

Report on the Deliberation Results

August 25, 2009

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

[Brand name]	(a) Januvia Tablets 25 mg, 50 mg, 100 mg (b) Glactiv Tablets 25 mg, 50 mg, 100 mg
[Non-proprietary name]	Sitagliptin Phosphate Hydrate (JAN*)
[Applicant]	(a) Banyu Pharmaceutical Co., Ltd. (b) Ono Pharmaceutical Co., Ltd.
[Date of application]	December 10, 2007

[Results of deliberation]

In the meeting held on July 24, 2009, 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.

In addition, the following conclusions were reached: the product is not classified as a biological product or a specified biological product; the re-examination period is 8 years; and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Review Report

July 8, 2009

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] Januvia Tablets 25 mg,¹⁾ 50 mg,¹⁾ 100 mg¹⁾
Glactiv Tablets 25 mg,²⁾ 50 mg,²⁾ 100 mg²⁾

[Non-proprietary name] Sitagliptin Phosphate Hydrate

[Applicant] Banyu Pharmaceutical Co., Ltd.¹⁾ Ono Pharmaceutical Co., Ltd.²⁾

[Date of application] December 10, 2007

[Dosage form/Strength] Each tablet contains Sitagliptin Phosphate Hydrate, equivalent to 25 mg, 50 mg, or 100 mg of Sitagliptin

[Application classification] Prescription drug (1) Drug with a new active ingredient

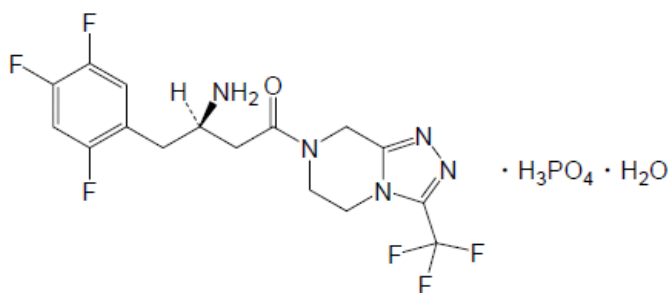
[Chemical structure]

Molecular formula $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$

Molecular weight 523.32

Chemical name (3R)-3-Amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one monophosphate monohydrate

Structural formula



[Items warranting special mention] None

[Reviewing office] Office of New Drug I

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Review Results

July 8, 2009

[Brand name] Januvia Tablets 25 mg,¹⁾ 50 mg,¹⁾ 100 mg¹⁾
Glactiv Tablets 25 mg,²⁾ 50 mg,²⁾ 100 mg²⁾
[Non-proprietary name] Sitagliptin Phosphate Hydrate
[Applicant] Banyu Pharmaceutical Co., Ltd.¹⁾ Ono Pharmaceutical Co., Ltd.²⁾
[Date of application] December 10, 2007
[Items warranting special mention] None

[Results of review]

It is concluded that the submitted data have demonstrated the efficacy and safety of the product in type 2 diabetes mellitus.

The efficacy of the product has been shown in phase III clinical studies (P054, P055, ONO-5435-08 to -10) etc.

No major safety problems have been identified in phase III clinical studies etc. Cardiovascular events and tumor development etc. during long-term use and the safety in patients with moderate renal insufficiency need to be investigated via post-marketing surveillance.

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

[Indication]

Type 2 diabetes mellitus;

Sitagliptin should be used only in patients who do not sufficiently respond to any one of the following treatments.

- (a) Dietary therapy and/or exercise therapy only
- (b) Use of sulfonylureas in addition to dietary therapy and/or exercise therapy
- (c) Use of thiazolidinediones in addition to dietary therapy and/or exercise therapy
- (d) Use of biguanides in addition to dietary therapy and/or exercise therapy

[Dosage and administration]

The usual adult dosage is 50 mg of Sitagliptin orally administered once daily. If the effect is insufficient, the dosage may be increased up to 100 mg once daily while closely observing the clinical course.

Review Report (1)

April 30, 2009

I. Product Submitted for Registration

[Brand name]	Januvia Tablets 25 mg, ¹⁾ 50 mg, ¹⁾ 100 mg ¹⁾ Glactiv Tablets 25 mg, ²⁾ 50 mg, ²⁾ 100 mg ²⁾
[Non-proprietary name]	Sitagliptin Phosphate Hydrate
[Applicant]	Banyu Pharmaceutical Co., Ltd. ¹⁾ Ono Pharmaceutical Co., Ltd. ²⁾
[Date of application]	December 10, 2007
[Dosage form/Strength]	Each tablet contains Sitagliptin Phosphate Hydrate, equivalent to 25 mg, 50 mg, or 100 mg of Sitagliptin
[Proposed indication]	Improvement of post-prandial hyperglycemia in type 2 diabetes mellitus; Sitagliptin should be used only in patients who do not sufficiently respond to any one of the following treatments. (a) Dietary therapy and/or exercise therapy only (b) Use of sulfonylureas in addition to dietary therapy and/or exercise therapy (c) Use of insulin-sensitizing agents in addition to dietary therapy and/or exercise therapy (d) Use of biguanides in addition to dietary therapy and/or exercise therapy
[Proposed dosage and administration]	The usual adult dosage is 50 mg of Sitagliptin orally administered once daily. If the effect is insufficient, the dosage may be increased up to 100 mg once daily while closely observing the clinical course.
[Items warranting special mention]	None

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

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

Incretins including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are gastrointestinal hormones, are peptide hormones released in active forms by the intestine in response to meal ingestion. When blood glucose concentrations are elevated, GLP-1 and GIP increase insulin release from pancreatic β cells. GLP-1 lowers glucagon secretion from pancreatic α cells. Due to their characteristic glucose-dependent action, the incretin hormones have been attracting attention as the target of a new class of antidiabetic agents with a lower risk of hypoglycemia. However, as the incretin hormones are rapidly inactivated by endogenous dipeptidyl

peptidase-4 (DPP-4), having very short elimination half-lives, these are unsuitable as a therapeutic drug.

Sitagliptin Phosphate Hydrate (Sitagliptin), the active ingredient of the 6 products submitted for registration (the product) including Januvia Tablet 25 mg and Glactiv Tablet 25 mg, is a DPP-4 inhibitor developed by Merck & Co., Inc., Whitehouse Station, N.J., U.S.A. and inhibits DPP-4, thereby increasing concentrations of the active forms of endogenous incretin hormones (GLP-1 and GIP). A study in DPP-4 deficient mice and studies using a DPP-4 inhibitor in rodents and humans have suggested that the stabilization of active GLP-1 by a DPP-4 inhibitor is useful for treating type 2 diabetes mellitus (Marguet D, *et al.*, *Proc Natl Acad Sci USA*, 2000; 97: 6874-6879, Ahrén B, *et al.*, *Diabetes Care*, 2002; 25: 869-875).

In Japan, Banyu Pharmaceutical Co., Ltd. solely initiated a clinical trial of Sitagliptin in 20[REDACTED] and then the drug was co-developed by Banyu Pharmaceutical Co., Ltd. and Ono Pharmaceutical Co., Ltd. at the stage of phase III clinical trials. Based on the usefulness of Sitagliptin confirmed in patients with type 2 diabetes mellitus, the applicant has filed a marketing application for the product.

Outside Japan, as of April 2009, Sitagliptin has been approved in over 80 countries/regions worldwide, including the US and Europe.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

The drug substance is registered in the Drug Master File (DMF) by Merck & Co., Inc. (DMF No. : 220MF10082). A summary of the submitted data pertaining to the drug substance and an outline of the review are as shown in the Appendix.

2.A.(2) Drug product

The drug product consists of film-coated tablets containing the drug substance, vehicle, disintegrant, lubricant, and film-coating agents and is manufactured by Merck Sharp & Dohme (Italia) S.p.A. (Italy), Banyu Pharmaceutical Co., Ltd., and Ono Pharmaceutical Co., Ltd. The proposed commercial formulation contains Sitagliptin Phosphate Hydrate, equivalent to 25 mg, 50 mg, or 100 mg of Sitagliptin free base. The 25 mg tablets are pink, the 50 mg tablets are light beige, and the 100 mg tablets are beige and the tablet cores before coating contain [REDACTED] [REDACTED]. The tablets are supplied in PTP-1 ([REDACTED] [REDACTED]) blister packages, PTP-2 ([REDACTED] [REDACTED]) blister packages, or HDPE (high density polyethylene) bottles [see “4.(i) Summary of biopharmaceutic studies and associated analytical methods” for the formulations used during the clinical research stages and the bioequivalence between these

formulations and the proposed commercial formulation].

The manufacturing process for the drug product consists of Step 1 (), Step 2 (), Step 3 (), Step 4 (), Step 5 (), Step 6-1 and -2 (), and Step 7 (testing, storage). Step and Step have been defined as critical process steps and for Step , as , (, hereinafter referred to as “ ”) and have been set. For Step , , (), and for have been set. Based on the results of an investigation in the manufacturing process development for the product, () has been established.

The specifications for the drug product have been set for description, identification (ultraviolet-visible spectrophotometry), purity, related substances (liquid chromatography [HPLC]), content uniformity, dissolution, and assay (HPLC). Though not included in the specifications, the drug product has been tested for water content and microbial limits. (), , , and () are by (identification [NIR], , assay [NIR]).

As the stability studies of the drug product, long-term testing (30°C/65%RH, 36 months), accelerated testing (40°C/75%RH, 6 months), and photostability testing (25°C/ambient humidity, open system, cool white fluorescent lamp and near ultraviolet lamp, an overall illumination of 1.2 million lux·h and an integrated near ultraviolet energy of 200 W·h/m²) were performed on the tablets packaged in HDPE bottles and in PTP-1 blisters (3 lots of each strength [25 mg, 50 mg, 100 mg tablets] for each package type) and the attributes tested were description, contents, related substances (individual and total [HPLC]), dissolution, disintegration, and water content. In long-term and accelerated testings, the hardness of tablets was also tested. As a result, under the long term and accelerated conditions, there were slight increases in water content for the tablets packaged in PTP-1 blisters and very slight changes were observed also for the tablets packaged in HDPE bottles. When the tablets packaged in PTP-1 blisters were stored for ≥ 12 months under the long-term condition or for 6 months under the accelerated condition, there were slight decreases in tablet hardness. Disintegration testing showed very slight reductions in disintegration time for the drug product stored for 36 months under the long-term condition, but these changes do not affect the physical and chemical stability of the drug product. There were no quality changes for other attributes tested. Long-term testing and accelerated testing were performed on the tablets packaged in PTP-2 blisters (3 lots each of 25 mg, 50 mg, and 100 mg tablets). The attributes tested were the same as those for the stability studies on the tablets packaged in HDPE bottles and in PTP-1 blisters. As of 20 , 18-month storage data at the long-term condition and 6-month storage data at the accelerated condition have been available, which both showed no quality changes. Furthermore, long-term testing and accelerated testing were performed on commercial scale lots (1 lot of 25 mg tablets, 1 lot of 50 mg tablets, and 3 lots of 100 mg tablets for

each package type [HDPE bottles and PTP-1 blisters]). The test attributes were description, contents, and related substances (individual and total [HPLC]). As of █ 20█, 24-month storage data at the long-term condition and 6-month storage data at the accelerated condition have been available, which both showed no quality changes. The long-term testings on the tablets packaged in PTP-2 blisters and on commercial scale lots will be continued up to 36 months.

Based on the above results, the proposed shelf life for the drug product is 3 years when stored in HDPE bottles, PTP-1 blister packages, or PTP-2 blister packages at room temperature.

2.B Outline of the review by PMDA

2.B.(1) Dissolution

PMDA asked the applicant to explain the relationship between dissolution and disintegration of the drug product and the reason for choosing disintegration testing to be included in the specifications.

The applicant responded as follows:

A dissolution test of the drug product (Basket Method █ rpm, █ rpm) showed rapid dissolution ($\geq$ █% in █ minutes) and a disintegration test also showed rapid disintegration (a mean disintegration time of █ to █ minutes). Also, with 100 mg film-coated tablets and uncoated tablets (6 tablets each), █ was performed using █, █ was █ at █ second interval up to █ minutes (█ seconds) and after █, █ was █ by █. As a result, at █ minutes (█ seconds), both █ and █ exhibited $\geq$ █% of █, demonstrating that after the disintegration of the tablet, the drug is rapidly dissolved. Therefore, considering that if it can be █ that █ within █ minutes by █, █ also █, disintegration testing was chosen taking also account of the convenience of operation in quality tests.

PMDA considers that disintegration testing can not distinguish changes in manufacturing process etc. affecting bioavailability because disintegration testing may be less discriminating as compared to the dissolution test conditions (█ rpm) and a relationship between dissolution and disintegration has not been established etc. PMDA instructed the applicant to include dissolution testing in the final drug product specifications in order to distinguish batches with unacceptable bioavailability and changes in formulation or manufacturing process affecting bioavailability, as indicated by “Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances” (PFSB/ELD Notification No. 568 dated May 1, 2001).

The applicant responded that dissolution testing will be included in the final drug product specifications and that █, █, █.

PMDA accepted the response.

2.B.(2) Uniformity of dosage units test

PMDA asked the applicant to explain the reason for selecting mass variation test.

The applicant responded as follows:

When the blend uniformity in the blending and lubrication blending processes was assessed, the uniformity was assured by blending at $\geq$ [REDACTED] rpm and $\geq$ [REDACTED] rpm, respectively, at a commercial production scale. Segregation during tableting was also investigated. As a result, at a commercial production scale, the active ingredient contents of all tablets obtained from the beginning until the end of tableting lied within the range of [REDACTED]% to [REDACTED]% ([REDACTED]) and the active ingredient contents of the tablets obtained from the beginning of tableting until [REDACTED] tablets compressed lied within the range of [REDACTED]% to [REDACTED]%. These test results [REDACTED]. Furthermore, as [REDACTED] [REDACTED] with [REDACTED] and [REDACTED] obtained from [REDACTED] and [REDACTED] by [REDACTED], mass variation test was selected.

PMDA instructed the applicant to include content uniformity testing in the final drug product specifications in order to distinguish changes in process parameters or manufacturing process affecting the uniformity of dosage units.

The applicant responded that content uniformity testing will be included in the final drug product specifications and that [REDACTED], [REDACTED].

PMDA accepted the response.

