.8	147 ± 50	137 ± 8	10.0 ± 2.0	13.3 ± 2.7	14.2 ± 2.8
$T_{1/2}$ (h)	5.0 ± 1.0	3.9 ± 0.3	4.9 ± 0.8	6.7[a)]	5.2[b)]	5.5 ± 1.7
$AUC_{0\text{-}24\ h}$ (ng·h/mL)	853 ± 113	1087 ± 214	1126 ± 200	104 ± 6	125 ± 16	130 ± 19

Mean ± SD

T_{max}, Time to reach the maximum plasma concentration; C_{max}, Maximum plasma concentration; $T_{1/2}$, Half-life; $AUC_{0\text{-}24\ h}$, Area under the plasma concentration-time curve from 0 to 24 hours

a) n = 2

b) n = 1

3.(ii).A.(2) Distribution (4.2.2.3-1, 4.2.2.3-4 to 4.2.2.3-7)

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male rats (n = 3/timepoint), radioactivity levels peaked at 1 hour post-dose in the intestinal wall, gastric wall, liver, adrenal gland, bladder, spleen, thyroid gland, and femur, while peaking at 6 hours post-dose in other tissues. Except for the gastrointestinal tract, high radioactivity levels were detected in the kidneys and liver. The highest radioactivity level in the kidneys was 30.0-fold that in plasma at 6 hours post-dose and the highest radioactivity level in the liver was 16.6-fold that in plasma at 1 hours post-dose. In most tissues, radioactivity levels declined over time after reaching the peak. Even at 168 hours post-dose, however, radioactivity was detected in some tissues. Those tissues were in descending order of the bladder, kidneys, lungs, intestinal wall, liver, heart, spleen, gastric wall, pancreas, testis, skin, submandibular gland, Harderian gland, thymus, and brain. The highest level of radioactivity was found in the bladder (13.6%), and the radioactivity levels in other tissues were ≤4.0%.

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male albino rats (n = 3/timepoint), plasma radioactivity levels (mean ± SD) peaked at 1 hour post-dose (0.114 ± 0.005 μg/mL) and remained constant even at 6 hours post-dose (0.104 ± 0.021 μg/mL). Radioactivity levels in the eyeball peaked at 6 hours post-dose (0.125 ± 0.015 μg/g). Radioactivity levels at 168 hours post-dose were below the

lower limits of quantitation both in plasma and in the eyeball. On the other hand, following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male pigmented rats (n = 3/timepoint), plasma radioactivity levels peaked at 1 hour post-dose (0.162 ± 0.021 μg/mL) and were below the lower limits of quantitation from 24 hours post-dose. Radioactivity levels in the eyeball peaked at 24 hours post-dose (1.242 ± 0.079 μg/g) and remained constant even at 72 hours post-dose (1.118 ± 0.014 μg/g); the radioactivity in the eyeball remained up to at least 4 weeks post-dose.

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in pregnant rats (gestation day 18, n = 3/timepoint), radioactivity levels in maternal plasma, the placenta, fetal plasma, and the fetuses peaked at 4 hours post-dose, and those in amnionic fluid peaked at 8 hours post-dose. Radioactivity levels were the highest in the placenta at all timepoints (approximately 3.5- to 8.5-fold radioactivity levels in maternal plasma). Radioactivity levels in the fetuses at 8, 24, and 48 hours post-dose were approximately 1.3-, 2.3-, and 3.0-fold, respectively, those in maternal plasma, and radioactivity levels in amnionic fluid at 24 hours post-dose were approximately 1.6-fold those in maternal plasma.

The mean protein binding (ultrafiltration method) of ^{14}C-trelagliptin (0.1-10 μg/mL) in plasma in male rats and male dogs was 24.1% to 54.7% and 22.8% to 25.2%, respectively. The mean distribution in blood in male rats and male dogs receiving a single oral dose of ^{14}C-trelagliptin 3 mg/kg was 27.9% to 30.9% and 45.4% to 48.3%, respectively.

3.(ii).A.(3) Metabolism (4.2.2.4-2 to 4.2.2.4-8)

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male rats (n = 3), unchanged trelagliptin, M-I (active metabolite), and other metabolites accounted for 80.7%, 9.1%, and 10.2%, respectively, of the total plasma radioactivity (based on $AUC_{0\text{-}24\ h}$). Similarly, following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male rats (n = 3), 38.4% of the administered radioactivity was excreted in urine up to 48 hours post-dose, and unchanged trelagliptin, M-I, and other metabolites accounted for 66.6%, 15.1%, and 18.3%, respectively, of the total urinary radioactivity. In addition, 60.1% of the administered radioactivity was excreted in feces up to 48 hours post-dose, and unchanged trelagliptin, M-I, and other metabolites accounted for 88.5%, 8.8%, and 2.7%, respectively, of the total fecal radioactivity. Following an intraduodenal dose of ^{14}C-trelagliptin 3 mg/kg in male rats with biliary fistula (n = 4), 20.0% of the administered radioactivity was detected in bile up to 24 hours post-dose, and unchanged trelagliptin, M-I, and other metabolites accounted for 25.0%, 3.0%, and 72.0%, respectively, of the total biliary radioactivity.

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male dogs (n = 4), unchanged trelagliptin, M-I, and other metabolites accounted for 43.3%, 51.9%, and 4.8%, respectively, of the total plasma radioactivity (based on $AUC_{0\text{-}24\ h}$). Similarly, following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male dogs (n = 4), 68.2% of the administered radioactivity was excreted in urine up to 72 hours post-dose, and unchanged trelagliptin, M-I, and other metabolites accounted for 35.0%, 50.2%, and 14.8%, respectively, of the total urinary radioactivity. In addition, 28.5% of the administered radioactivity was excreted in feces up to 72 hours post-dose, and unchanged trelagliptin, M-I, and other metabolites accounted for 15.9%, 61.4%, and 22.7%, respectively, of the total fecal radioactivity.

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male rats and dogs, (*S*)-SYR-472, an optical isomer of unchanged trelagliptin, was below the lower limits of quantitation up to 6 hours post-dose in plasma and up to 48 hours post-dose in urine.

The metabolism of ^{14}C-trelagliptin (10 μmol/L) was evaluated in rat and dog cryopreserved primary hepatocytes. Unchanged trelagliptin found in rat and dog cryopreserved primary hepatocytes accounted for 91.0% and 95.8%, respectively, of the total radioactivity at 6 hours after the start of incubation, which corresponded to the longest reaction time.

3.(ii).A.(4) Excretion (4.2.2.2-4, 4.2.2.5-1 to 4.2.2.5-5)

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male rats (n = 3), the cumulative excretion of radioactivity in urine and feces up to 72 hours post-dose (mean ± SD) accounted for 38.6% ± 3.4% and 60.3% ± 4.1%, respectively, of the administered radioactivity. Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in male dogs (n = 4), the cumulative excretion of radioactivity in urine and feces up

to 144 hours post-dose accounted for 68.8% ± 3.6% and 29.6% ± 2.8%, respectively, of the administered radioactivity.

Following an intraduodenal dose of ^{14}C-trelagliptin 3 mg/kg in bile duct cannulated male rats (n = 4), the cumulative excretion of radioactivity in urine, feces, and bile up to 24 hours post-dose accounted for 48.3% ± 3.2%, 25.4% ± 4.6%, and 20.0% ± 4.2%, respectively, of the administered radioactivity, with 3.6% ± 0.7% remaining in the carcass. The collected radioactive bile was administered intraduodenally (10 mL/kg) to a separate group of male rats with biliary fistula (n = 4). As a result, the cumulative excretion of radioactivity in urine and bile up to 24 hours post-dose accounted for 9.8% ± 0.5% and 14.0% ± 0.2%, respectively, of the administered radioactivity.

Following a single oral dose of ^{14}C-trelagliptin 3 mg/kg in lactating rats (day 14 postpartum, n = 4), the milk/plasma radioactivity ratio up to 1 to 48 hours post-dose was approximately 0.67 to 2.13.

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

3.(ii).B.(1) Melanin affinity of trelagliptin

Taking into account that the tissue distribution study in male pigmented rats has shown melanin affinity of trelagliptin as evidenced by a slower elimination from the eyeball than from plasma, PMDA asked the applicant to explain the ocular and skin safety of trelagliptin in Japanese patients.

The applicant responded as follows:
In various toxicity studies in mice, rats, rabbits, dogs, and monkeys, no trelagliptin-related changes suggestive of phototoxicity were observed in the eyes or skin. In addition, trelagliptin was tested negative for phototoxicity in the phototoxicity study using hairless mice (4.2.3.7.7-2).

In all the Japanese clinical studies of trelagliptin in patients with type 2 diabetes mellitus, no adverse events classified into the System Organ Class (SOC) “Eye disorders” were found in adverse events reported by ≥2% of subjects in any dose group for which a causal relationship to the study drug could not be ruled out. Although adverse events classified into the SOC “Skin and subcutaneous tissue disorders” were reported by 2 of 67 subjects (eczema [3.0%]) in the group receiving trelagliptin in combination with a short-acting insulin secretagogue (100 mg group) in the phase III long-term monotherapy/combination therapy study (Study OCT-001), no such events were reported in the trelagliptin 12.5, 25, 50, or 200 mg groups in the phase II dose-finding study (Study CCT-001). Based on the above non-clinical and clinical study data, the ocular and skin safety is secured.

PMDA accepted the applicant's response that clinically significant skin- or eye-related problems are unlikely to occur based on the results of non-clinical and clinical studies.

3.(ii).B.(2) Pharmacokinetic characteristics of trelagliptin

PMDA asked the applicant to explain the pharmacokinetic characteristics of trelagliptin in relation to the persistent inhibition of DPP-4 activity and the hypoglycemic activity, by examining the non-clinical pharmacokinetics (absorption, distribution, metabolism, and excretion) of trelagliptin versus those of alogliptin, a DPP-4 inhibitor with a similar structure[19] to trelagliptin.

The applicant responded as follows:
Following an oral dose of trelagliptin 3 mg/kg in rats and dogs, C_{max}, $AUC_{0\text{-}24\ h}$, and $T_{1/2}$ (mean ± SD) were 118 ± 36 ng/mL, 891 ± 107 ng·h/mL, and 3.6 ± 0.6 hours, respectively, for rats; and were 439 ± 196 ng/mL, 2410 ± 635 ng·h/mL, and 3.5 ± 0.6 hours, respectively, for dogs (4.2.2.2-1, 4.2.2.2-2). Similarly, C_{max}, $AUC_{0\text{-}24\ h}$, and $T_{1/2}$ following an oral dose of alogliptin 3 mg/kg were 68.1 ± 9.8 ng/mL, 368 ± 57 ng·h/mL, and 3.4 ± 0.3 hours, respectively, for rats; and were 244 ± 97.6 ng/mL, 991 ± 121 ng·h/mL, and 3.6 ± 3.8 hours,[20] respectively, for dogs. C_{max} and $AUC_{0\text{-}24\ h}$ of trelagliptin tended to be higher than those of alogliptin, but $T_{1/2}$ was almost comparable; therefore, both compounds are expected to be eliminated at a relatively rapid rate. The protein binding of trelagliptin determined *in vitro* at 0.1 to 10 μg/mL was 24.1% to 54.7% for rats, 22.8% to 25.2% for dogs, and 22.1% to 27.6% for humans, (4.2.2.3-4), and that of alogliptin was 25.2% to 36.2% for rats, 23.5% to 27.2% for dogs, and 28.2% to 32.3% for humans,[20] indicating low values with no substantial difference between the two compounds. The results of the *in vitro* metabolism study in rat, dog, and human cryopreserved primary

hepatocytes also showed that both compounds are hardly metabolized and that there is no substantial difference in CYP isoforms involved in metabolism, CYP inhibition, or CYP induction between the two compounds. In addition, following oral administration of radiolabeled trelagliptin or alogliptin, radiolabeled trelagliptin was almost completely recovered in excreta within 48 and 120 hours post-dose in rats and dogs, respectively (4.2.2.2-4, 4.2.2.5-1), and radiolabeled alogliptin was almost completely recovered in excreta within 72 and 120 hours post-dose,[20] respectively, indicating no persistence for both compounds. Based on the above results from non-clinical pharmacokinetic studies, trelagliptin and alogliptin have similar pharmacokinetic characteristics; therefore, the persistent inhibition of DPP-4 activity and the hypoglycemic activity are not attributable to the pharmacokinetics characteristic of trelagliptin. Given that trelagliptin continued to inhibit DPP-4 activity to a similar degree to alogliptin up to 8 hours post-dose at one-tenth the dose of alogliptin in a non-clinical study (4.2.1.1-8), trelagliptin may produce more persistent inhibition of DPP-4 activity than alogliptin when the 2 compounds are administered at the same dose level.

Also taking account of clinical study results, PMDA will review the relationships of the pharmacokinetic characteristics of trelagliptin with its persistent inhibition of DPP-4 activity and with its hypoglycemic activity in the clinical section [see "4.(ii).B.(1) Pharmacokinetic characteristics of trelagliptin"].

3.(iii) Summary of toxicology studies

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

Toxicity studies of trelagliptin conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies (phototoxicity study, skin toxicity studies in monkeys). Some studies were non-GLP studies and were handled by PMDA as reference data. In the following sections, dose levels of trelagliptin are expressed in terms of free base.

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

In a single-dose toxicity study, trelagliptin was administered orally to male and female SD rats at 0 (vehicle[8]), 600, or 2000 mg/kg. Salivation was observed immediately after administration of trelagliptin, but no deaths occurred. Thus, the approximate lethal dose was determined to be >2000 mg/kg.

In a dose escalation study, escalating single oral doses of trelagliptin (0 [control[24]], 30, 300, 2000 mg/kg) were administered to male and female beagle dogs. Vomiting, erythema and swelling of the auricle and face, salivation, and increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, and alkaline phosphatase (ALP) were observed in animals receiving ≥300 mg/kg and a decrease in locomotor activity, lateral position, and decreased body temperature were observed in animals receiving 2000 mg/kg, but no deaths were observed. Thus, the approximate lethal dose was determined to be >2000 mg/kg.

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

3.(iii).A.(2).1) Four-week repeated oral dose toxicity study in rats (4.2.3.2-3)

Male and female SD rats orally received daily trelagliptin at 0 (vehicle[8]), 50, 250, or 1000 mg/kg/day for 4 weeks. In addition, a recovery study was conducted in the 0 and 1000 mg/kg/day groups to assess the reversibility of toxicity after a 2-week recovery period.

Stained perianogenital fur; increases in neutrophil, lymphocyte, and white blood cell counts; increases in inorganic phosphorus, total cholesterol, and ALP; decreases in sodium, chloride, albumin, and total protein: a trend towards increased urine protein; an increase in liver weight; a decrease in thymus weight; centrilobular hepatocellular hypertrophy; and a decrease in lymphocytes in the thymic cortex were observed in the 1000 mg/kg/day group.

All findings were reversible after the 2-week recovery period.

As described above, stained fur associated with worsening of clinical signs and increased white blood cell count suggestive of inflammation were observed in the 1000 mg/kg/day group, and therefore the no observed adverse effect level (NOAEL) was determined to be 250 mg/kg/day.

[24] An empty gelatin capsule

3.(iii).A.(2).2) Thirteen-week repeated oral dose toxicity study in rats (4.2.3.2-4)
Male and female SD rats orally received daily trelagliptin at 0 (vehicle[8]), 80, 250, 750, or 1500 mg/kg/day for 13 weeks.

Findings observed were hyperplasias of monocytes and macrophages in the mesenteric lymph nodes in the ≥80 mg/kg/day groups; an increase in liver weight, centrilobular or panlobular hepatocellular hypertrophy in the ≥250 mg/kg/day groups; stained perianogenital or abdominal fur, increases in total cholesterol and ALP, an increase in thyroid weight, hepatic periportal vacuolation, and hypertrophies of pulmonary alveolar macrophages and thyroidal follicular cells in the ≥750 mg/kg/day groups; and unkept fur, reduced body weight gain, an increase in γ-glutamyl transpeptidase (γ-GTP), and an increase in mast cells in the mesenteric lymph nodes in the 1500 mg/kg/day group. The findings of the liver, thyroid, and mesenteric lymph nodes observed in the 80 and 250 mg/kg/day groups were minimal changes and were considered to have little toxicological significance.

Since worsening of clinical signs and biochemical and histopathological findings suggestive of hepatotoxicity were observed in the ≥750 mg/kg/day groups as described above, the NOAEL was determined to be 250 mg/kg/day.

3.(iii).A.(2).3) Twenty-six-week repeated oral dose toxicity study in rats (4.2.3.2-5)
Male and female SD rats orally received daily trelagliptin at 0 (vehicle[8]), 25, 75, 250, or 750 mg/kg/day for 26 weeks. In addition, a recovery study was conducted in the 0 and 750 mg/kg/day groups to assess the reversibility of toxicity after an 8-week recovery period.

Findings observed were salivation in the ≥75 mg/kg/day groups; an increased water consumption in the ≥250 mg/kg/day groups; and stained fur, reduced body weight gain, decreases in red blood cell count, hemoglobin concentration, and hematocrit value, increases in ALP, calcium, inorganic phosphorus, and total cholesterol, a decrease in urine pH, an increase in liver weight, and periportal vacuolation and centrilobular hepatocellular hypertrophy in the liver in the 750 mg/kg/day group. The findings of salivation, which was not found to be associated with histopathological changes of the salivary gland, and of an increased water consumption, which was found to be a mild change and which was not associated with changes in urine volume, were considered to have little toxicological significance.

All findings were reversible after the 8-week recovery period.

Based on the above, biochemical and histopathological findings suggestive of hepatotoxicity were observed in the ≥750 mg/kg/day groups, and therefore the NOAEL was determined to be 250 mg/kg/day. The exposure to unchanged trelagliptin ($AUC_{0\text{-}24\ h}$) on Day 181 in the 250 mg/kg/day group was 208,259 ng·h/mL in males and 221,250 ng·h/mL in females, which are approximately 39- and 42-fold, respectively, the plasma exposure to unchanged trelagliptin in humans receiving the recommended clinical dose (100 mg).[25]

3.(iii).A.(2).4) Two-week repeated oral dose toxicity study in dogs (4.2.3.2-6: Reference data)
Male and female beagle dogs orally received daily trelagliptin at 25, 75, or 250 mg/kg/day for 2 weeks. Vomiting, salivation, reddish discoloration of the auricle and abdomen, a decreased stool output, decreases in body weight and food consumption, and a decrease in reticulocyte count were observed in the 250 mg/kg/day group. The decreases in body weight and food consumption and the decrease in reticulocyte count were considered to constitute toxicity, and therefore the NOAEL was determined to be 75 mg/kg/day.

3.(iii).A.(2).5) Four-week repeated oral dose toxicity study in dogs (4.2.3.2-7)
Male and female beagle dogs orally received daily trelagliptin at 0 (control[24]), 25, 75, or 200 mg/kg/day for 4 weeks. In addition, a recovery study was conducted in the 0 and 200 mg/kg/day groups to assess the reversibility of toxicity after a 2-week recovery period.

[25] $AUC_{0\text{-}24\ h}$ on Day 14 (5293 ng·h/mL) in healthy Japanese adult subjects in the multiple dose study (Study CPH-002) in which the subjects received a single oral dose of trelagliptin 100 mg on Day 1, followed by multiple oral doses of trelagliptin 100 mg once daily from Day 4 to Day 14 for 11 days.

Findings observed were reddish discoloration of the auricle, orbit, nose, or lips, salivation, and a decrease in LDL cholesterol in the ≥25 mg/kg/day groups; a decrease in locomotor activity, decreased stool output, facial swelling, a decrease in thymus weight, and a decrease in thymic lymphocytes in the ≥75 mg/kg/day groups; and decreased skin elasticity attributed to vomiting, emaciation, and dehydration, decreases in body weight and food consumption, and an increase in HDL cholesterol in the 200 mg/kg/day group. The findings such as facial swelling were found to be transient and not associated with pathological changes of skin, the decrease in LDL cholesterol was not associated with pathological changes, and the findings of the thymus were considered as stress-induced. Therefore, these findings were considered to have little toxicological significance.

All findings were reversible after the 2-week recovery period.

Based on the above, decreases in body weight and food consumption were observed in the 200 mg/kg/day group, and therefore the NOAEL was determined to be 75 mg/kg/day.

3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity study in dogs (4.2.3.2-8)

Male and female beagle dogs orally received daily trelagliptin at 0 (control[24]), 10, 30, 100, or 300 mg/kg/day for 13 weeks. All animals in the 300 mg/kg/day group (n = 3/sex) were sacrificed moribund on Day 14 because decreases in body weight and food consumption were observed. Findings in that group were salivation, yellow watery or mucous stool, reddish or grayish discoloration of the auricle, nose, or orbit, a decrease in locomotor activity, decreased skin temperature, tremor, vomiting, peribulbar swelling, increases in red blood cell count, hemoglobin concentration, and hematocrit value, decreases in chloride, inorganic phosphorus, and potassium, and thymus atrophy.

At scheduled necropsy, findings included reddish discoloration of the auricle, reduced body weight gain, and decreased food consumption in the ≥30 mg/kg/day groups and salivation and decreased skin temperature in the 100 mg/kg/day group, but all of these changes were mild and considered to have little toxicological significance.

As described above, decreases in food consumption and body weight associated with trelagliptin, leading to early sacrifice, were observed in the 300 mg/kg/day group, and therefore the NOAEL was determined to be 100 mg/kg/day.

3.(iii).A.(2).7) Thirty-nine-week repeated oral dose toxicity study in dogs (4.2.3.2-9)

Male and female beagle dogs orally received daily trelagliptin at 0 (control[24]), 15, 50, or 150 mg/kg/day for 39 weeks. The dose was reduced to 100 mg/kg/day on Day 15 in the 150 mg/kg/day group (i.e., 150/100 mg/kg/day group) due to decreases in body weight and food consumption during the early phase of treatment. In addition, a recovery study was conducted in the 0 and 150/100 mg/kg/day groups to assess the reversibility of toxicity after a 13-week recovery period.

Facial swelling and reddish discoloration of skin in the ≥50 mg/kg/day groups and salivation in the 150/100 mg/kg/day group were observed, but all of these findings were non-serious and thus considered to have little toxicological significance. Decreases in body weight and food consumption were observed when animals were receiving 150 mg/kg/day (Weeks 1-2), but no effects on body weight or food consumption were observed after dose reduction to 100 mg/kg/day.

All findings were reversible after the 13-week recovery period.

Based on the fact that the decreases in body weight and food consumption observed in animals receiving 150 mg/kg/day resolved after dose reduction to 100 mg/kg/day, the NOAEL was determined to be 100 mg/kg/day. The exposure to unchanged trelagliptin ($AUC_{0\text{-}24\,h}$) on Day 273 in the 150/100 mg/kg/day group was 320,341 ng·h/mL in males and 308,888 ng·h/mL in females, which are approximately 61- and 58-fold, respectively, the plasma exposure to unchanged trelagliptin in humans receiving the clinical dose (100 mg).[25]

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

Bacterial reverse mutation assay, gene mutation assay with mouse lymphoma (L5178Y/TK$^{+/-}$), and mouse bone marrow micronucleus assay were conducted. The result showed trelagliptin to have no genotoxicity.

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

3.(iii).A.(4).1) Carcinogenicity dose-range finding study in mice (4.2.3.4.1-3) (4.2.3.4.1-1, 4.2.3.4.1-2, Reference data)

Male and female ICR mice orally received daily trelagliptin at 0 (vehicle[8]), 100, 300, 1000, or 2000 mg/kg/day for 1 week. Death occurred in 1 of 10 females in the 100 mg/kg/day group, 1 of 10 females in the 300 mg/kg/day group, 2 of 10 males and 1 of 10 females in the 1000 mg/kg/day group, and 1 of 10 males and 1 of 10 females in the 2000 mg/kg/day group. In addition, among animals evaluated for toxicokinetics, 1 of 21 females died in the 1000 mg/kg/day group and 1 of 21 males and 7 of 21 females died in the 2000 mg/kg/day group. The deaths observed in the 2000 mg/kg/day group were considered attributable to trelagliptin because of the high incidence of death. Findings in the 2000 mg/kg/day group were a decrease in locomotor activity, convulsion, abdominal distension, unkept fur, ataxia, decreased food consumption, decreases in lymphocyte and white blood cell counts, and increases in ALP, ALT, AST, and urea nitrogen.

Separately, an additional group of male and female ICR mice orally received daily 1000 mg/kg/day of trelagliptin for 1 week.

A decrease in locomotor activity, prone position, bradypnea, and hypothermia were observed after the first dose, but not after the second or subsequent doses. In addition, deaths or effects on body weight associated with trelagliptin were not noted.

Furthermore, male and female ICR mice orally received daily trelagliptin at 0 (vehicle[8]), 150, 300, 600, or 1200 mg/kg/day for 13 weeks.

No deaths associated with trelagliptin occurred, nor were any toxicological findings observed in clinical signs, body weight, food consumption, ophthalmology, haematology, clinical chemistry, organ weights, necropsy, or histopathology.

3.(iii).A.(4).2) Twenty-four-month repeated oral dose carcinogenicity study in mice (4.2.3.4.1-5) (4.2.3.4.1-4, Reference data)

An evaluation of carcinogenicity was scheduled following oral daily administration of trelagliptin at 0 (vehicle[8]), 100, 300, or 1000 mg/kg/day for 24 months to male and female ICR mice. However, death occurred in 4 of 60 males and 2 of 60 females in the control group, 2 of 60 males and 6 of 60 females in the 100 mg/kg/day group, 3 of 60 males and 14 of 60 females in the 300 mg/kg/day group, and 12 of 60 males and 17 of 60 females in the 1000 mg/kg/day group by Day 132. Among these deaths, 2 males and 2 females in the control group, 2 males and 6 females in the 100 mg/kg/day group, 1 male and 5 females in the 300 mg/kg/day group, and 3 males and 5 females in the 1000 mg/kg/day group were determined to have died due to a dosing error, but the cause of deaths of the remaining animals were unknown. The incidence of death up to Day 132 was evidently higher than that in other studies in mice, with some deaths being observed also in control animals, resulting in termination of this toxicity study.

Based on the above study results, male and female ICR mice in single-sex groups orally received daily trelagliptin at 0 (vehicle[8]), 100, 300, or 1000 mg/kg/day for 24 months. In males in the 1000 and 300 mg/kg/day groups, treatment was discontinued at Weeks 91 and 97, respectively, at which points the number of surviving animals decreased to ≤20 per group, and terminal necropsy was performed at Week 105. In females, terminal necropsy was performed at Week 102, at which point the number of surviving animals in the 1000 mg/kg/day group decreased to 15. Animals surviving at the time of final necropsy in the 0, 100, 300, and 1000 mg/kg/day groups were 21 of 60 males, 21 of 60 males, 17 of 60 males, and 16 of 60 males, respectively, and 25 of 60 females, 23 of 60 females, 17 of 60 females, and 15 of 60 females, respectively.

Histopathological examination showed no tumor lesions associated with trelagliptin. Other toxicological findings included renal amyloidosis, amyloidosis of the liver, spleen, and thyroid, hepatic extramedullary hematopoiesis, and skin ulcer in the ≥100 mg/kg/day groups; skin desquamation, splenic extramedullary hematopoiesis, and renal papillary necrosis in the ≥300 mg/kg/day groups; and stained abdominal fur, increases in body weight and food consumption, penile ulcer, dilatation of bladder lumen, and thymus atrophy in the 1000 mg/kg/day group.

Amyloidosis and skin ulcer were observed in males in the ≥100 mg/kg/day groups and females in the ≥300 mg/kg/day groups, and therefore the NOAEL was determined to be <100 mg/kg/day in males and 100 mg/kg/day in females. The maximal non-carcinogenic dose was 1000 mg/kg/day. The exposure to unchanged trelagliptin ($AUC_{0\text{-}24\ h}$) on Week 78 in the 1000 mg/kg/day group was 656,885 ng·h/mL in males and 677,293 ng·h/mL in females, which are approximately 124- and 128-fold, respectively, the plasma exposure to unchanged trelagliptin in humans receiving the recommended clinical dose (100 mg).[25]

3.(iii).A.(4).3) Twenty-four-month repeated oral dose carcinogenicity study in rats (4.2.3.4.1-6)

Trelagliptin was orally administered daily to male SD rats at 0 (vehicle[8]), 25, 75, 250, or 750 mg/kg/day and to female SD rats at 0 (vehicle), 50, 150, 500, or 1500 mg/kg/day for 24 months. Treatment was discontinued in groups in which the number of surviving animals per sex decreased to 20, and terminal necropsy was performed on animals at the time the number of surviving animals per sex in a group decreased to 15 or at Week 104. Consequently, male animals received treatment for 96 to 104 weeks and were subjected to terminal necropsy at Week 104, and female animals received treatment for 94 to 101 weeks and were subjected to terminal necropsy at Weeks 94 to 101. Surviving animals at the time of terminal necropsy were 23 of 60 males, 18 of 60 males, 18 of 60 males, 20 of 60 males, and 16 of 60 males in the 0, 25, 75, 250, and 750 mg/kg/day groups, respectively, and 21 of 60 females, 21 of 60 females, 19 of 60 females, 15 of 60 females, and 14 of 60 females in the 0, 50, 150, 500, and 1500 mg/kg/day groups, respectively.

Histopathological examination showed no tumor lesions associated with trelagliptin. Other toxicological findings in males included hypertrophy of thyroid follicular epithelial cells in the ≥75 mg/kg/day groups; echinocytosis, an increase in hepatocyte vacuolization and centrilobular to panlobular hepatocellular hypertrophy of the liver, sinus histiocytosis of the mesenteric lymph nodes, degeneration and atrophy of the seminiferous tubules, and a decrease in sperm count and cellular debris in the epididymis in the ≥250 mg/kg/day groups; and reduced body weight gain, hyperplasia of hepatic oval cells, hyperplasia of follicular epithelial cells and colloid mineralization of the thyroid, pulmonary alveolar histiocytosis, and a decrease in splenic lymphocytes in the 750 mg/kg/day group. For females, the findings included colloid mineralization of the thyroid in the ≥50 mg/kg/day groups; an increase in hepatocyte vacuolization, centrilobular to panlobular hepatocellular hypertrophy, multinucleated hepatocytes of the liver, hypertrophy of thyroid follicular epithelial cells in the ≥150 mg/kg/day groups; pulmonary alveolar histiocytosis in the ≥500 mg/kg/day groups; and reduced body weight gain, decreased food consumption, hyperplasia of hepatic oval cells, hyperplasia of thyroid follicular epithelial cells, sinus histiocytosis of the mesenteric lymph nodes, alopecia, and a decrease in splenic lymphocytes in the 1500 mg/kg/day group.