Based on the above, PMDA concluded that there are no particular problems with the specifications, storage, and shelf-life established for the drug product.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

As primary pharmacodynamic studies, *in vitro* affinity and selectivity for DPP-4 and *in vivo* improvement of glucose tolerance in various mouse models have been investigated. As secondary pharmacodynamic studies, the effects on the immune system and the DPP-4 selectivity of Sitagliptin vs. other DPP-4 inhibitors have been assessed. As safety pharmacology studies, the effects on the respiratory system, cardiovascular system, central nervous system, renal function, hemostasis, platelet function, and gastrointestinal function have been assessed. No pharmacodynamic drug interaction studies have been performed.

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

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

(a) Affinity for human and animal DPP-4 (4.2.1.1.1)

Using human recombinant DPP-4 produced in the baculovirus expression system, DPP-4 derived from CACO-2 extracts, and DPP-4 in serum from humans, mice, rats, and dogs, Sitagliptin was tested for the inhibitory activity against DPP-4. Sitagliptin inhibited the activity of human recombinant DPP-4 with an IC_{50} value (mean $\pm$ standard deviation [SD]) of 17.9 ± 7.4 nM and a K_i value of 8.9 nM and the inhibitory activity of Sitagliptin was competitive and reversible. The IC_{50} values against DPP-4 derived from CACO-2 extracts and DPP-4 in serum from humans, mice, rats, and dogs were 20.3, 12.9, 69.3, 52.4, and 16.3 nM, respectively.

(b) DPP-4 selectivity (4.2.1.1.1)

Sitagliptin was screened for activity against proteases other than DPP-4, ion channels, enzymes, and receptors. The IC_{50} values of Sitagliptin against proline specific proteases, i.e. QPP (quiescent cell proline dipeptidase), DPP-8, DPP-9, PEP (prolyl endopeptidase), APP (aminopeptidase P), and prolidase, were about 50 μ M or higher. The IC_{50} values of Sitagliptin against various proteases were > 10 μ M for γ -secretase, > 50 μ M for granzyme B and β -secretase, and > 100 μ M for other proteases. The IC_{50} values against ion channels (IKr, L-type Ca^{2+} channel, Na^+ channel site II) were 22 to 67 μ M. Sitagliptin bound to rat 5HT₂ and human 5HT_{2A} receptors with K_i values of 5.8 and 2.1 μ M, respectively, but no rat 5HT_{2A} receptor agonist activity was observed up to 10 μ M concentration.

The applicant explained as follows:

The C_{max} at the proposed clinical dose (maximum 100 mg/day) in humans is 0.9 μ M, which is about 0.4-fold the K_i value for the human 5HT_{2A} receptor. In a preliminary study by Merck & Co., Inc., Whitehouse Station, N.J., U.S.A., the distribution of 5HT_{2A} receptors in human tissue was determined. As a result, human 5HT_{2A} receptors were expressed mainly in the brain and were also expressed in macrophages and umbilical vein, but the levels of expression in these tissues were lower than in the

brain. In a rat pharmacokinetic study, the ratio of brain to plasma concentration of Sitagliptin was ≤ 0.1 , indicating low distribution into the brain (4.2.2.3.2, 4.2.2.3.7). Therefore, Sitagliptin is unlikely to exert a significant effect via the human 5HT_{2A} receptor in a clinical setting.

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

(a) Effect in oral glucose tolerance test in non-obese (normal) mice (4.2.1.1.1)

Male mice fasted overnight (n = 7 per group) were treated with a single oral dose of Sitagliptin (0.1, 0.3, 1, 3 mg/kg) or vehicle (0.25% methylcellulose) and then challenged with oral glucose (5 g/kg) at 1 hour post-dose. As a result, Sitagliptin inhibited blood glucose excursion after a glucose load in a dose-dependent manner and Sitagliptin 1 and 3 mg/kg achieved 46% and 55% inhibition of the blood glucose AUC_{0-120 min}, respectively, compared to the control group. As there were no changes in fasting blood glucose from baseline at 1 hour post-dose, the applicant explained that Sitagliptin is considered not to affect fasting blood glucose. Based on the results of a mouse pharmacokinetic study, the plasma Sitagliptin concentration at 1 hour post-dose (t_{max}) at a dose of 1 mg/kg was estimated to be about 150 nM.

(b) Pharmacodynamic evaluation in oral glucose tolerance test in non-obese (normal) mice (4.2.1.1.1)

Male mice fasted overnight (n = 20-28 per group) were treated with a single oral dose of Sitagliptin (0.1, 0.3, 1, 3 mg/kg) or vehicle (0.25% methylcellulose) and then challenged with oral glucose (5 g/kg) at 1 hour post-dose. As a result, Sitagliptin inhibited plasma DPP-4 activity and increased plasma active GLP-1 in a dose-dependent manner. Plasma Sitagliptin concentrations increased dose-dependently. At 3 mg/kg achieving maximal efficacy in inhibiting blood glucose excursion in oral glucose tolerance test, Sitagliptin resulted in plasma DPP-4 inhibition of about 80%, about a 3-fold increase in plasma active GLP-1 compared to the control group, and a plasma Sitagliptin concentration of 600 nM at 80 minutes post-dose (at 20 minutes after a glucose challenge).

(c) Effect on glucose tolerance in diet-induced obesity mice (4.2.1.1.1)

As mice fed high-fat diet (Diet-Induced Obesity mice [DIO mice]) develop obesity, hyperglycemia, and hyperinsulinemia and have impairment of blood glucose tolerance in response to a glucose challenge, the effect of Sitagliptin on blood glucose excursion after a glucose challenge was assessed using the DIO mice. Male DIO mice fasted overnight (n = 7-8 per group) were treated with a single oral dose of Sitagliptin (0.3, 3, 30 mg/kg) or vehicle (0.25% methylcellulose) and then challenged with oral glucose (2 g/kg) at 1 hour post-dose. As a result, glucose-induced blood glucose excursion was inhibited by Sitagliptin at all doses and the blood glucose AUC_{0-120 min} was inhibited by 68%, 90%, and 82% in the Sitagliptin 0.3, 3, and 30 mg/kg groups, respectively, compared to the vehicle control group. Based on the results of a pharmacokinetic study in DIO mice, the plasma Sitagliptin concentration at 1 hour post-dose (t_{max}) at a dose of 3 mg/kg was estimated to be about 700 nM.

(d) Effect on blood glucose in db/db mice (4.2.1.1.1)

The db/db mouse is a murine model of type 2 diabetes characterized by severe insulin resistance and marked hyperglycemia. The blood glucose-lowering effect of Sitagliptin was investigated in db/db mice. Male db/db mice (n = 7-8 per group) were treated with a single oral dose of Sitagliptin (3, 10, 30 mg/kg) or vehicle (0.5% methylcellulose). As a result, Sitagliptin at all doses significantly reduced blood glucose compared to the vehicle control and blood glucose was nearly normalized to normal controls (db/+ mice) at 4 hours post-dose. Based on the results of a pharmacokinetic study in db/db mice, the plasma Sitagliptin concentration at 1 hour post-dose ($t_{\max}$) at a dose of 3 mg/kg was estimated to be about 400 nM.

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

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

(a) Effects on T cell and B cell activation (4.2.1.1.1)

Since DPP-4 is identical to CD26, a T cell activation antigen and CD26 has been suggested to be involved in protective immunity (De Meester I, *et al.*, *Immunol Today*, 1999; 20: 367-375), the effects of Sitagliptin (12 nM to 50 μ M) on T cell- or B cell-dependent immune response were evaluated *in vitro*. As a result, Sitagliptin did not inhibit T-cell proliferation and IL-2 production in the mixed lymphocyte reaction or in response to antigen, phorbol myristate acetate- or IL-2-induced T-cell proliferation, or lipopolysaccharide-induced proliferation of B cells.

The applicant explained that as the IC_{50} value of Sitagliptin for *in vitro* inhibition of T-cell activation (> 50 μ M) was more than 1000-fold higher than the K_i value for DPP-4 (8.9 nM), Sitagliptin does not cause immunosuppression also at the proposed clinical dose inhibiting DPP-4 (maximum 100 mg/day; $C_{\max}$, 0.9 μ M).

(b) Selectivity of comparator compounds for DPP-4 (4.2.1.1.1)

Other DPP-4 inhibitors, including threo-Ile thia (L-threo-2S,3S-isoleucyl thiazolidine) and allo-Ile thia (allo-2S,3R-isoleucyl thiazolidine), are known to produce toxicity in non-clinical studies, including thrombocytopenia, anemia, multiple organ histopathology, and mortality (Lankas GR, *et al.*, *Diabetes*, 2005; 54: 2988-2994) and these toxicities are related to DPP-8 or DPP-9 inhibition. Thus, selectivity of Sitagliptin compared to other DPP-4 inhibitors was assessed. As a result, the IC_{50} values of Sitagliptin against DPP-4, DPP-8, DPP-9, and QPP were 0.018, 48, > 100, and > 100 μ M, respectively, while the IC_{50} values of threo-Ile thia were 0.42, 2.2, 1.6, and 14 μ M, respectively, and the IC_{50} values of allo-Ile thia were 0.46, 0.22, 0.32, and 18 μ M, respectively.

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

3.(i).A.(3).1 Safety pharmacology core battery

(a) Effects on respiratory function (4.2.1.3.3)

Following single oral administration of Sitagliptin (20, 60, 180 mg/kg) in conscious male rats (n = 6 per group), respiratory function (respiratory rate, tidal volume, minute ventilation, Penh) was evaluated using whole body plethysmography. As a result, there were no treatment-related effects on respiratory function.

(b) Cellular electrophysiological evaluation of Sitagliptin on hERG (4.2.1.3.5)

Using CHO-K1 cells expressing hERG channels, the effect of Sitagliptin on hERG channels was investigated by whole-cell voltage-clamp recordings. As a result, Sitagliptin inhibited hERG currents evoked by a step voltage protocol and a ramp voltage protocol with IC₅₀ values of 147 and 117 μ M, respectively. The inhibitory activity of Sitagliptin against hERG was almost reversible.

(c) Effects on cardiovascular function (4.2.1.3.2)

Conscious dogs (2 males and 2 females) were given single oral doses of Sitagliptin (2, 10, 50 mg/kg) and the effects on cardiovascular function (arterial pressure, heart rate, ECG parameters) were evaluated using telemetry. All dogs received all doses in a crossover fashion. As a result, there were no changes in heart rate or PR interval at the 2 and 10 mg/kg doses and there were no treatment-related effects on the mean arterial pressure, QRS interval, QT interval, or QT interval corrected for heart rate using Fridericia's formula. After the 50 mg/kg dose, the mean heart rate (mean $\pm$ standard error [SE]) increased from 94 $\pm$ 5 beats/min at baseline to 127 $\pm$ 9 beats/min at 4 hours post-dose, which resolved at about 6 hours post-dose. The tachycardia occurred with a concomitant slight shortening of the PR interval. The plasma Sitagliptin concentration at 1 hour post-dose was 1.60, 6.89, and 33.9 μ M at 2, 10, and 50 mg/kg, respectively.

(d) Effects on central nervous system (4.2.1.3.4)

Following single oral administration of Sitagliptin (20, 60, 180 mg/kg) in rats (5 males and 5 females per group), the effects on the central nervous system were assessed by a functional observational battery assay (home cage, hand-held, and open-field observations, stimulus activity responses, and grip strength, foot splay, and body temperature measurements). As a result, there were no treatment-related effects on the central nervous system.

3.(i).A.(3).2 Follow-up and supplemental safety pharmacology studies

(a) Cardiovascular effects: escalating dose study (4.2.1.3.1)

When anesthetized dogs (1 male, 2 females) were given an intravenous infusion of Sitagliptin yielding cumulative doses of 1, 3, 10, and 30 mg/kg over a 10 minute period, the effects on the cardiovascular system and ECG were assessed. As a result, no important changes in blood pressure, heart rate, blood

flow, or ECG parameters were observed at 1, 3, and 10 mg/kg and the mean $C_{\max}$ at 10 mg/kg was 58.7 μM . At 30 mg/kg, the $C_{\max}$ was within the range of 130 to 262 μM and blood pressure and heart rate decreased and the PR interval increased 7.4%, but there were no changes in other ECG parameters including heart rate-corrected QTc interval.

(b) Effects on renal function and electrolyte excretion (4.2.1.3.1)

A single oral dose of Sitagliptin (1 and 10 mg/kg) was administered to conscious female dogs ($n = 3$ per group). As a result, at 1 mg/kg, there were no effects on renal function, including glomerular filtration rate, effective renal plasma flow, electrolyte excretion, plasma electrolyte concentrations, and filtration fraction, and no emesis or changes in clinical observations were seen. At 10 mg/kg, 1 dog exhibited a slight increase in potassium excretion and 2 dogs showed a moderate decrease in potassium excretion. Slight decreases in plasma potassium concentrations were noted and the applicant discussed that this finding is likely to be associated with no supplementation of potassium ions. The $C_{\max}$ at 1 and 10 mg/kg was 0.576 to 0.634 and 8.69 to 9.46 μM , respectively.

(c) Effects on respiratory function, hemostasis, and platelet function (4.2.1.3.1)

A single intravenous dose of 10 mg/kg of Sitagliptin was administered to anesthetized male dogs ($n = 3$). As a result, Sitagliptin had no effects on peak expiratory flow, intrapulmonary pressure, lung compliance, tidal volume, and respiration rate. At 1 hour post-dose, there was a 65% increase in airway resistance and the applicant discussed that due to very low airway resistance values at baseline in 2 dogs, even a slight increase in the airway resistance value resulted in a high percent change. The mean maximum airway resistance value observed at 1 hour post-dose (2.83 $\text{cmH}_2\text{O/L/sec}$) was considered to be of little toxicological significance because its normal range for dogs of average size has been reported to be 0.6 to 3.7 $\text{cmH}_2\text{O/L/sec}$ (Stahl WR, *J Appl Physiol*, 1967; 22: 453-460) and the laboratory background data were 3.05 ± 2.59 $\text{cmH}_2\text{O/L/sec}$ (mean $\pm$ SD). A transient decrease in blood pressure and increase in heart rate were observed in 2 dogs, which resolved within 15 minutes. The mean arterial blood pH and blood gases were not meaningfully changed. Concerning effects on hemostasis, a significant reduction in activated partial thromboplastin time was noted but the change was ≤ 1.5 seconds on average, which was determined not to be physiologically meaningful. There were no effects on platelet function. The plasma Sitagliptin concentrations (mean $\pm$ SE) at 5 minutes post-dose and 1 hour post-dose were 37.8 ± 4.0 and 8.7 ± 0.24 μM , respectively.

(d) Effects on gastric acid secretion (4.2.1.3.1)

A single oral dose of 10 mg/kg of Sitagliptin was administered to conscious female dogs ($n = 6$). As a result, Sitagliptin had no effect on gastric acid secretion or gastrin-stimulated gastric acid output. No emesis or changes in clinical observations were seen.