As described above, hepatocyte vacuolization and degeneration of the seminiferous tubules were observed, and therefore the NOAEL was determined to be 75 mg/kg/day in males and 50 mg/kg/day in females. The maximal non-carcinogenic dose was 750 mg/kg/day in males and 1500 mg/kg/day in females. The exposure to unchanged trelagliptin ($AUC_{0\text{-}24\ h}$) on Week 78 in males in the 750 mg/kg/day group and females in the 1500 mg/kg/day group were 616,553 ng·h/mL and 1,062,392 ng·h/mL, respectively, which are approximately 116- and 201-fold, respectively, the plasma exposure to unchanged trelagliptin in humans receiving the recommended clinical dose (100 mg).[25]

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

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

Trelagliptin at 0 (vehicle[8]), 100, 300, or 1000 mg/kg/day was orally administered daily to male SD rats from 2 weeks before mating and throughout the mating period until the day before necropsy and to

female SD rats from 2 weeks before mating and throughout the mating period until gestation day 7. Male and female rats receiving the same dose were mated.

In males, reduced body weight gain and decreased food consumption were observed in the 1000 mg/kg/day, but no effects of trelagliptin were found at necropsy, or on the weight of reproductive organs or reproductive function (mean number of days until mating, number of mated animals, and number of pregnant animals). In females, reduced body weight gain and decreased food consumption were observed in the 1000 mg/kg/day group, but no effects of trelagliptin were found at necropsy, or on reproductive function (estrous cycle, copulation index, fertility index, corpora lutea count, number of implantation sites) or early embryonic development (preimplantation loss, postimplantation loss).

Based on the above, the NOAEL was determined to be 300 mg/kg/day for general toxicity of parent animals and 1000 mg/kg/day for reproductive functions and early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development study in rats (4.2.3.5.2-1)

Pregnant SD rats orally received daily trelagliptin at 0 (vehicle[8]), 100, 300, or 1000 mg/kg/day from gestation day 6 to gestation day17 and were subjected to caesarean section on gestation day 20.

As effects on maternal animals, reduced body weight gain and decreased food consumption were observed in the 1000 mg/kg/day group.

No effects of trelagliptin on embryo-fetal development were found in terms of the post-implantation loss, sex ratio, number of live fetuses, external surfaces, or visceral findings in the 1000 mg/kg/day group, but decreased fetal body weight and findings related to delayed ossification (unossified parietal bones, bent ribs, unossified sternebrae) were observed.

Based on the above, the NOAELs for maternal clinical signs and for embryo-fetal development were both determined to be 300 mg/kg/day. The exposure to unchanged trelagliptin ($AUC_{0\text{-}24\ h}$) at this dose was 166,650 ng·h/mL, which is approximately 31-fold the plasma exposure to unchanged trelagliptin in humans receiving the recommended clinical dose (100 mg).[25]

3.(iii).A.(5).3) Embryo-fetal development dose-range finding study in rabbits (4.2.3.5.2-2, Reference data)

Pregnant NZW rabbits orally received daily trelagliptin at 0 (vehicle[8]), 100, 250, 500, or 1000 mg/kg/day from gestation day 6 to gestation day 18 and were subjected to caesarean section on gestation day 29.

Death occurred in 4 of 6 rabbits in the 500 mg/kg/day group (3 pregnant rabbits, 1 non-pregnant rabbit) and 6 of 6 rabbits in the 1000 mg/kg/day group (3 pregnant rabbits, 3 non-pregnant rabbits). A total embryonic death was noted in 1 of the 2 animals subjected to caesarean section in the 500 mg/kg/day group.

As for effects on maternal animals, reduced body weight gain and decreases in food consumption and fecal volume were observed in the ≥250 mg/kg/day groups and body weight loss was observed in the ≥500 mg/kg/day groups. No effects of trelagliptin on embryo-fetal development were found in the 100 and 250 mg/kg/day groups, in which an adequate number of evaluable live fetuses was obtained.

3.(iii).A.(5).4) Embryo-fetal development study in rabbits (4.2.3.5.2-3)

Pregnant NZW rabbits orally received daily trelagliptin at 0 (vehicle[8]), 25, 80, or 250 mg/kg/day from gestation day 6 to gestation day 18 and were subjected to caesarean section on gestation day 29.

As for effects on maternal animals, deaths (2 of 23 animals), abortion (1 of 23 animals), reduced body weight gain, and decreased food consumption were noted in the 250 mg/kg/day group, but no effects of trelagliptin were found on necropsy findings, uterine weights, corpora lutea count, or number of implantation sites.

No effects of trelagliptin on embryo-fetal development were found in terms of the post-implantation loss, sex ratio, number of live fetuses, body weight, external surfaces, or visceral or skeletal findings.

Based on the above, the NOAEL was determined to be 80 mg/kg/day for maternal clinical signs and 250 mg/kg/day for embryo-fetal development. The exposure to unchanged trelagliptin ($AUC_{0\text{-}24\ h}$) on gestation day 18 in the 250 mg/kg/day group was 316,839 ng·h/mL, which is approximately 60-fold the plasma exposure to unchanged trelagliptin in humans receiving the recommended clinical dose (100 mg).[25]

3.(iii).A.(5).5) Study on prenatal and postnatal development including maternal function in rats (4.2.3.5.3-1)

Trelagliptin at 0 (vehicle[8]), 100, 300, or 1000 mg/kg/day was orally administered daily to pregnant SD rats from gestation day 6 to lactation day 20.

As for effects on maternal animals, trelagliptin-associated deaths occurred in 3 of 25 maternal animals in the 1000 mg/kg/day group. In this group, reduced body weight gain and decreased food consumption during pregnancy and decreased food consumption during lactation were also observed, but no effects of trelagliptin were found on the duration of pregnancy, rate of pregnancy, parturition, lactation, the number of implantation sites, or necropsy findings.

As for effects on the pups, an increase in stillbirth rate, decreases in survival rate and weaning rate until postnatal day 4, decreased pup body weight, and delays in pinna unfolding and cleavage of the balanopreputial gland were found in the 1000 mg/kg/day group, but no effects of trelagliptin were found on behavior or function of the offspring, learning/memory, reproductive function, or necropsy findings.

Based on the above, the NOAELs for dams and offspring were both determined to be 300 mg/kg/day.

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

3.(iii).A.(6).1) Phototoxicity study in hairless mice (4.2.3.7.7-2)

Male SKH1-*hr* hairless mice were treated with a single dose of trelagliptin at 0 (vehicle[8]), 500, 1000, or 2000 mg/kg and exposed to half the minimal erythema dose (MED) of artificial sunlight from 1 hour post-dose. Positive control animals received a single oral dose of lomefloxacin hydrochloride 200 mg/kg and were subjected to light exposure in the same manner from 30 minutes post-dose.

One of 10 animals in the 2000 mg/kg group died after the completion of light exposure. Erythema, as skin reactions, was observed in 2 of 10 animals in the 1000 mg/kg group on the following day of dosing, but these were not considered trelagliptin-induced changes because no such reactions were observed in the 2000 mg/kg group and because there was no dose-dependency.

Based on the above, trelagliptin was not considered phototoxic.

3.(iii).A.(6).2) Skin toxicity studies in monkeys (4.2.3.7.7-4, 4.2.3.7.7-5)

Because necrotizing lesions in monkey skin attributed to another DPP-4 inhibitor have been reported, trelagliptin at 0 (vehicle[8]), 5, 15, or 50 mg/kg/day was orally administered daily for 4 or 13 weeks to male and female cynomolgus monkeys, and skin toxicity was evaluated. The results showed no skin lesions associated with trelagliptin.

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

Cutaneous findings in dogs

Since reddish discoloration of body sites including the auricle, orbit, nose, and lips, and facial swelling were observed in the repeated oral dose toxicity studies in dogs, PMDA asked the applicant to explain the mechanism of these findings and the relevance to humans.

The applicant responded as follows:

Reddish discoloration of body sites including the auricle, orbit, nose, and lips, and facial swelling associated with trelagliptin were observed in dogs in the 250 mg/kg/day group in the 2-week repeated oral dose toxicity study, the ≥25 mg/kg/day groups in the 4-week study, the ≥30 mg/kg/day groups in the 13-week study, and the ≥50 mg/kg/day groups in the 39-week study. The detailed mechanism of these cutaneous findings is unknown. However, given the facts that similar symptoms have not been

observed in other species than dogs, and that the skins of the auricle, orbit, and face in dogs have a relatively high distribution density of mast cells and histamine content,[26] histamine released from mast cells may be involved in the mechanism. A secondary pharmacodynamic study (4.2.1.2-1) showed the absence of binding activity to human histamine H_1, H_2, or H_3 receptors, suggesting that trelagliptin has no agonistic or antagonistic activity on histamine receptors. On the basis of these findings, trelagliptin may be involved in the release of histamine from mast cells. In addition, no effects on the blood pressure or heart rate in dogs were found in a safety pharmacology study (4.2.1.3-2), thus, the above cutaneous findings may be attributed to localized effects on cutaneous microcirculation, rather than vasoactive effects that may impact the systemic circulation.

The highest dose that did not cause such findings in dogs was 15 mg/kg/day in the 39-week repeated oral dose toxicity study. The C_{max} (3263 ng/mL) and $AUC_{0\text{-}24\ h}$ (25,706 ng·h/mL) at this dose were approximately 5.4-fold and 4.9-fold, respectively, the human exposure (C_{max}, 603 ng/mL; $AUC_{0\text{-}24\ h}$, 5293 ng·h/mL)[27] at the recommended clinical dose (100 mg). Among adverse events classified into the SOC "Skin and subcutaneous tissue disorders" or hypersensitivity-related adverse events,[28] events reported by ≥2% of subjects in any of clinical studies of trelagliptin for which a causal relationship to the study drug could not be ruled out included eczema (2 of 67 subjects) in the short-acting insulin secretagogue combination therapy group (100 mg) in the phase III long-term monotherapy/combination therapy study (Study OCT-001), but no such events were reported in the 12.5, 25, 50, or 200 mg groups in the phase II dose-finding study (Study CCT-001).

Although the detailed mechanism of the cutaneous findings are unknown, these findings are unlikely to be relevant to humans because there is an approximately 5-fold safety margin and because no skin-related adverse events of concern were reported in clinical studies.

PMDA accepted the applicant's response. PMDA considers that there is no particular problem with the submitted data from a toxicological viewpoint.

4. Clinical data

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

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

Three types of film-coated tablets (Formulations A to C) were used in the clinical development of Zafatek. Details of the formulations used in clinical studies (evaluation data) are shown in Table 6. The level of formulation change between the two strengths (50 mg tablets, 100 mg tablets) of the proposed commercial formulation is Level [redacted] according to the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 0229-10, Attachment 1, dated February 29, 2012), and bioequivalence has been demonstrated by dissolution test; therefore, the two formulations were considered to be bioequivalent.

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[26] Emerson JL & Cross RF, *Am J Vet Res.* 1965;26:1379-82, Hidemasa Yamazaki, *Saishin Igaku.* 1961;11:3077-90

[27] C_{max} and $AUC_{0\text{-}24\ h}$ on Day 14 in healthy Japanese adult subjects in the multiple dose study (Study CPH-002) in which the subjects received a single oral dose of trelagliptin 100 mg on Day 1, followed by multiple oral doses of trelagliptin 100 mg once daily from Day 4 to Day 14 for 11 days.

[28] Defined as adverse event preferred terms classified into narrow scope Standardised MedDRA Queries (SMQs) of "Hypersensitivity" and "Angioedema" excluding those classified into the SOC "Skin and subcutaneous tissue disorders."

Table 6. Formulations used in clinical studies (evaluation data)

Formulation (strength)		Study (identifier)
Formulation A	3.125 mg	Phase I single-dose study (Study CPH-001)
	12.5 mg	Phase I single-dose study (Study CPH-001), Phase II dose-finding study (Study CCT-001)
	25 mg	Phase I single-dose study (Study CPH-001), Phase I multiple-dose study (Study CPH-002)
Formulation B	25 mg	Phase II dose-finding study (Study CCT-001)
	50 mg	Drug-drug interaction study (Study CPH-006), Phase II dose-finding study (Study CCT-001)
	100 mg	Phase II dose-finding study (Study CCT-001), Phase III confirmatory study (Study CCT-002) Phase III long-term monotherapy/combination therapy study (Study OCT-001) Phase III open-label study (Study OCT-002), Bioequivalence/food effect study (Study CPH-009), Thorough QT/QTc study (Study CPH-005)
Formulation C[a)]	50 mg	—
	100 mg	Bioequivalence/food effect study (Study CPH-009)

a) Proposed commercial formulation

Quantitation of the unchanged form of Trelagliptin Succinate (hereinafter "trelagliptin") and its metabolite (M-I) in human biomaterials was performed using high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). The lower limits of quantitation in plasma and urine were 1 and 5 ng/mL, respectively, for unchanged trelagliptin, and were 0.1 and 5 ng/mL, respectively, for the metabolite.

The results from the phase I single-dose study (Study CPH-001) and bioequivalence/food effect study (Study CPH-009) were submitted as the biopharmaceutic evaluation data. The results from the food effect study in non-Japanese subjects (Study 005) were submitted as the reference data. The results of the main studies are described below.

4.(i).A.(1) Bioequivalence/food effect study (5.3.1.1-1, Study CPH-009 [[redacted] to [redacted]])

4.(i).A.(1).1) Evaluation of bioequivalence

A randomized, open-label, two-treatment, two-period crossover study was conducted in healthy Japanese adult male subjects (target sample size, 24) to evaluate the bioequivalence between Formulations B and C.

In Periods I and II, subjects were randomly assigned to receive a single oral dose of trelagliptin 100 mg (Formulation B or C) under fasted conditions. The treatment periods were separated by a washout period of ≥13 days.

All of the 24 subjects treated were included in the pharmacokinetic and safety analysis sets.

A pharmacokinetic analysis showed that the adjusted mean ratios (Formulation C/Formulation B) [two-sided 90% confidence interval (CI)] for the maximum plasma concentration (C_{max}) of unchanged trelagliptin and the area under the plasma concentration-time curve from 0 to 168 hours ($AUC_{0\text{-}168\ h}$) were 1.09 [1.00, 1.18] and 0.99 [0.97, 1.00], respectively, meeting the acceptance criteria of bioequivalence specified in the "Guideline for Bioequivalence Studies of Generic Products" (PFSB/ELD Notification No. 0229-10, Attachment 1, dated February 29, 2012).

Safety analysis revealed that 1 adverse event (alanine aminotransferase [ALT] increased) was reported by 1 of 24 subjects receiving trelagliptin as Formulation B. A causal relationship between the study drug and the event was ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(i).A.(1).2) Evaluation of food effect

A randomized, open-label, two-treatment, two-period crossover study was conducted in healthy Japanese adult male subjects (target sample size, 12) to evaluate the food effect on pharmacokinetics and pharmacodynamics of trelagliptin following a single oral administration of Formulation C.

In Periods I and II, subjects was randomly assigned to receive a single oral dose of trelagliptin 100 mg (Formulation C) under fasted conditions or at 30 minutes after the start of breakfast (fed conditions). The treatment periods were separated by a washout period of ≥28 days.

All of the 12 subjects treated were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

Pharmacokinetic parameters (mean ± SD) of unchanged trelagliptin under fasted and fed conditions were 640 ± 189 and 734 ± 159 ng/mL, respectively, for C_{max}; 5906 ± 621 and 5762 ± 535 ng·h/mL, respectively, for $AUC_{0\text{-}168\ h}$; 1.3 ± 0.9 and 1.6 ± 0.5 hours, respectively, for time to reach the maximum plasma concentration (T_{max}); and 56.4 ± 6.7 and 53.4 ± 6.1 hours, respectively, for elimination half-life ($T_{1/2}$). The adjusted mean ratios (fed/fasted) [two-sided 90% CI] for C_{max} and $AUC_{0\text{-}168\ h}$ of unchanged trelagliptin in plasma were 1.17 [1.02, 1.34] and 0.98 [0.96, 1.00], respectively.

Analysis of pharmacodynamic effects showed that the maximum percent inhibition of plasma DPP-4 activity (E_{max}), the percent inhibition of plasma DPP-4 activity at 168 hours post-dose ($E_{168\ h}$), and $AUC_{0\text{-}168\ h}$ of the percent inhibition of plasma DPP-4 activity were all comparable between fasted and fed conditions.

No adverse events were reported.

4.(ii) Summary of clinical pharmacology studies

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

Results from studies using human biomaterials, 8 Japanese clinical studies (Studies CPH-001, CPH-002, CPH-006, CPH-009, CCT-001, CCT-002, OCT-001, and OCT-002), and 1 foreign clinical study (Study CPH-005) were submitted as evaluation data. Results from 9 foreign clinical studies (Studies 001 to 007, 101, and 102) were submitted as reference data. The results from the main studies are described below.

4.(ii).A.(1) Studies using human biomaterials (4.2.2.2-10, 4.2.2.2-11, 4.2.2.3-4, 4.2.2.3-5, 4.2.2.4-8 to 4.2.2.4-12, 4.2.2.6-1, 4.2.2.6-2)

The membrane permeability of ^{14}C-trelagliptin (3 μmol/L) was evaluated using Caco-2 cells. The results showed that the permeability coefficient (P_{app}) of ^{14}C-trelagliptin in the apical to basolateral direction (P_{app} A→B) and in the basolateral to apical direction (P_{app} B→A) after 2 hours of incubation was 2.00 and 6.42 × 10^{-6} cm/sec, respectively, with the P_{app} ratio (P_{app} B→A/P_{app} A→B) of 3.2. The ratio was 0.6 in the presence of quinidine, a P-glycoprotein inhibitor. The P_{app} A→B and P_{app} B→A of ^{14}C-mannitol (10 μmol/L) used as a low-permeability reference compound were found to be 0.75 and 0.82, respectively, and those of ^{14}C-antipyrine (10 μmol/L) used as a high-permeability reference compound were 49.0 and 49.5, respectively.

The effect of trelagliptin (0-500 μmol/L) on transport of ^{3}H-digoxin (3 μmol/L), a substrate for P-glycoprotein, both in the apical to basolateral direction (A→B) and in the basolateral to apical direction (B→A) was evaluated in Caco-2 cells that were incubated on transwell inserts. The results showed that the P_{app} ratio (P_{app} B→A/P_{app} A→B) after 2 hours of incubation was 6.7 to 3.8, showing a slight decrease in the ratio with increasing concentrations of trelagliptin.

The plasma protein binding was evaluated by adding ^{14}C-trelagliptin (0.1-10 μmol/L) to human plasma, and the binding was 22.1% to 27.6%.

The distribution in blood cells was evaluated by adding ^{14}C-trelagliptin (0.01-10 μmol/L) to human blood, and the distribution was 49.2% to 55.0%.

The metabolism of ^{14}C-trelagliptin (10 μmol/L) was evaluated in human cryopreserved primary hepatocytes. The results showed that unchanged trelagliptin accounted for 98.0% to 99.4% of the total radioactivity at 6 hours after the start of incubation, which corresponded to the longest reaction time.

Microsomes expressing human CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) were treated with ^{14}C-trelagliptin (10 μmol/L). The results showed that CYP2D6 played a major role in the formation of M-I and CYP3A4 mainly contributed to the formation of other metabolites.

The inhibitory effect of trelagliptin (0.1-100 μmol/L) on the metabolic activity of standard substrates for CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5) was evaluated in human liver microsomes. The results showed that CYP3A4/5-mediated midazolam 1'-hydroxylation was inhibited by 32%, but the IC_{50} values were all found to be >100 μmol/L. Inhibition of CYP isoforms by metabolites was evaluated by adding trelagliptin and nicotinamide adenine dinucleotide phosphate (NADPH)-generating system to the reaction system, pre-reacting them for 30 minutes, and adding individual CYP isoform substrates. The results showed that CYP3A4/5-mediated midazolam 1'-hydroxylation and testosterone 6β-hydroxylation were inhibited by 86% and 92%, respectively, and IC_{50} (mean ± SD) was 28 ± 2.0 μmol/L and 12 ± 1.0 μmol/L, respectively, while IC_{50} for inhibition of other CYP isoforms was >100 μmol/L.

Induction of CYP1A2, 2B6, and 3A4 in hepatocytes was evaluated by incubating primary human hepatocytes in media containing trelagliptin (1-100 μmol/L). The results showed no induction potential.

Inhibition of various transporters by trelagliptin (1-300 μmol/L) was evaluated in cells expressing breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, or organic cation transporter (OCT) 2. The results showed that trelagliptin inhibited the transport activity of OCT2 with IC_{50} of 55.9 μmol/L, but did not inhibit other transporters.

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 CPH-001 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy Japanese adult male subjects (target sample size, 110 subjects [10 subjects per step]) to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of a single dose of trelagliptin.

In Steps 1 to 9, a single oral dose of trelagliptin at a dose of 3.125, 6.25, 12.5, 25, 50, 100, 200, 400, or 800 mg was administered at 30 minutes before the start of breakfast. Separate groups were also set up to evaluate the food effect, and the subjects in the groups received a single oral dose of trelagliptin 12.5 or 100 mg under fasted conditions. Of 10 subjects included in each step, 8 subjects were allocated to the trelagliptin group and 2 subjects were allocated to the placebo group in a randomized manner.

All of the 110 subjects treated were included in the safety analysis set. Of these, 109 subjects were included in the pharmacodynamic analysis set, and the remaining 1 subject in the 12.5 mg group (fasted) was excluded from the analysis due to non-compliance with therapy. Of the 109 subjects, 107 subjects were included in the pharmacokinetic analysis set,[29] and the remaining 2 subjects (1 subject each in the 3.125 and 400 mg groups) were excluded from the analysis due to hemolysis of blood samples.

The pharmacokinetic parameters of unchanged trelagliptin after a single dose of trelagliptin were as shown in Table 7. The adjusted mean ratios (30 minutes before breakfast/fasted) [two-sided 90% CI] for C_{max} and $AUC_{0\text{-}168\ h}$ of unchanged trelagliptin in plasma were 1.43 [1.02, 2.00] and 0.95 [0.87, 1.05], respectively, after dosing at 12.5 mg and 1.17 [0.98, 1.41] and 1.01 [0.92, 1.10], respectively, after dosing at 100 mg.

[29] A total of 109 subjects were included in the urinary pharmacokinetic analysis set and 1 subject (non-compliance with therapy) in the 12.5 mg group (fasted) was excluded from the analysis.

Table 7. Pharmacokinetic parameters of unchanged trelagliptin following a single oral dose of trelagliptin

Dose	C_{max} (ng/mL)	$AUC_{0\text{-}168\ h}$ (ng·h/mL)	T_{max} (h)	$T_{1/2}$ (h)	CL/F (L/h)	$fe_{0\text{-}168\ h}$ (%)	CL_r (L/h)
3.125 mg	12.0 ± 2.7[a)]	250.5 ± 45.4[a)]	1.50 (1.00, 1.50)[a)]	38.4 ± 6.0[a)]	10.5 ± 1.7[a)]	64.5 ± 4.4	6.7 ± 1.3[a)]
6.25 mg	25.3 ± 4.9	466.5 ± 51.6	1.25 (1.00, 2.00)	43.2 ± 9.6	12.1 ± 1.6	66.5 ± 5.0	8.0 ± 1.3
12.5 mg	64.3 ± 30.7	789.2 ± 73.8	1.50 (1.00, 2.00)	43.8 ± 9.9	14.8 ± 1.4	72.5 ± 5.5	10.7 ± 1.2
25 mg	129.8 ± 41.8	1490.9 ± 217.3	1.25 (1.00, 2.50)	50.4 ± 11.7	16.3 ± 2.2	70.1 ± 5.4	11.4 ± 1.8
50 mg	268.3 ± 88.8	3001.4 ± 315.9	1.25 (1.00, 3.00)	53.9 ± 6.6	16.3 ± 1.7	71.5 ± 4.2	11.6 ± 1.4
100 mg	619.4 ± 77.3	6431.4 ± 792.2	1.25 (1.00, 2.00)	54.3 ± 7.9	15.4 ± 1.7	76.0 ± 5.2	11.6 ± 1.4
200 mg	1723.9 ± 512.5	13,347.4 ± 1057.7	1.25 (1.00, 3.00)	50.2 ± 9.2	14.8 ± 1.2	79.7 ± 2.9	11.8 ± 1.1
400 mg	3334.9 ± 788.1[a)]	25,046.6 ± 2483.9[a)]	1.00 (1.00, 2.50)[a)]	46.1 ± 4.2[a)]	16.0 ± 1.6[a)]	79.3 ± 8.3	12.6 ± 2.0[a)]
800 mg	7108.3 ± 1369.5	49,416.5 ± 3365.3	1.50 (1.00, 1.50)	39.0 ± 10.1	16.2 ± 1.1	81.7 ± 3.9	13.2 ± 1.3
12.5 mg (Fasted)	43.4 ± 12.9[a)]	831.7 ± 98.3[a)]	1.50 (1.00, 6.00)[a)]	44.9 ± 7.4[a)]	14.1 ± 1.7[a)]	68.3 ± 7.0[a)]	9.6 ± 0.8[a)]
100 mg (Fasted)	541.4 ± 155.7	6365.2 ± 490.5	1.75 (1.00, 4.00)	60.0 ± 6.8	15.4 ± 1.2	78.6 ± 4.0	12.1 ± 1.0

n = 8, mean ± SD, T_{max} is expressed as median (minimum, maximum).
C_{max}, Maximum plasma concentration; $AUC_{0\text{-}168\ h}$, Area under the plasma concentration-time curve from 0 to 168 hours; T_{max}, Time to reach the maximum plasma concentration; $T_{1/2}$, Elimination half-life; CL/F, Apparent systemic clearance; $fe_{0\text{-}168\ h}$, Cumulative urinary excretion rate up to 168 hours after dosing; CL_r, Renal clearance
a) n = 7

Pharmacodynamic effects was evaluated. The means of E_{max} and $E_{168\ h}$, as measures of inhibition of plasma DPP-4 activity, were found to be 95.0% to 99.9% and 14.2% to 86.9%, respectively, and the values increased in an almost dose-proportional manner. E_{max} and $E_{168\ h}$ were 98.7% and 49.7%, respectively, in the 50 mg group and 99.3% and 66.8%, respectively, in the 100 mg group. Change from baseline in $AUC_{11\text{-}24\ h}$ of plasma active GLP-1 concentrations adjusted based on baseline levels was used for analysis of variance with a dependent variable of $AUC_{11\text{-}24\ h}$ and a fixed effect of dose level. As a result, the concentrations were found to be significantly higher in all dose groups at 24 hours post-dose and only in the 800 mg group at 7 days post-dose as compared with the placebo group.

Safety analysis revealed 1 adverse event (syncope vasovagal) reported by 1 of 8 subjects in the 100 mg reported and 1 adverse event (puncture site pain) reported by 1 of 8 subjects in the 200 mg group. A causal relationship between the study drug and the events was ruled out. There were no deaths, 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 CPH-002 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in healthy Japanese adult male subjects (target sample size, 24 subjects [12 subjects per step]) to evaluate the safety, pharmacokinetics, and pharmacodynamic effects of multiple doses of trelagliptin.

Trelagliptin 100 or 200 mg was administered orally in a single dose at 30 minutes before breakfast, followed by a 2-day washout period, and the same dose was administered orally once daily at 30 minutes before breakfast from Day 4 to Day 14 for 11 days. Of 12 subjects included in each step, 9 subjects were allocated to the trelagliptin group and 3 subjects to the placebo group in a randomized manner.

All of the 24 subjects treated were included in the safety analysis set. Of these, 23 subjects were included in the urinary pharmacokinetic/pharmacodynamic analysis sets and the remaining 1 subject in the 200 mg group was excluded from the analysis (treatment discontinuation due to an adverse event). Of the 23 subjects, 22 subjects were included in the plasma pharmacokinetic analysis set, and the remaining 1 subject in the 100 mg group was excluded from the analysis due to hemolysis of blood samples.

The plasma pharmacokinetic parameters of unchanged trelagliptin after the initial dose (Day 1) and last dose (Day 14) were as shown in Table 8. The accumulation ratio[30] (last dose/initial dose, mean ± SD) for AUC in the 100 and 200 mg groups was 1.32 ± 0.11 and 1.16 ± 0.09, respectively, and that for C_{max} was 1.14 ± 0.32 and 1.16 ± 0.30, respectively.

Table 8. Plasma pharmacokinetic parameters of unchanged trelagliptin after the initial dose (Day 1) and last dose (Day 14)

Parameter	Initial dose (Day 1)		Last dose (Day 14)	
	100 mg (n = 8)	200 mg (n = 8)	100 mg (n = 8)	200 mg (n = 8)
C_{max} (ng/mL)	554.25 ± 121.97	1243.63 ± 243.28	602.63 ± 149.53	1388.63 ± 196.99
$AUC_{0\text{-inf}}$ (ng·h/mL)	5572.27 ± 793.19	11,364.85 ± 1024.33	-	-
$AUC_{0\text{-tau}}$ (ng·h/mL)	-	-	5292.95 ± 613.82	10,094.86 ± 889.87
T_{max} (h)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 3.00)	1.00 (1.00, 3.00)
$T_{1/2}$ (h)	17.89 ± 2.07	15.37 ± 1.31	35.12 ± 3.95	32.51 ± 3.16
CL/F (L/h)	18.26 ± 2.53	17.70 ± 1.59	19.14 ± 2.29	19.93 ± 1.73
fe (%)	5.89 ± 0.36[a)]	6.33 ± 0.32	71.73 ± 8.70[a)]	78.91 ± 4.81
CL_r (L/h)	12.88 ± 1.18	13.47 ± 1.35	14.11 ± 1.01	16.09 ± 1.97

Mean ± SD, T_{max} is expressed as median (minimum, maximum). -: Not calculated
C_{max}, Maximum plasma concentration; $AUC_{0\text{-inf}}$, Area under the plasma concentration-time curve from time 0 to infinity (extrapolated value); $AUC_{0\text{-tau}}$, Area under the plasma concentration-time curve from time 0 to tau hours; T_{max}, Time to reach the maximum plasma concentration; $T_{1/2}$, Elimination half-life; CL/F, Apparent systemic clearance; fe, Cumulative urinary excretion rate (% of total dose; from 0 to 72 hours for the initial dose, from the initial dose up to 72 hours post-dose for the last dose); CL_r, Renal clearance.
a) n = 9

Pharmacodynamic effects were evaluated in terms of inhibition of plasma DPP-4 activity. E_{max} (mean ± SD) following the initial dose in the placebo, 100 mg, and 200 mg groups was 1.72% ± 1.58%, 99.2% ± 0.33%, and 99.3% ± 0.33%, respectively, and E_{max} following the last dose was 5.88% ± 6.51%, 99.38% ± 0.37%, and 99.24% ± 0.16%, respectively. $E_{168\ h}$ (mean ± SD) following the last dose was −1.67% ± 9.01%, 81.3% ± 13.9%, and 81.2% ± 6.77%, respectively, and $AUC_{0\text{-}168\ h}$ (mean ± SD) of the percent inhibition of plasma DPP-4 activity following the last dose was -452 ± 1383% inhibition·h, 15,471 ± 835% inhibition·h, and 15,385 ± 324% inhibition·h, respectively.

Safety analysis revealed 1 adverse event (blood creatine phosphokinase increased) reported by 1 of 6 subjects in the placebo group and 1 adverse event (rash) reported by 1 of 9 subjects in the 200 mg group. Of these events, rash was assessed as an adverse event for which a causal relationship to the study drug could not be ruled out (i.e., adverse drug reaction). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

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

4.(ii).A.(3).1) Phase II dose-finding study (5.3.5.1-1, Study CCT-001 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with type 2 diabetes mellitus (target sample size, 306 subjects [51 subjects per group]) to determine the clinical dose of trelagliptin [for details of study design and the results of efficacy and safety, see "4.(iii).A.(1) Phase II dose-finding study"].

Following an 8-week run-in period, placebo or trelagliptin 12.5, 25, 50, 100, or 200 mg was orally administered once weekly before breakfast for 12 weeks.

Pharmacokinetics was evaluated. Pre-dose plasma concentrations of unchanged trelagliptin at each timepoint and plasma concentrations of unchanged trelagliptin obtained during a meal tolerance test at Week 8 were shown in Table 9.

[30] Defined as $AUC_{0\text{-tau}}$ (Day 14)/$AUC_{0\text{-}24\ h}$ (Day 1) and C_{max} (Day 14)/C_{max} (Day 1)

Table 9. Pre-dose plasma concentrations of unchanged trelagliptin at each timepoint and plasma concentrations of unchanged trelagliptin obtained during a meal tolerance test at Week 8

		12.5 mg	25 mg	50 mg	100 mg	200 mg
Pre-dose	Week 2	2.29 ± 3.59 (n = 51)	2.69 ± 3.95 (n = 50)	3.89 ± 7.72 (n = 45)	10.18 ± 25.75 (n = 52)	22.31 ± 101.90 (n = 52)
	Week 4	1.42 ± 1.64 (n = 54)	2.66 ± 4.16 (n = 51)	3.03 ± 3.71 (n = 51)	3.91 ± 3.14 (n = 55)	10.68 ± 23.53 (n = 54)
	Week 8	1.50 ± 2.13 (n = 53)	3.61 ± 8.34 (n = 51)	2.96 ± 3.86 (n = 51)	4.08 ± 4.90 (n = 54)	11.75 ± 23.85 (n = 54)
	Week 12	1.24 ± 1.51 (n = 53)	1.59 ± 1.38 (n = 50)	2.22 ± 1.06 (n = 51)	6.06 ± 14.66 (n = 53)	9.13 ± 26.91 (n = 52)
Meal tolerance test (Week 8)	Pre-dose[a)]	1.09 ± 0.85 (n = 41)	1.50 ± 0.79 (n = 37)	2.35 ± 1.06 (n = 45)	3.30 ± 1.23 (n = 43)	4.85 ± 4.23 (n = 46)
	0.5 hours after the start of meals	72.56 ± 31.00 (n = 41)	148.07 ± 61.13 (n = 37)	371.24 ± 162.02 (n = 44)	690.19 ± 329.69 (n = 43)	1699.97 ± 714.92 (n = 45)
	1 hour after the start of meals	70.48 ± 27.06 (n = 41)	130.46 ± 40.35 (n = 37)	300.31 ± 101.69 (n = 45)	643.96 ± 241.72 (n = 43)	1423.59 ± 485.51 (n = 45)
	2 hours after the start of meals	55.16 ± 15.01 (n = 41)	103.44 ± 27.90 (n = 37)	229.04 ± 72.21 (n = 45)	497.79 ± 172.87 (n = 43)	991.17 ± 359.44 (n = 45)

Unit: ng/mL, mean ± SD
a) Trelagliptin was administered at 0.5 hours before the start of meals.

Pharmacodynamic effects were evaluated. The percent inhibition of plasma DPP-4 activity (mean ± SD) 7 days after the last dose of the 12-week treatment was 2.43% ± 15.5% in the placebo group, 38.6% ± 20.9% in the 12.5 mg group, 55.4% ± 18.5% in the 25 mg group, 63.6% ± 15.7% in the 50 mg group, 77.4% ± 11.5% in the 100mg group, and 84.2% ± 6.82% in the 200 mg group. In the meal tolerance test, the percent inhibition of plasma DPP-4 activity following administration of placebo or trelagliptin 12.5 to 200 mg (0.5, 1, and 2 hours after the start of meals) was determined at Week 8, and the values ranged from 1.73% ± 11.4% to 4.45% ± 11.2% in the placebo group and from 94.3% ± 14.4% to 99.0% ± 2.39% in the trelagliptin groups. The changes in $AUC_{0\text{-}2\,h}$ (mean ± SD) of plasma active GLP-1 concentrations were 0.33 ± 2.79 pmol·h/L in the placebo group and 1.52 ± 2.96 to 4.80 ± 4.90 pmol·h/L in the trelagliptin groups.

4.(ii).A.(3).2) Phase III long-term monotherapy/combination therapy study (5.3.5.2-1, Study OCT-001 [[redacted] to [redacted]])

An open-label, uncontrolled, long-term treatment study was conducted in Japanese patients with type 2 diabetes mellitus who had an inadequate response to diet and exercise therapy alone or to one of existing oral hypoglycemic agents in addition to diet and exercise therapy (target sample size, 622 subjects [227 subjects in the trelagliptin alone group, 143 subjects in the trelagliptin plus sulfonylureas (SU) group, 63 subjects each in the trelagliptin plus short-acting insulin secretagogues (glinides), α-glucosidase inhibitors (α-GI), biguanides (BG), or thiazolidines (TZD) group]) to evaluate the long-term safety and efficacy of trelagliptin alone or in combination with other drugs [for details of study design and the results of efficacy and safety, see "4.(iii).A.(2).2) Phase III long-term monotherapy/combination therapy study"].

Following a 2-week run-in period, 100 mg of trelagliptin was orally administered once weekly before breakfast for 52 weeks.

Pharmacokinetics were evaluated, and plasma concentrations of unchanged trelagliptin at each timepoint in the treatment period were as shown in Table 10.

Table 10. Plasma concentrations of unchanged trelagliptin at each timepoint in the treatment period

Timepoint	Trelagliptin alone	Trelagliptin + SU	Trelagliptin + glinide	Trelagliptin + α-GI	Trelagliptin + BG	Trelagliptin + TZD
Week 2[a)]	521.51 ± 212.04 (n = 233)	503.71 ± 167.88 (n = 143)	500.01 ± 211.76 (n = 62)	368.45 ± 167.15 (n = 59)	489.72 ± 149.40 (n = 61)	468.18 ± 180.40 (n = 67)
Week 4[b)]	5.66 ± 11.20 (n = 246)	5.14 ± 9.63 (n = 153)	7.77 ± 15.26 (n = 66)	5.95 ± 9.85 (n = 64)	8.08 ± 13.26 (n = 68)	9.50 ± 16.70 (n = 72)
Week 8[b)]	6.46 ± 13.36 (n = 244)	9.41 ± 28.34 (n = 153)	6.90 ± 12.77 (n = 65)	7.50 ± 12.60 (n = 62)	7.25 ± 16.01 (n = 66)	6.77 ± 12.27 (n = 71)
Week 12[b)]	5.31 ± 10.51 (n = 243)	5.57 ± 11.17 (n = 151)	10.24 ± 25.66 (n = 65)	6.20 ± 12.40 (n = 62)	22.55 ± 80.16 (n = 65)	8.62 ± 17.17 (n = 71)

Unit: ng/mL, mean ± SD
a) Measured at 60 to 130 minutes after dosing of trelagliptin.
b) Measured before dosing of trelagliptin.

Pharmacodynamic effects were evaluated, and the percent inhibition of plasma DPP-4 activity (mean ± SD) after the end of the treatment period (52 weeks) was 79.0% ± 15.6% in the trelagliptin alone group, 76.5% ± 18.7% in the trelagliptin plus SU group, 78.9% ± 15.8% in the trelagliptin plus glinide group, 78.3% ± 18.3% in the trelagliptin plus α-GI group, 76.6% ± 19.6% in the trelagliptin plus BG group, and 79.6% ± 14.7% in the trelagliptin plus TZD group.

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

4.(ii).A.(4).1) Pharmacokinetic study in subjects with renal impairment (5.3.3.3-1, Study 101 [[redacted] to [redacted]], Reference data)

An open-label, parallel-group, comparative study was conducted in non-Japanese adult male and female subjects (target sample size, 48 subjects) to evaluate the effect of renal function on the pharmacokinetics and pharmacodynamic effect of a single dose of trelagliptin.

A single oral dose of trelagliptin 50 mg was administered under fasted conditions.

All of the 48 subjects treated (24 subjects with normal renal function [creatinine clearance[31] (Ccr) >80 mL/min], 6 subjects with mild renal impairment [Ccr >50 and ≤80 mL/min], 6 subjects with moderate renal impairment [Ccr ≥30 and ≤50 mL/min], 6 subjects with severe renal impairment [Ccr <30 mL/min], 6 patients with end-stage renal failure requiring hemodialysis) were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets. For each group of subjects with renal impairment, the study included control groups each consisting of 6 subjects with normal renal function matched for age, sex, body weight, and race.

The plasma pharmacokinetic parameters of unchanged trelagliptin after a single oral dose of trelagliptin 50 mg were as shown in Table 11. The adjusted mean ratios (subjects with renal impairment/subjects with normal renal function) [90% CI] for C_{max} and $AUC_{0\text{-}tlqc}$ of unchanged trelagliptin were 1.36 [1.00, 1.85] and 1.56 [1.26, 1.93], respectively, for subjects with mild renal impairment, 1.13 [0.82, 1.55] and 2.06 [1.69, 2.50], respectively, for subjects with moderate renal impairment, 1.09 [0.69, 1.73] and 3.01 [2.56, 3.54], respectively, for subjects with severe renal impairment, and 0.86 [0.61, 1.22] and 3.68 [2.94, 4.61], respectively, for patients with end-stage renal failure.

[31] Ccr calculated from the Cockcroft-Gault formula.

Table 11. Pharmacokinetic parameters of unchanged trelagliptin in plasma following a single oral dose of trelagliptin 50 mg

Parameter	Subjects with mild renal impairment (n = 6)	Subjects with moderate renal impairment (n = 6)	Subjects with severe renal impairment (n = 6)	Patients with end-stage renal failure[a] (n = 5)
	Subjects with normal renal function[b] (n = 6)	Subjects with normal renal function[b] (n = 6)	Subjects with normal renal function[b] (n = 6)	Subjects with normal renal function[b] (n = 6)
C_{max} (ng/mL)	245.33 (27.517)	277.67 (32.544)	256.67 (43.935)	157.40 (22.257)
	176.67 (21.139)	241.00 (25.973)	236.67 (32.764)	187.33 (33.488)
AUC_{0-tlqc} (ng·h/mL)	4856.23 (19.068)	7277.39 (14.760)	10,518.28 (16.102)	10,929.92 (16.565)
	3152.64 (21.013)	3570.50 (20.739)	3429.65 (9.814)	3001.39 (19.401)
T_{max} (h)	3.250 (1.000, 4.000)	1.750 (0.500, 3.000)	3.000 (1.500, 8.000)	6.000 (3.500, 6.000)
	2.750 (2.000, 4.000)	2.000 (0.500, 3.000)	2.250 (1.500, 4.000)	2.500 (1.000, 3.500)
$T_{1/2}$ (h)	67.82 (48.737)	82.60 (30.774)	88.45 (12.996)	107.97 (9.322)
	55.56 (35.879)	64.68 (43.789)	56.43 (14.060)	56.75 (31.847)
CL/F (L/h)	10.25 (17.458)	6.64 (13.958)	4.60 (20.047)	4.17 (19.274)
	15.66 (18.063)	13.91 (23.610)	14.00 (9.638)	16.46 (21.230)
Vz/F (L)	1038.17 (62.148)	788.98 (35.465)	579.83 (14.817)	647.02 (19.178)
	1193.74 (21.674)	1248.52 (32.761)	1135.46 (14.371)	1334.46 (41.023)
$Ae_{0-120\ h}$ (μg)	26,456.34 (31.006)	21,393.64 (34.053)	13,820.39 (35.476)	-
	25,825.10 (16.183)	28,258.48 (17.580)	26,438.85 (16.855)	31,070.20 (15.685)
$Fe_{0-120\ h}$ (%)	52.91 (31.006)	42.79 (34.053)	27.64 (35.476)	-
	51.65 (16.183)	56.52 (17.580)	52.88 (16.855)	62.14 (15.685)
CL_r (L/h)	5.23 (23.281)	2.88 (39.494)	1.30 (46.476)	-
	8.15 (28.016)	7.99 (35.989)	7.36 (14.861)	10.02 (14.054)

Mean (coefficient of variation [CV]%); T_{max} is expressed as median (minimum, maximum); -, Not calculated; Upper columns, Data from subjects with renal impairment; Lower columns, Data from subjects with normal renal function

C_{max}, Maximum plasma concentration; AUC_{0-tlqc}, Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; T_{max}, Time to reach the maximum plasma concentration; $T_{1/2}$, Elimination half-life; CL/F, Apparent systemic clearance; Vz/F, Apparent volume of distribution; $Ae_{0-120\ h}$, Cumulative urinary excretion up to 120 hours after dosing; $Fe_{0-120\ h}$, Cumulative urinary excretion rate up to 120 hours after dosing; CL_r, Renal clearance

a) Excluding 1 subject for whom plasma concentration measurements at all timepoints were determined as "No Recorded Result" due to defective chromatograms for determination of plasma pharmacokinetic parameters.

b) Subjects with normal renal function matched with subjects with renal impairment for age, sex, body weight, and race.

The plasma unbound fraction (mean) of trelagliptin at 3 hours post-dose in subjects with mild, moderate, and severe renal impairment and patients with end-stage renal failure was 74% to 76%, while that in subjects with normal renal function matched for baseline characteristics with each group of subjects with renal impairment was 76% to 79%.

The pharmacodynamic parameters related to inhibition of plasma DPP-4 activity following a single oral dose of trelagliptin 50 mg were as shown in Table 12.

Table 12. Parameters related to inhibition of plasma DPP-4 activity following a single oral dose of trelagliptin 50 mg

Parameter	Subjects with mild renal impairment (n = 6)	Subjects with moderate renal impairment (n = 6)	Subjects with severe renal impairment (n = 6)	Patients with end-stage renal failure (n = 6)
	Subjects with normal renal function[a] (n = 6)	Subjects with normal renal function[a] (n = 6)	Subjects with normal renal function[a] (n = 6)	Subjects with normal renal function[a] (n = 6)
E_{max} (%)	97.32 ± 0.47	97.77 ± 0.54	97.05 ± 1.10	96.12 ± 1.09
	97.23 ± 0.75	97.73 ± 0.50	97.55 ± 0.79	97.48 ± 0.61
$E_{168\ h}$ (%)	68.00 ± 11.03	81.97 ± 8.04	84.07 ± 4.33	87.92 ± 1.71
	49.90 ± 21.29	60.67 ± 23.49	64.78 ± 12.02	51.08 ± 20.54
$AUEC_{0-tlqc}$ (%inhibition·h)	21,222.98 ± 8.58	25,272.60 ± 7.12	26,769.88 ± 3.34	27,318.09 ± 1.56
	17,534.41 ± 11.72	20,305.87 ± 11.90	20,352.13 ± 8.98	18,093.49 ± 12.94

Mean ± CV%; Upper columns, Data from subjects with renal impairment; Lower columns, Data from subjects with normal renal function

E_{max}, Maximum inhibition rate of plasma DPP-4 activity; $E_{168\ h}$, Percent inhibition of plasma DPP-4 activity at 168 hours post-dose; $AUEC_{0-tlqc}$, Area under the effect-time curve of the inhibition of plasma DPP-4 activity from time 0 to the time of the last quantifiable concentration

a) Subjects with normal renal function matched for age, sex, body weight, and race with subjects with renal impairment.

Safety analysis revealed 1 adverse event (bradycardia) reported by1 of 24 subjects with normal renal function, 1 adverse event (oedema peripheral) reported by 1 of 6 subjects with moderate renal impairment, 1 adverse event (hyperkalaemia) reported by 1 of 6 subjects with severe renal impairment, and 1 adverse event (contusion) reported by 1 of 6 patients with end-stage renal failure. A causal relationship between the study drug and all these events was ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(4).2) Pharmacokinetic study in subjects with hepatic impairment (5.3.3.3-2, Study 102 [[redacted] to [redacted]], Reference data)

An open-label, parallel-group, comparative study was conducted in non-Japanese adult male and female subjects (target sample size, 16 subjects) to evaluate the effect of hepatic function on the pharmacokinetics and pharmacodynamic effects of a single dose of trelagliptin.

A single oral dose of trelagliptin 50 mg was administered under fasted conditions.

All of the 16 subjects treated (8 subjects with normal hepatic function, 8 subjects with moderate hepatic impairment[32]) were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

The pharmacokinetic parameters of unchanged trelagliptin in plasma following a single oral dose of trelagliptin 50 mg were as shown in Table 13. The adjusted mean ratios (subjects with moderate hepatic impairment/subjects with normal hepatic function) [90% CI] for C_{max} and $AUC_{0\text{-}tlqc}$ of unchanged trelagliptin were 0.96 [0.65, 1.40] and 1.03 [0.82, 1.30], respectively.

Table 13. Pharmacokinetic parameters of unchanged trelagliptin following a single oral dose of trelagliptin 50 mg

Parameter	Subjects with normal hepatic function (n = 7)[a)]	Subjects with moderate hepatic impairment (n = 8)
C_{max} (ng/mL)	145.71 (18.03)	171.91 (38.85)
$AUC_{0\text{-}tlqc}$ (ng·h/mL)	2245.29 (17.57)	2427.20 (21.52)
T_{max} (h)	3.00 (2.00, 6.00)	2.00 (0.75, 3.00)
$T_{1/2}$ (h)	22.60 (9.14)	24.92 (23.02)
CL/F (L/h)	21.08 (16.97)	19.18 (22.06)
Vz/F (L)	689.32 (20.73)	679.45 (25.39)
$Ae_{0\text{-}72\ h}$ (μg)	27,522.80 (38.35)	36,016.83 (42.72)
$Fe_{0\text{-}72\ h}$ (%)	55.05 (38.35)	72.03 (42.72)

Mean (CV%); T_{max} is expressed as median (minimum, maximum).
C_{max}, Maximum plasma concentration; $AUC_{0\text{-}tlqc}$, Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; T_{max}, Time to reach the maximum plasma concentration; $T_{1/2}$, Elimination half-life; CL/F, Apparent systemic clearance; Vz/F, Apparent volume of distribution; $Ae_{0\text{-}72\ h}$, Cumulative urinary excretion up to 72 hours after dosing; $Fe_{0\text{-}72\ h}$, Cumulative urinary excretion rate up to 72 hours after dosing
a) Excluding 1 subject with notably lower plasma concentrations of trelagliptin than other subjects.

Pharmacodynamic effects were analyzed in terms of inhibition of plasma DPP-4 activity in subjects with normal hepatic function and those with moderate hepatic impairment, the results was as follows: E_{max} (mean ± coefficient of variation [CV]%) was 96.8% ± 0.40% and 96.8% ± 1.03%, respectively; the percent inhibition of plasma DPP-4 activity up to 72 hours post-dose ($E_{72\ h}$) was 79.8% ± 5.63% and 79.8% ± 7.33%, respectively; and the area under the effect-time curve of the inhibition of plasma DPP-4 activity from time 0 to the time of the last quantifiable concentration ($AUEC_{0\text{-}tlqc}$) was 6344 ± 1.38% inhibition·h and 6340 ± 2.12% inhibition·h, respectively.

No adverse events were reported.

4.(ii).A.(5) Drug-drug interaction study (5.3.3.4-1, Study CPH-006 [[redacted] to [redacted]]; 5.3.3.4-2, Study 003 [[redacted] to [redacted]], Reference data; 5.3.3.4-3, Study 004 [[redacted]], Reference data)

Study CPH-006 was the only drug interaction study conducted in healthy Japanese adult male subjects, and the remaining studies (Studies 003 and 004) were conducted in healthy non-Japanese adult male and female subjects. The results of the individual studies were as shown in Table 14.

[32] Defined as subjects having hepatic impairment with a Child-Pugh score of 7 to 9

Table 14. Results of drug-drug interaction studies

Study No.	Dose of trelagliptin	Name and dose of concomitant drug	Analyte in plasma	Plasma pharmacokinetic parameters following monotherapy and combination therapy	
				C_{max}	$AUC_{0\text{-inf}}$
Study CPH-006[a)]	200 mg	Glimepiride 1 mg	Unchanged trelagliptin (n = 8)	1.04 [0.95, 1.15]	1.00 [0.97, 1.02][d)]
			Unchanged glimepiride (n = 8)	1.22 [1.10, 1.35]	1.04 [0.99, 1.08]
			Glimepiride metabolite (M1) (n = 8)	1.14 [1.08, 1.20]	1.05 [1.00, 1.11]
			Glimepiride metabolite (M2) (n = 8)	1.20 [1.09, 1.33]	1.10 [1.04, 1.17]
Study 003[b)]	100 mg	Metformin hydrochloride 2000 mg	Unchanged trelagliptin (n = 24)	1.08 [1.01, 1.17]	1.05 [1.02, 1.08][e)]
			Unchanged metformin (n = 24)	0.73 [0.67, 0.81]	0.90 [0.84, 0.97][e)]
Study 004[c)]	100 mg	Caffeine 200 mg	Unchanged caffeine (n = 18)	0.90 [0.85, 0.96]	0.97 [0.87, 1.08]
			1,7-Paraxanthine (n = 18)	0.91 [0.86, 0.95]	0.93 [0.86, 1.00]
		Tolbutamide 500 mg	Unchanged tolbutamide (n = 18)	0.96 [0.90, 1.02]	0.96 [0.90, 1.01]
			4-Hydroxy tolbutamide (n = 18)	0.90 [0.84, 0.97]	0.93 [0.91, 0.96]
			Carboxytolbutamide (n = 18)	1.02 [0.96, 1.09]	0.98 [0.96, 0.99]
		Dextromethorphan 30 mg	Unchanged dextromethorphan (n = 18)	1.11 [0.95, 1.30]	1.10 [0.95, 1.28]
			Dextrorphan (n = 18)	0.92 [0.87, 0.96]	0.97 [0.93, 1.00]
		Midazolam 4 mg	Unchanged midazolam (n = 18)	1.08 [1.01, 1.15]	1.07 [1.00, 1.14]
			1-Hydroxymidazolam (n = 18)	1.08 [1.00, 1.17]	0.98 [0.91, 1.06]

The adjusted mean ratio (combination therapy/monotherapy) [90% CI] for plasma pharmacokinetic parameters of unchanged trelagliptin or concomitant drug

a) Subjects received a single oral dose of glimepiride 1 mg at 30 minutes before breakfast on Day 1, oral doses of trelagliptin 200 mg at 30 minutes before breakfast on Day 3 to Day 12, and a single oral dose of trelagliptin 200 mg and glimepiride1 mg at 30 minutes before breakfast on Day 13. No treatment was administered on Day 2.

b) For assessment of the effect of metformin on the pharmacokinetics of trelagliptin, in Periods I and II, subjects were assigned to receive once-daily oral doses of trelagliptin 100 mg alone or in combination with twice-daily oral doses of metformin hydrochloride 1000 mg (administered once in the morning on Day 12 only), both for 12 days. The treatment periods were separated by a 9-day washout period. In addition, for assessment of the effect of trelagliptin on the pharmacokinetics of metformin hydrochloride, in Periods I and II, subjects were assigned to receive oral doses of metformin hydrochloride 1000 mg twice daily (administered once in the morning on Day 12 only) alone or in combination with oral doses of trelagliptin 100 mg once daily, both for 12 days. The treatment periods were separated by a 9-day washout period.

c) Subjects received a single dose of a CYP substrate cocktail (caffeine, tolbutamide, dextromethorphan, midazolam) on Day 1, oral doses of trelagliptin 100 mg once daily on Day 4 to Day 13, and single oral doses of trelagliptin 100 mg and the CYP substrate cocktail on Day 14. No treatment was administered on Days 2 and 3.

d) $AUC_{0\text{-}24\ h}$

e) $AUC_{0\text{-tau}}$

4.(ii).A.(6) Pharmacodynamic studies

Thorough QT/QTc study (5.3.3.1-5, Study CPH-005 [[redacted] to [redacted]])

A randomized, double-blind, parallel-group, placebo- and moxifloxacin-controlled study [33] was conducted in healthy non-Japanese adult male and female subjects (target sample size, 260 subjects) to evaluate the effect of trelagliptin 200 or 800 mg on the QT/QTc interval.

A single oral dose of placebo, trelagliptin 200 or 800 mg, or moxifloxacin 400 mg was administered 1.0 to 1.5 hours after meals.

All of the 260 subjects treated were included in the safety analysis set. Of these, 226 subjects were included in the pharmacodynamic analysis set and the remaining 34 subjects[34] were excluded from the

[33] Moxifloxacin, which was selected as a positive control, was administered in an open-label manner.

[34] Subjects who received a prohibited concomitant medication (6 subjects in the placebo group, 12 subjects in the trelagliptin 200 mg group, 5 subjects in the trelagliptin 800 mg group, and 11 subjects in the moxifloxacin group) were excluded.

analysis. Of the 226 subjects, 213 subjects were included in the pharmacokinetic analysis set and the remaining 13 subjects[35] were excluded from the analysis.

Plasma pharmacokinetic parameters of unchanged trelagliptin in the trelagliptin 200 and 800 mg groups were as follows: C_{max} (mean ± SD), 1001 ± 242 and 5186 ± 1378 ng/mL, respectively; $AUC_{0\text{-inf}}$ (mean ± SD), 12,288 ± 1945 and 52,311 ± 9833 ng·h/mL, respectively; CL/F (mean ± SD), 16.7 ± 2.75 and 15.8 ± 2.82 L/h, respectively; and T_{max} (median [minimum, maximum]), 2.05 [1.02, 6.03] and 2.52 [1.02, 4.02] hours, respectively.

An analysis of pharmacodynamic effects in terms of inhibition of plasma DPP-4 activity revealed that $E_{168\ h}$ (mean ± SD) in the trelagliptin 200 and 800 mg groups was 78.3% ± 8.59% and 87.7% ± 3.23%, respectively.

As for the electrocardiogram (ECG), the maximum upper limit of the 90% CI of the difference in the least squares mean change from baseline in QTcF interval between the trelagliptin and placebo groups (ΔΔQTcF) was 5.85 msec in the trelagliptin 200 mg group (6 hours post-dose) and 13.77 msec in the trelagliptin 800 mg group (2 hours post-dose), resulting in the upper limit of the CI of >10 msec in the trelagliptin 800 mg group. In the moxifloxacin group, the lower limit of the 90% CI of the ΔΔQTcF was in the range of 5.57 to 7.51 msec at 2 to 6 hours post-dose, resulting in the lower limit of the CI of >5 msec.

Safety analysis revealed 51 adverse events reported by 27 of 64 subjects in the placebo group, 68 adverse events reported by 35 of 66 subjects in the trelagliptin 200 mg group, 47 adverse events reported by 26 of 65 subjects in the 800 mg group, and 61 adverse events reported by 35 of 65 subjects in the moxifloxacin group. Adverse drug reactions were reported by 16 of 64 subjects (hunger [5 subjects], and rash, dizziness, abdominal discomfort, vasodilatation, mouth ulceration, ALT increased, abdominal pain upper, diarrhoea, dizziness/hunger/headache, hunger/abdominal discomfort/headache, and vision blurred/chest pain/dysgeusia [1 subject each]) in the placebo group; 17 of 66 subjects (hunger [7 subjects], dizziness [3 subjects], and chest discomfort, headache, dizziness/headache, constipation/headache, respiratory tract irritation/upper respiratory tract infection, abdominal pain/headache, and dysgeusia/headache [1 subject each]) in the trelagliptin 200 mg group; 16 of 65 subjects (hunger [4 subjects], headache, dizziness, and dysgeusia [2 subjects each], and lethargy, hunger/back pain, dizziness/vasodilatation, dysgeusia/chest pain, dysgeusia/ALT increased/aspartate aminotransferase (AST) increased, and lethargy/hunger/headache [1 subject each]) in the 800 mg group; and 20 of 65 subjects (hunger [5 subjects], headache [3 subjects], lethargy and dizziness [2 subjects each], and dyspepsia, epistaxis, erythema, rash, vision blurred, hunger/dizziness, headache/lethargy, and lethargy/gingival bleeding/meteorism [1 subject each]) in the moxifloxacin group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(7) Other studies

Population pharmacokinetic analysis (5.3.3.5-1)

Using plasma unchanged trelagliptin concentration data at 5132 sampling points obtained from 3 Japanese studies (Studies CCT-001, OCT-001, and CPH-001), a population pharmacokinetic (PPK) analysis was performed using nonlinear mixed effects modeling (NONMEM software ver.7) based on a 2-compartment model with first-order absorption and elimination to evaluate the effects of subject-specific variable factors and concomitant drugs on the pharmacokinetics of unchanged trelagliptin. The PPK analysis included 974 subjects (678 male subjects and 296 female subjects) with the following baseline characteristics (mean [minimum, maximum]): age, 58.2 [20, 89] years; body weight, 67.3 [33.3, 124.6] kg; BMI, 25.1 [15.2, 43.9] kg/m^2; lactate dehydrogenase (LDH), 179.0 [97, 357] U/L; Ccr, 109.5 [27, 399] mL/min; and body surface area, 1.72 [1.1, 2.5] m^2.

[35] Subjects with one or more missing or rejected data due to inadequacy in pharmacokinetic testing and observation (4 subjects in the placebo group, 2 subjects in the trelagliptin 200 mg group, 3 subjects in the trelagliptin 800 mg group, and 4 subjects in the moxifloxacin group) were excluded. These subjects also included dropouts and those who withdrew from treatment during the period from hospitalization to the completion of examination at 8 days post-dose (2 subjects in the placebo group, 1 subject in the trelagliptin 800 mg group, and 1 subject in the moxifloxacin group).