(e) Effects on gastrointestinal motility (4.2.1.3.1)

A single oral dose of 10 mg/kg of Sitagliptin was administered to conscious female mice (n = 10). As a result, Sitagliptin had no effect on intestinal transit and did not affect clinical observations during the 80-minute exposure period.

(f) Effects on behavior and other central nervous system function (4.2.1.3.1)

A single oral dose of 100 mg/kg of Sitagliptin was administered to conscious female mice (n = 10). As a result, Sitagliptin had no effect on central nervous system function, behavior, motor activity, or thermoregulation.

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

As DPP-4 is identical to CD26, a T-cell activation antigen and DPP-4 and CD26 are present on various cells etc. in the body, PMDA asked the applicant to discuss the potential for Sitagliptin to affect various cells.

The applicant responded as follows:

3.(i).B.(1) Discussion from the viewpoint of animals lacking the gene encoding DPP-4

Although DPP-4 has been suggested to be multifunctional, the physiological role has been elucidated only for the regulation of the activities of GLP-1 and GIP, incretin hormones. The phenotypic change observed in DPP-4 deficient animals is the improved glucose tolerance (Marguet D, *et al.*, *Proc Natl Acad Sci USA*, 2000; 97: 6874-6879). Compared to wild-type animals, DPP-4 knockout mice have higher plasma concentrations of active GLP-1 and insulin and lower plasma concentrations of glucagon after a glucose challenge, resulting in reduced blood glucose excursions after a glucose challenge. In addition, DPP-4 knockout mice are resistant to diet-induced obesity and drug-induced diabetes (Conarello SL, *et al.*, *Proc Natl Acad Sci USA*, 2003; 100: 6825-6830). DPP-4 has been suggested to have several functions other than the regulation of incretin activity, of which its involvement in the immune function is of greatest interest (De Meester I, *et al.*, *Immunol Today*, 1999; 20: 367-375). However, there is no definite evidence that the immune function etc. are altered in DPP-4 knockout mice, and DPP-4 knockout mice develop normally and are also fertile. Therefore, the regulation of incretin activity as observed in DPP-4 knockout mice is considered to be the major physiological function of DPP-4.

3.(i).B.(2) Effects on the immune function

Generally, T-cell activation requires an antigen-specific signal triggered by the ligation of the T cell receptor complex by the specific peptide antigen-major histocompatibility complex (MHC) molecule and a second signal from a co-stimulatory receptor. *In vitro* T-cell activation assays suggested that DPP-4 may serve as a co-stimulatory receptor. However, there is no definite evidence that DPP-4 is involved in T-cell activation *in vivo*. Most of the extracellular part of DPP-4, including the active site,

can be deleted without affecting its co-stimulatory activity (Hühn J, *et al.*, *Immunol Lett*, 2000; 72: 127-132), indicating that DPP-4 enzymatic activity is not essential for co-stimulation in T-cell proliferation as observed in *in vitro* studies and a site other than the active site of DPP-4 is involved. According to a recent report, caveolin-1 on antigen-presenting cells has been identified as a promising ligand for DPP-4 on T cells, suggesting that DPP-4 may transduce proliferative signals, regardless of enzymatic activity (Ohnuma K, *et al.*, *Trends Immunol*, 2008; 29: 295-301).

It is expected that even if Sitagliptin binds to the DPP-4 active site reversibly, DPP-4 functions except for enzymatic activity will not be altered. Indeed, a recent study conducted by Merck & Co., Inc., Whitehouse Station, N.J., U.S.A. has also shown that genetic deficiency of DPP-4 or inhibition of its enzymatic activity has no apparent effect on T cell- or B cell-dependent immune response in mice.

Using drugs categorized as selective DPP-4 inhibitors, an involvement of DPP-4 in the immune function has been investigated, which has demonstrated the effects of these drugs on immune cells (growth inhibition, cytokine production, hyperphosphorylation of p56^{lck}, induction of TGF- β secretion, etc.) (Reinhold D, *et al.*, *Biol Chem*, 2002; 383: 1133-1138). However, according to a study done by Merck & Co., Inc., Whitehouse Station, N.J., U.S.A., it has been discussed that as these drugs showed non-specific effects other than DPP-4 inhibition, the study results were interpreted differently (Lankas GR, *et al.*, *Diabetes*, 2005; 54: 2988-2994). Especially, the drugs used in these studies were found to inhibit not only DPP-4, but also DPP-8 and DPP-9. In order to investigate the involvement of DPP-8 and DPP-9 in immune cells reported with these drugs, selective inhibitors of DPP-8 and DPP-9 were synthesized and the effects on T-cell activation were assessed *in vitro*. As a result, selective DPP-8 and DPP-9 inhibitors were found to attenuate T-cell activation *in vitro*. Furthermore, a highly selective inhibitor of DPP-4 was shown to have no effect on T-cell proliferation *in vitro* (Lankas GR, *et al.*, *Diabetes*, 2005; 54: 2988-2994).

3.(i).B.(3) Tumor invasion and metastases

It has been confirmed that when normal cells transform into malignant tumor cells, the expression of multiple ectopeptidases (CD26/DPP-4, CD10/NEP, CD13/APN, seprase/FAP, etc.) increases/decreases (Iwata S & Morimoto C, *J Exp Med*, 1999; 190: 301-5). Changes in the expression of these peptidases (increase or decrease) vary depending on the types of tissue and cells. For example, an increase in the expression of DPP-4 due to malignant transformation has been demonstrated in T-cell lymphoma, T-cell acute lymphocytic leukaemia, cell-derived thyroid cancer, basal cell carcinoma, and breast cancer. While DPP-4 expression is seen in melanocytes *in vitro*, *in vitro* transformed melanomas lack DPP-4 expression. Constitutive expression of DPP-4 inhibited the invasiveness of melanoma cell lines, but the enzymatic activity was not required for its anti-invasive activity (Pethiyagoda CL, *et al.*, *Clin Exp Metastasis*, 2000; 18: 391-400), suggesting that DPP-4 enzymatic activity is not important for malignant transformation of melanocytes. So far, there have been no reported data suggesting that

altered DPP-4 activity affects tumor development/metastases *in vivo*.

Although it has been reported that DPP-4 on endothelial cells serves as an adhesion receptor for fibronectin on the surface of cancer cells and is involved in cancer metastases (Cheng HC, *et al.*, *J Biol Chem*, 1998; 273: 24207-24215), the fibronectin binding domain of DPP-4 is distinct from its active site and specific serine protease inhibitors have been shown to have no effect on the binding of DPP-4 to fibronectin (Cheng HC, *et al.*, *J Biol Chem*, 1998; 273: 24207-24215). Therefore, even if Sitagliptin binds to the active site of DPP-4 *in vivo*, the binding of DPP-4 to fibronectin will not be affected.

Based on the above, DPP-4 enzymatic activity is unrelated to tumor invasion and metastases and Sitagliptin should have no potential to affect tumor invasion and metastases.

3.(i).B.(4) Regulation of proteins/peptides other than GLP-1/GIP

There are multiple peptides or proteins that are efficiently degraded *in vitro* by DPP-4, e.g. glucagon-family peptides, neuropeptides, and chemokines. Due to the lack of suitable assays for measurement of the endogenous levels of these peptides or proteins and their putative degradation products, whether these molecules that are *in vitro* DPP-4 substrates are also regulated by DPP-4 *in vivo* has not been determined yet. Furthermore, in addition to DPP-4, other peptidases are involved in the degradation of these peptides or proteins and it is generally recognized that several protein degradation pathways are involved in the clearance of many bioactive peptides.

DPP-4 knockout mice are healthy and fertile, suggesting that DPP-4 inhibition is well tolerated (Marguet D, *et al.*, *Proc Natl Acad Sci USA*, 2000; 97: 6874-6879, Conarello SL, *et al.*, *Proc Natl Acad Sci USA*, 2003; 100: 6825-6830). Even with DPP-4 inhibition-related changes in peptide concentrations, there are no serious effects on development or fertility etc. in DPP-4 knockout mice. Moreover, except for non-clinical studies at exposures > 58 times the exposure at the clinical dose, non-clinical studies of Sitagliptin and the safety information from clinical studies have shown no severe toxicities associated with Sitagliptin. However, the applicant fully assessed *in vitro* substrate specificity of DPP-4 and selected most important substrates to be closely examined based on the assessment results, and then discussed as follows.

3.(i).B.(4).1) Glucagon-family peptides

In addition to GLP-1 and GIP, some bioactive peptides of the glucagon family, e.g. growth hormone-releasing hormone (GHRH) and GLP-2, are *in vitro* DPP-4 substrates. *In vitro* cleavage of these peptides alters their bioactivity as well.

GHRH is a substrate cleaved most efficiently by DPP-4 *in vitro* and stimulates the release of growth

hormone and insulin-like growth factor-1 (IGF-1) from the pituitary gland. However, as continuous inhibition of DPP-4 over 70 hours (91% inhibition of plasma DPP-4 activity) did not increase plasma IGF-1 concentrations in pigs (Faidley TD, *et al.*, *Exp Biol Med*, 2006; 231: 1373-1378) and Sitagliptin did not affect plasma IGF-1 concentrations in clinical studies (5.3.3.1.5, 5.3.3.3.2), Sitagliptin is unlikely to affect GHRH function. These findings suggest that *in vitro* cleavage of a peptide by DPP-4 does not always translate into *in vivo* regulation of its bioactivity. It can also be said that there were no major changes in GHRH action because other peptidases were more important than DPP-4 for the *in vivo* regulation of the bioactivity of this peptide.

Another substrate cleaved by DPP-4 *in vitro* is GLP-2. GLP-2 is secreted from entero-endocrine L cells and is involved in intestinal growth and motility etc. (Dubé PE & Brubaker PL, *Am J Physiol Endocrinol Metab*, 2007; 293: E460-465). Following intravenous administration of GLP-1 and GIP to DPP-4 knockout mice, plasma concentrations of the active peptides were elevated, but intravenous administration of GLP-2 did not result in a marked increase in active GLP-2 levels (an in-house preliminary study, Merck & Co., Inc., Whitehouse Station, N.J., U.S.A.), suggesting that the bioactivity of GLP-2 is not regulated by DPP-4 *in vivo*. Also, there have been no abnormal histopathologic findings in the gastrointestinal tract in DPP-4 knockout mice or non-clinical toxicity studies of Sitagliptin. Therefore, GLP-2 is not regulated by DPP-4 *in vivo* and Sitagliptin is unlikely to affect the bioactivity of GLP-2.

3.(i).B.(4).2) Substance P and bradykinin

Substance P (SP) is a neuropeptide involved in pain sensation, intestinal smooth muscle contraction, and immune regulation and is widely distributed in the body. It is said that SP is also degraded by DPP-4, as well as by angiotensin-converting enzyme and neutral endopeptidase. However, skin reaction or increased saliva etc. in which SP is known to be involved, was not observed after oral administration of Sitagliptin in toxicity studies (4.2.3.1.1-5, 4.2.3.2.1-15). Some peptidases are believed to be involved in bradykinin degradation as well. However, DPP-4 is not directly involved in the degradation of bradykinin and bradykinin is first cleaved by APP to form an inactive product, which is degraded by DPP-4 (Ryan JW, *et al.*, *J Pharmacol Exp Ther*, 1994; 269: 941-947). Therefore, DPP-4 inhibition is unlikely to affect bradykinin activity.

3.(i).B.(4).3) Chemokines

Chemokines are chemotactic cytokines that function as chemotactic factors for leukocytes and lymphocytes etc. Many chemokines possess an N-terminal penultimate proline and are considered to be protected from cleavage by non-specific aminopeptidases, but are efficiently cleaved by DPP-4 *in vitro*. Degradation of chemokines, e.g. RANTES, LD78- β , MDC, eotaxin, and SDF-1 α , by DPP-4 results in changes in their chemotactic activity or activity in a signaling assay and altered receptor selectivity. Of these chemokines, SDF-1 α plays an important role in the homing of murine

hematopoietic stem cells and progenitor cells to the bone marrow and their migration from the bone marrow and it has been reported that degradation of SDF-1 α by DPP-4 reduces the ability of hematopoietic stem cells and progenitor cells to migrate *in vitro* (Proost P, *et al.*, *FEBS Lett*, 1998; 432: 73-76, Christopherson KW, *et al.*, *Science*, 2004; 305: 1000-1003). However, the *in vivo* significance of DPP-4 action on these chemokines is unknown.

PMDA considers as follows:

As described in the above response, DPP-4 actions *in vivo* are not fully understood and the possibility that Sitagliptin, a DPP-4 inhibitor, has some effects can not be excluded, but no clinically relevant pharmacological effects have been observed to date.

3.(ii) Summary of pharmacokinetic studies

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

The single intravenous and oral dose pharmacokinetics of Sitagliptin or ¹⁴C-labeled Sitagliptin in rats and dogs were investigated. Based on toxicokinetics in repeated oral dose toxicity studies in dogs and monkeys, the repeat-dose pharmacokinetics of Sitagliptin were assessed and the metabolism in mice, rats, rabbits, dogs, and monkeys, placental transfer in rats and rabbits, and milk excretion in rats were also studied. Plasma concentrations of Sitagliptin were quantitated by liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification of 1.0 and 5.0 ng/mL in rat and dog plasma, respectively. The doses are expressed as free base and measurements are expressed as mean $\pm$ SD.

3.(ii).A.(1) Absorption (4.2.2.1.1, 4.2.2.2.1, 4.2.2.2.2)

The pharmacokinetic parameters of Sitagliptin following a single intravenous or oral dose of Sitagliptin in male and female rats and male dogs are shown in Table 1. After intravenous dosing, the mean plasma clearance (Cl_p) was about 45 mL/min/kg in rats and about 9 mL/min/kg in dogs, the elimination half-life ($t_{1/2}$) was about 2 to 4 hours, and the steady-state volume of distribution (V_{ss}) was about 7 to 9 L/kg in rats and about 3 L/kg in dogs. After oral dosing, the maximum plasma concentration (C_{max}) was reached at 15 minutes to 4 hours post-dose and the area under the plasma concentration-time curve ($AUC_{0-\infty}$) was dose-proportional within the dose range tested in dogs while the ratio of $AUC_{0-\infty}$ between the doses was more than the ratio of the doses in rats. The absolute bioavailability of an oral dose was 59% in male rats and 82% in female rats at 2 mg/kg and 89% and 97% in male dogs at 0.4 and 1.6 mg/kg, respectively. The renal clearance (Cl_R) of Sitagliptin (unbound) in rats was high at about 34 mL/min/kg and this value exceeded the glomerular filtration rate (about 5 mL/min/kg), indicating that Sitagliptin is subject to active tubular secretion.