Covariates on the parameter estimates (clearance [CL], central compartment volume of distribution [V2]) of each individual to be included in the established basic model were selected using forward selection and backward elimination approaches from the following patients' baseline parameters: sex, age, body weight, BMI, body surface area, Ccr, and laboratory values (hematocrit, hemoglobin, ALT, AST, γ-glutamyl transpeptidase [γ-GTP], alkaline phosphatase [ALP], total bilirubin, total protein, albumin, creatinine, blood urea nitrogen [BUN], creatinine kinase [CK], LDH). As a result, Ccr and LDH were identified as covariates on CL, and body surface area was identified as a covariate on V2. In addition, subject type (patients with type 2 diabetes mellitus or healthy adults) was identified as another covariate on V2.

The results of the PPK analysis showed that V2 was higher in healthy adult subjects by 17.1% than in patients with type 2 diabetes mellitus. In addition, CL increased from 7.74 to 14.74 L/h with increasing Ccr from 30 to 100 mL/min, and decreased from 16.40 to 13.85 L/h with increasing LDH from 132 to 235 U/L. Furthermore, V2 increased from 117.71 to 225.49 L with increasing body surface area from 1.41 to 2.04 m^2. As shown above, there was a tendency toward an increase in plasma concentrations of unchanged trelagliptin with decreasing Ccr or body surface area or with increasing LDH. In addition, the relative bioavailability of unchanged trelagliptin after the concomitant use of trelagliptin with α-GI was shown to be 24.9% lower than that after trelagliptin monotherapy.

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

4.(ii).B.(1) Pharmacokinetic characteristics of trelagliptin

PMDA asked the applicant to discuss the pharmacokinetics (absorption, distribution, metabolism, and excretion) of trelagliptin versus those of alogliptin benzoate ("alogliptin"), a DPP-4 inhibitor with a similar structure[19] to trelagliptin, in clinical studies, and then to explain the pharmacokinetic characteristics of trelagliptin in relation to the persistent inhibition of DPP-4 activity and hypoglycemic activity etc.

The applicant responded as follows:
A comparison of the pharmacokinetic parameters of trelagliptin and alogliptin calculated from data up to 72 hours post-dose obtained from phase I single-dose studies (Study CPH-001 for trelagliptin and Study CPH-001 [SYR-322] for alogliptin) revealed no substantial difference in the pharmacokinetic parameters related to absorption or excretion. As for distribution, a comparison of the plasma unbound fractions of trelagliptin and alogliptin obtained from clinical pharmacology studies in subjects with renal impairment (Foreign Study 101 for trelagliptin and Foreign Study 006 [SYR-322] for alogliptin) revealed no substantial difference between the two studies and no impact of renal impairment in both studies. As for metabolism, a metabolite M-I, which is produced by N-demethylation and which has pharmacological activity, was identified as a major metabolite of trelagliptin, but AUC of the metabolite M-I was <1% of that of trelagliptin. As major metabolites of alogliptin, M-I, which is produced by N-demethylation and which has pharmacological activity, and M-II, which is produced by N-acetylation and which has no pharmacological activity, were identified, but AUCs of metabolites M-I and M-II were <1% and <6%, respectively, of that of alogliptin. Based on the above, trelagliptin and alogliptin are considered to have similar pharmacokinetic characteristics.

The relationship of pharmacodynamic effects with hypoglycemic activity was evaluated. Trough plasma concentrations of trelagliptin at 7 days post-dose were lower[36] than those of alogliptin at 24 hours after administration at the recommended clinical dose, but there was no substantial difference between trelagliptin and alogliptin in the inhibition of DPP-4 activity or hypoglycemic activity (as reflected by fasting blood glucose etc.) at the respective trough point.[37] The above findings suggest that trelagliptin can exert persistent hypoglycemic activity up to 7 days post-dose due to its potent inhibition of DPP-4 activity even at a lower plasma concentration.

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[36] The plasma concentration of unchanged trelagliptin at 7 days after the last dose of trelagliptin 100 mg administered once weekly for 12 weeks was 6.062 ng/mL, while the plasma alogliptin concentration at 1 day after the last dose of alogliptin 25 mg administered once daily for 12 weeks was 25.0 ng/mL.

[37] The percent inhibition of DPP-4 activity and the change in fasting blood glucose (means) were 78.1% and -11.5 mg/dL, respectively, at 7 days after the last dose of trelagliptin 100 mg administered once weekly for 12 weeks and 81.3% and -17.5 mg/dL, respectively, at 1 day after the last dose of alogliptin 25 mg administered once daily for 12 weeks.

PMDA considers as follows:
The applicant's explanation on the relationships of pharmacokinetics and pharmacodynamic effects with hypoglycemic activity is understandable. However, the marked increase in plasma trelagliptin concentrations associated with high-dose intermittent administration (trelagliptin 100 mg once weekly) and long-term effects of persistent inhibition of DPP-4 activity will be further reviewed in the clinical sections in terms of safety [see "4.(iii).B.(6) Dosage and administration" and "4.(iii).B.(3) Safety"].

4.(ii).B.(2) Pharmacokinetics in subjects with renal or hepatic impairment
4.(ii).B.(2).1) Subjects with renal impairment
Foreign Study 101 showed a tendency toward increased exposure to trelagliptin (plasma concentrations of unchanged trelagliptin) and increased half-life of trelagliptin with increasing severity of renal impairment. PMDA asked the applicant to explain the cause of the tendency.

The applicant responded as follows:
Plasma concentration-time profile of trelagliptin is characterized by increased elimination time with increasing severity of renal impairment. In addition, a correlation is observed between Ccr and $AUC_{0\text{-}tlqc}$ of trelagliptin, indicating an increasing trend in $AUC_{0\text{-}tlqc}$ of trelagliptin with decreasing Ccr. Since trelagliptin has a low protein binding and is predominantly excreted from the kidneys as unchanged trelagliptin with being little metabolized, its CLr in Foreign Study 101 decreased depending on severity of renal impairment, with the mean value being 5.23, 2.88, and 1.30 L/h in subjects with mild, moderate, and severe renal impairment, respectively (5.3.3.3-1). However, the mean plasma unbound fraction of trelagliptin was 74% to 76% in subjects with renal impairment and 76% to 79% in healthy adult subjects matched for baseline characteristics (5.3.3.3-1), indicating no impact of renal impairment.

Based on the above, the observed increase in AUC and $T_{1/2}$ associated with severity of renal impairment is considered attributable to the delayed excretion of trelagliptin due to a decrease in renal function.

The applicant explains that the estimated trelagliptin exposures in subjects with mild renal impairment receiving trelagliptin 100 mg once weekly for 12 weeks and subjects with moderate renal impairment receiving trelagliptin 50 mg once weekly for 12 weeks were almost comparable to those in subjects with normal renal function. Thus, PMDA asked the applicant to discuss the estimated trelagliptin exposures in subjects with severe renal impairment and patients with end-stage renal failure receiving multiple doses of trelagliptin 25, 50, or 100 mg and to compare those in subjects with normal renal function, thereby explaining the appropriateness of the precautions for treatment of patients with mild, moderate, or severe renal impairment and patients with end-stage renal failure.

The applicant responded as follows:
The pharmacokinetic parameters were estimated by fitting the 2-compartment model with first-order absorption and elimination to the single-dose trelagliptin plasma concentration data from subjects with severe renal impairment and patients with end-stage renal failure in Foreign Study 101 and from subjects with normal renal function matched for baseline characteristics with the subjects with renal impairment for each subject. The pharmacokinetic parameters were used to predict plasma concentration-time profiles after 12-week treatment with once-weekly trelagliptin 25, 50, and 100 mg. The results showed that a steady state was expected to be nearly reached after 12-week treatment with once-weekly trelagliptin in subjects with severe renal impairment or patients with end-stage renal failure. In addition, an evaluation of accumulation ratio following multiple doses of trelagliptin 100 mg revealed that the mean ratio for $AUC_{0\text{-}168\ h}$ (steady state [after 12 weeks of treatment]/initial dose [up to 168 hours post-dose]) in subjects with normal renal function, subjects with severe renal impairment, and patients with end-stage renal failure was 1.03 to 1.05, 1.21, and 1.37, respectively, and the mean ratio for C_{max} was 1.01, 1.11, and 1.25, respectively, indicating a trend towards a slightly higher ratio in subjects with severe renal impairment and patients with end-stage renal failure than in subjects with normal renal function.

$AUC_{0\text{-}168\ h}$ in subjects with severe renal impairment or patients with end-stage renal failure receiving 12-week treatment with trelagliptin 50 or 100 mg was higher than that in subjects with normal renal function receiving multiple doses of trelagliptin 100 mg. However, $AUC_{0\text{-}168\ h}$ in subjects with severe renal impairment and in patients with end-stage renal failure receiving 12-week treatment with trelagliptin 25

mg was 0.77- and 0.94-fold, respectively, that in subjects with normal renal function receiving multiple-dose treatment with trelagliptin 100 mg; thus, the exposures were expected to be almost comparable to that in healthy adult subjects. C_{max} in subjects with severe renal impairment or patients with end-stage renal failure receiving 12-week treatment with trelagliptin 100 mg was comparable to that in subjects with normal renal function, while C_{max} in subjects with severe renal impairment or patients with end-stage renal failure receiving 12-week treatment with trelagliptin 25 or 50 mg was lower than that in subjects with normal renal function receiving multiple doses of trelagliptin 100 mg.

Based on the consideration on single- and multiple-dose pharmacokinetics evaluated in Foreign Study 101 (5.3.3.3-1) and the effect of renal impairment on safety in Japanese clinical studies (Studies CCT-001, CCT-002, OCT-001, and OCT-002) (5.3.5.3-1), adjustment of the regimen of trelagliptin for subjects with mild renal impairment was considered unnecessary, and one-half (50 mg) of the recommended dose (100 mg) was selected for subjects with moderate renal impairment. However, given the facts that there is almost no experience with use of trelagliptin in subjects with severe renal impairment or patients with end-stage renal failure and that trelagliptin is the world's first once-weekly oral hypoglycemic agent and at the same time is a renally excreted drug, trelagliptin should be contraindicated in these patient populations at present.

Taking account of these points, in the draft package insert, the Precautions for Dosage and Administration and Careful Administration sections include proper precautionary statements that blood concentrations of trelagliptin would increase due to delayed excretion in patients with moderate renal impairment and that trelagliptin should be used carefully with reduced dose as appropriate in patients with moderate renal impairment. The Pharmacokinetics section includes the pharmacokinetic study data of trelagliptin in patients with renal impairment to provide information. In addition, given the observed increase in blood concentrations of trelagliptin in proportion to the severity of renal impairment and the limited number of patients with moderate renal impairment who participated in the previous clinical studies, safety information on patients with moderate renal impairment will be collected via post-marketing surveillance.

4.(ii).B.(2).2) Subjects with hepatic impairment

PMDA asked the applicant to explain why precautions should be given for the use of trelagliptin in subjects with severe hepatic impairment, discussing the effect of renal impairment on the pharmacokinetics of and the safety of trelagliptin in subjects with severe hepatic impairment.

The applicant responded as follows:

The effect of hepatic impairment on the pharmacokinetics is associated with decreases in the amount of drug-metabolizing enzymes such as CYPs and plasma proteins. However, after oral administration of trelagliptin 100 mg in healthy adult subjects, $AUC_{0\text{-}inf}$ of unchanged trelagliptin and metabolite M-I was 6601.739 and 21.8729 ng·h/mL, respectively, and the cumulative urinary excretion rate was 75.96% and 0.26%, respectively, indicating that trelagliptin hardly undergoes metabolism and predominantly excreted through the kidneys as unchanged trelagliptin (5.3.3.1-1). In addition, protein binding of trelagliptin was 22.1% to 27.6% (4.2.2.3-4), showing a low protein binding in human plasma. The results of a clinical pharmacology study in subjects with hepatic impairment (Foreign Study 102) showed no substantial difference in C_{max} or AUC of unchanged trelagliptin between subjects with moderate hepatic impairment and healthy adult subjects, indicating no effect of hepatic impairment on the pharmacokinetics of trelagliptin. Although studies in subjects with severe hepatic impairment have not been conducted, the above findings suggest that the pharmacokinetics of trelagliptin is virtually unchanged even in subjects with severe hepatic impairment receiving trelagliptin. In addition, safety analysis of adverse events in patients who received trelagliptin alone or in combination with other drugs indicates that the risk of specific adverse events is unlikely to be increased depending on the presence or absence of hepatic impairment. The applicant therefore considers that adjustment of the regimen is unnecessary even in subjects with severe hepatic impairment in light of the effect of renal impairment on the pharmacokinetics of and the safety of trelagliptin, and thus that precautions for the use of trelagliptin in patients with hepatic impairment including patients with severe hepatic impairment is unnecessary.

From a pharmacokinetic viewpoint, PMDA accepted the applicant's following responses about the use of trelagliptin in patients with renal or hepatic impairment: (1) no adjustment of the regimen of trelagliptin is required for patients with mild renal impairment; (2) one-half of the recommended dose should be used in patients with moderate renal impairment; (3) at present, trelagliptin should be contraindicated in patients with severe renal impairment or end-stage renal failure; and (4) no precautions are required for the use of trelagliptin in patients with hepatic impairment. However, these points will be further discussed in the clinical section in terms of safety [see "4.(iii).B.(7) Use in special populations"].

4.(ii).B.(3) QT interval prolongation

The applicant explained as follows:

In the thorough QT/QTc study, the maximum upper limit of the 90% CI of ΔΔQTcF was <10 msec in subjects receiving 200 mg, while >10 msec in subjects receiving 800 mg (2 hours post-dose). C_{max} (mean ± SD) of unchanged trelagliptin in plasma at 200 and 800 mg of trelagliptin was 1001 ± 242 and 5186 ± 1378 ng/mL, respectively, and T_{max} (median [minimum, maximum]) of unchanged trelagliptin in plasma was 2.05 [1.02, 6.03] and 2.52 [1.02, 4.02] hours, respectively. A PPK analysis of 3 Japanese studies (Studies CCT-001, OCT-001, and CPH-001) was used to estimate the maximum plasma trelagliptin concentration in patients with type 2 diabetes mellitus receiving trelagliptin 100 mg. As a result, the maximum plasma trelagliptin concentration was estimated to be 1134 ng/mL in patients with type 2 diabetes mellitus who had potential factors contributing to an increase in the maximum plasma trelagliptin concentrations, i.e., low body surface area (a minimum of 1.11 m^2), low Ccr (a minimum of 27 mL/min), and high LDH (a maximum of 357 IU/L). In addition, based on data from the thorough QT/QTc study, plasma trelagliptin concentration at which the upper limit of the 90% CI of ΔΔQTcF falls slightly below 10 msec was estimated using mixed effects modeling with time-matched change from baseline in QTcF interval as a response variable, plasma trelagliptin concentrations as a fixed effect, and subjects as a random effect. As a result, the "estimated maximum plasma trelagliptin concentration that would have no impact on the QT/QTc interval" was 4363 ng/mL. The "maximum plasma trelagliptin concentration expected to be found in patients with type 2 diabetes mellitus receiving 100 mg (1134 ng/mL)" was approximately one-fourth of the "estimated maximum plasma trelagliptin concentration that would have no impact on the QT/QTc interval (4363 ng/mL)." In addition, the "maximum plasma concentration expected to be found in patients with type 2 diabetes mellitus receiving 100 mg" (1134 ng/mL) was not substantially different from the mean C_{max} (1001 ng/mL) in subjects in the 200 mg group, in whom no QT/QTc interval prolongation was observed, in Study CPH-005. Therefore, the risk of QT/QTc interval prolongation or proarrhythmia caused by trelagliptin 100 mg is considered unlikely.

PMDA accepted the applicant's explanation. However, the risk of QT/QTc interval prolongation or proarrhythmia will be reviewed in the clinical section [see "4.(iii).B.(3).4) Proarrhythmic risk associated with QT/QTc interval prolongation"].

4.(iii) Summary of clinical efficacy and safety

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

The evaluation data submitted consisted of the results from a phase II dose-finding study (Study CCT-001), phase III confirmatory study (Study CCT-002), phase III long-term monotherapy/combination therapy study (Study OCT-001), and phase III open-label study (Study OCT-002) conducted in Japanese patients with type 2 diabetes mellitus. The reference data submitted consisted of the results from foreign phase II dose-finding studies in patients with type 2 diabetes mellitus (Foreign Studies 007 and 006). The results from the main studies are described below. The data use HbA1c as defined by the Japanese Diabetes Society (JDS), unless otherwise noted.

4.(iii).A.(1) Phase II dose-finding study (5.3.5.1-1, Study CCT-001 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with type 2 diabetes mellitus[38] (target sample size, 306 subjects [51 subjects per group]) to determine the clinical dose of trelagliptin.

[38] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 years; who have received a specific diet and exercise therapy (if any) for ≥4 weeks prior to the start of the run-in period (at 8 weeks before randomization); with HbA1c of ≥6.5% and <10.0% at 4 weeks after the start of the run-in period (at 4 weeks before randomization); for whom change in HbA1c between at 4 weeks after the start of the run-in period and at the start of the run-in period is >10.0% of HbA1c at the start of the run-in period.

Following an 8-week run-in period, placebo or trelagliptin 12.5, 25, 50, 100, or 200 mg was orally administered before breakfast once weekly for 12 weeks.

Of 322 subjects treated, 321 subjects were included in the safety analysis set and full analysis set (FAS), and the FAS was the primary efficacy analysis set. The remaining 1 subject in the 200 mg group was excluded from the analysis (due to major GCP violation [verbal consent only]). The reasons for study discontinuation (11 subjects) were adverse events (1 subject in the placebo group, 1 subject in the 100 mg group, 2 subjects in the 200 mg group), lack of efficacy (3 subjects in the placebo group), voluntary withdrawal (1 subject in the 12.5 mg group, 1 subject in the 25 mg group), a major protocol deviation (1 subject in the 25 mg group), and others[39] (1 subject in the 100 mg group).

The changes in HbA1c from the end of the run-in period to the end of the treatment period (Week 12), the primary efficacy endpoint, were as shown in Table 15. In order to determine the clinical dose of trelagliptin, all trelagliptin groups and the placebo group were compared using a closed testing procedure. The results showed a significant reduction in HbA1c in all trelagliptin groups relative to the placebo group (contrast test using an analysis of covariance [ANCOVA] model, $P < 0.0001$ for all comparisons).

Table 15. Change in HbA1c from the end of the run-in period to the end of the treatment period (Week 12) (FAS)

	Placebo	Trelagliptin				
		12.5 mg	25 mg	50 mg	100 mg	200 mg
End of run-in period	7.74 ± 0.937 (n = 55)	7.78 ± 0.889 (n = 54)	7.59 ± 0.770 (n = 52)	7.67 ± 0.852 (n = 51)	8.00 ± 0.956 (n = 55)	7.44 ± 0.764 (n = 54)
End of treatment period (Week 12)	8.08 ± 1.336 (n = 55)	7.40 ± 0.854 (n = 54)	7.26 ± 0.926 (n = 51)[a)]	7.25 ± 0.811 (n = 51)	7.45 ± 0.955 (n = 55)	6.90 ± 0.770 (n = 54)
Change [95% CI][b)]	0.34 ± 0.067 [0.210, 0.474] (n = 55)	-0.37 ± 0.068 [-0.502, -0.236] (n = 54)	-0.32 ± 0.070 [-0.459, -0.184] (n = 51)	-0.42 ± 0.070 [-0.554, -0.280] (n = 51)	-0.54 ± 0.068 [-0.671, -0.404] (n = 55)	-0.55 ± 0.068 [-0.689, -0.420] (n = 54)
P-value[c)]	-	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$

Unit: %, mean ± SD. Data are expressed as adjusted mean ± standard error (SE) for change.

a) One subject was excluded because the data at the end of the treatment period were unavailable.

b) ANCOVA model with change in HbA1c at the end of the treatment period as a response variable, and treatment and HbA1c at the end of the run-in period as covariates.

c) Contrast test versus placebo, adjustment of multiplicity by closed testing procedure evaluating the highest dose first, two-sided significance level of 0.05

The results for major secondary endpoints were as shown in Table 16.

Table 16. Results for major secondary endpoints (FAS)

		Placebo	Trelagliptin				
			12.5 mg	25 mg	50 mg	100 mg	200 mg
Fasting blood glucose (mg/dL)	End of run-in period	163.8 ± 40.00 (n = 55)	162.2 ± 31.34 (n = 54)	162.6 ± 28.66 (n = 52)	165.7 ± 37.47 (n = 51)	170.0 ± 37.27 (n = 55)	158.3 ± 32.35 (n = 54)
	End of treatment period (Week 12)	173.6 ± 46.26 (n = 55)	156.8 ± 33.46 (n = 54)	152.1 ± 25.55 (n = 51)	158.0 ± 40.32 (n = 51)	158.5 ± 34.85 (n = 55)	145.9 ± 30.78 (n = 54)
	Change	9.8 ± 20.70 (n = 55)	-5.4 ± 15.10 (n = 54)	-10.5 ± 19.65 (n = 51)	-7.6 ± 33.59 (n = 51)	-11.5 ± 22.63 (n = 55)	-12.4 ± 20.22 (n = 54)
2-hour postprandial blood glucose (mg/dL)	End of run-in period	258.6 ± 61.57 (n = 55)	252.9 ± 53.94 (n = 54)	241.3 ± 54.23 (n = 52)	256.8 ± 60.19 (n = 51)	269.9 ± 54.71 (n = 55)	243.7 ± 53.72 (n = 54)
	End of treatment period (Week 12)	268.3 ± 73.08 (n = 53)	230.6 ± 55.10 (n = 53)	214.3 ± 51.38 (n = 49)	237.7 ± 53.25 (n = 51)	238.02 ± 59.57 (n = 54)	205.9 ± 48.13 (n = 53)
	Change	16.0 ± 48.57 (n = 53)	-23.1 ± 30.43 (n = 53)	-25.7 ± 37.18 (n = 49)	-19.1 ± 49.25 (n = 51)	-32.4 ± 36.61 (n = 54)	-37.5 ± 31.69 (n =53)
Percentage of subjects who achieved HbA1c <6.5% at the end of the treatment period		0.0 (0/55)	5.6 (3/54)	21.6 (11/51)	11.8 (6/51)	12.7 (7/55)	33.3 (18/54)

Mean ± SD, % of subjects (No. of subjects who achieved HbA1c <6.5%/No. of subjects evaluated)

[39] Due to difficulty in scheduling the subject's hospital visit

Safety analysis was performed. The incidence of adverse events in the placebo and the trelagliptin 12.5, 25, 50, 100, and 200 mg groups was 43.6% (24 of 55 subjects), 37.0% (20 of 54 subjects), 40.4% (21 of 52 subjects), 39.2% (20 of 51 subjects), 50.9% (28 of 55 subjects), and 50.0% (27 of 54 subjects), respectively. The incidence of adverse drug reactions in the placebo and the trelagliptin 12.5, 25, 50, 100, and 200 mg groups was 3.6% (2 of 55 subjects), 7.4% (4 of 54 subjects), 9.6% (5 of 52 subjects), 11.8% (6 of 51 subjects), 9.1% (5 of 55 subjects), and 5.6% (3 of 54 subjects), respectively. Adverse events reported by >3% of subjects in any group were as shown in Table 17.

Table 17. Adverse events reported by >3% of in any group (safety analysis set)

Adverse event	Placebo (n = 55)	Trelagliptin				
		12.5 mg (n = 54)	25 mg (n = 52)	50 mg (n = 51)	100 mg (n = 55)	200 mg (n = 54)
All events	43.6 (24)	37.0 (20)	40.4 (21)	39.2 (20)	50.9 (28)	50.0 (27)
Nasopharyngitis	20.0 (11)	11.1 (6)	19.2 (10)	17.6 (9)	20.0 (11)	22.2 (12)
Constipation	1.8 (1)	0.0 (0)	1.9 (1)	0.0 (0)	0.0 (0)	5.6 (3)
Gastroenteritis	3.6 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	3.7 (2)
Conjunctivitis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	3.7 (2)
Diarrhoea	0.0 (0)	0.0 (0)	3.8 (2)	0.0 (0)	0.0 (0)	1.9 (1)
Back pain	3.6 (2)	0.0 (0)	0.0 (0)	3.9 (2)	0.0 (0)	1.9 (1)
Abdominal discomfort	0.0 (0)	0.0 (0)	1.9 (1)	0.0 (0)	3.6 (2)	1.9 (1)
Eczema	0.0 (0)	1.9 (1)	0.0 (0)	0.0 (0)	3.6 (2)	1.9 (1)
Carotid arteriosclerosis	0.0 (0)	1.9 (1)	1.9 (1)	3.9 (2)	1.8 (1)	0.0 (0)
Pharyngitis	1.8 (1)	1.9 (1)	3.8 (2)	2.0 (1)	1.8 (1)	0.0 (0)
Arteriosclerosis	0.0 (0)	3.7 (2)	1.9 (1)	2.0 (1)	1.8 (1)	0.0 (0)
Upper respiratory tract inflammation	0.0 (0)	3.7 (2)	0.0 (0)	0.0 (0)	1.8 (1)	0.0 (0)
Cystitis	0.0 (0)	0.0 (0)	0.0 (0)	3.9 (2)	0.0 (0)	0.0 (0)
Insomnia	0.0 (0)	0.0 (0)	0.0 (0)	3.9 (2)	0.0 (0)	0.0 (0)
Fall	3.6 (2)	1.9 (1)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)
Arthralgia	0.0 (0)	3.7 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Blood triglycerides increased	5.5 (3)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence in % (No. of subjects with events), MedDRA/J ver.13.0

No deaths were reported. Serious adverse events were reported by 1 subject in the 50 mg group (enterocolitis) and 1 subject in the 200 mg group (diabetic gangrene). A causal relationship between the study drug and these events was ruled out.

Adverse events leading to study drug discontinuation were reported by 1 subject in the placebo group (diabetes mellitus), 1 subject in the 100 mg group (toxic skin eruption), and 2 subjects in the 200 mg group (diabetic gangrene, eczema). Toxic skin eruption noted in the 100 mg group was assessed as an adverse drug reaction.

No events of hypoglycaemia were reported.

Among vital signs, hypertension was reported by 1 subject each in the 12.5, 25, and 50 mg groups and blood pressure increased was reported by 1 subject in the 12.5 mg group. All but blood pressure increased reported by 1 subject in the 12.5 mg group were assessed as adverse drug reactions, but were mild in severity. Among 12-lead ECG findings, inverted T waves were reported by 1 subject in the placebo group, ventricular extrasystoles were reported by 1 subject each in the 12.5 and 25 mg groups, supraventricular tachycardia was reported by 1 subject in the 25 mg group, and atrial fibrillation was reported by 1 subject in the 50 mg group. All these events were assessed as adverse drug reactions, but were mild in severity.

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

4.(iii).A.(2).1) Phase III confirmatory study (5.3.5.1-4, Study CCT-002 [[redacted] to [redacted]])

A randomized, double-blind, parallel-group, placebo- and active-controlled study was conducted in Japanese patients with type 2 diabetes mellitus[40] (target sample size, 240 subjects [48 subjects in the

[40] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 years; who have received a specific diet and exercise therapy (if any) from 4 weeks prior to the start of the run-in period (at 8 weeks before randomization) to the end of the run-in period; with HbA1c of ≥6.5% and <10.0% at 4 weeks after the start of the run-in period (at 4 weeks before randomization); for whom change in HbA1c between at 4 weeks after the start of the run-in period and at the start of the run-in period is >10.0% of HbA1c at the start of the run-in period.

placebo group, 96 subjects in the trelagliptin 100 mg group, and 96 subjects in the alogliptin 25 mg group[41]]) to evaluate the efficacy and safety of trelagliptin. The placebo group was used as a control group for reference purposes.

Following an 8-week run-in period, once-weekly trelagliptin 100 mg or its matching placebo, or once-daily alogliptin 25 mg or its matching placebo was orally administered before breakfast. The duration of treatment was to be 24 weeks.

Of 245 subjects treated, 1 subject was double-counted in both the trelagliptin and placebo groups resulting in an overlapping enrollment; therefore, 1 subject in the trelagliptin group and 1 subject in the placebo group were excluded from the analysis and the remaining 243 subjects were included in the safety analysis set and FAS. The FAS was the primary efficacy analysis set. A total of 16 subjects discontinued the study, and the reasons for study discontinuation were pretreatment events (PTEs)[42] or adverse events in 8 subjects (1 subject in the placebo group, 6 subjects in the trelagliptin group, and 1 subject in the alogliptin group), voluntary withdrawal in 3 subjects (1 subject in the placebo group and 2 subjects in the trelagliptin group), lack of efficacy in 4 subjects (3 subjects in the placebo group and 1 subject in the trelagliptin group), and lost to follow-up in 1 subject (1 subject in the alogliptin group).

The changes in HbA1c from the end of the run-in period to the end of the treatment period (Week 24), the primary efficacy endpoint, were as shown in Table 18. The adjusted mean difference between treatment groups [two-sided 95% CI] in change in HbA1c at the end of the treatment period (trelagliptin group minus alogliptin group) was 0.11% [-0.053, 0.282]. Because the upper limit of the two-sided 95% CI fell below the pre-specified non-inferiority margin (0.40%), the non-inferiority of trelagliptin to alogliptin was demonstrated.

Table 18. Change in HbA1c from the end of the run-in period to the end of the treatment period (Week 24) (FAS)

	Placebo (n = 50)	Trelagliptin (n = 101)	Alogliptin (n = 92)
End of run-in period	7.31 ± 0.766	7.33 ± 0.845	7.47 ± 0.856
End of treatment period (Week 24)	7.55 ± 0.924	7.01 ± 0.876	7.01 ± 0.949
Change [95% CI]	0.24 ± 0.523 [0.090, 0.386][a)]	-0.33 ± 0.059 [-0.449, -0.218]	-0.45 ± 0.061 [-0.569, -0.327]
Difference between the trelagliptin and alogliptin groups[b)] [95% CI]	-	0.11 [-0.053, 0.282]	-
Difference from placebo[b)] [95% CI]	-	-0.56 [-0.753, -0.367]	-0.70 [-0.905, -0.493]

Unit: %, mean ± SD. Data are expressed as adjusted mean ± SE for change. -: Not applicable.

a) Mean ± SD

b) ANCOVA model with a change in HbA1c at the end of the treatment period as a response variable, and treatment and HbA1c at the end of the run-in period as covariates

The results for major secondary endpoints were as shown in Table 19.