Table 1. Single-dose pharmacokinetic parameters of Sitagliptin

Animal species	Route	Dose (mg/kg)	Sex	N	t _{max} (h)	C _{max} (μM)	AUC _{0-∞} (μM·h)	F (%)	Cl _p (mL/min/kg)	V _{ss} (L/kg)	t _{1/2} (h)
Rat	i.v.	0.5	M	4			0.46 ± 0.10		46 ± 8.2	8.8 ± 3.4	1.7 ± 0.3
		2	M	4			2.05 ± 0.05		40 ± 1.0	8.1 ± 2.0	1.9 ± 0.3
		5	M	4			4.28 ± 0.32		48 ± 3.6	7.4 ± 1.2	1.8 ± 0.2
	p.o.	2	F	4			1.23 ± 0.14		67 ± 7.1	9.0 ± 2.0	2.1 ± 0.1
		2	M	3	0.5-4	0.21 ± 0.13	1.20 ± 0.18	59			2.6 ± 0.4
		20	M	4	0.5-1	4.00 ± 0.38	15.2 ± 2.04	NC			2.1 ± 0.3
		60	M	4	0.5-1	17.1 ± 6.57	60.9 ± 6.78	NC			2.3 ± 0.6
		180	M	4	0.5-2	27.8 ± 6.73	217 ± 26.9	NC			4.0 ± 0.2
		2	F	4	0.5-2	0.21 ± 0.05	1.01 ± 0.13	82			2.4 ± 0.2
		180	F	4	0.25-2	34.1 ± 4.81	161 ± 34.5	NC			2.9 ± 0.3
	i.v.	0.5	M	6			2.20 ± 0.36		9.3 ± 1.3	3.2 ± 0.1	4.0 ± 0.4
		1.5	M	3			7.11 ± 1.35		8.8 ± 1.5	3.4 ± 0.5	4.2 ± 0.2
Dog	i.v.	0.4	M	3	1-2	0.25 ± 0.08	1.62 ± 0.50	89 ± 20			3.8 ± 0.6
		1.6	M	6	0.5-1	1.32 ± 0.24	7.18 ± 1.56	97 ± 29			4.5 ± 0.8
	p.o.	10	M	3	0.5-1	10.3 ± 2.05	54.2 ± 13.4	NC			4.7 ± 1.8
		30	M	3	0.5-1	26.5 ± 6.23	156 ± 29.2	NC			4.7 ± 0.3

Mean ± SD (range for t_{max})t_{max}: Time to reach maximum plasma concentration, C_{max}: Maximum plasma concentration, AUC: Area under the plasma concentration-time curve, F: Absolute bioavailability, Cl_p: Plasma clearance, V_{ss}: Volume of distribution, t_{1/2}: Elimination half-life, NC: Not calculated

Following 14-week, repeated oral administration of Sitagliptin (2, 10, 50 mg/kg/day) in male dogs, the t_{max} ranged from 0.5 to 1 hour and the mean C_{max} and AUC_{0-24h} were 1.70 μM and 9.88 μM·h, respectively, on Day 1 and 1.67 μM and 9.41 μM·h, respectively, in Week 13 at 2 mg/kg/day, 7.35 μM and 41.3 μM·h, respectively, on Day 1 and 8.22 μM and 47.6 μM·h, respectively, in Week 13 at 10 mg/kg/day, and 39.3 μM and 217 μM·h, respectively, on Day 1 and 40.2 μM and 220 μM·h, respectively, in Week 13 at 50 mg/kg/day. Following 14-week, repeated oral administration of Sitagliptin (10, 30, 100 mg/kg/day) in male monkeys, the t_{max} ranged from 0.5 to 3 hours and the mean C_{max} and AUC_{0-24h} were 3.76 μM and 12.4 μM·h, respectively, on Day 1 and 3.57 μM and 15.0 μM·h, respectively, in Week 12 at 10 mg/kg/day, 11.6 μM and 45.2 μM·h, respectively, on Day 1 and 13.6 μM and 46.0 μM·h, respectively, in Week 12, at 30 mg/kg/day, and 37.6 μM and 171 μM·h, respectively, on Day 1 and 42.5 μM and 246 μM·h, respectively, in Week 12 at 100 mg/kg/day. A similar trend was observed also for female dogs and female monkeys and it was considered that in dogs and monkeys, the pharmacokinetics of Sitagliptin are not affected by repeated administration.

3.(ii).A.(2) Distribution (4.2.2.3.1-9)

Following a single intravenous dose of 2 mg/kg or a single oral dose of 5 mg/kg of ¹⁴C-labeled Sitagliptin in male rats (n = 3 per route), radioactivity was rapidly distributed systemically and a similar trend was observed for distribution following intravenous and oral dosing. The tissue/plasma ratio of radioactivity was higher than 1 in most tissues up to 4 hours following intravenous dosing and up to 8 hours following oral dosing. The ratio was high, especially in the liver (the ratio was about 12-35 up to 4 hours after intravenous dosing; the ratio was about 22-31 up to 8 hours after oral dosing), kidney (about 13-25 and about 15-28, respectively), and bladder (about 6-23 and about 4-10, respectively). The ratio was low in the brain (about 0.1 and about 0.1, respectively), fat tissue (about 0.6-1 and about 0.7-1, respectively), and eye (about 1 and about 0.4-0.6, respectively). Radioactivity

levels declined over time and the recovery of radioactivity from all tissues was about 1.9% of the dose administered at 24 hours after an intravenous dose.

When pregnant rats (n = 4 per group) received oral doses of Sitagliptin (250 and 1000 mg/kg/day) from gestation days 6 to 20 and pregnant rabbits (n = 4) received oral doses of 125 mg/kg/day of Sitagliptin from gestation days 7 to 20, Sitagliptin crossed the placenta and the mean fetal/maternal plasma concentration ratios were about 0.45 at 2 hours post-dose and about 0.8 at 24 hours post-dose at both doses in rats and about 0.66 at 2 hours post-dose and about 0.3 at 24 hours post-dose in rabbits.

The mean plasma protein binding of Sitagliptin (0.02-200 μ M, *in vitro*) was low at 32% to 33% in mice, rats, rabbits, and dogs and the blood/plasma Sitagliptin concentration ratios in rats and dogs (0.1-10 μ M, *in vitro*) were about 1 and it was inferred that blood clearance will approximate plasma clearance.

Using LLC-PK1 cells expressing murine P-glycoprotein (P-gp), the transcellular transport of Sitagliptin (10 μ M) was investigated. As a result, time-dependent, unidirectional transport was observed and Sitagliptin was considered to serve as a substrate for P-gp [see “4.(ii).A.(1) *In vitro* studies using human biomaterials” for human data].

3.(ii).A.(3) Metabolism (4.2.2.4.1-9)

Sitagliptin is minimally metabolized and metabolite excretion in rats and dogs accounted for about 5% to 9% of the dose. When the metabolism of 14 C-labeled Sitagliptin (10 μ M) was investigated using hepatocytes and liver microsomes from mice, rats, rabbits, dogs, and monkeys, Sitagliptin was minimally metabolized. As the metabolites of Sitagliptin, M1, M4, M6 (2 regioisomers), M2 and M5 formed by N-sulfation of the primary amine, N-carbamoyl glucuronidation, hydroxylation of the triazolopiperazine ring, and oxidative desaturation of the piperazine ring followed by intramolecular cyclization via the primary amine, respectively, were mainly detected, but these metabolites were at low concentrations in plasma. All metabolites identified in human plasma, urine, and feces were also present in animals [see “4.(ii).A.(1) *In vitro* studies using human biomaterials” for human data].

3.(ii).A.(4) Excretion (4.2.2.3.2, 4.2.2.3.9, 4.2.2.4.1, 4.2.2.4.2, 4.2.2.5.1)

Following a single intravenous dose of 2 mg/kg or a single oral dose of 5 mg/kg of 14 C-labeled Sitagliptin in male rats (n = 3 per route), 53.5% or 37.3%, respectively, of radioactivity was recovered in urine and 40.2% or 58.9%, respectively, in the feces up to 120 hours post-dose. Twenty-one percent of the administered radioactivity following an intravenous dose of 2 mg/kg and 22% and 29% of the administered radioactivity following oral doses of 5 and 20 mg/kg, respectively, were recovered in bile of bile duct cannulated male rats (n = 3 per group). Following a single intravenous dose of 0.5 mg/kg or a single oral dose of 2 mg/kg of 14 C-labeled Sitagliptin in male dogs (n = 3 per group), 62.0% or

64.6%, respectively, of radioactivity was recovered in urine and 9.8% or 17.3%, respectively, in the feces up to 96 hours post-dose. Following a single oral dose of 2 mg/kg in bile duct cannulated male dogs (n = 3), 77%, 7.8%, and 4.2% of radioactivity were recovered in urine, bile, and feces, respectively, up to 120 hours post-dose.

After pregnant rats (n = 4 per group) received oral doses of Sitagliptin (250 and 1000 mg/kg/day) from gestation day 6 to lactation day 14, the Sitagliptin concentration in milk at 2 hours after the last dose was about 4-fold the plasma concentration at both doses and Sitagliptin was considered to be excreted in maternal milk.

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

PMDA asked the applicant to explain the distribution of Sitagliptin into tissues where DPP-4 is present.

The applicant responded as follows:

DPP-4 is an enzyme that is widely distributed and expressed and exists as both a membrane-bound form and a circulating form. It has been reported that membrane-bound DPP-4 is found in the brush border of epithelial cells (hepatocytes, small intestinal epithelial cells, pancreatic duct cells, salivary duct cells), endothelial cells (renal medulla, heart and skeletal muscles, splenic red pulp, capillaries in other tissues), and lymphocytes (thymic lymphocytes, splenic and lymph node T cells) and that Western blot analysis demonstrated that DPP-4 protein level was highest in the kidney, small intestine, and lung, followed by the liver, spleen, and heart in rats (McCaughan GW, *et al.*, *Hepatology*, 1990; 11: 534-544, Hong WJ, *et al.*, *Exp Cell Res*, 1989; 182: 256-266). In rats, the tissue/plasma radioactivity ratios at 1 and 4 hours after an intravenous dose of 2 mg/kg of ¹⁴C-labeled Sitagliptin tended to be high in the tissues where high levels of DPP-4 expression are found, but the sequence was not always the same and there was no clear relationship between the tissue distribution of Sitagliptin and the tissue distribution of DPP-4.

PMDA asked the applicant to explain the melanin affinity of Sitagliptin.

The applicant responded as follows:

Since Sitagliptin shows only a single absorption peak at around [REDACTED] nm and ophthalmologic and histopathological examinations revealed no toxicological findings in dog repeated oral dose toxicity studies, an investigation of the melanin affinity of Sitagliptin using pigmented animals has not been performed. In order to assess the risk associated with melanin affinity, eye and skin adverse events reported in clinical studies were investigated. The incidences of adverse events and adverse drug reactions in the Sitagliptin group across all clinical studies in Japanese type 2 diabetes mellitus patients were 6.4% (76 of 1190 subjects) and 0.2% (2 of 1190 subjects), respectively, for eye disorders,

and 9.8% (117 of 1190 subjects) and 0.6% (7 of 1190 subjects), respectively, for skin and subcutaneous tissue disorders. Adverse events with a high incidence in the Sitagliptin group were eczema (2.9%) (35 of 1190 subjects), diabetic retinopathy (1.8%) (21 of 1190 subjects), and rash (1.2%) (14 of 1190 subjects), of which 2 cases of diabetic retinopathy and 4 cases of rash only were classified as adverse drug reactions. The incidences of adverse events at Week 12 across Japanese double-blind comparative studies (6 studies: A201, A202, and P054 with a treatment period of 12 weeks, and P055, ONO-5435-08, and ONO-5435-09 with a treatment period of 12 weeks + 40 weeks) were 3.7% (13 of 356 subjects) in the placebo group, 3.3% (15 of 449 subjects) in the 50 mg group, and 3.4% (5 of 145 subjects) in the 100 mg group for eye disorders, and 4.2% (15 of 356 subjects) in the placebo group, 4.9% (22 of 449 subjects) in the 50 mg group, and 3.4% (5 of 145 subjects) in the 100 mg group for skin and subcutaneous tissue disorders, and there were no dose-dependent increases in the incidence. No adverse events of pigmentation disorder were reported. Across foreign phase II and phase III studies (12 studies, treatment periods of 18-106 weeks), the incidences of adverse events (placebo or active control, 100 mg, 200 mg) were 4.1% (112 of 2724 subjects), 4.1% (140 of 3415 subjects), and 4.2% (19 of 456 subjects), respectively, and the incidences of adverse drug reactions were 0.2% (6 of 2724 subjects), 0.1% (2 of 3415 subjects), and 0.4% (2 of 456 subjects), respectively, for eye disorders; and the incidences of adverse events were 6.2% (169 of 2724 subjects), 7.3% (248 of 3415 subjects), and 6.1% (28 of 456 subjects), respectively, and the incidences of adverse drug reactions were 1.3% (36 of 2724 subjects), 1.2% (40 of 3415 subjects), and 0.9% (4 of 456 subjects), respectively, for skin and subcutaneous tissue disorders. Adverse events of pigmentation occurred in 5 subjects, of which post inflammatory pigmentation change only was classified as an adverse drug reaction. As described in the above, based on the investigation of adverse events in type 2 diabetes mellitus patients treated with Sitagliptin in Japanese clinical studies, Sitagliptin does not appear to affect melanin or melanocytes and there is no safety concern on this matter, and the incidences of adverse events and adverse drug reactions categorized as eye disorders and skin and subcutaneous tissue disorders were similar between Japanese and foreign clinical studies.

Concerning the tissue distribution and melanin affinity of Sitagliptin, PMDA considers as follows:

In non-clinical pharmacokinetic studies of Sitagliptin, melanin affinity in pigmented animals etc. has not been investigated and there are no sufficient data supporting the applicant's explanation that the skin lesions observed with other DPP-4 inhibitors reported to the FDA were due to DPP-8 and DPP-9 inhibition [see "3.(iii).B.(4) Studies for effects on skin in monkeys"]. However, taking account of the similar incidences of eye and skin adverse events between Sitagliptin and placebo in Japanese clinical studies and the nature of the reported events etc., although it is necessary to collect safety information on skin problems etc. after the market launch, as a caution statement about skin disorders has been included in the package insert (draft), there should be no clinically relevant problems [see "3.(iii) Summary of toxicology studies" and "4.(iii) Summary of clinical efficacy and safety"].

3.(iii) Summary of toxicology studies

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

3.(iii).A.(1) Single-dose toxicity (4.2.3.1.1-4, 4.2.3.2.9)

In a single oral dose, toxicokinetic study in mice, Sitagliptin (██████) was administered at 0 (control), 250, 500, 1000, 2000, and 4000 mg/kg and the approximate lethal dose was determined to be 2000 mg/kg. A study of Sitagliptin (██████) at 250, 500, and 1000 mg/kg was also conducted. As a result, no major differences were seen in the plasma exposure (AUC and C_{max}) compared to the mouse single oral dose, toxicokinetic study of Sitagliptin (██████) and ██████ and ██████ were determined to be bioequivalent up to a 1000 mg/kg dose.

In a single oral dose toxicokinetic study in rats, Sitagliptin (██████) at 750, 1500, and 3000 mg/kg was administered. Deaths, decreased activity, labored breathing, hypothermia, and reddish discharge from nose were observed and the approximate lethal dose was determined to be 3000 mg/kg.

Acute toxicity of Sitagliptin in dogs was assessed in a 2-week repeated oral dose toxicity study and no death occurred at 50 mg/kg.

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

Repeat-dose toxicity studies were conducted in mice (14 weeks), rats (2, 14, 27 weeks), dogs (2, 14, 27, 53 weeks), and monkeys (14 weeks). Sitagliptin dissolved in deionized water/0.1 mM hydrochloric acid or suspended in 0.5% (w/v) methylcellulose/5 mM hydrochloric acid aqueous solution was administered by oral gavage.

As the major toxicological findings, centrilobular hepatocellular hypertrophy/necrosis and renal tubular necrosis in mice and rats and deterioration in clinical observations including tremor and open-mouthed breathing and skeletal myofiber degeneration in dogs were observed. The effects of Sitagliptin on the skin and kidney were assessed in monkeys, which revealed no toxicological findings. The no observed adverse effect level (NOAEL) was determined to be 250 mg/kg/day in mice (males), 180 mg/kg/day (2, 14, 27 weeks) in rats, 2 mg/kg/day (27 weeks) in dogs, and 100 mg/kg/day (for skin and kidney toxicity) in monkeys. The NOAELs in mice and rats both provide an about 23-fold multiple of the human exposure (AUC) at the proposed clinical dose (maximum 100 mg/day). Likewise, the NOAEL in dogs provides an about 1-fold multiple of the human exposure.

3.(iii).A.(2).1 Mouse 14-week oral toxicity study (4.2.3.2.2)

Mice (15 males and 15 females/group) were treated with Sitagliptin 0 (control), 75, 250, 500, 750, and 1000 mg/kg/day. As a result, as an increase in deaths was noted in females treated with 1000 mg/kg/day, treatment was discontinued at Week 2. There were centrilobular hepatocellular hypertrophy in males at 1000 mg/kg/day and increased kidney weight and renal pelvis dilatation in

females at 750 mg/kg/day and males at ≥ 500 mg/kg/day. The NOAEL was determined to be 250 mg/kg/day in males and 500 mg/kg/day in females.

3.(iii).A.(2).2) Rat 2-, 14-, and 27-week oral toxicity studies (4.2.3.2.4, 4.2.3.2.5, 4.2.3.2.7)

Rats (2 and 14 weeks, 15 males and 15 females/group; 27 weeks, 20 males and 20 females/group) were treated with Sitagliptin 0 (control), 20, 60, and 180 mg/kg/day. As a result, there were no drug-related effects and the NOAELs for both males and females were determined to be ≥ 180 mg/kg/day.

3.(iii).A.(2).3) Rat 14-week oral toxicity study (4.2.3.2.6)

In order to determine the toxicological profile of Sitagliptin, a study at higher doses than the studies in the above 3.(iii).A.(2).2) was conducted.

Rats (15 males and 15 females/group) were treated with Sitagliptin 0 (control), 500, 1000, 1500, and 2000 mg/kg/day. As a result, 6 males and 1 female in the 2000 mg/kg/day group and 1 male in the 1500 mg/kg/day group were found dead/sacrificed early due to the effects of Sitagliptin and they all had renal tubular necrosis. At 2000 mg/kg/day, centrilobular hepatocellular degeneration and lymphoid depletion of lymph nodes, the spleen, and the thymus were observed and decreased prostate gland weight was found in males. At ≥ 1500 mg/kg/day, decreased pituitary weight, renal tubular degeneration, and centrilobular hepatocellular necrosis etc. were noted and increased adrenal gland weight, myocardial degeneration/necrosis etc., and necrosis of lobules of mammary gland and of bone marrow occurred in males and uterine atrophy occurred in females. At ≥ 1000 mg/kg/day, ALT and alkaline phosphatase increased, and increased thyroid gland weight and follicular cell hypertrophy were seen in females. In rats treated with Sitagliptin, alopecia, increased cholesterol, increased liver weight and inflammatory cell infiltration, and centrilobular hepatocellular hypertrophy were observed and reductions in body weight gain etc. occurred in males. Since the Sitagliptin-related toxicological findings in various organs were not present in the 180 mg/kg/day groups of the rat 2-, 14-, and 27-week oral toxicity studies and the corresponding $C_{\max}$ of Sitagliptin (25.8 μM) was well above the IC_{50} against rat DPP-4 (52.4 nM), it has been discussed that these findings were due to effects other than DPP-4 inhibition. The NOAEL in this study was determined to be < 500 mg/kg/day.

3.(iii).A.(2).4) Dog 2-, 14-, 27-, and 53-week oral toxicity studies (4.2.3.2.9-12)

Beagle dogs (4 males and 4 females/group) were treated with Sitagliptin 0 (control), 2, 10, and 50 mg/kg/day for 2, 14, 27, and 53 weeks. As a result, at the dose of 50 mg/kg/day in these studies, reduced activity, tremor, and open-mouthed breathing with bronchial sounds (the 2-, 27-, 53-week studies) etc. and hunched position/recumbency or head tilt etc. as deterioration in clinical observations and skeletal myofiber degeneration (the 14- and 27-week studies) were observed. In addition, at 50 mg/kg/day, eyelid swelling and increased ALT (both in the 2-week study) and reductions in body weight gain (the 53-week study) were noted.

In the 27-week study, 2 males in the 10 mg/kg/day group exhibited opened mouth breathing with intermittent bronchial sounds between Treatment Week 14 or 23 and the end of treatment. Although the reason that this finding occurred in only males in the 27-week study at 10 mg/kg/day is unknown, as this finding was not observed in females in the same dose group or at the same dose in the 53-week study, it has been discussed that this may be attributable to differences in sensitivity among individuals.

The NOAELs in the 2-, 14-, and 53-week studies were determined to be 10 mg/kg/day and the NOAEL in the 27-week study was determined to be 2 mg/kg/day.

3.(iii).A.(2).5) Monkey 14-week oral toxicity study (4.2.3.2.15)

As the US Food and Drug Administration (FDA) requested assessment of the effects of Sitagliptin on the skin in a 3-month repeated oral dose toxicity study in monkeys, this study was conducted. Histopathological assessment of the kidney was also performed to determine the renal toxicity.

Rhesus monkeys (3 males and 3 females/group) were treated with Sitagliptin 0 (control), 10, 30, and 100 mg/kg/day. As a result, there were no drug-related effects on clinical observations, body weight, food consumption, and skin and kidney weight and histopathology. The mean exposure of Sitagliptin (AUC, C_{max}) increased in a dose-dependent manner and the exposure (AUC) following 12-week administration of 100 mg/kg/day was about 28-fold the human exposure at the proposed clinical dose (maximum 100 mg/day). At 2 to 24 hours after the administration of Sitagliptin, plasma DPP-4 inhibition of 97.2% to 98.3% was observed.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1.1-3, 4.2.3.3.2.1)

A bacterial reverse mutation assay, an *in vitro* alkaline elution assay and chromosomal aberration assay using cultured mammalian cells, and a rodent micronucleus assay were performed. As a result, Sitagliptin was not genotoxic.

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

Carcinogenicity studies were conducted in mice and rats. Sitagliptin suspended in 0.5% (w/v) methylcellulose/5 mM hydrochloric acid aqueous solution was administered by oral gavage.

3.(iii).A.(4).1) Mouse 106-week oral carcinogenicity study (4.2.3.4.1.1)

ICR mice (50 males and 50 females/group) were given 0 (control 1, control 2), 50, 125, 250, and 500 mg/kg/day of Sitagliptin. As a result, there was no treatment-related increase in the incidence of tumors in any organ. As non-neoplastic changes, treatment-related deaths, renal hydronephrosis, and centrilobular hepatocellular hypertrophy occurred at 500 mg/kg/day.

3.(iii).A.(4).2) Rat 106-week oral carcinogenicity study (4.2.3.4.1.3)

SD rats (50 males and 50 females/group) were given 0 (control 1, control 2), 50, 150, and 500 mg/kg/day of Sitagliptin. As a result, there was a treatment-related increase in the incidence of hepatocellular carcinomas in males and females and of hepatocellular adenomas in males at 500 mg/kg/day. A decrease in the incidence of pituitary adenoma and of breast cancer was observed at 500 mg/kg/day and it has been discussed that based on overall evaluation of the results of rat repeat-dose toxicity and reproductive and developmental toxicity studies, this finding is unlikely to be due to the direct effects of Sitagliptin on the hypothalamic-pituitary-gonadal system, but the decrease in the incidence of pituitary adenoma in female rats may have contributed to the decreased incidence of breast cancer.

As non-neoplastic changes, eosinophilic and basophilic cellular alternations and cystic degeneration in the liver were observed at 500 mg/kg/day.

It has been discussed that the increased incidence of hepatocellular tumors was due to non-genotoxic tumorigenesis secondary to chronic hepatocellular injury by Sitagliptin because Sitagliptin is not genotoxic; there was no increase in the incidence of tumors in the carcinogenicity study (4.2.3.4.1.1) in mice sensitive to tumor promoter effect in the liver; the rat 14-week oral toxicity study (4.2.3.2.6) showed dose-dependent occurrence of hepatocellular toxicity such as hepatocellular hypertrophy, necrosis, and degeneration at ≥ 500 mg/kg/day and according to a report of the US National Toxicology Program (NTP) etc., there is a correlation between liver tumor development in rodents and hepatocellular toxicity; and the incidence of liver tumors did not rise significantly in the 150 mg/kg/day group exhibiting no hepatocellular toxicity in this study. It has been explained that in foreign clinical pharmacology studies using doses up to 800 mg/day that is 8-fold the proposed clinical dose (maximum 100 mg/day) (P004 and P032) and Japanese and foreign clinical studies (Japanese clinical studies, A201, A202, A203, P054, P055, ONO-5435-08 to -10, P046; foreign clinical studies, P010, P014, P019, P020, P021, P023, P024, P035, P036, P040, P052, P053), the liver function tests revealed no hepatotoxicity and the exposure (AUC) in the 150 mg/kg/day group exhibiting no liver tumors in this study is about 19 times the human exposure at the proposed clinical dose (maximum 100 mg/day).

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

Reproductive and developmental toxicity studies were conducted in rats and rabbits. Sitagliptin suspended in 0.5% (w/v) methylcellulose/5 mM hydrochloric acid aqueous solution was administered by oral gavage.

In an embryo-fetal development study, the incidence of fetal rib malformations (absent rib, hypoplastic

rib) and variations (wavy ribs) increased at 1000 mg/kg/day. In a study on pre- and postnatal development, including maternal function, body weight gain was reduced in pups at 1000 mg/kg/day. Sitagliptin has been shown to cross the placenta into the fetus in rats and rabbits (4.2.2.3.8, 4.2.2.3.9) and has been shown to be excreted in maternal milk in rats (4.2.2.3.9).

3.(iii).A.(5).1) Rat study of fertility and early embryonic development to implantation (4.2.3.5.1.1, 4.2.3.5.1.2)

Rats (24 males and 24 females/group) were treated orally with 0 (control), 125, 250, and 1000 mg/kg/day of Sitagliptin (male rats dosed from 29 days prior to mating through 1 day prior to scheduled necropsy, female rats dosed from 14 days prior to mating through gestation day 7). As a result, body weight gain was reduced in males at ≥ 250 mg/kg/day. There was a trend towards increased embryonic resorption in females at ≥ 250 mg/kg/day (6.8%-9.1%), but it has been discussed that this finding is not related to Sitagliptin because the incidences were within the laboratory background range (20% to 20%, mean 6.31%, maximum 12.71%) and were not dose-dependent while the exposure increased almost dose-dependently at 20 to 1500 mg/kg/day of Sitagliptin in the rat repeat-dose toxicity studies. The NOAELs were determined to be 125 mg/kg/day for paternal general toxicity and 1000 mg/kg/day for maternal general toxicity and paternal and maternal reproductive toxicity.

3.(iii).A.(5).2) Rat embryo-fetal development study (4.2.3.5.2.1)

Pregnant rats (n = 22/group) were treated orally with 0 (control), 125, 250, and 1000 mg/kg/day of Sitagliptin from gestation days 6 to 20. As a result, there was a trend towards increased embryonic resorption in dams at 1000 mg/kg/day (4.6%), but it has been discussed that this finding is not related to Sitagliptin because the incidence was within the laboratory background range (20%-20%, mean 3.86%, maximum 8.06%) and the incidence of resorptions in the control group (2.1%) was slightly lower than the above background data. The incidences of absent rib (1 of 343 fetuses)/hypoplastic rib (5 of 343 fetuses, 3 litters) and of wavy ribs (5 of 343 fetuses, 2 litters) increased in the fetuses from different dams at 1000 mg/kg/day, which has been discussed to be related to Sitagliptin. Fetal rib malformations and variations have been discussed to be attributable to effects other than DPP-4 inhibition because in the pharmacokinetic study in pregnant rats (4.2.2.3.9), it is estimated that the exposure in the 250 mg/kg/day group that did not exhibit these findings (C_{24h} in dams, 1.33 μ M; placental transfer, 46%-81%) exceeded the IC_{50} against rat DPP-4 (52.4 nM). The NOAELs were determined to be 1000 mg/kg/day for maternal general and reproductive toxicity and 250 mg/kg/day for the fetus.