41 Subjects received alogliptin benzoate equivalent to 25 mg of alogliptin.

42 Defined as any untoward medical event occurring before the start of treatment in a subject who gave informed consent.

Table 19. Results for major secondary endpoints (FAS)

		Placebo	Trelagliptin	Alogliptin
Fasting blood glucose (mg/dL)	End of run-in period	167.4 ± 38.92 (n = 50)	157.3 ± 30.19 (n = 101)	165.9 ± 41.25 (n = 92)
	End of treatment period (Week 24)	161.9 ± 31.01 (n = 50)	150.9 ± 27.95 (n = 101)	151.0 ± 34.86 (n = 92)
	Change	-5.5 ± 30.92 (n = 50)	-6.4 ± 21.20 (n = 101)	-14.9 ± 27.04 (n = 92)
2-hour postprandial blood glucose (mg/dL)	End of run-in period	242.4 ± 53.43 (n = 50)	239.7 ± 50.91 (n = 101)	251.4 ± 58.13 (n = 92)
	End of treatment period (Week 24)	238.3 ± 55.03 (n = 46)	222.9 ± 51.21 (n = 97)	221.8 ± 61.54 (n = 90)
	Change	-2.2 ± 42.06 (n = 46)	-17.2 ± 47.65 (n = 97)	-29.2 ± 42.24 (n = 90)
Percentage of subjects who achieved HbA1c <6.5% at the end of the treatment period		10.0 (5/50)	26.7 (27/101)	32.6 (30/92)

Mean ± SD (No. of subjects), % of subjects (No. of subjects who achieved HbA1c <6.5%/No. of subjects evaluated)

Safety analysis was performed. The incidence of adverse events was 64.0% (32 of 50 subjects) in the placebo group, 66.3% (67 of 101 subjects) in the trelagliptin group, and 62.0% (57 of 92 subjects) in the alogliptin group. The incidence of adverse drug reactions was 6.0% (3 of 50 subjects) in the placebo group, 5.0% (5 of 101 subjects) in the trelagliptin group, and 7.6% (7 of 92 subjects) in the alogliptin group. Adverse events reported by >3% of subjects in any group were as shown in Table 20.

Table 20. Adverse events reported by >3% of subjects in any group (safety analysis set)

Adverse event	Placebo (n = 50)	Trelagliptin (n = 101)	Alogliptin 25 mg (n = 92)
All events	64.0 (32)	66.3 (67)	62.0 (57)
Nasopharyngitis	18.0 (9)	22.8 (23)	20.7 (19)
Blood creatine phosphokinase increased	6.0 (3)	5.9 (6)	6.5 (6)
Back pain	0.0 (0)	4.0 (4)	2.2 (2)
Arthralgia	2.0 (1)	4.0 (4)	1.1 (1)
Influenza	0.0 (0)	4.0 (4)	1.1 (1)
Blood triglycerides increased	4.0 (2)	2.0 (2)	3.3 (3)
Diarrhoea	2.0 (1)	2.0 (2)	3.3 (3)
Rash	0.0 (0)	2.0 (2)	3.3 (3)
Dyslipidaemia	4.0 (2)	2.0 (2)	0.0 (0)
Fall	2.0 (1)	1.0 (1)	4.3 (4)
Lipase increased	0.0 (0)	1.0 (1)	3.3 (3)
Constipation	4.0 (2)	1.0 (1)	2.2 (2)
Upper respiratory tract inflammation	6.0 (3)	1.0 (1)	1.1 (1)
Contusion	2.0 (1)	0.0 (0)	3.3 (3)
Bronchitis	4.0 (2)	0.0 (0)	0.0 (0)

Incidence in % (No. of subjects with events), MedDRA/J ver.16.0

No deaths were reported. Serious adverse events were reported by 1 subject in the placebo group (subarachnoid haemorrhage), 4 subjects in the trelagliptin group (acute kidney injury, prostate cancer, colon cancer/large intestine polyp, angina unstable), and 2 subjects in the alogliptin group (intervertebral disc protrusion, cerebral infarction). A causal relationship between the study drug and all these events was ruled out.

Adverse events leading to study drug discontinuation were reported by 1 subject in the placebo group (subarachnoid haemorrhage), 6 subjects in the trelagliptin group (brain natriuretic peptide increased, rash, renal failure acute, prostate cancer, colon cancer, angina unstable), and 1 subject in the alogliptin group (cerebral infarction). Rash noted in the trelagliptin group was assessed as an adverse drug reaction.

Hypoglycaemia was reported by 1 subject in the alogliptin group and was assessed as an adverse drug reaction, but was mild in severity.

Among vital signs, hypertension was reported by 1 subject in the placebo group, 2 subjects in the trelagliptin group, and 1 subject in the alogliptin group, and blood pressure increased was reported by 1 subject each in the trelagliptin and alogliptin groups, but all were mild in severity. Hypertension (1

subject) in the placebo group was assessed as an adverse drug reaction. Among 12-lead ECG findings, atrial fibrillation was reported by 1 subject in the alogliptin group and ventricular extrasystoles was reported by 1 subject in the trelagliptin group. A causal relationship to the study drug was ruled out for both events.

4.(iii).A.(2).2) Phase III long-term monotherapy/combination therapy study (5.3.5.2-1, Study OCT-001 [[redacted] to [redacted]])

An open-label, uncontrolled, long-term treatment study was conducted in Japanese patients with type 2 diabetes mellitus[43] who had an inadequate response to the diet and exercise therapy alone or to one of existing oral hypoglycemic agents in addition to diet and exercise therapy (target sample size, 622 subjects [227 subjects in the trelagliptin alone group, 143 subjects in the trelagliptin + SU group, and 63 subjects each in the trelagliptin + glinides, α-GI, BG, or TZD groups]) to evaluate the long-term safety and efficacy of trelagliptin alone or in combination with other drugs.

Following a 2-week run-in period, trelagliptin 100 mg was orally administered once weekly before breakfast for 52 weeks.

All of the 680 subjects treated (248 subjects in the trelagliptin alone group, 158 subjects in the trelagliptin + SU group, 67 subjects in the trelagliptin + glinide group, 65 subjects in the trelagliptin + α-GI group, 70 subjects in the trelagliptin + BG group, 72 subjects in the trelagliptin + TZD group) were included in the safety analysis set and FAS, and the FAS was the primary efficacy analysis set. A total of 79 subjects discontinued the study, and the reasons for study discontinuation were PTEs or adverse events in 40 subjects (9 subjects in the trelagliptin alone group, 10 subjects in the trelagliptin + SU group, 5 subjects in the trelagliptin + glinide group, 6 subjects in the trelagliptin + α-GI group, 5 subjects in the trelagliptin + BG group, 5 subjects in the trelagliptin + TZD group), voluntary withdrawal in 13 subjects (4 subjects in the trelagliptin alone group, 3 subjects in the trelagliptin + SU group, 3 subjects in the trelagliptin + α-GI group, 1 subject in the trelagliptin + BG group, 2 subjects in the trelagliptin + TZD group), lack of efficacy in 24 subjects (5 subjects in the trelagliptin alone group, 6 subjects in the trelagliptin + SU group, 6 subjects in the trelagliptin + glinide group, 1 subject in the trelagliptin + α-GI group, 4 subjects in the trelagliptin + BG group, 2 subjects in the trelagliptin + TZD group), and others in 2 subjects (2 subjects in the trelagliptin + BG group).

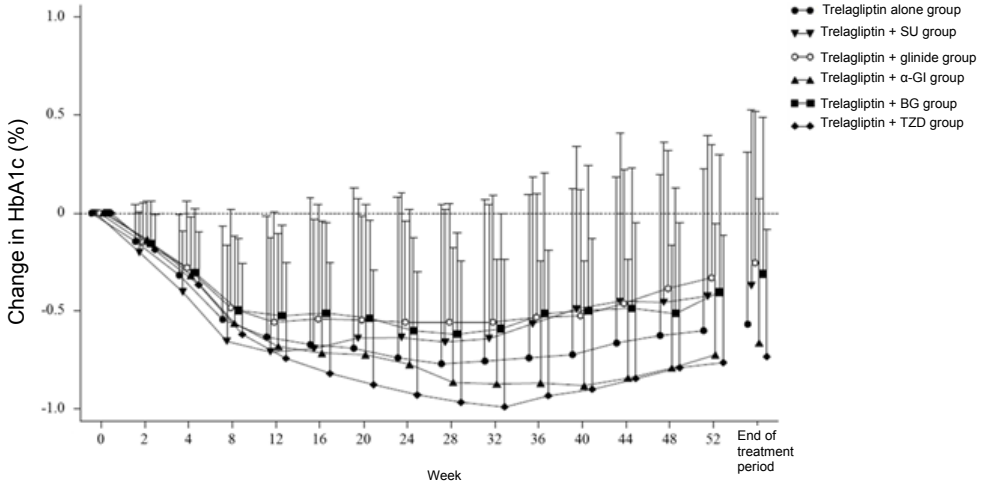
The results of measurements of HbA1c and their change, an efficacy endpoint, were as shown in Table 21. The change in HbA1c over time was as shown in Figure 1.

Table 21. Measurements of HbA1c and their change (FAS)

	Trelagliptin alone (n = 248)	Trelagliptin + SU (n = 158)	Trelagliptin + glinide (n = 67)	Trelagliptin + α-GI (n = 65)	Trelagliptin + BG (n = 70)	Trelagliptin + TZD (n = 72)
End of run-in period	7.47 ± 0.869	7.69 ± 0.836	7.47 ± 0.778	7.67 ± 0.971	7.42 ± 0.939	7.51 ± 0.951
End of treatment period (Week 52)	6.90 ± 0.937	7.32 ± 1.092	7.21 ± 1.158[a)]	7.00 ± 0.968	7.11 ± 1.340	6.78 ± 0.913
Change	-0.57 ± 0.878	-0.37 ± 0.897	-0.26 ± 0.777[a)]	-0.66 ± 0.736	-0.31 ± 0.802	-0.73 ± 0.649

Unit: %, mean ± SD
a) n = 66

[43] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 years; with HbA1c of ≥6.5% and <10.0% at the start of the run-in period (2 weeks before the start of study treatment); who have received a specific diet and exercise therapy (if any) from 10 weeks prior to the start of the run-in period until the start of study treatment. In the combination therapy groups, patients who have received an existing oral hypoglycemic agent at a specified dosage regimen from 10 weeks (14 weeks for patients who have received a TZD concomitantly) prior to the start of the run-in period until the start of study treatment.



Trelagliptin alone group	248	248	246	245	244	243	242	238	237	236	235	233	232	231	230	248
Trelagliptin + SU group	158	157	154	154	152	151	150	150	149	149	147	146	144	140	139	158
Trelagliptin + glinide group	67	66	66	66	65	65	64	64	61	59	58	56	57	57	56	66
Trelagliptin + α-GI group	65	65	64	63	62	62	62	62	60	60	58	57	56	55	55	65
Trelagliptin + BG group	70	70	68	66	65	64	62	62	61	60	60	60	60	59	58	70
Trelagliptin + TZD group	72	72	72	72	71	70	69	69	69	69	67	66	66	64	63	72

Figure 1. Change in HbA1c over time (mean + SD) (FAS)

The results for other efficacy endpoints were as shown in Table 22.

Table 22. Results for other efficacy endpoints (FAS)

		Trelagliptin alone (n = 248)	Trelagliptin + SU (n = 158)	Trelagliptin + glinide (n = 67)	Trelagliptin + α-GI (n = 65)	Trelagliptin + BG (n = 70)	Trelagliptin + TZD (n = 72)
Fasting blood glucose (mg/dL)	End of run-in period	160.5 ± 35.56	168.5 ± 33.07	173.1 ± 33.64	170.4 ± 37.74	157.8 ± 36.13	157.8 ± 34.92
	End of treatment period (Week 52)	150.6 ± 33.39	167.6 ± 41.52	167.7 ± 42.21[a)]	156.9 ± 35.92	155.4 ± 39.00	147.2 ± 32.11
	Change	-10.0 ± 31.17	-0.8 ± 35.53	-4.8 ± 33.38[a)]	-13.5 ± 31.39	-2.4 ± 29.32	-10.6 ± 22.65
Percentage of subjects who achieved HbA1c <6.5% at the end of the treatment period		36.3 (90/248)	20.3 (32/158)	25.8 (17/66)	35.4 (23/65)	38.6 (27/70)	44.4 (32/72)

Mean ± SD, % of subjects (No. of subjects who achieved HbA1c <6.5%/No. of subjects evaluated)
a) n = 66

Safety analysis was performed. The incidence of adverse events was 79.8% (198 of 248 subjects) in the trelagliptin alone group, 87.3% (138 of 158 subjects) in the trelagliptin + SU group, 77.6% (52 of 67 subjects) in the trelagliptin + glinide group, 81.5% (53 of 65 subjects) in the trelagliptin + α-GI group, 64.3% (45 of 70 subjects) in the trelagliptin + BG group, and 84.7% (61 of 72 subjects) in the trelagliptin + TZD group. The incidence of adverse drug reactions was 15.7% (39 of 248 subjects) in the trelagliptin alone group, 10.8% (17 of 158 subjects) in the trelagliptin + SU group, 11.9% (8 of 67 subjects) in the trelagliptin + glinide group, 6.2% (4 of 65 subjects) in the trelagliptin + α-GI group, 11.4% (8 of 70 subjects) in the trelagliptin + BG group, and 13.9% (10 of 72 subjects) in the trelagliptin + TZD group. Adverse events reported by >3% of subjects in any group were as shown in Table 23.

Table 23. Adverse events reported by >3% of subjects in any group (safety analysis set)

Adverse event	Trelagliptin alone (n = 248)	Trelagliptin + SU (n = 158)	Trelagliptin + glinide (n = 67)	Trelagliptin + α-GI (n = 65)	Trelagliptin + BG (n = 70)	Trelagliptin + TZD (n = 72)
All events	79.8 (198)	87.3 (138)	77.6 (52)	81.5 (53)	64.3 (45)	84.7 (61)
Nasopharyngitis	28.2 (70)	27.8 (44)	23.9 (16)	44.6 (29)	22.9 (16)	30.6 (22)
Upper respiratory tract inflammation	8.9 (22)	14.6 (23)	4.5 (3)	6.2 (4)	4.3 (3)	8.3 (6)
Back pain	6.9 (17)	3.8 (6)	6.0 (4)	3.1 (2)	5.7 (4)	5.6 (4)
Contusion	6.0 (15)	5.1 (8)	9.0 (6)	3.1 (2)	1.4 (1)	2.8 (2)
Bronchitis	5.6 (14)	5.7 (9)	3.0 (2)	3.1 (2)	1.4 (1)	0.0 (0)
Fall	5.2 (13)	5.1 (8)	9.0 (6)	0.0 (0)	1.4 (1)	6.9 (5)
Influenza	4.4 (11)	4.4 (7)	3.0 (2)	3.1 (2)	1.4 (1)	1.4 (1)
Headache	4.0 (10)	0.0 (0)	3.0 (2)	1.5 (1)	1.4 (1)	1.4 (1)
Blood CPK increased	3.6 (9)	6.3 (10)	7.5 (5)	7.7 (5)	0.0 (0)	12.5 (9)
Dental caries	3.6 (9)	3.2 (5)	3.0 (2)	3.1 (2)	0.0 (0)	0.0 (0)
Constipation	3.2 (8)	2.5 (4)	11.9 (8)	4.6 (3)	0.0 (0)	1.4 (1)
Diarrhoea	3.2 (8)	1.9 (3)	4.5 (3)	1.5 (1)	0.0 (0)	2.8 (2)
Amylase increased	3.2 (8)	1.3 (2)	1.5 (1)	3.1 (2)	2.9 (2)	0.0 (0)
Eczema	3.2 (8)	5.1 (8)	7.5 (5)	0.0 (0)	2.9 (2)	2.8 (2)
Hypertension	3.2 (8)	1.9 (3)	3.0 (2)	3.1 (2)	1.4 (1)	6.9 (5)
Pharyngitis	3.2 (8)	3.2 (5)	10.4 (7)	3.1 (2)	1.4 (1)	2.8 (2)
Arthralgia	2.8 (7)	5.1 (8)	4.5 (3)	0.0 (0)	0.0 (0)	4.2 (3)
Lipase increased	2.8 (7)	2.5 (4)	3.0 (2)	1.5 (1)	5.7 (4)	2.8 (2)
Myalgia	2.4 (6)	3.2 (5)	1.5 (1)	6.2 (4)	0.0 (0)	5.6 (4)
Gastritis	2.4 (6)	3.8 (6)	1.5 (1)	1.5 (1)	1.4 (1)	1.4 (1)
Periodontitis	2.4 (6)	0.6 (1)	4.5 (3)	1.5 (1)	0.0 (0)	0.0 (0)
Gastroenteritis	2.0 (5)	3.2 (5)	3.0 (2)	0.0 (0)	1.4 (1)	2.8 (2)
Rhinitis allergic	1.6 (4)	0.6 (1)	1.5 (1)	3.1 (2)	1.4 (1)	0.0 (0)
Arthropod sting	1.6 (4)	0.6 (1)	1.5 (1)	3.1 (2)	1.4 (1)	1.4 (1)
Cataract	1.6 (4)	0.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	4.2 (3)
Insomnia	1.6 (4)	0.0 (0)	1.5 (1)	4.6 (3)	0.0 (0)	2.8 (2)
Abdominal pain	1.2 (3)	0.6 (1)	1.5 (1)	3.1 (2)	0.0 (0)	0.0 (0)
Cystitis	1.2 (3)	3.2 (5)	1.5 (1)	1.5 (1)	0.0 (0)	1.4 (1)
Blood triglycerides increased	1.2 (3)	3.8 (6)	1.5 (1)	1.5 (1)	1.4 (1)	0.0 (0)
Blood urine present	1.2 (3)	1.3 (2)	3.0 (2)	3.1 (2)	0.0 (0)	2.8 (2)
γ-GTP increased	1.2 (3)	1.9 (3)	1.5 (1)	3.1 (2)	0.0 (0)	1.4 (1)
Pain in extremity	1.2 (3)	3.8 (6)	1.5 (1)	1.5 (1)	0.0 (0)	0.0 (0)
Malaise	0.8 (2)	0.6 (1)	3.0 (2)	3.1 (2)	0.0 (0)	0.0 (0)
Excoriation	0.8 (2)	1.3 (2)	4.5 (3)	0.0 (0)	0.0 (0)	1.4 (1)
Osteoarthritis	0.8 (2)	0.0 (0)	1.5 (1)	0.0 (0)	1.4 (1)	4.2 (3)
Spinal osteoarthritis	0.8 (2)	0.0 (0)	4.5 (3)	0.0 (0)	0.0 (0)	2.8 (2)
Herpes zoster	0.4 (1)	0.0 (0)	3.0 (2)	3.1 (2)	0.0 (0)	0.0 (0)
ALT increased	0.4 (1)	2.5 (4)	3.0 (2)	0.0 (0)	1.4 (1)	4.2 (3)
AST increased	0.4 (1)	1.9 (3)	1.5 (1)	0.0 (0)	1.4 (1)	4.2 (3)
Pancreatic enzymes increased	0.4 (1)	0.6 (1)	0.0 (0)	3.1 (2)	1.4 (1)	0.0 (0)
Hypoglycaemia	0.4 (1)	4.4 (7)	1.5 (1)	1.5 (1)	1.4 (1)	1.4 (1)
Dyslipidaemia	0.4 (1)	0.6 (1)	4.5 (3)	1.5 (1)	0.0 (0)	1.4 (1)
Abdominal discomfort	0.0 (0)	2.5 (4)	4.5 (3)	1.5 (1)	1.4 (1)	0.0 (0)
Pancreatic enzyme abnormality	0.0 (0)	0.6 (1)	0.0 (0)	3.1 (2)	0.0 (0)	1.4 (1)
Chillblains	0.0 (0)	0.0 (0)	0.0 (0)	3.1 (2)	0.0 (0)	0.0 (0)
VIIth nerve paralysis	0.0 (0)	0.0 (0)	0.0 (0)	3.1 (2)	0.0 (0)	0.0 (0)

Incidence in % (No. of subjects with events), MedDRA/J ver.16.0
CPK, Creatine phosphokinase; ALT, Alanine aminotransferase; GTP, Glutamyltransferase; AST, Aspartate aminotransferase

No deaths were reported. Serious adverse events were reported by 9 subjects in the trelagliptin alone group (cerebral infarction [2 subjects], transient ischaemic attack, pneumonia, calculus ureteric, inguinal hernia, calculus urinary, large intestine polyp, and gastroenteritis [1 subject each]), 11 subjects in the trelagliptin + SU group (macular hole, colon adenoma, angina pectoris, gastrointestinal tract adenoma, pyelonephritis acute, alveolitis allergic, complicated fracture, mental disorder due to a general medical condition, cerebral infarction, myocardial ischaemia/cellulitis, cholecystitis acute), 5 subjects in the trelagliptin + glinide group (ileus/colon cancer, coronary artery stenosis, acute myocardial infarction, bronchiolitis, rib fracture/radius fracture), 3 subjects in the trelagliptin + α-GI group (tibia fracture, pyelonephritis, pneumonia), 1 subject in the trelagliptin + BG group (cholecystitis), and 4 subjects in the trelagliptin + TZD group (back pain, colon cancer, bladder cancer/arteriovenous malformation, pancreatitis/cholelithiasis/wound complication). Of these, ileus reported in the trelagliptin + glinide group, cholecystitis reported in the trelagliptin + BG group, and bladder cancer reported in the trelagliptin + TZD group were assessed as adverse drug reactions.

Adverse events leading to study drug discontinuation were reported by 9 subjects in the trelagliptin alone group (pneumonia, lipase increased, cerebral infarction, pancreatic enzymes increased, eczema, blood glucose increased/thirst, rash, cellulitis/skin ulcer, pruritus generalized/erythema/papule), 9 subjects in the trelagliptin + SU group (colon adenoma, hypoglycaemia, angina pectoris, pyelonephritis acute, complicated fracture, mental disorder due to a general medical condition, cerebral infarction, cellulitis, amylase increased), 5 subjects in the trelagliptin + glinide group (intestinal obstruction, ileus, eczema, acute myocardial infarction, bronchiolitis), 5 subjects in the trelagliptin + α-GI group (tibia fracture, muscle spasms, liver function test abnormal, pneumonia, VIIth nerve paralysis), 5 subjects in the trelagliptin + BG group (cholecystitis, pancreatic enzymes increased, eczema, plasma cell myeloma, polyarthritis), and 5 subjects in the trelagliptin + TZD group (AST increased/ALT increased, colon cancer, haematospermia/diabetic neuropathy, bladder cancer, pancreatitis/cholelithiasis). Of these, the events reported by 7 subjects in the trelagliptin alone group (lipase increased, pancreatic enzymes increased, eczema, blood glucose increased/thirst, rash, cellulitis/skin ulcer, pruritus generalized/erythema/papule), 1 subject in the trelagliptin + SU group (hypoglycaemia), 3 subjects in the trelagliptin + glinide group (intestinal obstruction, ileus, eczema), 1 subject in the trelagliptin + α-GI group (muscle spasms), 4 subjects in the trelagliptin + BG group (cholecystitis, eczema, plasma cell myeloma, polyarthritis), and 2 subjects in the trelagliptin + TZD group (haematospermia, bladder cancer) were assessed as adverse drug reactions.

The incidence of hypoglycaemia was 0.4% (1 of 248 subjects) in the trelagliptin alone group, 4.4% (7 of 158 subjects) in the trelagliptin + SU group, 1.5% (1 of 67 subjects) in the trelagliptin + glinide group, 1.5% (1 of 65 subjects) in the trelagliptin + α-GI group, 1.4% (1 of 70 subjects) in the trelagliptin + BG group, and 1.4% (1 of 72 subjects) in the trelagliptin + TZD group, but all were mild in severity. Except for the events reported by 2 subjects in the trelagliptin + SU group and 1 subject in the trelagliptin + α-GI group, all were assessed as adverse drug reactions.

Adverse events related to vital signs were analyzed. The incidence of hypertension was 3.2% (8 of 248 subjects) in the trelagliptin alone group, 1.9% (3 of 158 subjects) in the trelagliptin + SU group, 3.0% (2 of 67 subjects) in the trelagliptin + glinide group, 3.1% (2 of 65 subjects) in the trelagliptin + α-GI group, 1.4% (1 of 70 subjects) in the trelagliptin + BG group, and 6.9% (5 of 72 subjects) in the trelagliptin + TZD group. The incidence of blood pressure increased was 1.2% (3 of 248 subjects) in the trelagliptin alone group, 0.6% (1 of 158 subjects) in the trelagliptin + SU group, 3.0% (2 of 67 subjects) in the trelagliptin + glinide group, and 1.4% (1 of 72 subjects) in the trelagliptin + TZD group, and in addition, orthostatic hypotension was reported by 1 subject each in the trelagliptin alone and trelagliptin + TZD groups and blood pressure decreased and blood pressure fluctuation were reported by 1 subject each in the trelagliptin alone group. All the events were mild in severity and their causal relationship to the study drug was ruled out. Among adverse events related to 12-lead ECG, bundle branch block right was reported by 1 subject in the trelagliptin alone group, ventricular extrasystoles was reported by 1 subject in the trelagliptin + SU group, supraventricular extrasystoles was reported by 1 subject in the trelagliptin + α-GI group, atrial fibrillation was reported by 1 subject in the trelagliptin + BG group, and atrial fibrillation was reported by 1 subject in the trelagliptin + TZD group, but all were mild in severity.

4.(iii).A.(2).3) Phase III open-label study (5.3.5.2-2, Study OCT-002 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in Japanese patients with type 2 diabetes mellitus[44] on once-daily treatment with a DPP-4 inhibitor (sitagliptin phosphate hydrate[45]) (target sample size, 14 subjects) to evaluate the efficacy and safety of switching to once-weekly trelagliptin 100 mg from another DPP-4 inhibitor.

Once-daily sitagliptin 50 mg was to be switched to once-weekly oral trelagliptin 100 mg before breakfast for 12 weeks.

All of the 14 subjects treated were included in the safety analysis set and FAS, and the FAS was the primary efficacy analysis set. No subjects discontinued the study.

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[44] Key inclusion criteria: Patients with type 2 diabetes mellitus aged ≥20 years on once-daily treatment with 50 mg of sitagliptin; with HbA1c of ≥5.8% and <8.0% at the start of the run-in period (2 weeks before the start of study treatment); who have received a specific diet and exercise therapy (if any) from 10 weeks prior to the start of the run-in period until the start of study treatment.

[45] Subjects received sitagliptin phosphate hydrate equivalent to 50 mg of sitagliptin.

The time-course changes of blood glucose levels obtained in a meal tolerance test, primary efficacy endpoint, were as shown in Table 24. No major changes were observed in the pre- or post-prandial blood glucose at each timepoint after switching to trelagliptin.

Table 24. Time-course changes of blood glucose levels obtained in a meal tolerance test (FAS)

	Baseline value[a)] (n = 14)	Change from baseline to the date of the first dose of trelagliptin (n = 14)	Change from baseline to 2 days after dosing of trelagliptin (n = 14)	Change from baseline to 3 days after dosing of trelagliptin (n = 14)	Change from baseline to 7 days after dosing of trelagliptin (n = 14)
Before breakfast	140.9 ± 23.70 [127.18, 154.54]	-0.4 ± 6.71 [-4.23, 3.52]	-6.2 ± 5.42 [-9.35, -3.08]	-3.0 ± 7.98 [-7.61, 1.61]	-1.7 ± 13.21 [-9.34, 5.91]
2 hours after the start of breakfast	202.1 ± 38.30 [179.96, 224.18]	-4.4 ± 17.88 [-14.75, 5.89]	-1.6 ± 30.78 [-19.41, 16.13]	7.0 ± 31.93 [-11.43, 25.43]	-8.7 ± 25.38 [-23.37, 5.94]

Unit, mg/dL; Upper column, Mean ± SD; Lower column, [two-sided 95% CI]

a) Measurements obtained from a meal tolerance test where sitagliptin 50 mg was administered 1 day prior to the first dose of the study drug.

Evaluations of other efficacy endpoints showed that the change in HbA1c (mean ± SD) from the date of the first dose of trelagliptin to the end of the treatment period (Week 12) in the FAS was 0.04% ± 0.359%, and the change in fasting blood glucose (mean ± SD) over the same interval was -1.6 ± 13.93 mg/dL.

Safety analysis revealed 10 adverse events (pharyngitis/blood creatine phosphokinase increased, sinusitis, lipase increased, protein urine present/periodontitis, spinal osteoarthritis/dry eye, diabetic nephropathy/blood urine present) reported by 6 of 14 subjects. Of these, lipase increased reported by 1 of 14 subjects was assessed as an adverse drug reaction.

There were no deaths, serious adverse events, or adverse events leading to study drug discontinuation.

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

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

PMDA asked the applicant to explain the clinical positioning of trelagliptin.

The applicant responded as follows:
Since once-weekly trelagliptin allows a reduced dosing frequency as compared with existing oral hypoglycemic agents, a better medication adherence can be expected. As a new treatment option for patients with type 2 diabetes mellitus, trelagliptin is considered to be particularly useful in patients who will begin the treatment with trelagliptin alone or those who require medication support (e.g., dementia patients).

PMDA considers as follows:
The efficacy of once-weekly treatment with trelagliptin has been demonstrated [see "4.(iii).B.(2) Efficacy"] and its safety is acceptable [see "4.(iii).B.(3) Safety"]. Trelagliptin can therefore be a treatment option for patients with type 2 diabetes mellitus, on the premise that precautions are appropriately provided to address safety issues [see "4.(iii).B.(3) Safety"], that adequate information is collected via post-marketing surveillance [see "4.(iii).B.(8) Post-marketing obligations"], and that measures for the proper use of trelagliptin are taken in an appropriate manner [see "4.(iii).B.(4) Measures for the proper use of the product"].

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

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

PMDA considers as follows:
The applicant's explanation for the non-inferiority margin (0.40%) selected for the phase III confirmatory study (Study CCT-002) is acceptable for the following reasons: (i) the draft guidance issued by the US Food and Drug Administration[46] states that a non-inferiority margin for HbA1c (as a primary endpoint) of 0.3% to 0.4% is acceptable for a study in patients with type 2 diabetes mellitus,

[46] Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention (DRAFT GUIDANCE), FDA. 2008

and (ii) the value 0.4% is below one half (0.415%) of the absolute value of the point estimate (-0.83%) of the mean difference in the change in HbA1c between the alogliptin 25 mg and placebo groups at the end of the treatment period (Week 12) in the Japanese phase II dose-finding study evaluating alogliptin (Study CCT-001 [SYR-322]). In the phase III confirmatory study (Study CCT-002), the difference [two-sided 95% CI] in the change in HbA1c from baseline to the end of the treatment period (Week 24) between the trelagliptin and alogliptin groups (the primary endpoint) was 0.11% [-0.053, 0.282]. Because the upper limit of the two-sided 95% CI was below the non-inferiority margin (0.40%), the non-inferiority of trelagliptin to alogliptin has been demonstrated [Table 18]. The mean changes [95% CI] in fasting blood glucose and in 2-hour postprandial blood glucose from the end of the run-in period to the end of the treatment period (Week 24) (the secondary endpoints) were -6.4 [-10.55, -2.18] and -17.2 [-26.76, -7.55] mg/dL, respectively, in the trelagliptin group, and -14.9 [-20.55, -9.35] and -29.2 [-38.09, -20.40] mg/dL in the alogliptin group, respectively, showing smaller changes in the trelagliptin group than in the alogliptin group. However, the proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period (Week 24) was similar between the trelagliptin (26.7%) and alogliptin (32.6%) groups. In the phase II dose-finding study (Study CCT-001), an analysis of the change in HbA1c from the end of the run-in period to the end of the treatment period (Week 12) showed that all the trelagliptin groups had statistically significant decreases in HbA1c compared to the placebo group [Table 15]. In addition, in the trelagliptin monotherapy group in the phase III long-term monotherapy/combination therapy study (Study OCT-001), the change (mean ± SD) in HbA1c from the end of the run-in period to the end of the treatment period (Week 52) was -0.57% ± 0.878% and the proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period (Week 52) was 36.3%, indicating the persistent efficacy up to the end of the treatment period (Week 52). Based on the above, the efficacy of trelagliptin monotherapy has been demonstrated.