3.(iii).A.(5).3) Rabbit embryo-fetal development study (4.2.3.5.2.3)

Pregnant rabbits were treated orally with 0 (control), 62.5, 125 (n = 18/group), and 500 mg/kg/day (n = 19/group) of Sitagliptin from gestation days 7 to 20. As a result, 2 dams in the 500 mg/kg/day group

(gestation day 16) died due to the effects of Sitagliptin and weight loss and reduced food intake were noted also in other animals in the same dose group, which were determined to be excessive maternal toxicity. Thus, the 500 mg/kg/day group was terminated on gestation days 15 to 18 and embryo-fetal toxicity evaluation was not performed. There were no treatment-related findings including fertility at 62.5 and 125 mg/kg/day. The NOAELs for maternal general and reproductive toxicity and the fetus were all determined to be 125 mg/kg/day. The exposure (AUC) at the NOAEL was about 22-fold the human exposure at the proposed clinical dose (maximum 100 mg/day).

3.(iii).A.(5).4 Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1)

Pregnant rats (n = 22/group) were treated orally with 0 (control), 125, 250, and 1000 mg/kg/day of Sitagliptin from gestation day 6 to lactation day 20. As a result, decreased body weight gain and reduced food intake in dams at ≥ 250 mg/kg/day and reduced body weight gain persisting to the post-weaning stage in males of the F₁ generation at 1000 mg/kg/day were observed. There were no treatment-related effects in the F₂ generation. The NOAELs were determined to be 125 mg/kg/day for maternal general toxicity and 250 mg/kg/day for reproductive toxicity and pups. The exposure (AUC) at the NOAEL for reproductive toxicity (250 mg/kg/day) was about 32-fold the human exposure at the proposed clinical dose (maximum 100 mg/day).

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

3.(iii).A.(6).1 Toxicity studies using non-selective DPP-4 inhibitors

Skin lesions in monkeys treated with other DPP-4 inhibitors were reported to the FDA. As no skin lesions were found following the administration of Sitagliptin at doses almost completely inhibiting plasma DPP-4 activity in the monkey 14-week oral toxicity study (4.2.3.2.15), the following 2 studies using non-selective DPP-4 inhibitors (Compound 1 and Compound 2) were conducted in order to further investigate whether the skin lesions in monkeys observed with other DPP-4 inhibitors reported to the FDA are associated with the inhibition of DPP-8 and DPP-9, which are dipeptidases similar to DPP-4. The IC₅₀ values of Sitagliptin and these compounds against DPP-4, DPP-8, and DPP-9 are as shown in Table 2.

Table 2. IC₅₀ values against DPP-4, DPP-8, and DPP-9

Drug	IC ₅₀ value (μM)		
	DPP-4	DPP-8	DPP-9
Sitagliptin	0.018	48	> 100
Compound 1	0.43	1.2 (DPP-8 and DPP-9)	
Compound 2	30	0.038	0.055

(a) Monkey 12-week oral toxicity study of Compound 1 (4.2.3.7.7.9)

Rhesus monkeys (3 males and 3 females/group) were treated with Compound 1 at 0 (control), 50, 150, and 450 mg/kg/day. As a result, 2 of the 3 males at 450 mg/kg/day, 1 male and 3 females at 150

mg/kg/day, and 1 female at 50 mg/kg/day were found dead/sacrificed early. One male at 450 mg/kg/day and 1 female at 50 mg/kg/day had focally extensive areas of hemorrhage in their brains and extensive degeneration and necrosis of nervous tissue etc., which were considered related to Compound 1. As skin lesions, excessive scratching at 450 mg/kg/day, edema/inflammation of the subcutaneous tissue and saponification of fat tissue at ≥ 150 mg/kg/day, and redness/swelling of the skin etc. in the Compound 1 groups were observed. As renal lesions, multifocal inflammation with aggregation of mononuclear inflammatory cells, renal tubular dilatation, and glomerulopathy etc. were noted. Significant inhibition of DPP-4 activity of about $\geq 98\%$ was observed at 2 hours after dosing in the Compound 1 groups compared to the control group.

(b) Monkey 23-week oral toxicity study of Compound 2 (4.2.3.7.7.10)

Rhesus monkeys (3 males and 3 females/group) were treated with Compound 2 at 0 (control), 3, 1 $\rightarrow$ 12.5 (increased in Week 9), and 10 $\rightarrow$ 30 (increased in Week 4) mg/kg/day. As a result, 1 male in the 10 $\rightarrow$ 30 mg/kg/day group was sacrificed early. As skin lesions, swelling in the hind limb area etc. and edema/inflammation of the subcutaneous tissue were observed in males in the 10 $\rightarrow$ 30 mg/kg/day group. As renal lesions, renal tubular degeneration and glomerulopathy in males in the 10 $\rightarrow$ 30 mg/kg/day group and mild multifocal inflammation in the Compound 2 groups were noted. Plasma DPP-4 activity was comparable to control except that it was inhibited by about 64.2% compared to control at 2 hours after dosing in the 10 $\rightarrow$ 30 mg/kg/day group.

The applicant has discussed that based on the results of the monkey 14-week oral toxicity study (4.2.3.2.15) and of (a) and (b) studies using non-selective DPP-4 inhibitors, the skin lesions reported to the FDA are associated with DPP-8 and DPP-9 inhibition, but not DPP-4 inhibition.

3.(iii).A.(6).2) Dog repeat-dose toxicity studies in combination with metformin

Since Sitagliptin may be used in combination with metformin in a clinical setting, the following studies were conducted to evaluate the potential toxicity and toxicokinetic interactions of Sitagliptin in combination with metformin.

(a) 14-week oral toxicity study (4.2.3.7.7.13)

Beagle dogs (3 males and 3 females/group) were treated with Sitagliptin + metformin at 0 + 50 (Sitagliptin dose + metformin dose), 2 + 50, 10 + 50, and 50 + 50 mg/kg/day. As a result, 2 females each in the 10 + 50 and 50 + 50 mg/kg/day group and 1 female each in the 0 + 50 and 2 + 50 mg/kg/day group were found dead/sacrificed early. One animal sacrificed early in the 0 + 50 mg/kg/day group exhibited decreased serum bicarbonate and increased plasma lactate, indicative of lactic acidosis. Ataxia, tremors, and increased plasma lactate in the 50 + 50 mg/kg/day group and deterioration in clinical observations including unformed stools, lateral recumbency, and prostration, and vacuolation and neuronal necrosis etc., in the cerebral cortex and hippocampus in the $\geq 10 + 50$

mg/kg/day groups were observed. The ataxia and tremors observed in the 50 + 50 mg/kg/day group were determined to be drug-related.

(b) 16-week oral toxicity study (4.2.3.7.7.14)

In order to evaluate the toxicity of Sitagliptin in combination with low-dose metformin, female dogs (n = 5/group) were treated with Sitagliptin + metformin at 0 + 20, 2 + 20, 10 + 20, and 50 + 20 mg/kg/day. As a result, transient ataxia and tremors occurred in the 50 + 20 mg/kg/day group.

Based on the results of the above 2 studies, the NOAEL for the combination of Sitagliptin and metformin was determined to be 10 mg/kg/day for Sitagliptin and 20 mg/kg/day for metformin. There were no significant differences in toxicokinetic parameters (AUC_{0-24h} and C_{max}) between the combination and Sitagliptin or metformin alone.

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

3.(iii).B.(1) Reversibility of toxicity of Sitagliptin

Since no recovery study has been performed in repeat-dose toxicity studies, PMDA asked the applicant to explain how to assure the reversibility of toxicity of Sitagliptin.

The applicant responded as follows:

Among the major toxicological findings in the rat repeated oral dose toxicity study, liver findings were observed at ≥ 500 mg/kg/day and the hepatocellular hypertrophy and inflammatory cell infiltration in the liver noted at 500 mg/kg/day were not serious injuries, which should be suggestive of reversibility. Kidney findings were observed at ≥ 1500 mg/kg/day and at 1500 mg/kg/day, 1 animal sacrificed early had renal tubular necrosis and 5 surviving animals had mild renal tubular degeneration. The exposure (AUC) at 1500 mg/kg/day resulting in irreversible changes such as death was about 180 times the human exposure at the proposed clinical dose (maximum 100 mg/day).

Changes in clinical observations including tremors and abnormal respiration characterized by open-mouthed breathing observed at ≥ 10 mg/kg/day in the dog repeated oral dose toxicity studies resolved between 7 hours post-dose and the end of observation period each day, which should be indicative of reversibility. Skeletal myofiber degeneration noted at 50 mg/kg/day in the 14- and 27-week studies was slight in severity and degenerated myofibers surrounded by muscle satellite cells in the perimysium were seen, which should be suggestive of myofiber regeneration. Furthermore, as this finding was not observed in the 53-week study, it is considered that skeletal myofiber degeneration does not progress and is reversible. All of the above findings can be monitored easily in humans.

Although the applicant explained that if the findings noted in dogs occur in humans, these findings can

be monitored easily, the NOAEL for abnormal respiration is 2 mg/kg/day, which provides an exposure (AUC) that is almost comparable to the human exposure at the proposed clinical dose (maximum 100 mg/day). PMDA asked the applicant to explain the necessity of including a caution statement in the package insert, taking also account of this point.

The applicant responded as follows:

Changes in clinical observations including abnormal respiration, tremors, and decreased activity observed in the dog repeated oral dose toxicity studies are considered to be related to the central nervous system. Sitagliptin is a substrate for P-gp transport system (2.6.4.4.5) and is considered to be excreted from the brain, but the CNS-related effects may have occurred due to transient elevations of Sitagliptin concentrations in the brain, resulting from saturation of excretion via P-gp transport after the administration of 10 and 50 mg/kg/day to dogs (C_{max} , 8 and 38 μ M, respectively). While tremors occurred at ≥ 1500 mg/kg/day (C_{max} , about 100 μ M) in the rat 14-week oral toxicity study (4.2.3.2.6), CNS-related findings in clinical observations or skeletal myofiber degeneration were not observed in repeat-dose toxicity studies in other animal species and it is considered that dogs are sensitive species or these findings are specific to dogs. Furthermore, in Japanese double-blind comparative studies (A201, A202, P054, P055, ONO-5435-08, ONO-5435-09), the incidences of adverse events categorized as nervous system disorders, respiratory disorders, and musculoskeletal disorders were similar between the Sitagliptin and placebo groups. Therefore, as the CNS-related findings in clinical observations and skeletal myofiber degeneration observed in dogs are unlikely to occur in humans, there is no need to include a caution statement in the package insert.

PMDA considers as follows:

In each repeat-dose toxicity study, the reversibility of toxicity has not been evaluated based on “Partial revision of the guideline for repeat-dose toxicity studies” (PMSB/ELD Notification No. 655 dated April 5, 1999). However, although it has been indicated that the hepatotoxicity observed in rats treated with 500 mg/kg/day is related to hepatocellular tumors in the carcinogenicity study, there were no drug-related effects including other findings noted at ≥ 500 mg/kg/day in the ≤ 180 mg/kg/day groups and the exposure (AUC) at 180 mg/kg/day is about 23 times the human exposure at the proposed clinical dose (maximum 100 mg/day). Thus, the findings noted in rats are unlikely to occur in humans. Although the exposure (AUC) at the NOAEL of 2 mg/kg/day in the dog repeat-dose toxicity study is almost comparable to the human exposure at the proposed clinical dose (maximum 100 mg/day), since abnormal respiration resolved by the end of observation period each day; safety pharmacology studies (4.2.1.3.3 and 4.2.1.3.4) showed no effects on respiratory function or central nervous system; skeletal myofiber degeneration tended to be reversible; any of the symptoms did not worsen with prolonged duration of treatment; and the incidences of adverse events categorized as nervous system disorders, respiratory disorders, and musculoskeletal disorders were similar between the Sitagliptin and placebo groups in clinical studies, the findings observed in dogs are unlikely to occur in humans.

Then, PMDA accepted the response.

3.(iii).B.(2) Liver carcinogenicity in rats

PMDA asked the applicant to explain the possibility that the increased incidence of hepatocellular tumors observed in the rat carcinogenicity study was not secondary to hepatocellular injury associated with Sitagliptin and a potential concern about the safety in humans, from the standpoint of hepatocellular toxicity and the doses in this study and the rat 14-week oral toxicity study (4.2.3.2.6).

The applicant responded as follows:

The liver findings observed at ≥ 500 mg/kg/day in the rat 14-week oral toxicity study were the changes suggestive of hepatic enzyme induction and hepatocellular injury and increased thyroid gland weight and follicular epithelial cell hypertrophy etc. were considered to be induced by or secondary to hepatic enzyme induction.

In the rat carcinogenicity study, eosinophilic and basophilic cellular alternations and cystic degeneration in the liver were noted at 500 mg/kg/day, but centrilobular hepatocellular hypertrophy and cellular infiltration observed in the 14-week study were similar between the Sitagliptin and control groups. However, it is inferred that these changes had occurred in the early phase of the carcinogenicity study and the increased incidence of eosinophilic and basophilic cellular alternations is considered to be a change suggestive of hepatic enzyme induction. Based on the analysis of carcinogenicity studies by NTP, it has been reported that there is a significant correlation between hepatocellular hypertrophy and increased liver weight in a rat repeat-dose toxicity study and an increased incidence of liver tumors in a carcinogenicity study. Therefore, also in the carcinogenicity study of Sitagliptin, the combined findings, e.g. hepatocellular hypertrophy due to hepatic enzyme induction and cellular infiltration due to hepatocellular injury that had occurred early, may have increased the incidence of hepatocellular adenomas and carcinomas.

In Japanese and foreign clinical studies, the incidence of laboratory adverse events affecting liver function (Japanese clinical studies, A201, A202, P054, P055, ONO-5435-08, ONO-5435-09; foreign clinical studies, P010, P014, P019, P020, P021, P023, P024, P035, P036, P040, P052, P053) and the change from baseline (Japanese clinical studies [data up to Treatment Week 12], A201, A202, A203, P054, P055, ONO-5435-08 to -10, P046; foreign clinical studies, P010, P014, P019, P020, P021, P023, P024, P035, P036, P040, P052, P053) etc. were similar between the Sitagliptin and control (placebo or active comparator) groups. There is an adequate safety margin (about 19-fold) between the highest dose producing no liver tumors in rats and the clinical dose based on plasma concentration. Sitagliptin at the clinical dose does not induce the primary metabolic enzyme, CYP3A4 (4.2.2.4.6). Therefore, Sitagliptin is unlikely to be carcinogenic in humans.

PMDA asked the applicant to explain specific data suggesting hepatic enzyme induction by Sitagliptin.