4.(iii).B.(2).2) Efficacy of combination therapies

In the phase III long-term monotherapy/combination therapy study (Study OCT-001), the change in HbA1c from the end of the run-in period tended to be smaller in the trelagliptin + SU, trelagliptin + glinide, and trelagliptin + BG groups than in the trelagliptin alone group and the groups receiving trelagliptin in combination with the other concomitant drugs [Table 21]. PMDA asked the applicant to explain the cause for the smaller change.

The applicant responded as follows:

Data from Study OCT-001 were evaluated to determine whether or not baseline characteristics (age, sex, BMI, duration of type 2 diabetes mellitus, creatinine clearance, HbA1c, fasting blood glucose, HOMA-R, and HOMA-β) and interruption of prior antidiabetic medication affected the change in HbA1c. The results showed no reduction in HbA1c at the end of the treatment period in the following subjects: those with baseline "BMI ≥30.0 kg/m^2" in the trelagliptin + SU group; those with baseline "BMI ≥25.0 and <30.0 kg/m^2" or "BMI ≥30.0 kg/m^2," "duration of type 2 diabetes mellitus ≤60 months," and baseline "HOMA-R ≥4.0" in the trelagliptin + glinide group; and those with baseline "HOMA-R ≥4.0" in the trelagliptin + BG group. However, subgroup analyses of Studies CCT-001 and CCT-002 (randomized controlled studies) for these patient characteristics (BMI, duration of type 2 diabetes mellitus, and HOMA-R) showed a greater reduction in HbA1c in the 100 mg group than in the placebo group for all the subgroups. In Study OCT-001, HbA1c at the end of the treatment period was lower than that at the end of the run-in period in all the combination therapy groups [Table 21].

PMDA considers as follows:

Given the results of Study OCT-001 showing a reduction in HbA1c [Table 21] and its persistence up to the end of the treatment period [Figure 1, Table 22] in each combination therapy group, the efficacy of each combination therapy examined in the study has been demonstrated. Although attention should be paid to the observed tendency toward a smaller reduction in HbA1c in the trelagliptin + SU, trelagliptin + glinide, and trelagliptin + BG groups than in the groups receiving trelagliptin in combination with the other concomitant drugs, no major problems are expected because the draft package insert includes a precautionary statement to the effect that switching to a more appropriate therapy should be considered for patients with inadequate response to a therapy.

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

The applicant explained as follows:

The incidence of adverse events and adverse drug reactions reported in the trelagliptin monotherapy group in Japanese clinical studies in patients with type 2 diabetes mellitus (Studies CCT-001, CCT-002, OCT-001, and OCT-002) was as shown in Table 25. The incidence of adverse events and adverse drug reactions by treatment group was as shown in Table 26. No specific safety concerns were noted with monotherapy or any of the combination therapies. In addition, the results from Study OCT-002 showed no major safety problems associated with switching from a daily-dose preparation to trelagliptin [see "4.(iii).A.(2).3) Phase III open-label study"], although the number of subjects evaluated was limited.

Table 25. Adverse events and adverse drug reactions reported by subject receiving monotherapy in Japanese clinical studies (pooled analysis,[a)] safety analysis set)

	Placebo (n = 105)	Trelagliptin					Alogliptin 25 mg (n = 92)
		12.5 mg (n = 54)	25 mg (n = 52)	50 mg (n = 51)	100 mg (n = 418)	200 mg (n = 54)	
Adverse events	56 (53.3) 95 [258.3]	20 (37.0) 30 [223.2]	21 (40.4) 35 [270.0]	20 (39.2) 43 [334.0]	299 (71.5) 875 [283.1]	27 (50.0) 38 [282.7]	57 (62.0) 111 [250.4]
Adverse drug reactions	5 (4.8) 6 [16.3]	4 (7.4) 5 [37.2]	5 (9.6) 5 [38.6]	6 (11.8) 10 [77.7]	50 (12.0) 80 [25.9]	3 (5.6) 3 [22.3]	7 (7.6) 7 [15.8]
Serious adverse events	1 (1.0) 1 [2.7]	0 (0.0) 0 [0.0]	0 (0.0) 0 [0.0]	1 (2.0) 1 [7.8]	13 (3.1) 14 [4.5]	1 (1.9) 1 [7.4]	2 (2.2) 2 [4.5]
Adverse events leading to treatment discontinuation	2 (1.9) 2 [5.4]	0 (0.0) 0 [0.0]	0 (0.0) 0 [0.0]	0 (0.0) 0 [0.0]	16 (3.8) 20 [6.5]	2 (3.7) 2 [14.9]	1 (1.1) 1 [2.3]

Upper column: No. of subjects with events (incidence %). Lower column: No. of events [No. of events per unit time (events/100 patient-years)]

a) Pooled analysis of the monotherapy groups in Studies CCT-001, CCT-002, and OCT-001 and all subjects in Study OCT-002.

Table 26. Adverse events and adverse drug reactions reported in Japanese clinical studies by treatment group (Study OCT-001, safety analysis set)

Endpoint	Trelagliptin alone (n = 248)	Trelagliptin + SU (n = 158)	Trelagliptin + glinide (n = 67)	Trelagliptin + α-GI (n = 65)	Trelagliptin + BG (n = 70)	Trelagliptin + TZD (n = 72)
Adverse events	198 (79.8)	138 (87.3)	52 (77.6)	53 (81.5)	45 (64.3)	61 (84.7)
Adverse drug reactions	39 (15.7)	17 (10.8)	8 (11.9)	4 (6.2)	8 (11.4)	10 (13.9)
Serious adverse events	9 (3.6)	11 (7.0)	5 (7.5)	3 (4.6)	1 (1.4)	4 (5.6)
Adverse events leading to treatment discontinuation	9 (3.6)	9 (5.7)	5 (7.5)	5 (7.7)	5 (7.1)	5 (6.9)

No. of subjects with events (incidence %)

PMDA asked the applicant to discuss the impact of type or dose level of concomitant oral hypoglycemic agents on safety.

The applicant responded as follows:

The incidence of adverse events in the trelagliptin + SU group in Study OCT-001 by type of SU was 66.7% (4 of 6 subjects) for glibenclamide, 66.7% (4 of 6 subjects) for gliclazide, and 89.0% (130 of 146 subjects) for glimepiride. There was no substantial difference between treatment groups although interpretation of the results is limited by some groups consisting of a small number of subjects. The incidence of adverse events in the trelagliptin + SU group by dose level of glimepiride was 88.9% (112 of 126 subjects) at ≤2 mg/day and 90.0% (18 of 20 subjects) at >2 mg/day; the incidence of hypoglycaemia was 3.2% (4 of 126 subjects) at ≤2 mg/day and 5.0% (1 of 20 subjects) at >2 mg/day. Thus, no substantial difference was observed between treatment groups.

The incidence of adverse events in the trelagliptin + glinide group by type of glinide was 76.2% (32 of 42 subjects) for mitiglinide calcium hydrate and 80.0% (20 of 25 subjects) for nateglinide, showing a similar incidence in both subgroups. The incidence of adverse events in the trelagliptin + α-GI group by type of α-GI was 85.7% (6 of 7 subjects) for acarbose, 73.7% (14 of 19 subjects) for miglitol, and 84.6% (33 of 39 subjects) for voglibose. There was no substantial difference between treatment groups although interpretation of the results is limited by some groups consisting of a small number of subjects. The incidence of adverse events in the trelagliptin + BG group by dose level of metformin hydrochloride was 69.4% (25 of 36 subjects) at ≤750 mg/day and 58.8% (20 of 34 subjects) at >750 mg/day, showing no increasing trend with increasing dose level. The incidence of adverse events in the trelagliptin + TZD

group by dose level of pioglitazone hydrochloride was 93.1% (27 of 29 subjects) at ≤15 mg/day and 79.1% (34 of 43 subjects) at >15 mg/day, showing no increasing trend with increasing dose level.

Based on the above, the type or dose level of oral hypoglycemic agents used concomitantly with trelagliptin is not considered to have a substantial impact on the safety.

PMDA considers as follows:
PMDA accepted the applicant's view that no specific safety concerns were noted based on the incidence of adverse events and adverse drug reactions reported in the monotherapy and combination therapy groups in Japanese clinical studies. However, given that some of the oral hypoglycemic agents used concomitantly with trelagliptin have been evaluated in a limited number of subjects, collection of information on the safety should be continued in post-marketing surveillance.

PMDA reviewed events of special interest for safety, and the review results are summarized in 4.(iii).B.(3).1) to 7). In addition, given the once-weekly regimen of trelagliptin, the impact of plasma trelagliptin level elevation resulting from high-dose intermittent administration on the safety will be reviewed in the dosage and administration section [see "4.(iii).B.(6) Dosage and administration"].

4.(iii).B.(3).1) Hypoglycaemia
The applicant explained as follows:
In Japanese clinical studies, hypoglycaemia was reported by only 1 subject in the alogliptin group in Study CCT-002, and no such events were reported by subjects in the placebo or trelagliptin group in this study. In Study OCT-001, the incidence of hypoglycaemia was 0.4% (1 of 248 subjects) in the trelagliptin alone group, 4.4% (7 of 158 subjects) in the trelagliptin + SU group, 1.5% (1 of 67 subjects) in the trelagliptin + glinide group, 1.5% (1 of 65 subjects) in the trelagliptin + α-GI group, 1.4% (1 of 70 subjects) in the trelagliptin + BG group, and 1.4% (1 of 72 subjects) in the trelagliptin + TZD group, showing no substantial between-therapy difference. No hypoglycaemia was reported in Study CCT-001 or OCT-002. All events of hypoglycaemia reported in Japanese clinical studies were mild in severity and non-serious. In foreign clinical studies, hypoglycaemia was reported by 2 subjects (both in the 200 mg group) in Foreign Study 007.[47] In Foreign Study 006[48] in which daily dosing was evaluated, the incidence of hypoglycaemia was 1.6% (1 of 63 subjects) in the placebo group, 3.1% (2 of 65 subjects) in the 3.125 mg group, 0.0% (0 of 67 subjects) in the 12.5 mg group, 1.6% (1 of 64 subjects) in the 50 mg group, 0.0% (0 of 65 subjects) in the 100 mg group, and 1.6% (1 of 61 subjects) in the sitagliptin 100 mg group. Severe or serious events were not reported in either foreign study.

Events of hypoglycaemia reported in Study OCT-001 were analyzed by time to onset. The results revealed that early-onset hypoglycaemia (defined as occurring within 84 days after the start of treatment) was observed in the trelagliptin alone group (1 event [29 days after the start of treatment]), in the trelagliptin + SU group (6 events [4 events occurring 1 to 14 days after the start of treatment, 1 event occurring 15 to 28 days after the start of treatment, and 1 event occurring 57 to 84 days after the start of treatment]), in the trelagliptin + glinide group (1 event [27 days after the start of treatment]), and in the trelagliptin + BG group (1 event [84 days after the start of treatment]). No early-onset hypoglycaemia was reported in the trelagliptin + α-GI group (160 days after the start of treatment) or trelagliptin + TZD group (197 days after the start of treatment).

Because of the low incidence of hypoglycaemia associated with trelagliptin, used either alone or in combination with other drugs, serious hypoglycaemia is unlikely to occur. However, since serious hypoglycaemia has been reported with other DPP-4 inhibitors used concomitantly with an SU, "hypoglycaemia" will be included in the safety specification of the risk management plan, and precautionary statements will be included in the Precautions section of the package insert.

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[47] A placebo-controlled, randomized, double-blind study in which non-Japanese patients with type 2 diabetes mellitus who experienced inadequate glycemic control with diet and exercise therapy or metformin monotherapy received placebo or trelagliptin 25, 50, 100, or 200 mg once a week orally before breakfast for 12 weeks.

[48] A placebo-controlled, randomized, double-blind study in which non-Japanese patients with type 2 diabetes mellitus who experienced inadequate glycemic control with diet and exercise therapy or metformin monotherapy received placebo, trelagliptin 3.125, 12.5, 50, or 100 mg, or sitagliptin 100 mg once daily orally before breakfast for 12 weeks.

PMDA considers as follows:
Since the results of Study OCT-001 revealed a trend towards a higher incidence of hypoglycaemia with trelagliptin + SU therapy than with other therapies, an appropriate caution should be provided. In addition, collection of information on hypoglycaemia should be continued in post-marketing surveillance.

4.(iii).B.(3).2) Skin disorder-related events and hypersensitivity
The applicant explained as follows:
The incidence of skin disorder-related adverse events[49] in Japanese clinical studies was analyzed. In Study CCT-001, the incidence of such events was 0.0% (0 of 55 subjects) in the placebo group, 1.9% (1 of 54 subjects) in the 12.5 mg group, 0.0% (0 of 52 subjects) in the 25 mg group, 2.0% (1 of 51 subjects) in the 50 mg group, 9.1% (5 of 55 subjects) in the 100 mg group, and 1.9% (1 of 54 subjects) in the 200 mg group, showing a similar incidence in all the trelagliptin groups except the 100 mg group; the 100 mg group showed a higher incidence as compared with the placebo group. In Study CCT-002, the incidence was 6.0% (3 of 50 subjects) in the placebo group, 4.0% (4 of 101 subjects) in the trelagliptin group, and 6.5% (6 of 92 subjects) in the alogliptin group, showing no substantial difference between treatment groups. In Study OCT-001, the incidence was 12.5% (31 of 248 subjects) in the trelagliptin alone group, 10.1% (16 of 158 subjects) in the trelagliptin + SU group, 14.9% (10 of 67 subjects) in the trelagliptin + glinide group, 10.8% (7 of 65 subjects) in the trelagliptin + α-GI group, 7.1% (5 of 70 subjects) in the trelagliptin + BG group, and 12.5% (9 of 72 subjects) in the trelagliptin + TZD group, showing no substantial difference between therapies. There was no report of such events in Study OCT-002. Adverse events leading to study drug discontinuation were reported by 1 subject in the 100 mg group (toxic skin eruption) and 1 subject in the 200 mg group (eczema) in Study CCT-001, 1 subject in the trelagliptin group (rash) in Study CCT-002, and 4 subjects in the trelagliptin alone group (eczema, rash, skin ulcer, pruritus generalized/erythema/papule), 1 subject in the trelagliptin + glinide group (eczema), and 1 subject in the trelagliptin + BG group (eczema) in Study OCT-001. All but eczema reported by 1 subject in the 200 mg group in Study CCT-001 were assessed as adverse drug reactions. No serious or severe adverse events were reported.

The incidence of hypersensitivity-related adverse events[50] (excluding those included in the skin-related events) in Japanese clinical studies was 0.0% (0 of 50 subjects) in the placebo group, 2.0% (2 of 101 subjects) in the trelagliptin 100 mg group, and 2.2% (2 of 95 subjects) in the alogliptin 25 mg group in Study CCT-002. All of these events were mild in severity and their causal relationship to the study drug was ruled out. In Study OCT-001, the incidence was 2.0% (5 of 248 subjects) in the trelagliptin alone group, 1.9% (3 of 158 subjects) in the trelagliptin + SU group, 3.0% (2 of 67 subjects) in the trelagliptin + glinide group, 3.1% (2 of 65 subjects) in the trelagliptin + α-GI group, 1.4% (1 of 70 subjects) in the trelagliptin + BG group, and 1.4% (1 of 72 subjects) in the trelagliptin + TZD group. Alveolitis allergic reported by 1 subject in the trelagliptin + SU group was moderate in severity and considered to be a serious adverse event, but its causal relationship to the study drug was ruled out. There was no report of hypersensitivity-related adverse events in Study CCT-001 or OCT-002. Adverse events leading to study drug discontinuation were not reported.

Based on the above, trelagliptin, used either alone or in combination with other drugs, is unlikely to cause clinically relevant skin disorder or hypersensitivity. However, in consideration of reports on other DPP-4 inhibitors, “skin disorder” will be included in the safety specifications of the risk management plan, and precautionary statements will be included in the Precautions section of the package insert.

PMDA considers as follows:
There are no particular problems with the applicant's explanation that the clinical study data showed no possible trend towards an increased risk of skin disorder- or hypersensitivity-related adverse events associated with trelagliptin. However, since skin disorder as an adverse drug reaction leading to study drug discontinuation was reported in Japanese clinical studies and since the number of subjects studied

[49] Adverse events classified under the SOC “skin and subcutaneous tissue disorders”

[50] Defined as events (preferred terms) included in narrow scope standardized MedDRA queries (SMQs) of “Hypersensitivity” and “Angioedema” excluding those classified under the SOC “Skin and subcutaneous tissue disorders”

and treatment duration in clinical studies were limited, collection of information on skin disorder and hypersensitivity should be continued in post-marketing surveillance.

4.(iii).B.(3).3) Cardiovascular risk

PMDA asked the applicant to discuss cardiovascular risk associated with trelagliptin based on the clinical study data.

The applicant responded as follows:

The incidence of adverse events related to cardiovascular risk (cardiovascular adverse events,[51] adverse events related to vital signs,[52] adverse events reported during ECG interpretation[53] or ECG-related adverse events,[54] lipid metabolism-related adverse events[55]) based on pooled data from Japanese clinical studies[56] and on pooled data from Japanese and foreign clinical studies[57] was as shown in Table 27.

Table 27. Adverse events related to cardiovascular risk in clinical studies (pooled analyses, safety analysis set)

	Pooled data from Japanese clinical studies[a)]			Pooled data from Japanese and foreign clinical studies[b)]	
	Placebo group (n = 105)	Combined trelagliptin group (n = 1061)	Alogliptin 25 mg group (n = 92)	Placebo group (n = 242)	Combined trelagliptin group (n = 1616)
Cardiovascular adverse events	4 (3.8) 6 [16.3]	64 (6.0) 70 [9.0]	8 (8.7) 8 [18.0]	4 (1.7) 6 [8.5]	65 (4.0) 71 [7.8]
Adverse events related to vital signs	1 (1.0) 1 [2.7]	39 (3.7) 49 [6.3]	2 (2.2) 2 [4.5]	2 (0.8) 2 [2.8]	49 (3.0) 59 [6.5]
Adverse events reported during ECG interpretation or ECG-related adverse events	1 (1.0) 1 [2.7]	9 (0.8) 9 [1.2]	1 (1.1) 1 [2.3]	1 (0.4) 1 [1.4]	14 (0.9) 14 [1.5]
Lipid metabolism-related adverse events	7 (6.7) 8 [21.8]	28 (2.6) 34 [4.4]	3 (3.3) 3 [6.8]	12 (5.0) 13 [18.4]	48 (3.0) 57 [6.3]

Upper column, No. of subjects with events (incidence %); Lower column, No. of events (incidence rate [events per 100 patient-years])

a) Pooled analysis of data from Studies CCT-001, CCT-002, OCT-001, and OCT-002

b) Pooled analysis of data from Studies CCT-001, CCT-002, OCT-001, and OCT-002, and Foreign Studies 007 and 006

Based on the pooled data from Japanese clinical studies, the incidence and the incidence rate (the number of events per unit of time) of each adverse event related to cardiovascular risk in the combined trelagliptin group were not substantially different from those in the placebo or alogliptin 25 mg group. The most commonly reported cardiovascular adverse event was blood creatine phosphokinase increased. All these events were mild in severity, and a causal relationship to the study drug was ruled out for all the events except for 5 events. Serious cardiovascular adverse events were reported by 5 subjects in the combined trelagliptin group (cerebral infarction [3 subjects], transient ischaemic attack [1 subject], acute myocardial infarction [1 subject]), but a causal relationship to the study drug was ruled out for all these events. The pooled data from Japanese and foreign clinical studies also showed no substantial difference in the incidence of cardiovascular adverse events between the combined trelagliptin group and the placebo group.

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51 Defined as events (preferred terms) classified under the broad scope SMQs of "Myocardial infarction" or "Central nervous system haemorrhages and cerebrovascular conditions"

52 Defined as events (preferred terms) classified under the narrow scope SMQ of "Hypertension" or HLT "Vascular tests NEC (incl. blood pressure)" for events related to blood pressure, as events (preferred terms) classified under the HLT "Heart rate and pulse investigations" for events related to pulse rate, and as events (preferred term) that includes the word "weight" for events related to body weight.

53 Defined as events reported during ECG interpretation for a clinical study. All ECGs interpreted as "abnormal and clinically relevant" that were obtained at any timepoint after the start of study treatment in a subject who had a baseline ECG interpreted as "within normal range" or "abnormal but clinically irrelevant" were reported as adverse events, except that reported by 1 subject each in the 25 mg group in Foreign Study 007 and in the 3.125 mg group in Foreign Study 006.

54 Defined as events (preferred terms) classified under the HLT "ECG investigations." Such events were reported by 1 subject in the placebo group (electrocardiogram T wave inversion) in Study CCT-001; 1 subject in the 50 mg group (electrocardiogram QT prolonged) and 2 subjects in the 100 mg group (electrocardiogram PR prolongation) in Foreign Study 007; and 1 subject in the sitagliptin 100 mg group (QRS axis abnormal) in Foreign Study 006. All these adverse events except the one reported by 1 subject in the 100 mg group (electrocardiogram PR prolongation) in Foreign Study 007 were reported during ECG interpretation.

55 Defined as events (preferred terms) classified under the narrow scope SMQ of "Dyslipidaemia" or the HLGT "Lipid analyses"

56 Pooled analysis of data from Studies CCT-001, CCT-002, OCT-001, and OCT-002

57 Pooled analysis of data from Studies CCT-001, CCT-002, OCT-001, and OCT-002, and Foreign Studies 007 and 006

An analysis of the changes in vital signs (blood pressure, pulse rate, body weight) in Japanese clinical studies revealed no substantial difference between the placebo and trelagliptin groups or between the monotherapy and combination therapy groups for blood pressure and pulse rate. Body weight significantly increased in the trelagliptin group compared to the placebo group in Studies CCT-001 and CCT-002, but the change was not clinically relevant because the point estimate of the between-group difference was as small as 0.693 kg at most. An analysis of ECG findings in Japanese phase III studies revealed no clinically meaningful difference in the mean changes in ECG parameters (RR, PR, QRS, QT, and QTc intervals) in any of the studies. In addition, there was no substantial difference between the placebo and trelagliptin groups or between the monotherapy and combination therapy groups. The change in lipid metabolism markers[58] was small and not clinically relevant in any of the Japanese phase II and III studies. In addition, there was no substantial difference between the placebo and trelagliptin groups or between the long-term monotherapy and long-term combination therapy groups.

Based on the above results, trelagliptin was very unlikely to have an impact on adverse events related to the cardiovascular system, vital signs, ECG, or lipid metabolism, or on the values of vital signs, ECG parameters, or lipid metabolism markers; therefore, trelagliptin is very unlikely to increase cardiovascular risk as well.

PMDA considers as follows:
Since the clinical study data showed no trend toward an increased risk of cardiovascular adverse events as compared with other DPP-4 inhibitors, there is no particular problem that requires a similar precautionary statement to that for other approved drugs of the same class. However, the number of subjects studied and treatment duration in clinical studies were limited, and collection of information on cardiovascular risk should be continued in post-marketing surveillance.

4.(iii).B.(3).4) Proarrhythmic risk associated with QT/QTc interval prolongation
The applicant explained as follows:
Proarrhythmic risk associated with QT/QTc interval prolongation was evaluated based on the data from the foreign thorough QT/QTc study conducted in healthy adult subjects (Study CPH-005). The results revealed that QT/QTc interval prolongation was not observed in subjects receiving trelagliptin 200 mg (double the recommended dose) but was observed in subjects receiving 800 mg. In addition to the ECG interpretation, evaluation of ECG parameters, including a categorical analysis of QTcF interval and a subgroup analysis on the change in QTcF interval, was performed in Japanese phase III clinical studies; the results showed no QT/QTc interval prolongation. In addition, an analysis of adverse events related to proarrhythmia associated with QT/QTc interval prolongation[59] revealed that loss of consciousness occurred in 1 subject in the trelagliptin + glinide group in Study OCT-001. The event was severe, but its causal relationship to the study drug was ruled out because this was considered by the investigator as a transient event due to hot flash induced by prolonged bathing. In foreign clinical studies, electrocardiogram QT prolonged was reported by 1 subject (a 63-year-old woman with a history of arrhythmia, hypertension, and hyperlipidaemia) at Week 2 in the 50 mg group in Foreign Study 007.[47] The event was moderate in severity and was assessed as an adverse drug reaction, but the subject recovered and completed the study. The subject's QTcF at Week 2 was 512 msec (increased from baseline by 69 msec), but became 454 msec at Week 12.

Based on the above findings, once-weekly trelagliptin 100 mg is unlikely to cause proarrhythmia associated with QT/QTc interval prolongation. Nevertheless, “proarrhythmia associated with QT/QTc interval prolongation” will be included in the safety specification of the risk management plan.

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[58] Consisting of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

[59] Including the following adverse events (preferred terms): Torsade de pointes, sudden death, cardiac death, sudden cardiac death, cardiac arrest, cardio-respiratory arrest, ventricular tachycardia, ventricular tachyarrhythmia, ventricular arrhythmia, ventricular fibrillation, cardiac fibrillation, ventricular flutter, altered state of consciousness, syncope, loss of consciousness, convulsion, epilepsy, electrocardiogram QT prolonged, long QT syndrome, long QT syndrome congenital, electrocardiogram QT interval abnormal, electrocardiogram repolarisation abnormality, and electrocardiogram U-wave abnormality

PMDA considers as follows:
No apparent increase in proarrhythmic risk associated with QT/QTc interval prolongation was observed in clinical studies. The applicant's response on information collection that would be continued in post-marketing surveillance is appropriate and acceptable because QT/QTc interval prolongation may cause life-threatening arrhythmia.

4.(iii).B.(3).5) Gastrointestinal disorders (including pancreatitis)
The applicant explained as follows:
An analysis was performed on adverse events classified under the SOC "gastrointestinal disorders" in Japanese clinical studies. In Study CCT-001, the incidence of such events was 7.3% (4 of 55 subjects) in the placebo group, 5.6% (3 of 54 subjects) in the 12.5 mg group, 7.7% (4 of 52 subjects) in the 25 mg group, 7.8% (4 of 51 subjects) in the 50 mg group, 7.3% (4 of 55 subjects) in the 100 mg group, and 13.0% (7 of 54 subjects) in the 200 mg group, showing a similar incidence in all the trelagliptin groups except the 200 mg group; the incidence was slightly higher in the 200 mg group than in the placebo group. The incidence of the events in Study CCT-002 was 10.0% (5 of 50 subjects) in the placebo group, 12.9% (13 of 101 subjects) in the trelagliptin group, and 10.9% (10 of 92 subjects) in the alogliptin group, showing no substantial difference between treatment groups. The incidence in Study OCT-001 was 18.1% (45 of 248 subjects) in the trelagliptin alone group, 22.2% (35 of 158 subjects) in the trelagliptin + SU group, 29.9% (20 of 67 subjects) in the trelagliptin + glinide group, 18.5% (12 of 65 subjects) in the trelagliptin + α-GI group, 4.3% (3 of 70 subjects) in the trelagliptin + BG group, and 16.7% (12 of 72 subjects) in the trelagliptin + TZD group. The incidence was slightly higher in the trelagliptin + glinide group and slightly lower in the trelagliptin + BG group than in the trelagliptin alone group. There was no report of such events in Study OCT-002. Serious adverse events of gastrointestinal disorders were enterocolitis (1 subject) in the 50 mg group in Study CCT-001; large intestine polyp (1 subject) in the trelagliptin group in Study CCT-002; and inguinal hernia and large intestine polyp (1 subject each) in the trelagliptin alone group, ileus (1 subject) in the trelagliptin + glinide group, and pancreatitis (1 subject) in the trelagliptin + TZD group in Study OCT-001. Ileus reported by 1 subject in the trelagliptin + glinide group was assessed as an adverse drug reaction.

No adverse events related to acute pancreatitis[60] occurred in Study CCT-001. In Study CCT-002, the incidence was 2.0% (1 of 50 subjects) in the placebo group, 5.9% (6 of 101 subjects) in the trelagliptin group, and 5.4% (5 of 92 subjects) in the alogliptin group, showing no substantial difference between the trelagliptin and alogliptin groups. All these events were mild in severity. Only 1 event reported by 1 subject in the alogliptin group (hyperlipasaemia) was assessed as an adverse drug reaction. In Study OCT-001, the incidence was 5.6% (14 of 248 subjects) in the trelagliptin alone group, 5.1% (8 of 158 subjects) in the trelagliptin + SU group, 4.5% (3 of 67 subjects) in the trelagliptin + glinide group, 9.2% (6 of 65 subjects) in the trelagliptin + α-GI group, 7.1% (5 of 70 subjects) in the trelagliptin + BG group, and 5.6% (4 of 72 subjects) in the trelagliptin + TZD group. Pancreatitis reported by 1 subject in the trelagliptin + TZD group was severe in severity, but other events were mild or moderate in severity. Adverse events related to acute pancreatitis were assessed as adverse drug reactions, which consisted of lipase increased (4 subjects), amylase increased (2 subjects), hyperbilirubinaemia(1 subject), and pancreatic enzymes increased (1 subject) in the trelagliptin alone group; lipase increased (2 subjects), pancreatic enzyme abnormality (1 subject), amylase increased (1 subject), and pancreatic enzymes increased (1 subject) in the trelagliptin + SU group, and lipase increased (1 subject) in the trelagliptin + α-GI group. No substantial difference in incidence was observed among the treatment groups. In Study OCT-002, lipase increased was reported by 1 subject and was assessed as an adverse drug reaction, but was mild in severity. In Japanese clinical studies, the adverse event classified under the narrow scope Standardized MedDRA Queries (SMQ) of "Acute pancreatitis" was pancreatitis reported by only 1 subject in the trelagliptin + TZD group in Study OCT-001. The event was severe and determined to be caused by bile-duct stones, and its causal relationship to the study drug was ruled out. No adverse events related to acute pancreatitis were reported in foreign clinical studies.

[60] Defined as all adverse events (preferred terms) classified under the narrow scope SMQ of "acute pancreatitis," and adverse events (preferred terms) related to laboratory parameters (hematology, urinalysis) classified under the broad scope SMQ of "acute pancreatitis" (i.e., pancreatic enzymes abnormal, pancreatic enzymes increased, pancreatic enzyme abnormality, hyperamylasaemia, amylase abnormal, amylase increased, hyperbilirubinaemia, bilirubin conjugated abnormal, blood bilirubin increased, blood trypsin increased, hyperlipasaemia, lipase abnormal, lipase increased, lipase urine increased).

As described above, the incidence of adverse events related to gastrointestinal disorders and acute pancreatitis with trelagliptin used alone was comparable to that with placebo or the comparator and not substantially different from that with trelagliptin used with any of the concomitant drugs, no concerns are considered to exist associated with trelagliptin monotherapy or combination therapies. However, in consideration of reports on other DPP-4 inhibitors, "acute pancreatitis" and "intestinal obstruction" will be included in the safety specification of the risk management plan, and precautionary statements will be included in the Precautions section of the package insert.

PMDA considers as follows:
PMDA accepted the applicant's explanation that no clinically relevant concerns were identified in the clinical study data because many of the gastrointestinal disorders observed in the clinical studies were mild in severity and because events related to acute pancreatitis were reported by a small number of subjects. However, since a serious adverse drug reaction (ileus) was reported in a Japanese clinical study and since the number of subjects studied in clinical studies was limited, the package insert should include appropriate precautionary statements, and collection of information on the incidence of gastrointestinal disorders and acute pancreatitis should be continued in post-marketing surveillance.

4.(iii).B.(3).6) Tumor risk
PMDA asked the applicant to explain the tumor risk associated with trelagliptin.

The applicant responded as follows:
Based on the pooled data from Japanese clinical studies, adverse events classified under "neoplasms benign, malignant and unspecified (incl. cysts and polyps)" include 1 event reported by 1 subject in the placebo group (haemangioma of liver) and 12 events reported by 10 subjects in the 100 mg group (3 events of colon cancer in 3 subjects, 2 events of colon adenoma in 1 subject, and 1 event each of adrenal neoplasm/bladder cancer, gastrointestinal tract adenoma, plasma cell myeloma, prostate cancer, seborrhoeic keratosis, and skin papilloma in 1 subject each). Based on foreign study data, such an event was reported by 1 subject in the 25 mg group (haemangioma) in Foreign Study 007 and 1 subject each in the placebo (skin papilloma), 12.5 mg (basal cell carcinoma), and sitagliptin 100 mg (benign lung neoplasm) groups in Foreign Study 006. The incidence rate of adverse events classified under "neoplasms benign, malignant and unspecified (incl. cysts and polyps)" based on the pooled data from Japanese and foreign clinical studies[57] was 2.8 events per 100 patient-years in the placebo group and 1.5 events per 100 patient-years in the combined trelagliptin group, showing no substantial difference between treatment groups.

Based on the above, at present, trelagliptin is unlikely to cause clinically relevant problems in terms of tumor risk. However, in consideration of the facts that there is no consensus about causal relationship between incretin-based therapy and pancreatic carcinoma and that systemic effects of long-term inhibition of DPP-4 activity remain unclear even using information obtained from overseas on other drugs of the same class, "malignant tumors" will be included in the safety specification of the risk management plan.

PMDA considers as follows:
The applicant's explanation is acceptable at present. However, since the number of subjects studied and treatment duration in Japanese and foreign clinical studies were limited, collection of information on the incidence of malignant tumors should be continued in post-marketing surveillance.

4.(iii).B.(3).7) Immune system disorders and infections
The applicant explained as follows:
The effect of trelagliptin on the immune system was evaluated based on the incidence of adverse events classified under the SOC "immune system disorders" and "infections and infestations" using the clinical study data.

Analysis was performed on adverse events classified under "immune system disorders" which had been reported in the Japanese clinical studies. Seasonal allergy occurred in 1 subject only in the 200 mg group in Study CCT-001. The event was mild in severity and its causal relationship to the study drug was ruled out. In Study CCT-002, seasonal allergy occurred in 3 subjects only in the trelagliptin group. All of these

events were mild in severity and their causal relationship to the study drug was ruled out. In Study OCT-001, events in this category were reported by 6 subjects in the trelagliptin alone group, 3 subjects in the trelagliptin + SU group, and 2 subjects in the trelagliptin + glinide group. All of the events were mild in severity and their causal relationship to the study drug was ruled out. There was no report on such events in Study OCT-002.

Analysis was performed on adverse events classified under "infections and infestations" which had been reported in the Japanese clinical studies. In Study CCT-001, the incidence of events in this category was 27.3% (15 of 55 subjects) in the placebo group, 16.7% (9 of 54 subjects) in the 12.5 mg group, 25.0% (13 of 52 subjects) in the 25 mg group, 25.5% (13 of 51 subjects) in the 50 mg group, 30.9% (17 of 55 subjects) in the 100 mg group, and 27.8% (15 of 54 subjects) in the 200 mg group, showing a similar incidence in all the trelagliptin groups except the 12.5 mg group; the incidence of the events was slightly lower in the 12.5 mg group than in the placebo group. A causal relationship between the study drug and all these events was ruled out. No severe events were reported. Diabetic gangrene reported by 1 subject in the 200 mg group was assessed as a serious adverse event and led to study drug discontinuation. In Study CCT-002, the incidence of events in this category was 24.0% (12 of 50 subjects) in the placebo group, 31.7% (32 of 101 subjects) in the trelagliptin group, and 28.3% (26 of 92 subjects) in the alogliptin group, showing a similar incidence in the trelagliptin group to that in the placebo and alogliptin groups. A causal relationship between the study drug and all these events was ruled out. No severe events were reported. In Study OCT-001, the incidence was 44.4% (110 of 248 subjects) in the trelagliptin alone group, 48.1% (76 of 158 subjects) in the trelagliptin + SU group, 43.3% (29 of 67 subjects) in the trelagliptin + glinide group, 58.5% (38 of 65 subjects) in the trelagliptin + α-GI group, 32.9% (23 of 70 subjects) in the trelagliptin + BG group, and 40.3% (29 of 72 subjects) in the trelagliptin + TZD group. Severe adverse events were reported by 1 subject in the trelagliptin + SU group (cellulitis) and 1 subject in the trelagliptin + glinide group (bronchiolitis). Serious adverse events included pneumonia and gastroenteritis (1 subject each) in the trelagliptin alone group, cellulitis and pyelonephritis acute (1 subject each) in the trelagliptin + SU group, bronchiolitis (1 subject) in the trelagliptin + glinide group, and pneumonia and pyelonephritis (1 subject each) in the trelagliptin + α-GI group. In Study OCT-002, periodontitis, pharyngitis, and sinusitis occurred in 1 subject. All of these events were mild in severity and their causal relationship to the study drug was ruled out.

Based on the above, the currently available data have not suggested a possible effect of trelagliptin on immune function, and thus trelagliptin is unlikely to pose clinically relevant safety problems. However, there are many reports about the effect of DPP-4 activity on immune function, but no consensus has been reached on its impact on infection risk. Therefore, in consideration of a possible effect of inhibition of DPP-4 activity on the immune system and a possible increase in infection risk, "infections" will be included in the safety specification of the risk management plan.

PMDA considers as follows:
The applicant's explanation is reasonable at present. Since the number of subjects studied and treatment duration in Japanese and foreign clinical studies were limited, collection of post-marketing information should be continued to evaluate the effect on the immune system and the incidence of infections.

4.(iii).B.(4) Measures for the proper use of the product
4.(iii).B.(4).1) Actions to be taken in the case of an overdose or missed dose
Trelagliptin may inadvertently be used daily or omitted due to the facts that all existing oral hypoglycemic agents are daily-dose products and that many patients concomitantly use daily-dose drugs for complications. For this reason, PMDA asked the applicant to explain measures for the proper use of trelagliptin.

The applicant responded as follows:
In Studies CCT-002, OCT-001, and OCT-002, concomitant daily-dose medication(s) were used by ≥80% of subjects. Among 795 subjects who received trelagliptin, only 6 subjects in Study OCT-001 (5 subjects in the trelagliptin alone group and 1 subject in the trelagliptin + BG group) had overdose (1 occasion each). All of the 6 subjects took 200 mg, which is double the recommended dose. Of these 6 subjects, 5 took 100 mg of trelagliptin twice within a week and the remaining 1 subject took 100 mg of trelagliptin twice in a day. Of these subjects, 4 experienced an adverse event(s) after the overdose (nasopharyngitis,

periodontitis, headache/hepatic function abnormal/arthralgia, and cough/back pain). All of these events were mild in severity and their causal relationship to the study drug was ruled out. There were no serious adverse events or adverse events leading to study drug discontinuation.

In terms of the safety of trelagliptin at a dose level exceeding the specified dose level, the data from Study CCT-001 and Foreign Study 007 showed that the incidence of adverse events associated with trelagliptin 200 mg once weekly was not substantially different from that with placebo treatment or trelagliptin 100 mg once weekly. In addition, the incidence of adverse events in Foreign Study 006, in which daily dosing at 100 mg for 12 weeks was evaluated, was not substantially different from that with placebo treatment [Table 28].

Table 28. Adverse events occurring in studies evaluating once-weekly trelagliptin 200 mg or daily trelagliptin 100 mg

	Study CCT-001 (once-weekly administration)			Foreign Study 007 (once-weekly administration)			Foreign Study 006 (daily administration)	
	Placebo (n = 55)	Trelagliptin 100 mg (n = 55)	Trelagliptin 200 mg (n = 54)	Placebo (n = 74)	Trelagliptin 100 mg (n = 74)	Trelagliptin 200 mg (n = 74)	Placebo (n = 63)	Trelagliptin 100 mg (n = 65)
Adverse events	24 (43.6)	28 (50.9)	27 (50.0)	31 (41.9)	27 (36.5)	29 (39.2)	31 (49.2)	38 (58.5)
Adverse drug reactions	2 (3.6)	5 (9.1)	3 (5.6)	9 (12.2)	15 (20.3)	12 (16.2)	8 (12.7)	14 (21.5)
Serious adverse events	0 (0.0)	0 (0.0)	1 (1.9)	2 (2.7)	1 (1.4)	0 (0.0)	1 (1.6)	0 (0.0)
Adverse events leading to treatment discontinuation	1 (1.8)	1 (1.8)	2 (3.7)	2 (2.7)	0 (0.0)	0 (0.0)	2 (3.2)	4 (6.2)

No. of subjects with events (incidence %)

Based on the above, an inadvertent daily administration or overdosing of trelagliptin is unlikely to cause major safety issues. However, because special precautions would be needed to avoid an inadvertent daily administration of trelagliptin, the Precautions for Dosage and Administration section of the package insert will include precautionary statements that trelagliptin should be used once a week on the same day of the week and that the dose of trelagliptin should not exceed the specified dose level. In addition, a precautionary statement describing the action to be taken when a dose of trelagliptin is inadvertently omitted will be provided, stating that patients should just take the specified dose at the time of noticing a missed dose, and take trelagliptin on a predetermined day of the week thereafter. Furthermore, measures will be taken including packaged PTP sheets which directly indicate timing of dosing and precautions and supportive materials such as a patient information leaflet in order to prevent unintentionally missed doses and/or overdoses resulting from daily dosing, and information will be provided to healthcare professionals and patients on how to deal with a missed dose (as described above) or overdose (i.e., patients should stop taking trelagliptin at the time of becoming aware of an overdose, and consult with a physician or pharmacist).

4.(iii).B.(4).2) Switching from trelagliptin to an existing daily-dose oral hypoglycemic agent

In light of the prolonged action of trelagliptin, PMDA asked the applicant to explain the necessity of providing a precaution about switching from trelagliptin to a daily-dose antidiabetic agent.

The applicant responded as follows:

Even at 7 days post-dose, blood trelagliptin concentrations would remain high enough to maintain approximately ≥70% inhibition of DPP-4 activity, thus promoting hypoglycemic activity. The Important Precautions section of the package insert will therefore include a precautionary statement to the effect that the starting timing and dose level of another antidiabetic agent in switching from trelagliptin should be selected in consideration of the persistence of hypoglycemic activity even at 168 hours after administration of trelagliptin.

PMDA considers that there is no major problem with the applicant's response about the measures for the proper use of trelagliptin described in 4.(iii).B.(4).1) and 4.(iii).B.(4).2) above. However, details of the

actions will be reviewed and the final decision on their appropriateness will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.(5) Indication

PMDA considers as follows:

"On release of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents" (PFSB/ELD Notification No. 0709-1 dated July 9, 2010, [OAD Guideline]) states that when an investigational drug is confirmed to be useful in clinical studies of two-drug combination therapies with the investigational drug and the approved oral hypoglycaemic agents (combination therapies expected to be administered to patients in clinical practice) conducted based on the OAD Guideline, the appropriate description of the indication is "type 2 diabetes mellitus." Because the data submitted in this application demonstrate the efficacy of monotherapy and combination therapies through clinical studies conducted in accordance with the OAD Guideline [see "4.(iii).B.(2) Efficacy"] and their safety is acceptable [see "4.(iii).B.(3) Safety"], PMDA considers that there is no problem with the proposed indication of "type 2 diabetes mellitus."

4.(iii).B.(6) Dosage and administration

The applicant explained as follows:

Based on the comparison of data between the foreign phase II dose-finding studies in patients with type 2 diabetes mellitus (Foreign Study 007 evaluating once-weekly treatment for 12 weeks and Foreign Study 006 evaluating once-daily treatment for 12 weeks), the efficacy of trelagliptin has been demonstrated for once-weekly 100 mg (Foreign Study 007) and daily 100 mg (Foreign Study 006), with no substantial difference in the safety as compared with placebo treatment. On this basis, once-weekly dosing regimen was considered appropriate. In addition, in the phase II dose-finding study in Japanese patients with type 2 diabetes mellitus (Study CCT-001), HbA1c at the end of the treatment period decreased almost proportionally with increasing dose levels within the range of 12.5 to 200 mg (once-weekly administration), while no substantial difference in the change in HbA1c was observed between the 100 mg and 200 mg groups. As for safety, the incidence of adverse events was similar between the placebo and each of the trelagliptin groups, with no major problems noted. In addition, the mean percent inhibition of DPP-4 activity at 7 days after the last dose in subjects receiving 100 mg remained at ≥70% (specifically 77.43%), which was comparable to the trough level of inhibition of DPP-4 activity (approximately ≥70%) achieved with existing daily-dose DPP-4 inhibitors. Since trelagliptin is an oral hypoglycemic agent intended for once-weekly administration, a dosage regimen different from that of other drugs, and therefore, may possibly inadvertently be used daily, the appropriate recommended dose of trelagliptin would be 100 mg once weekly, which gives the lower exposure. The results from the phase III confirmatory study in Japanese patients with type 2 diabetes mellitus (Study CCT-002) confirmed the non-inferiority of once-weekly trelagliptin 100 mg to once-daily alogliptin 25 mg, showing the efficacy of the trelagliptin monotherapy. An analysis of the safety revealed that the incidence of adverse events was similar to that in the placebo and alogliptin groups, with no major problems noted. In addition, the effect of the persistent inhibition of DPP-4 activity by trelagliptin on the safety was evaluated based on the incidence of adverse events by elapsed days from the previous dosing of trelagliptin or its matching placebo [Table 29]. The results showed that the incidence of adverse events was the highest on Day 1 in all treatment groups, and the incidence on Day 1 was similar among the trelagliptin, placebo, and alogliptin groups. The incidence in the trelagliptin group tended to be higher than that in the alogliptin group on Day 4 and from Day 8 onward, and higher than that in the placebo group on Days 6 and 7. However, in terms of the incidence of adverse events by SOC and preferred term, no tendency was observed in the trelagliptin group for the incidence of specific adverse events to increase with elapsed days as compared with the alogliptin or placebo group.

Table 29. Adverse events by elapsed days from the previous dosing of trelagliptin or its matching placebo (Study CCT-002)

Elapsed days from the previous dosing of the study drug	Placebo[a)] (n = 50)	Trelagliptin (n = 101)	Alogliptin[a)] (n = 92)
Subjects experiencing any adverse event	32 (64.0)	67 (66.3)	57 (62.0)
1	11 (22.0)	29 (28.7)	28 (30.4)
2	10 (20.0)	11 (10.9)	6 (6.5)
3	5 (10.0)	6 (5.9)	11 (12.0)
4	4 (8.0)	11 (10.9)	5 (5.4)
5	5 (10.0)	13 (12.9)	11 (12.0)
6	2 (4.0)	20 (19.8)	10 (10.9)
7	4 (8.0)	16 (15.8)	11 (12.0)
≥8	5 (10.0)	15 (14.9)	7 (7.6)

No. of subjects with events (%)
a) Placebo matching to trelagliptin was administered.

In addition, in the phase III long-term monotherapy/combination therapy study (Study OCT-001), the efficacy of once-weekly trelagliptin 100 mg was demonstrated in monotherapy and the combination therapies, with no major problems with the safety of monotherapy or combination therapies. In Japanese Study CPH-009, the timing of dosing was evaluated using the 100 mg formulation proposed for marketing in Japan. The results suggested that food intake would not affect the PK/PD of trelagliptin.

Based on the above, the proposed dosage and administration of trelagliptin is "the usual adult dosage is 100 mg of trelagliptin orally administered once weekly" for both monotherapy and combination therapies.

PMDA considers as follows:
Given the clinical study data evaluating the pharmacokinetics, pharmacodynamic effects, efficacy, and safety, there is no major problem with selecting "100 mg of trelagliptin orally administered once weekly." Although there was a concern about the impact of high-dose intermittent administration-induced elevation of plasma trelagliptin levels on safety, no particular problems were observed through the analysis of the incidence of adverse events by elapsed days from administration of trelagliptin using data from Study CCT-002 [Table 29]. Although trelagliptin was to be administered before breakfast in the clinical studies evaluating the efficacy and safety (except Foreign Studies 006 and 007, in which trelagliptin was to be administered before the first meal of the day), there is no need to specify the time of dosing in light of the results of the food effect study and pharmacodynamic effects including inhibition of DPP-4 activity [for dose levels in patients with renal or hepatic impairment, see "4.(iii).B.(7) Use in special populations"]. The final decision on the above issues will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.(7) Use in special populations
4.(iii).B.(7).1) Patients with renal impairment
PMDA asked the applicant to explain the safety of trelagliptin in patients with renal impairment.

The applicant responded as follows:
Based on pooled data from the monotherapy groups in the Japanese clinical studies in Japanese patients with type 2 diabetes mellitus and on data by treatment group from Study OCT-001, the incidence of adverse events was examined by severity of renal impairment (normal renal function, Ccr ≥80 mL/min; mild renal impairment, Ccr ≥50 and <80 mL/min; moderate to severe renal impairment, Ccr <50 mL/min).

The pooled data from monotherapy groups showed no substantial difference in the incidence of adverse events between subjects with normal renal function and patients with mild renal impairment as shown in Table 30. The data from monotherapy groups in Study OCT-001 showed no consistent trend in the incidence of adverse events, adverse drug reactions, serious adverse events, adverse events leading to study drug discontinuation, or hypoglycaemia according to the severity of renal impairment for any of the treatment groups as shown in Table 31. Of 20 subjects (1 subject in the placebo group, 15 subjects in the 100 mg group, 3 subjects in the 200 mg group, and 1 subject in the alogliptin group) who had

moderate renal impairment (Ccr ≥30 and <50 mL/min), 13 subjects in the 100 mg group and 1 subject in the 200 mg group experienced adverse events. Severe adverse events were not reported. Serious adverse events were reported by 2 subjects (macular hole in the trelagliptin + SU group, acute myocardial infarction in the trelagliptin + glinide group), but their causal relationship to the study drug was ruled out. Only 1 subject (in the trelagliptin + glinide group in Study OCT-001) had severe renal impairment (Ccr <30 mL/min). This subject discontinued study treatment due to an adverse drug reaction of eczema (non-serious and moderate in severity) occurred on Day 144.

Table 30. Adverse events by severity of renal impairment (pooled analysis on monotherapy from Japanese clinical studies)

Type of event	Renal function	Placebo (n = 105)	Trelagliptin					Alogliptin 25 mg (n = 92)
			12.5 mg (n = 54)	25 mg (n = 52)	50 mg (n = 51)	100 mg (n = 418)	200 mg (n = 54)	
All adverse events	Normal	31/68 (45.6) [209.1]	15/40 (37.5) [212.4]	15/42 (35.7) [219.3]	16/39 (41.0) [346.3]	232/327 (70.9) [273.3]	21/37 (56.8) [327.9]	43/73 (58.9) [242.3]
	Mild renal impairment	25/36 (69.4) [351.9]	5/14 (35.7) [253.3]	6/10 (60.0) [484.8]	4/12 (33.3) [294.6]	63/85 (74.1) [324.6]	5/14 (35.7) [198.4]	14/18 (77.8) [296.7]
	Moderate to severe renal impairment	0/1 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	4/6 (66.7) [239.3]	1/3 (33.3) [131.4]	0/1 (0.0) [0.0]
All adverse drug reactions	Normal	2/68 (2.9) [8.5]	4/40 (10.0) [50.6]	3/42 (7.1) [28.6]	5/39 (12.8) [91.7]	41/327 (12.5) [28.0]	2/37 (5.4) [21.9]	6/73 (8.2) [17.1]
	Mild renal impairment	3/36 (8.3) [30.6]	0/14 (0.0) [0.0]	2/10 (20.0) [80.8]	1/12 (8.3) [32.7]	9/85 (10.6) [19.4]	1/14 (7.1) [28.3]	1/18 (5.6) [11.4]
	Moderate to severe renal impairment	0/1 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/6 (0.0) [0.0]	0/3 (0.0) [0.0]	0/1 (0.0) [0.0]
Serious adverse events	Normal	1/68 (1.5) [4.3]	0/40 (0.0) [0.0]	0/42 (0.0) [0.0]	1/39 (2.6) [10.2]	10/327 (3.1) [4.5]	1/37 (2.7) [10.9]	2/73 (2.7) [5.7]
	Mild renal impairment	0/36 (0.0) [0.0]	0/14 (0.0) [0.0]	0/10 (0.0) [0.0]	0/12 (0.0) [0.0]	3/85 (3.5) [4.8]	0/14 (0.0) [0.0]	0/18 (0.0) [0.0]
	Moderate to severe renal impairment	0/1 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/6 (0.0) [0.0]	0/3 (0.0) [0.0]	0/1 (0.0) [0.0]
Adverse events leading to treatment discontinuation	Normal	1/68 (1.5) [4.3]	0/40 (0.0) [0.0]	0/42 (0.0) [0.0]	0/39 (0.0) [0.0]	12/327 (3.7) [6.6]	2/37 (5.4) [21.9]	1/73 (1.4) [2.9]
	Mild renal impairment	1/36 (2.8) [7.7]	0/14 (0.0) [0.0]	0/10 (0.0) [0.0]	0/12 (0.0) [0.0]	4/85 (4.7) [6.5]	0/14 (0.0) [0.0]	0/18 (0.0) [0.0]
	Moderate to severe renal impairment	0/1 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/6 (0.0) [0.0]	0/3 (0.0) [0.0]	0/1 (0.0) [0.0]
Hypoglycaemia	Normal	0/68 (0.0) [0.0]	0/40 (0.0) [0.0]	0/42 (0.0) [0.0]	0/39 (0.0) [0.0]	1/327 (0.3) [0.4]	0/37 (0.0) [0.0]	0/73 (0.0) [0.0]
	Mild renal impairment	0/36 (0.0) [0.0]	0/14 (0.0) [0.0]	0/10 (0.0) [0.0]	0/12 (0.0) [0.0]	0/85 (0.0) [0.0]	0/14 (0.0) [0.0]	1/18 (5.6) [11.4]
	Moderate to severe renal impairment	0/1 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/0 (0.0) [0.0]	0/6 (0.0) [0.0]	0/3 (0.0) [0.0]	0/1 (0/1) [0.0]

Upper column, No. of subjects with events/No. of subjects included in the analysis set; Middle column, (incidence %); Lower column, [No. of events per unit time (events/100 patient-years)]; MedDRA/J ver.16.0

Table 31. Adverse events by severity of renal impairment (Study OCT-001)

Type of event	Renal function	Trelagliptin alone (n = 248)	Trelagliptin + SU (n = 158)	Trelagliptin + glinide (n = 67)	Trelagliptin + α-GI (n = 65)	Trelagliptin + BG (n = 70)	Trelagliptin + TZD (n = 72)
All adverse events	Normal	151/195 (77.4)	113/128 (88.3)	38/51 (74.5)	38/49 (77.6)	40/61 (65.6)	49/58 (84.5)
	Mild renal impairment	45/49 (91.8)	22/27 (81.5)	10/12 (83.3)	12/13 (92.3)	5/9 (55.6)	12/14 (85.7)
	Moderate to severe renal impairment	2/4 (50.0)	3/3 (100.0)	4/4 (100.0)	3/3 (100.0)	0/0 (0.0)	0/0 (0.0)
All adverse drug reactions	Normal	30/195 (15.4)	16/128 (12.5)	4/51 (7.8)	1/49 (2.0)	8/61 (13.1)	7/58 (12.1)
	Mild renal impairment	9/49 (18.4)	0/27 (0.0)	3/12 (25.0)	3/13 (23.1)	0/9 (0.0)	3/14 (21.4)
	Moderate to severe renal impairment	0/4 (0.0)	1/3 (33.3)	1/4 (25.0)	0/3 (0.0)	0/0 (0.0)	0/0 (0.0)
Serious adverse events	Normal	7/195 (3.6)	6/128 (4.7)	2/51 (3.9)	2/49 (4.1)	1/61 (1.6)	2/58 (3.4)
	Mild renal impairment	2/49 (4.1)	4/27 (14.8)	2/12 (16.7)	1/13 (7.7)	0/9 (0.0)	2/14 (14.3)
	Moderate to severe renal impairment	0/4 (0.0)	1/3 (33.3)	1/4 (25.0)	0/3 (0.0)	0/0 (0.0)	0/0 (0.0)
Adverse events leading to treatment discontinuation	Normal	6/195 (3.1)	6/128 (4.7)	2/51 (3.9)	2/49 (4.1)	5/61 (8.2)	1/58 (1.7)
	Mild renal impairment	3/49 (6.1)	3/27 (11.1)	1/12 (8.3)	3/13 (23.1)	0/9 (0.0)	4/14 (28.6)
	Moderate to severe renal impairment	0/4 (0.0)	0/3 (0.0)	2/4 (50.0)	0/3 (0.0)	0/0 (0.0)	0/0 (0.0)
Hypoglycaemia	Normal	1/195 (0.5)	7/128 (5.5)	1/51 (2.0)	0/49 (0.0)	1/61 (1.6)	0/58 (0.0)
	Mild renal impairment	0/49 (0.0)	0/27 (0.0)	0/12 (0.0)	1/13 (7.7)	0/9 (0.0)	1/14 (7.1)
	Moderate to severe renal impairment	0/4 (0.0)	0/3 (0.0)	0/4 (0.0)	0/3 (0.0)	0/0 (0.0)	0/0 (0.0)

No. of subjects with events/No. of subjects included in the analysis set (incidence %), MedDRA/J ver.16.0

In the foreign clinical pharmacology study in subjects with renal impairment (Foreign Study 101), pharmacokinetics following a single dose of trelagliptin 50 mg were evaluated in healthy adult subjects (Ccr >80 mL/min), subjects with mild renal impairment (Ccr >50 and ≤80 mL/min), subjects with moderate renal impairment (Ccr ≥30 and ≤50 mL/min), subjects with severe renal impairment (Ccr <30 mL/min without hemodialysis), and patients with end-stage renal failure requiring hemodialysis. $AUC_{0\text{-}tlqc}$ of unchanged trelagliptin in subjects with mild renal impairment, subjects with moderate renal impairment, subjects with severe renal impairment, and patients with end-stage renal failure was 1.56-, 2.06-, 3.01-, and 3.68-fold, respectively, that in healthy adult subjects [see "4.(ii).A.(4).1) Pharmacokinetic study in subjects with renal impairment"]. Based on the population pharmacokinetic analysis in Japanese patients with type 2 diabetes mellitus, AUC of unchanged trelagliptin in subjects with mild renal impairment and subjects with moderate renal impairment was estimated to be approximately 1.12- to 1.43-fold and 1.43- to 1.86-fold, respectively, that in healthy adult subjects. Analysis was performed to evaluate the possibility of accumulation of trelagliptin administered in multiple doses. No accumulation of trelagliptin was expected regardless of the severity of renal impairment because a steady state was nearly reached after 12-week treatment.

The above subgroup analyses by severity of renal impairment using data from Japanese clinical studies showed no apparent trend in the incidence of adverse events according to the severity of renal impairment, although the number of patients with moderate to severe renal impairment was limited. However, pharmacokinetic study data in subjects with renal impairment showed that the adjusted mean $AUC_{0\text{-}tlqc}$ in subjects with mild renal impairment and subjects with moderate renal impairment was approximately 1.56- and 2.06-fold, respectively, that in subjects with normal renal function; therefore, adjustment of the dosage regimen of trelagliptin for patients with mild renal impairment is considered unnecessary, while a dose reduction to one-half (i.e., 50 mg) of the recommended dose is required for patients with moderate renal impairment. The optimal dose in patients with severe renal impairment or patients with end-stage renal failure is estimated to be 25 mg based on $AUC_{0\text{-}tlqc}$ of unchanged trelagliptin (3.01- and 3.68-fold, respectively, that in subjects with normal renal function) in Foreign Study 101. However, there is almost no clinical experience in a patient population with severe renal impairment or with end-stage renal failure. In addition, trelagliptin is the world's first once-weekly oral

hypoglycemic agent and at the same time is a renally excreted drug. Elevated blood trelagliptin concentrations are expected in the patient populations when they are treated with trelagliptin 50 mg once weekly, but the safety of the drug in such patients has not been determined. At present, therefore, trelagliptin should be contraindicated in patients with severe renal impairment and those with end-stage renal failure. Although there would be no major safety problems with recommending a dose regimen of 50 mg once weekly in patients with moderate renal impairment, such patients will be listed in the Careful Administration section, and safety information on such patients will be identified as important missing information because of the paucity of information due to the limited number of patients treated with trelagliptin.