The applicant responded as follows:

As CYP or UDP-GT was not evaluated and thyroid or thyroid-stimulating hormone etc. was not measured in rat repeat-dose toxicity studies, there are no direct or indirect data on hepatic enzyme induction. Since Sitagliptin is primarily excreted unchanged and metabolism contributes little to elimination clearance, even if hepatic enzyme induction occurs, there will be no marked decrease in the plasma concentration. Although there are no direct data showing hepatic enzyme induction by Sitagliptin, the liver and thyroid gland findings observed in rats should be suggestive of hepatic enzyme induction by Sitagliptin.

PMDA considers as follows:

The data supporting the applicant's view that the hepatocellular tumors observed in rats were secondary to hepatic enzyme induction and hepatocellular injury by Sitagliptin are not necessarily sufficient. However, since Sitagliptin is not genotoxic; hepatocellular tumors observed in rats did not affect the survival rate as the direct cause of death in the carcinogenicity study and moreover, histopathological changes were similar between the Sitagliptin and control groups and no metastatic focus was identified; and the exposure (AUC) at the highest dose producing no hepatotoxicity or liver tumors in rats (150 mg/kg/day) was about 19-fold the human exposure at the proposed clinical dose (maximum 100 mg/day), liver tumors observed in rats are unlikely to occur in humans.

3.(iii).B.(3) Toxicologic evaluation in rabbit reproductive and developmental toxicity study

In the rabbit embryo-fetal development study (4.2.3.5.2.3), the high dose (500 mg/kg/day) group was terminated due to excessive maternal toxicity and developmental toxicity was not evaluated. Thus, PMDA asked the applicant to discuss developmental toxicity in rabbits, using the results from a preliminary study as reference data.

The applicant responded as follows:

In a dose-ranging study in pregnant rabbits (n = 10/group) (4.2.3.5.2.4), Sitagliptin 0, 62.5, 125, 250, and 500 mg/kg/day were administered orally from gestation days 7 to 20. As a result, body weight loss and reduced food intake and a spontaneous abortion were observed in 1 maternal animal in the 500 mg/kg/day group. In other 4 maternal animals in the 500 mg/kg/day group, food intake decreased transiently, which resolved during the dosing period. As to embryo-fetal toxicity, there were no treatment-related effects except for slight reductions in live fetal weight at ≥ 250 mg/kg/day. The fetuses were not examined for the sex ratio or skeletal and visceral malformations/variations. In addition to the above results, there were no treatment-related findings in any of the developmental toxicity parameters at 62.5 and 125 mg/kg/day in the embryo-fetal development study. Therefore, in

rabbit embryos/fetuses, Sitagliptin caused reduced body weight at ≥ 250 mg/kg/day, but did not induce embryo-fetal death or external abnormalities and the NOAEL for the fetus was determined to be 125 mg/kg/day.

Embryo-fetal toxicity was evaluated using 2 dose levels in the embryo-fetal development study, which was not in accordance with “Revision of the Guideline for Detection of Toxicity to Reproduction for Medicinal Products” (PMSB/ELD Notification No. 1834 dated December 27, 2000). However, as no toxicologically significant developmental toxicity was observed at 125 mg/kg/day in the dose-ranging study and the embryo-fetal development study, and developmental toxicity can be evaluated based on the results of these two studies, PMDA accepted the response.

3.(iii).B.(4) Studies for effects on skin in monkeys

PMDA asked the applicant to explain the basis for discussing that the skin lesions in monkeys observed with other DPP-4 inhibitors reported to the FDA are associated with DPP-8 and DPP-9 inhibition, but not DPP-4 inhibition.

The applicant responded as follows:

Based on the IC_{50} values and plasma exposures of Compound 1 and Compound 2, it is inferred that DPP-8 and DPP-9 were both inhibited sufficiently, although *in vivo* activity could not be determined as DPP-8 and DPP-9 are endoenzymes. As the *in vitro* percent inhibition of DPP-8 and DPP-9 are higher with Compound 2 than Compound 1, more serious skin lesions were predicted for Compound 2, but the skin lesions produced by Compound 2 were mild in severity, which may be attributed to the possibility that DPP-8 and DPP-9 were inhibited insufficiently due to low cellular permeability of Compound 2 or that the skin lesions reported to the FDA were caused by effects other than DPP-8 and DPP-9 inhibition. There should be no relationship between DPP-4 inhibition and the skin lesions reported to the FDA because Sitagliptin has been confirmed to be distributed in the skin (4.2.2.3.2) and the toxicity studies using Sitagliptin and Compound 1 showed DPP-4 inhibition of $\geq 98\%$ at their respective highest doses, but skin lesions were not observed in the Sitagliptin group.

PMDA asked the applicant to explain the possible development of skin lesions in humans due to a difference in the selectivity for enzyme inhibition between humans and monkeys.

The applicant responded as follows:

As the percent inhibition of monkey DPP-4 activity is not available, the difference in DPP-4 selectivity between monkeys and humans is unknown. However, the incidence of adverse events categorized as skin and subcutaneous tissue disorders in Japanese clinical studies (A201, A202, P054, P055, ONO-5435-08, ONO-5435-09) and the incidence of eczema and rash in foreign clinical studies (P010, P014, P019, P020, P021, P023, P024, P035, P036) were similar between the Sitagliptin and

placebo groups. Based on the results from the monkey 14-week oral toxicity study of Sitagliptin (4.2.3.2.15), skin lesions, as seen with the non-selective DPP-4 inhibitors, are unlikely to develop in humans following the administration of Sitagliptin.

PMDA considers as follows:

With respect to the relationship between the skin lesions in monkeys and the plasma exposures of the non-selective DPP-4 inhibitors (Compound 1 and Compound 2) in the toxicity studies, comparative discussion can not be made based on the percent inhibition of DPP-8 and DPP-9 activities because, although skin lesions worsened in a dose-dependent manner at AUC of $\geq 105 \mu\text{M}\cdot\text{h}$ and C_{max} of $\geq 38 \mu\text{M}$, the data on *in vivo* percent inhibition of DPP-8 and DPP-9 are not available and each enzyme in cells may not have been sufficiently inhibited at the low and mid doses of Compound 2. Therefore, the non-clinical data obtained so far are not sufficient to support the applicant's view that the skin lesions observed in monkeys treated with other DPP-4 inhibitors reported to the FDA are associated with DPP-8 and DPP-9 inhibition, but the possibility that DPP-8 and DPP-9 inhibition are associated with the skin lesions can not be ruled out. In the monkey 14-week oral toxicity study of Sitagliptin, the highest dose resulted in the plasma exposures of $236 \mu\text{M}$ AUC and $40.9 \mu\text{M}$ C_{max} , but no skin lesions were found and there is an adequate safety margin relative to the plasma concentration in humans at the proposed clinical dose (maximum 100 mg/day) (AUC, about 28-fold; C_{max} , about 45-fold). There were no differences in the incidence of adverse events categorized as skin tissue disorders between the Sitagliptin and placebo groups in clinical studies. A caution statement that if skin disorders (hypersensitivity reactions) develop, administration should be discontinued has been included in the package insert (draft). Therefore, the development of skin lesions is unlikely to become an obstacle to the clinical use of Sitagliptin.

4. Clinical data

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

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

In the clinical development of Sitagliptin, 2 types of the drug substance (■■■■, ■■■■) and of the drug product (capsule formulation, tablet formulation) were used. The formulations used in Japanese clinical studies (Evaluation data) are presented in Table 3.

Table 3. Formulations used in Japanese clinical studies (Evaluation data)

Development phase of study	Study Number	Drug substance	Drug product
Phase I	P013, A111, A112	■■■■	Capsule formulation (■■■■) and film-coated tablet formulation (■■■■)
Phase II	A201to203	■■■■	Film-coated tablet formulation (■■■■)
Phase III	P054, P055, ONO-5435-08 to -10		Proposed commercial formulation (■■■■) (■■■■) (■■■■) (■■■■), (■■■■) (■■■■)
Phase I	P046, P076		

Sitagliptin in human biomaterials was quantitated by LC-MS/MS and the lower limit of quantitation was 0.5 ng/mL for plasma, 0.1 µg/mL for urine, and 0.01 ng/mL for dialysate.

The results from the following biopharmaceutic studies were submitted: 1 Japanese clinical study (P076) and 4 foreign clinical studies (P006, P016, P027, P029). The main study results are described below.

4.(i).A.(1) Pharmacokinetic and food effect study of the proposed commercial formulation (5.3.3.4.2, P076 [■■■ 20■■■])

A randomized, open-label, 2-period, crossover study in Japanese healthy adult male subjects (target number of cases of 12) was conducted to assess the pharmacokinetics of the proposed commercial formulation (a 50-mg tablet) and food effect on the pharmacokinetics.

A single oral dose of 50 mg of Sitagliptin as the proposed commercial formulation was to be administered once daily in the morning under fasted condition or after a standard Japanese-style breakfast and a 7-day washout period was included between the two periods.

All of the 12 treated subjects were included in the pharmacokinetic and safety analyses.

Pharmacokinetic analysis showed that the geometric mean (geometric standard deviation) of C_{max} was 366 (92.9) nM and the geometric mean of $AUC_{0-\infty}$ was 4.08 (0.52) µM·h after fasted administration of a 50-mg tablet. The geometric mean ratios of $AUC_{0-\infty}$ and C_{max} (fed/fasted) with their 90% confidence intervals were 0.98 [0.94, 1.02] and 1.37 [1.15, 1.62], respectively, and the median t_{max} (min, max) was 2.5 hours (1.5 hours, 6 hours) in the fasted state and 2 hours (0.5 hours, 6 hours) in the fed state.

Regarding safety, 3 clinical adverse events occurred in 3 subjects (fasted administration, ventricular extrasystoles, stomatitis; fed administration, nasopharyngitis), but a causal relationship to the study drug was denied for all events. There were no deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation. With respect to clinical laboratory values, vital signs, ECG, and physical findings, there were no clinically meaningful changes or treatment-related changes.

4.(i).A.(2) Formulation comparison study (5.3.1.2.1, P006 [■ to ■ 20■], Reference data)

A randomized, open-label, 2-period, crossover study in foreign healthy adult male and female subjects was conducted to investigate the influence of formulation (capsule formulation, tablet formulation) on the pharmacokinetics of Sitagliptin.

A single oral dose of 50 mg of Sitagliptin as either the capsule formulation or the tablet formulation was to be administered, separated by a washout period of 7 days.

All of the 12 treated subjects were included in the pharmacokinetic and safety analyses.

Pharmacokinetic analysis showed that the $AUC_{0-\infty}$ ratio (tablet/capsule) with its 90% confidence interval were 1.04 [1.02, 1.07] and the C_{max} ratio with its 90% confidence interval were 1.21 [1.10, 1.33]. The tablet formulation had a slightly shorter t_{max} (median, 3.0 hours) compared to the capsule formulation (median, 4.5 hours).

Regarding safety, 13 clinical adverse events occurred in 7 subjects (4 subjects [6 events] after the administration of the capsule formulation; 5 subjects [7 events] after the administration of the tablet formulation). Headache was a commonly reported adverse event after the administration of each formulation (4 subjects [5 events] after the administration of the capsule formulation; 4 subjects [4 events] after the administration of the tablet formulation, all mild in severity), of which 5 events of headache reported in 4 subjects (2 subjects [3 events] after the administration of the capsule formulation; 2 subjects [2 events] after the administration of the tablet formulation) were regarded as adverse events for which a causal relationship to the study drug could not be denied (hereinafter referred to as “adverse drug reactions”). As to clinical laboratory values, serum potassium increased was observed up to 24 hours post-dose in 2 subjects (1 subject each after the administration of the capsule formulation and of the tablet formulation), which were both classified as adverse drug reactions, but were not serious, requiring no treatment. There were no deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

4.(i).A.(3) Bioequivalence study (5.3.1.2.2, P027 [■ 20■], Reference data)

A randomized, open-label, 2-period, crossover study in foreign healthy adult male and female subjects was conducted to establish the bioequivalence of tablet formulations containing ■ and ■ of Sitagliptin.

A single oral dose of 100 mg of Sitagliptin as either the tablet formulation containing ■ or ■ was to be administered and there was a 7-day washout interval between the two periods.

All of the 12 treated subjects were included in the pharmacokinetic and safety analyses.

Pharmacokinetic analysis showed that the $AUC_{0-\infty}$ and C_{max} ratios (tablet formulation containing ■/tablet formulation containing ■) with corresponding 90% confidence intervals were 1.05 [1.02, 1.07] and 1.07 [0.94, 1.22], respectively. The t_{max} and $t_{1/2}$ were similar between the two formulations.

Regarding safety, 13 clinical adverse events occurred in 5 subjects (3 subjects [5 events] after the administration of the tablet formulation containing ■; 4 subjects [8 events] after the administration of the tablet formulation containing ■). Of which, headache and light headedness (1 subject had headache [1 event] after the administration of the tablet formulation containing ■, 1 subject had light headedness [1 event] after the administration of the tablet formulation containing ■, both mild in severity) were classified as adverse drug reactions. There were no deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation. With respect to clinical laboratory values, vital signs, and ECG, there were no study drug-related changes.

4.(i).A.(4) Bioavailability and food effect study (5.3.1.1.2, P029 [■ to ■ 20■], Reference data)

A randomized, placebo-controlled, double-blind study (Part I) and a randomized, open-label, 3-period, crossover study (Part II) in foreign healthy adult male and female subjects were conducted to evaluate the absolute bioavailability of Sitagliptin (tablet formulation) and food effect.

In Part I, escalating single intravenous doses of Sitagliptin (25 mg, 50 mg, 100 mg) or placebo were to be given and in Part II, single doses of 100 mg of Sitagliptin were to be given (an oral dose in the fasted state or after a high-fat meal, or an intravenous dose), and there was a 5-day washout period between doses.

All of the 22 treated subjects (Part I, 10 subjects; Part II, 12 subjects) were included in the safety analysis, of which 20 subjects who received Sitagliptin (10 subjects in each Part) were all included in the pharmacokinetic analysis.

According to pharmacokinetic analysis, in Part I, the $AUC_{0-\infty}$ of Sitagliptin was dose-proportional, the plasma clearance (Cl_p) was 413 to 421 mL/min (geometric mean), the renal clearance (Cl_R) was 249 to 340 mL/min (geometric mean), the volume of distribution was 198 to 262 L (arithmetic mean), and the fraction of dose excreted unchanged in urine ($f_{e, 0-\infty}$) was 0.654 to 0.828 (arithmetic mean). In Part II, the absolute bioavailability of Sitagliptin after oral administration was 87%, the $AUC_{0-\infty}$ and C_{max} geometric mean ratios (fed/fasted) with corresponding 90% confidence intervals were 1.03 [0.97, 1.11] and 0.94 [0.86, 1.03], respectively, and the t_{max} and $t_{1/2}$ in the fasted state were similar to those after a high-fat meal.