PMDA considers as follows:
The proposed regimen of trelagliptin 100 mg once weekly (i.e., the recommended dosage) in patients with mild renal impairment is appropriate, because data from the Japanese clinical studies showed no trend towards a particularly increased risk in patients with mild renal impairment as compared with patients with normal renal function during the trelagliptin monotherapy or combination therapies. Although data from the Japanese clinical studies showed no particular trend suggesting a safety concern in patients with moderate renal impairment, a dose reduction to trelagliptin 50 mg once weekly should be recommended in such patients in light of the pharmacokinetics of trelagliptin. In addition, given the paucity of information due to the limited number of patients treated with trelagliptin, such patients should be listed in the Careful Administration section and safety information should be collected on such patients via post-marketing surveillance. PMDA accepted the applicant's explanation that at present, trelagliptin should be contraindicated in patients with severe renal impairment and patients with end-stage renal failure because (1) the safety of trelagliptin, which is a renally excreted drug, has not been determined in these patient populations who have a risk of elevated blood trelagliptin concentrations since no lower dosage strength is proposed for use in patients with high exposure, and (2) trelagliptin is an once-weekly oral hypoglycemic agent with sustained glucose-lowering effects. The dosage regimen and safety of trelagliptin in patients with renal impairment and specific measures for calling attention to such patients will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(7).2) Patients with hepatic impairment
PMDA asked the applicant to explain the safety of trelagliptin in patients with hepatic impairment.

The applicant responded as follows:
Based on the pooled analysis of data from the monotherapy subgroups in the Japanese clinical studies and on the analysis by treatment group using data from Study OCT-001, the incidence of adverse events was examined according to the presence or absence of hepatic impairment (comorbidity included in the SOC “hepatobiliary disorders” at screening).

The pooled analysis of data from monotherapy groups showed no substantial difference in the incidence of adverse events in each treatment group according to the presence or absence of hepatic impairment, as shown in Table 32. The analysis by treatment group (Study OCT-001) showed no consistent trend in the incidence of adverse events for any of the treatment groups regardless of hepatic impairment, although the number of subjects with events was limited for some of the treatment group (see Table 33).

Based on the above, in patients receiving trelagliptin monotherapy or combination therapy, the risk of specific adverse events is unlikely to be increased depending on the presence or absence of hepatic impairment.

Table 32. Adverse events by the presence or absence of hepatic impairment[a)] (pooled analysis on monotherapy from Japanese clinical studies)

Type of event	Hepatic impairment[a)]	Placebo (n = 105)	Trelagliptin 12.5 mg (n = 54)	Trelagliptin 25 mg (n = 52)	Trelagliptin 50 mg (n = 51)	Trelagliptin 100 mg (n = 418)	Trelagliptin 200 mg (n = 54)	Alogliptin 25 mg (n = 92)
All adverse events	Yes	18/45 (40.0) [216.9]	6/23 (26.1) [155.9]	7/23 (30.4) [187.9]	12/22 (54.5) [466.4]	123/167 (73.7) [321.5]	12/30 (40.0) [242.2]	26/34 (76.5) [351.6]
	No	38/60 (63.3) [283.3]	14/31 (45.2) [273.8]	14/29 (48.3) [337.7]	8/29 (27.6) [232.9]	176/251 (70.1) [259.0]	15/24 (62.5) [332.8]	31/58 (53.4) [190.5]
All adverse drug reactions	Yes	0/45 (0.0) [0.0]	1/23 (4.3) [17.3]	2/23 (8.7) [34.2]	2/22 (9.1) [71.8]	20/167 (12.0) [27.7]	1/30 (3.3) [13.5]	5/34 (14.7) [30.3]
	No	5/60 (8.3) [26.1]	3/31 (9.7) [52.2]	3/29 (10.3) [42.2]	4/29 (13.8) [82.2]	30/251 (12.0) [24.7]	2/24 (8.3) [33.3]	2/58 (3.4) [7.2]
Serious adverse events	Yes	0/45 (0.0) [0.0]	0/23 (0.0) [0.0]	0/23 (0.0) [0.0]	0/22 (0.0) [0.0]	7/167 (4.2) [6.7]	1/30 (3.3) [13.5]	1/34 (2.9) [6.1]
	No	1/60 (1.7) [4.4]	0/31 (0.0) [0.0]	0/29 (0.0) [0.0]	1/29 (3.4) [13.7]	6/251 (2.4) [3.2]	0/24 (0.0) [0.0]	1/58 (1.7) [3.6]
Adverse events leading to treatment discontinuation	Yes	1/45 (2.2) [7.2]	0/23 (0.0) [0.0]	0/23 (0.0) [0.0]	0/22 (0.0) [0.0]	8/167 (4.8) [9.2]	1/30 (3.3) [13.5]	0/34 (0.0) [0.0]
	No	1/60 (1.7) [4.4]	0/31 (0.0) [0.0]	0/29 (0.0) [0.0]	0/29 (0.0) [0.0]	8/251 (3.2) [4.7]	1/24 (4.2) [16.6]	1/58 (1.7) [3.6]
Hypoglycaemia	Yes	0/45 (0.0) [0.0]	0/23 (0.0) [0.0]	0/23 (0.0) [0.0]	0/22 (0.0) [0.0]	1/167 (0.6) [0.8]	0/30 (0.0) [0.0]	1/34 (2.9) [6.1]
	No	0/60 (0.0) [0.0]	0/31 (0.0) [0.0]	0/29 (0.0) [0.0]	0/29 (0.0) [0.0]	0/251 (0.0) [0.0]	0/24 (0.0) [0.0]	0/58 (0.0) [0.0]

Upper column, No. of subjects with events/No. of subjects included in the analysis set; Middle column, (incidence %); Lower column, (No. of events per unit time [events/100 patient-years]); MedDRA/J ver.16.0

a) The presence or absence of a comorbidity included in the SOC "hepatobiliary disorders" at screening.

Table 33. Adverse events by the presence or absence of hepatic impairment (by treatment group in Study OCT-001)

Type of event	Hepatic impairment[a)]	Trelagliptin alone (n = 248)	Trelagliptin + SU (n = 158)	Trelagliptin + glinide (n = 67)	Trelagliptin + α-GI (n = 65)	Trelagliptin + BG (n = 70)	Trelagliptin + TZD (n = 72)
All adverse events	Yes	80/95 (84.2)	52/59 (88.1)	27/31 (87.1)	21/26 (80.8)	14/20 (70.0)	21/24 (87.5)
	No	118/153 (77.1)	86/99 (86.9)	25/36 (69.4)	32/39 (82.1)	31/50 (62.0)	40/48 (83.3)
All adverse drug reactions	Yes	16/95 (16.8)	8/59 (13.6)	6/31 (19.4)	0/26 (0.0)	3/20 (15.0)	3/24 (12.5)
	No	23/153 (15.0)	9/99 (9.1)	2/36 (5.6)	4/39 (10.3)	5/50 (10.0)	7/48 (14.6)
Serious adverse events	Yes	4/95 (4.2)	1/59 (1.7)	3/31 (9.7)	2/26 (7.7)	1/20 (5.0)	1/24 (4.2)
	No	5/153 (3.3)	10/99 (10.1)	2/36 (5.6)	1/39 (2.6)	0/50 (0.0)	3/48 (6.3)
Adverse events leading to treatment discontinuation	Yes	5/95 (5.3)	2/59 (3.4)	4/31 (12.9)	3/26 (11.5)	2/20 (10.0)	1/24 (4.2)
	No	4/153 (2.6)	7/99 (7.1)	1/36 (2.8)	2/39 (5.1)	3/50 (6.0)	4/48 (8.3)
Hypoglycaemia	Yes	1/95 (1.1)	5/59 (8.5)	1/31 (3.2)	1/26 (3.8)	1/20 (5.0)	0/24 (0.0)
	No	0/153 (0.0)	2/99 (2.0)	0/36 (0.0)	0/39 (0.0)	0/50 (0.0)	1/48 (2.1)

No. of subjects with events/No. of subjects included in the analysis set (incidence %), MedDRA/J ver.16.0

a) The presence or absence of a comorbidity included in the SOC "hepatobiliary disorders" at screening.

PMDA considers as follows:

No trend towards a particularly increased risk was found in subjects receiving monotherapy or any of the combination therapies in the Japanese clinical studies, regardless of hepatic impairment (comorbidity included in the SOC "hepatobiliary disorders" at screening). The applicant considered that no dose adjustment is required in patients with hepatic impairment also in terms of the pharmacokinetics of

trelagliptin in such patients, and the applicant's view is appropriate. However, the clinical studies excluded patients with clinically evident hepatic impairment, indicating insufficient evaluation of patients with hepatic impairment. Therefore, collection of information on the safety in patients with hepatic impairment should be continued in post-marketing surveillance.

4.(iii).B.(7).3) Elderly patients

PMDA asked the applicant to explain the safety of trelagliptin in elderly patients.

The applicant responded as follows:

Based on the pooled analysis of data from the monotherapy groups in the Japanese clinical studies and on the analysis by treatment group using data from Study OCT-001, the incidence of adverse events was examined according to age subgroup (<65, ≥65, or ≥75 years of age).

The pooled analysis of data from monotherapy groups in the Japanese clinical studies showed no substantial difference among the age subgroups in the incidence of adverse events in each treatment group as shown in Table 34. The analysis by treatment group using data from Study OCT-001 showed no consistent age-related trend in the incidence of adverse events for all the treatment groups except α-GI combination therapy, with which the incidence was higher in subjects aged ≥65 years than in subjects aged <65 years, as shown in Table 35. Although the number of subjects having any event was limited for some of the treatment groups, no consistent age-related trend in the incidence of adverse drug reactions, serious adverse events, adverse events leading to treatment discontinuation, or hypoglycaemia was observed for any of the treatment groups.

Based on the above analysis by age subgroup (<65, ≥65, or ≥75 years of age) that showed no substantial difference in the safety, the age is unlikely to affect the safety of trelagliptin.

Table 34. Adverse events by age subgroup (<65, ≥65, or ≥75 years of age) (pooled analysis on monotherapy from Japanese clinical studies)

Type of event	Age	Placebo (n = 105)	Trelagliptin					Alogliptin 25 mg (n = 92)
			12.5 mg (n = 54)	25 mg (n = 52)	50 mg (n = 51)	100 mg (n = 418)	200 mg (n = 54)	
All adverse events	<65	32/64 (50.0) [216.4]	14/34 (41.2) [213.3]	9/35 (25.7) [149.1]	13/31 (41.9) [357.0]	207/283 (73.1) [280.0]	19/32 (59.4) [354.9]	39/67 (58.2) [233.0]
	≥65	24/41 (58.5) [321.9]	6/20 (30.0) [240.0]	12/17 (70.6) [518.8]	7/20 (35.0) [298.2]	92/135 (68.1) [289.7]	8/22 (36.4) [180.2]	18/25 (72.0) [296.8]
	≥75	6/8 (75.0) [267.1]	1/3 (33.3) [264.7]	1/3 (33.3) [135.8]	2/3 (66.7) [647.6]	12/17 (70.6) [315.5]	0/4 (0.0) [0.0]	2/4 (50.0) [310.4]
All adverse drug reactions	<65	1/64 (1.6) [4.5]	3/34 (8.8) [47.4]	3/35 (8.6) [34.4]	3/31 (9.7) [38.2]	35/283 (12.4) [28.0]	2/32 (6.3) [25.3]	5/67 (7.5) [15.5]
	≥65	4/41 (9.8) [34.2]	1/20 (5.0) [20.0]	2/17 (11.8) [47.2]	3/20 (15.0) [139.2]	15/135 (11.1) [21.3]	1/22 (4.5) [18.0]	2/25 (8.0) [16.5]
	≥75	2/8 (25.0) [100.2]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/17 (0.0) [0.0]	0/4 (0.0) [0.0]	1/4 (25.0) [51.7]
Serious adverse events	<65	1/64 (1.6) [4.5]	0/34 (0.0) [0.0]	0/35 (0.0) [0.0]	1/31 (3.2) [12.7]	10/283 (3.5) [4.8]	1/32 (3.1) [12.7]	2/67 (3.0) [6.2]
	≥65	0/41 (0.0) [0.0]	0/20 (0.0) [0.0]	0/17 (0.0) [0.0]	0/20 (0.0) [0.0]	3/135 (2.2) [4.1]	0/22 (0.0) [0.0]	0/25 (0.0) [0.0]
	≥75	0/8 (0.0) [0.0]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/17 (0.0) [0.0]	0/4 (0.0) [0.0]	0/4 (0.0) [0.0]
Adverse events leading to treatment discontinuation	<65	1/64 (1.6) [4.5]	0/34 (0.0) [0.0]	0/35 (0.0) [0.0]	0/31 (0.0) [0.0]	9/283 (3.2) [6.2]	2/32 (6.3) [25.3]	1/67 (1.5) [3.1]
	≥65	1/41 (2.4) [6.8]	0/20 (0.0) [0.0]	0/17 (0.0) [0.0]	0/20 (0.0) [0.0]	7/135 (5.2) [7.1]	0/22 (0.0) [0.0]	0/25 (0.0) [0.0]
	≥75	0/8 (0.0) [0.0]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/17 (0.0) [0.0]	0/4 (0.0) [0.0]	0/4 (0.0) [0.0]
Hypoglycaemia	<65	0/64 (0.0) [0.0]	0/34 (0.0) [0.0]	0/35 (0.0) [0.0]	0/31 (0.0) [0.0]	1/283 (0.4) [0.5]	0/32 (0.0) [0.0]	0/67 (0.0) [0.0]
	≥65	0/41 (0.0) [0.0]	0/20 (0.0) [0.0]	0/17 (0.0) [0.0]	0/20 (0.0) [0.0]	0/135 (0.0) [0.0]	0/22 (0.0) [0.0]	1/25 (4.0) [8.2]
	≥75	0/8 (0.0) [0.0]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/3 (0.0) [0.0]	0/17 (0.0) [0.0]	0/4 (0.0) [0.0]	1/4 (25.0) [51.7]

Upper column, No. of subjects with events/No. of subjects included in the analysis set; Middle column, (incidence %); Lower column, (No. of events per unit time [events/100 patient-years]); MedDRA/J ver.16.0

Table 35. Adverse events by age subgroup (<65, ≥65, or ≥75 years of age) (Study OCT-001)

Type of event	Age	Trelagliptin alone (n = 248)	Trelagliptin + SU (n = 158)	Trelagliptin + glinide (n = 67)	Trelagliptin + α-GI (n = 65)	Trelagliptin + BG (n = 70)	Trelagliptin + TZD (n = 72)
All adverse events	<65	136/170 (80.0)	93/108 (86.1)	35/43 (81.4)	29/40 (72.5)	35/55 (63.6)	35/43 (81.4)
	≥65	62/78 (79.5)	45/50 (90.0)	17/24 (70.8)	24/25 (96.0)	10/15 (66.7)	26/29 (89.7)
	≥75	9/11 (81.8)	5/5 (100.0)	5/6 (83.3)	4/4 (100.0)	-	6/6 (100.0)
All adverse drug reactions	<65	28/170 (16.5)	10/108 (9.3)	4/43 (9.3)	1/40 (2.5)	7/55 (12.7)	7/43 (16.3)
	≥65	11/78 (14.1)	7/50 (14.0)	4/24 (16.7)	3/25 (12.0)	1/15 (6.7)	3/29 (10.3)
	≥75	0/11 (0.0)	1/5 (20.0)	1/6 (16.7)	1/4 (25.0)	-	1/6 (16.7)
Serious adverse events	<65	8/170 (4.7)	2/108 (1.9)	2/43 (4.7)	2/40 (5.0)	1/55 (1.8)	1/43 (2.3)
	≥65	1/78 (1.3)	9/50 (18.0)	3/24 (12.5)	1/25 (4.0)	0/15 (0.0)	3/29 (10.3)
	≥75	0/11 (0.0)	2/5 (40.0)	1/6 (16.7)	0/4 (0.0)	-	1/6 (16.7)
Adverse events leading to treatment discontinuation	<65	5/170 (2.9)	2/108 (1.9)	2/43 (4.7)	3/40 (7.5)	4/55 (7.3)	2/43 (4.7)
	≥65	4/78 (5.1)	7/50 (14.0)	3/24 (12.5)	2/25 (8.0)	1/15 (6.7)	3/29 (10.3)
	≥75	0/11 (0.0)	1/5 (20.0)	2/6 (33.3)	0/4 (0.0)	-	2/6 (33.3)
Hypoglycaemia	<65	1/170 (0.6)	2/108 (1.9)	1/43 (2.3)	0/40 (0.0)	1/55 (1.8)	0/43 (0.0)
	≥65	0/78 (0.0)	5/50 (10.0)	0/24 (0.0)	1/25 (4.0)	0/15 (0.0)	1/29 (3.4)
	≥75	0/11 (0.0)	0/5 (0.0)	0/6 (0.0)	0/4 (0.0)	-	1/6 (16.7)

No. of subjects with events/No. of subjects included in the analysis set (incidence %), MedDRA/J ver.16.0
-: Not calculated because n = 0.

PMDA considers as follows:
PMDA accepted the applicant's explanation that no trend towards a particularly increased risk was found in elderly patients receiving monotherapy or any of the combination therapies in the Japanese clinical studies. However, because the once-weekly trelagliptin allows a reduced dosing frequency as compared with existing oral hypoglycemic agents, trelagliptin may be used in elderly patients requiring medication assistance due to dementia etc. Elderly patients often have renal impairment. Furthermore, the number of elderly patients aged ≥75 years studied in the clinical studies was limited. Therefore, collection of information on the safety in elderly patients should be continued in post-marketing surveillance etc.

4.(iii).B.(8) Post-marketing obligations
The applicant explained as follows:
A post-marketing surveillance study with an observation period of 3 years and a target sample size of 3000 patients will be conducted to evaluate the long-term safety and efficacy of trelagliptin. This survey will evaluate the impact on the occurrence of hypoglycaemia, skin disorders, acute pancreatitis, proarrhythmia associated with QT/QTc interval prolongation, intestinal obstruction, infections, and malignant tumors, as well as the safety in patients with moderate renal impairment and safety in the case of overdose. In addition, a Japanese clinical study will be conducted to evaluate the efficacy and safety of trelagliptin in combination with an insulin product because trelagliptin is expected to be used concomitantly with an insulin product.

PMDA considers as follows:
Information should be collected to evaluate the impact of type or dose level of concomitant drugs on safety, cardiovascular risk, and the safety and efficacy in patients with renal or hepatic impairment and elderly patients. The final decision on details of the post-marketing surveillance will be made, 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 inspection and data integrity assessment

Document-based compliance 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, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-4, 5.3.5.2-1). As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, PMDA has concluded that the efficacy of trelagliptin (Zafatek) in patients with type 2 diabetes mellitus has been demonstrated and its safety is acceptable in view of its observed benefits. Zafatek, a once-weekly DPP-4 inhibitor, provides a new option for treatment of type 2 diabetes mellitus. Use of Zafatek in patients with renal impairment, post-marketing obligations, and measures for the proper use of the product need to be further evaluated.

PMDA considered that Zafatek may be approved if it can be concluded based on the comments from the Expert Discussion that there are no particular problems.

Review Report (2)

January 9, 2015

I. Product Submitted for Registration

[Brand name]	Zafatek Tablets 50 mg
	Zafatek Tablets 100 mg
[Non-proprietary name]	Trelagliptin Succinate
[Applicant]	Takeda Pharmaceutical Company Limited
[Date of application]	March 7, 2014

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) are 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 the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

1) Efficacy of monotherapy

PMDA considers as follows:

In the phase III confirmatory study (Study CCT-002), the non-inferiority of trelagliptin to alogliptin has been demonstrated for the change in HbA1c from the end of the run-in period to the end of the treatment period (Week 24), the primary endpoint (Table 18). An evaluation of the changes in fasting blood glucose and in 2-hour postprandial blood glucose from the end of the run-in period to the end of the treatment period (Week 24), the secondary endpoints, revealed that reductions in the mean changes and their 95% CIs tended to be smaller in the trelagliptin group than in the alogliptin group, but the proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period (Week 24) was similar between the trelagliptin and alogliptin groups. Also in the phase II dose-finding study (Study CCT-001), an evaluation of the change in HbA1c from the end of the run-in period to the end of the treatment period (Week 12) showed that HbA1c significantly decreased in all trelagliptin groups compared to the placebo group (Table 15). In addition, in the monotherapy group in the phase III long-term monotherapy/combination therapy study (Study OCT-001), the proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period (Week 52) was 36.3%, demonstrating the persistent efficacy up to the end of the treatment period (Week 52). Based on the above, the efficacy of trelagliptin monotherapy has been demonstrated.

The above conclusion by PMDA was supported by the expert advisors.

2) Efficacy of combination therapies

PMDA considers as follows:

The results of Study OCT-001 showed that HbA1c levels were reduced in all combination therapy groups (Table 21) and the reduced HbA1c levels were maintained up to the end of the treatment period (Figure 1). This can be interpreted as the demonstration of the efficacy of the combination therapies examined in the study. Although attention should be paid to the tendency toward a smaller reduction in HbA1c in subjects receiving trelagliptin in combination with any of sulfonylureas, short-acting insulin secretagogues, and biguanides, there is no major problem with this matter because the draft package insert includes a precautionary statement to the effect that switching to a more appropriate therapy should be considered for patients who have inadequate response to the current therapy.

The above conclusion by PMDA was supported by the expert advisors.

(2) Safety

PMDA considers as follows:

Based on the incidence of adverse events and adverse drug reactions in the monotherapy group and combination therapy groups in Japanese clinical studies, the safety of trelagliptin is acceptable on the premise that appropriate precautions are provided regarding events such as hypoglycaemia and skin disorders. Meanwhile, as with other existing dipeptidyl peptidase-4 (DPP-4) inhibitors, collection of information on the safety should be continued in post-marketing surveillance. Such information includes that on hypoglycaemia, skin disorder-related adverse events, adverse events of hypersensitivity, cardiovascular risk, gastrointestinal disorders (including pancreatitis), tumor risk, immune system disorders, infections, and proarrhythmic risk associated with QT/QTc interval prolongation.

The above conclusion by PMDA was supported by the expert advisors.

Based on the above, PMDA instructed the applicant to include such precautions in the package insert, and confirmed that the applicant did so accordingly [for post-marketing obligations, see "(7) Risk management plan (draft)"].

(3) Measures for the proper use of trelagliptin

PMDA considers as follows:

Trelagliptin is Japan's first once-weekly oral hypoglycemic agent. There is, however, no major problem with measures proposed by applicant for provision of information to patients and healthcare professionals through materials including the package insert, packaged PTP sheets, and patient information leaflets. In addition, no major problem is found with the applicant's measures with regard to switching to an existing daily-dose oral hypoglycemic agent; specifically, the Important Precautions section of the package insert includes a precautionary statement to the effect that starting timing and dose level of another antidiabetic agent in switching from trelagliptin should be selected in consideration of the persistence of hypoglycemic activity even at 168 hours after administration of trelagliptin.

The above conclusion by PMDA was supported by the expert advisors. There was a comment from the expert advisors that since trelagliptin is intended for once-weekly administration, it is important to provide patients and healthcare professionals with information on how to cope with the case of an overdose or missed dose.

Based on the above, PMDA instructed the applicant to provide information to patients and healthcare professionals by producing leaflets describing information about the proper use of trelagliptin, e.g., how to cope with the case of an overdose or missed dose.

The applicant responded as follows:

Measures to prevent the occurrence of overdose and hypoglycaemia will be taken because trelagliptin is intended for once-weekly administration unlike existing oral hypoglycemic agents. Because discrimination from other oral hypoglycemic agents is critical, custom-designed features, such as characteristic font, color, and inclusion of a column to entry medication schedule, will be placed on the packaged PTP sheets for the convenience of elderly patients and patients with reduced visual acuity, who are relatively often found in the patient population with type 2 diabetes mellitus. Besides the above features of the drug package, instructions will be provided to patients by producing materials describing information for preventing hypoglycaemia, initial symptoms of hypoglycaemia, and a way to handle hypoglycaemia. Instructions for healthcare professionals will be provided by producing materials describing information including currently available study data, the contents of the Precautions section of the package insert, and precautions for use of trelagliptin as an once-weekly oral hypoglycemic agent.

PMDA accepted the applicant's response.

(4) Indication

PMDA concluded that there is no problem with the proposed indication of "type 2 diabetes mellitus," because the efficacy of trelagliptin monotherapy and combination therapies has been demonstrated through clinical studies conducted in accordance with the "On release of the Guideline for Clinical

Evaluation of Oral Hypoglycemic Agents" (PFSB/ELD Notification No. 0709-1 dated July 9, 2010) and its safety is acceptable.

The above conclusion by PMDA was supported by the expert advisors.

(5) Dosage and administration

PMDA considers as follows:

Although there was a concern about the impact of elevated plasma trelagliptin levels resulting from high-dose intermittent administration (i.e., trelagliptin 100 mg once weekly) on safety, no particular problems were shown through the analysis of the incidence of adverse events by elapsed days from administration of trelagliptin in Study CCT-002 (Table 29). On the basis of the clinical study data evaluating the pharmacokinetics, pharmacodynamic effects, efficacy, and safety of trelagliptin, there is no major problem with selecting once-weekly trelagliptin 100 mg as the dosage regimen. Although trelagliptin was to be administered before breakfast in the clinical studies evaluating the efficacy and safety (except Foreign Studies 006 and 007, in which trelagliptin was to be administered before the first meal of the day), there is no need to limit the timing of dosing in light of the results of the food effect study and pharmacodynamic effects including the inhibition of DPP-4 activity, as described by the applicant.

The above conclusion by PMDA was supported by the expert advisors.

(6) Use in special populations

1) Patients with renal impairment

PMDA considers as follows:

Because data from the Japanese clinical studies showed no trend toward a particularly increased risk in patients with mild renal impairment as compared with patients with normal renal function during trelagliptin monotherapy or combination therapy, the proposed regimen of 100 mg once weekly (i.e., the recommended dosage) in patients with mild renal impairment is appropriate. Data from the Japanese clinical studies showed no particular trend suggesting a safety concern in patients with moderate renal impairment. However, a dose reduction to trelagliptin 50 mg once weekly should be recommended in such patients because the data from Foreign Study 101 showed an approximately 2-fold higher exposure in subjects with moderate renal impairment than that in subjects with normal renal function (Table 11). Also, given the paucity of information due to the limited number of patients treated with trelagliptin, patients with moderate renal impairment should be listed in the Careful Administration section, and safety information should be collected on such patients via post-marketing surveillance. The applicant's explanations that at present, trelagliptin should be contraindicated in patients with severe renal impairment and patients with end-stage renal failure is acceptable, because (1) the safety of trelagliptin, which is a renally excreted drug, has not been determined in these patient populations who have a risk of elevated blood trelagliptin concentrations since no lower dosage strength is proposed for use in patients with high exposure, and (2) trelagliptin is a once-weekly oral hypoglycemic agent with sustained glucose-lowering effects.

The above conclusion by PMDA was supported by the expert advisors [for post-marketing obligations, see "(7) Risk management plan (draft)"].

2) Patients with hepatic impairment

PMDA considers as follows:

No trend towards a particularly increased risk was found in subjects receiving monotherapy or any of the combination therapies in the Japanese clinical studies, regardless of hepatic impairment. The applicant considered that no dose adjustment is required in patients with hepatic impairment also in terms of the pharmacokinetics of trelagliptin in such patients, and the applicant's view is appropriate. However, the clinical studies excluded "patients with clinically evident hepatic impairment," indicating insufficient evaluation of patients with hepatic impairment. Therefore, collection of information on the safety in patients with hepatic impairment should be continued in post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors [for post-marketing obligations, see "(7) Risk management plan (draft)"].

3) Elderly patients

PMDA considers as follows:

PMDA accepted the applicant's explanation that no trend towards a particularly increased risk was found in elderly patients receiving monotherapy or any of the combination therapies in the Japanese clinical studies. However, because once-weekly trelagliptin allows a reduced dosing frequency as compared with existing oral hypoglycemic agents, trelagliptin may be used in elderly patients requiring medication assistance due to dementia etc. Elderly patients often have renal impairment. Furthermore, the number of elderly patients aged ≥75 years studied in the clinical studies was limited. Therefore, collection of information on the safety in elderly patients should be continued in post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors [for post-marketing obligations, see "(7) Risk management plan (draft)"].

(7) Risk management plan (draft)

Based on the review in "4.(iii).B.(8) Post-marketing obligations" of the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the following points should be additionally evaluated in the risk management plan.

- Safety in patients with hepatic impairment
- Safety in elderly patients
- Effects on cardiovascular risk

PMDA instructed the applicant to take actions on the above points. The applicant accordingly presented the summary of the risk management plan (draft) [Table 36, Table 37] and an outline of the specified drug use-results surveys (draft) [Table 38], as shown below. PMDA confirmed that there were no problems with the contents.

Table 36. Safety and efficacy specifications of risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypoglycaemia	• Skin disorders • Acute pancreatitis • Proarrhythmia associated with QT/QTc interval prolongation • Intestinal obstruction • Infections • Malignant tumors • Overdose-related events	• Safety in patients with renal impairment • Safety in patients with hepatic impairment • Safety in elderly patients • Safety of concomitant use of trelagliptin with an insulin product • Impact on cardiovascular risk
Efficacy specifications		
• Long-term efficacy of trelagliptin in routine clinical settings • Efficacy of trelagliptin in combination with an insulin product		

Table 37. Summary of additional pharmacovigilance activities and risk minimization actions in risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization actions
• Early post-marketing phase vigilance • Specified drug use-results survey of long-term treatment • Clinical study(ies) of trelagliptin in combination with an insulin product[a)]	• Preparation and distribution of informative materials for patients • Preparation and distribution of informative materials for healthcare professionals • Custom-designed features of the packaging form of trelagliptin[b)] • Information provision via early post-marketing phase vigilance

a) Planned to be conducted as a post-marketing clinical study(ies) after approval of trelagliptin.

b) Because trelagliptin is the first once-weekly oral hypoglycemic agent, custom-designed features such as blister card packaging will be employed to ensure proper drug use.

Table 38. Outline of specified drug use-results survey of long-term treatment (draft)

Objective	To evaluate the long-term safety and efficacy of trelagliptin in patients with type 2 diabetes mellitus in routine clinical settings
Survey method	Central registry system
Target patient population	Patients with type 2 diabetes mellitus
Observation period	3 years
Target sample size	3000 patients
Main information to be collected	Patient characteristics, details on administration of trelagliptin, concomitant drugs, safety evaluation (hypoglycaemia, skin disorders, acute pancreatitis, proarrhythmia associated with QT/QTc interval prolongation, intestinal obstruction, infections, malignant tumors, overdose-related events, and other adverse events), efficacy evaluation (HbA1c)

III. Overall Evaluation

As a result of the above review, PMDA has concluded that Zafatek (trelagliptin) may be approved for the indication and the dosage and administrations as shown below, with the following conditions. 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

[Dosage and administration] The usual adult dosage is 100 mg of trelagliptin orally administered once weekly.

[Conditions for approval] The applicant is required to establish a risk management plan and implement it appropriately.