Regarding safety, 6 clinical adverse events occurred in 4 subjects (after a 25 mg dose in Part I, increased hunger, drowsiness; after a 100 mg dose in Part I, dizziness and nausea, menstrual spotting with sporadic clots; after a 100 mg intravenous dose in Part II, headache). All of these events except for menstrual spotting with sporadic clots were classified as adverse drug reactions, but were mild in severity. There were no laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

4.(i).B *Outline of the review by PMDA*

Food effect

Food effect was evaluated in Japanese and foreign clinical studies (Japanese Study P076, Foreign Study P029). While the 90% confidence intervals for the $AUC_{0-\infty}$ and C_{max} geometric mean ratios (fed/fasted) following a 100-mg oral dose both fell within the bioequivalence acceptance ranges in Study P029, the 90% confidence interval for the C_{max} geometric mean ratio (fed/fasted) following a 50-mg dose fell outside the bioequivalence acceptance range in Study P076. PMDA asked the applicant to explain its reason and the potential effect of increased C_{max} after a meal observed in Japanese subjects.

The applicant responded as follows:

In Study P029, a 100-mg tablet of Sitagliptin was given to foreign subjects in the fasted state or after a high-fat meal. The $AUC_{0-\infty}$ and C_{max} under these conditions fell within the bioequivalence acceptance ranges. On the other hand, in Study P076, a 50-mg tablet of Sitagliptin was given to Japanese subjects in the fasted state or after a Japanese-style meal and the $AUC_{0-\infty}$ and C_{max} geometric mean ratios (fed/fasted) with their 90% confidence intervals were 0.98 [0.94, 1.02] and 1.37 [1.15, 1.62], respectively. In both studies, a meal was served as breakfast at about 30 minutes prior to the scheduled time of drug administration and was consumed completely within about 25 minutes. Only male subjects were enrolled into Study P076 and the mean age and BMI were lower than in Study P029, but other subject background factors, inclusion/exclusion criteria, pharmacokinetic sampling points, and

the management of subjects etc. were similar between the studies. As to the background factors, there are data showing that BMI had little effect on the pharmacokinetics of Sitagliptin and that C_{max} was higher in females than in males and in the elderly than in the non-elderly (P003). Although the definite reason for the increased C_{max} in Study P076 only is unknown, the increased C_{max} observed in Study P076 should have no potential for a clinically meaningful effect, because the acceptance criteria were met for AUC^1 , which is considered important for assessing the clinically meaningful effects of Sitagliptin; the C_{max} in Study P076 (366 nM in the fasted state, 500 nM in the fed state) is expected to achieve almost maximal efficacy based on the data on the percent inhibition of DPP-4 activity by Sitagliptin; and the safety of Sitagliptin up to 200 mg (Japanese type 2 diabetes mellitus patients) or 400 mg (Japanese healthy adult male subjects) has been confirmed in Japanese clinical studies (P013, A111, A112, A202).

PMDA considers that the possibility that the differences in the results between the Japanese and foreign clinical studies were associated with the differences in the subject background due to partially different study conditions (e.g. Study P029 included female and elderly subjects who have been shown to exhibit higher C_{max} values in Study P003) can not be excluded, but accepted the applicant's response that the increased C_{max} observed in the Japanese food effect study should have no potential for a clinically meaningful effect, taking account of the discussion on the efficacy and safety of Sitagliptin based on clinical studies.¹

¹ The applicant explained that the most relevant pharmacokinetic parameter to assess a clinically meaningful change is AUC based on the mode of action, PK/PD analyses, and clinical efficacy/safety profile of Sitagliptin and the applicant had specified the range for Sitagliptin pharmacokinetic studies for lack of a clinically meaningful change for the AUC geometric mean ratio as 0.5-2. Meanwhile, in some drug interaction studies etc., other bounds that are different from the pre-specified range for Sitagliptin pharmacokinetic studies or the bioequivalence acceptance ranges (as specified in the "Guideline for Bioequivalence Testing of Generic Drugs" [PFSB/ELD Notification No. 1124004 dated November 24, 2006] and the "Methods of Drug Interaction Studies" [PFSB/ELD Notification No. 813 dated June 4, 2001]) were set for assessment. PMDA checked the rationale for these ranges specified by the applicant. In evaluating drug interaction, PMDA assessed the data based on the bioequivalence acceptance ranges as specified in the notification "Methods of Drug Interaction Studies", and made inquiries about individual deviations of the parameter values, taking into account the efficacy and safety information from the relevant study and other clinical studies, etc.

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data, the results from Japanese phase I clinical studies in healthy adult subjects (P013, A111, A112), Japanese phase II clinical studies in patients with diabetes mellitus (A201-A203), and a Japanese drug interaction study (P046) were submitted. As the reference data, the results from foreign clinical studies (P001-P005, P007-P012, P014, P017, P018, P022, P025, P026, P031-P034, P037) were submitted. The main study results are described below.

4.(ii).A.(1) *In vitro* studies using human biomaterials (4.2.2.3.1, 4.2.2.3.3 to 4.2.2.3.6, 4.2.2.4.4 to 4.2.2.4.6, 4.2.2.4.9)

The human plasma protein binding of Sitagliptin (0.02-200 μM , *in vitro*) was about 38% and the human blood/plasma ratio of Sitagliptin (0.1-10 μM , *in vitro*) was 1.21 and it was inferred that blood clearance will approximate plasma clearance.

Using LLC-PK1 cells expressing human P-gp, the transcellular transport of Sitagliptin (10 μM) was investigated. As a result, time-dependent, unidirectional transport was observed and Sitagliptin was considered to be a substrate for the human P-gp. Sitagliptin (0.3-500 μM) had no inhibitory effect on the P-gp-mediated transport of digoxin, verapamil, ritonavir, and vinblastine and inhibited the transport of quinidine by about 30% at 500 μM . Cyclosporine, a P-gp inhibitor, inhibited the P-gp-mediated transport of Sitagliptin with an IC_{50} value of 1.1 μM .

Using cell lines expressing hOCT2, hOAT1, hOAT3, and hOAT4, and hPEPT1, uptake of Sitagliptin (10 μM for CHO-K1 cells expressing hOAT3; 5 or 100 μM for other cell lines) was investigated. As a result, Sitagliptin was considered to be a substrate of hOAT3 and hOAT3-mediated Sitagliptin uptake was inhibited by probenecid, ibuprofen, furosemide, fenofibric acid, quinapril, indapamide, and cimetidine (with IC_{50} values of 5.6, 3.7, 1.7, 2.2, 6.2, 11.1, and 78.6 μM , respectively). When the effects of Sitagliptin on hOAT1/3 substrates were investigated, at concentrations of 0.1 to 500 μM , Sitagliptin did not inhibit ^3H -cidofovir uptake, but it showed weak inhibition of ^3H -cimetidine uptake ($\text{IC}_{50} = 160 \mu\text{M}$).

The metabolism of ^{14}C -Sitagliptin (10 μM) was studied in human hepatocytes and microsomes. The results demonstrated minimal metabolism of Sitagliptin and it was considered that CYP3A4 is primarily involved in the formation of the metabolites of Sitagliptin, i.e. M2, M5, and M6 and CYP2C8 is partially involved in the formation of M2 and M5. The IC_{50} values of Sitagliptin for human liver microsomal CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) were all $> 100 \mu\text{M}$ and Sitagliptin was not a time-dependent inhibitor of human liver CYP3A4 activity. The potential of Sitagliptin to induce CYP3A4 in human hepatocytes was evaluated. As a result, CYP3A4 mRNA expression and enzyme activity were not affected in response to Sitagliptin treatment (1 and 10 μM)

and comparison with the positive control rifampicin (10 μ M) suggested that Sitagliptin has no potential to induce CYP3A4.

4.(ii).A.(2) Human pharmacokinetics

4.(ii).A.(2).1 Pharmacokinetics in healthy adult subjects

(a) Phase I single oral dose study (5.3.3.1.1, Study Number P013 [■■■ to ■■■ 20■■■])

A randomized, placebo-controlled, double-blind, crossover, panel, single escalating dose study in Japanese healthy adult male subjects living in the US (target number of cases of 16; 8 cases per panel) was conducted to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of 5 mg, 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg of Sitagliptin.

In Panel A, single oral doses of placebo or Sitagliptin 5 mg, 25 mg, and 100 mg were to be administered in the fasted state in Period 1, Period 2, and Period 3, respectively, in a dose escalating manner, and a single oral dose of placebo or Sitagliptin 25 mg was to be administered after a standard Japanese-style breakfast in Period 4. In Panel B, single oral doses of placebo or Sitagliptin 12.5 mg, 50 mg, 200 mg, and 400 mg were to be administered in the fasted state in Period 1, Period 2, Period 3, and Period 4, respectively, in a dose escalating manner. There was at least a 1-week interval between dose escalations.

All of the 18 treated subjects were included in the safety analysis, of which 17 subjects excluding 1 subject who did not receive Sitagliptin were included in the pharmacokinetic and pharmacodynamic analyses.

Pharmacokinetic parameters are presented in Table 4.

Table 4. Pharmacokinetic parameters following single oral doses of Sitagliptin to Japanese healthy adult male subjects

Parameter	5 mg Fasted (n = 6)	12.5 mg Fasted (n = 6)	25 mg Fasted (n = 6)	50 mg Fasted (n = 6)	100 mg Fasted (n = 6)	200 mg Fasted (n = 6)	400 mg Fasted (n = 6)	25 mg Fed (n = 6)	Mean ratio* [95% CI]
AUC _{0-∞} (μ M·h)	0.499	0.960	2.04	3.76	8.65	16.5	32.0	2.23	1.12 [1.05, 1.19]
C _{max} (nM)	26.9	59.4	149	309	959	1970	3950	171	1.18 [1.00, 1.39]
t _{max} (h)	6	4	5	2	2	3	2	5	
t _{1/2} (h)	13.8	12.3	11.6	11.4	9.56	9.14	9.07	11.8	
f _{e,0-∞}	0.730	0.850	0.787	0.851	0.878	0.954	1.00	0.856	
Cl _R (mL/min)	299	445	397	464	415	475	513	391	

Geometric least-squares mean for AUC_{0-∞}, C_{max} and Cl_R; median for t_{max}; harmonic mean for t_{1/2}; arithmetic least-squares mean of fraction of dose excreted unchanged in urine extrapolated to infinity for f_{e,0-∞}

*Geometric mean ratio (fed/fasted)

The AUC_{0-∞} was dose-proportional and the C_{max} increased in a slightly greater than dose proportional manner. There was a trend towards shorter t_{max} and t_{1/2} with increasing dose. The mean fraction of dose excreted unchanged in urine was 0.73 to 1.0 and the mean Cl_R was 299 to 513 mL/min and this value exceeded the typical glomerular filtration rate, indicating that Sitagliptin is subject to active tubular secretion [see “4.(i).A.(1) Pharmacokinetic and food effect study of the proposed commercial

formulation” for the pharmacokinetics of the proposed commercial formulation].

Pharmacodynamic analysis showed that Sitagliptin inhibited plasma DPP-4 activity in a dose-dependent manner. When the relationship between plasma Sitagliptin concentrations and the percent inhibition of plasma DPP-4 activity was analyzed using an $E_{\max}$ model, the EC_{50} was estimated to be 26.2 nM.

Regarding safety, 26 clinical adverse events occurred in 12 subjects. Of which, 3 events of drowsiness/headache and somnolence were classified as adverse drug reactions. As laboratory adverse events, ALT increased (about 6 times the upper limit of normal [ULN]), AST increased (6.5 times the ULN), ALP increased (about twice the ULN), and γ GTP increased (about 5 times the ULN) were observed in 1 subject at 1 week after the administration of 5 mg of Sitagliptin in Period 1 or on the following day of placebo administration in Period 2 and treatment was discontinued, but their causal relationship to the study drug was judged as “unlikely.” In this subject, all laboratory parameters except for γ GTP returned to normal after study drug discontinuation. There were no deaths or serious adverse events (including laboratory test abnormalities) and hypoglycaemia was not reported.

(b) Phase I multiple oral dose study (5.3.3.1.2, Study Number A111 [■■■ 20■■■ to ■■■ 20■■■])

A randomized, placebo-controlled, double-blind, 5-panel, inter-subject dose escalation, parallel-group study in Japanese healthy adult male subjects (target number of cases of 50, 10 cases per panel) was conducted to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple oral doses of 25 mg, 50 mg, 100 mg, and 200 mg of Sitagliptin once daily for 10 days and of 50 mg of Sitagliptin twice daily for 10 days.

In successive Panels A, B, C, and D, each subject was to orally receive Sitagliptin 25 mg, 50 mg, 100 mg, or 200 mg, respectively, once daily in the morning in the fasted state from Day 1 to Day 10. In Panel E, each subject was to receive a single oral dose of 50 mg of Sitagliptin in the morning in the fasted state in Part 1, undergo a 72-hour washout period, and then receive multiple oral doses of 50 mg of Sitagliptin twice daily (in the morning in the fasted state and 12 hours later) from Day 4 until the morning of Day 13 in Part 2. Two subjects received placebo in each panel.

All of the 50 treated subjects (total 10 subjects treated with placebo [2 subjects in each panel], total 40 subjects treated with Sitagliptin [8 subjects in each panel]) were included in the safety analysis, of which 49 subjects excluding 1 subject in Panel B (as consent was withdrawn after study drug administration on Day 8, the subject had no pharmacokinetic or pharmacodynamic data after Day 9) were included in the pharmacokinetic and pharmacodynamic analyses.

According to pharmacokinetic analysis, plasma Sitagliptin trough concentrations reached a

steady-state by Day 2 of repeated administration in both once-daily and twice-daily regimens. With once-daily dosing, the AUC_{0-24} was dose-proportional and the AUC_{0-24} ratio (Day 10/Day 1) was 1.03 to 1.19 and there was no evidence of accumulation. The mean fraction of dose excreted unchanged in urine was 0.71 to 0.81 and the mean Cl_R was 355 to 395 mL/min.

According to pharmacodynamic analysis, with once-daily repeated administration, the percent inhibition of plasma DPP-4 activity increased in a dose-dependent manner, but the percent inhibition was similar between Day 10 and Day 1. When the relationship between plasma Sitagliptin concentrations and plasma DPP-4 inhibition was analyzed on Day 1 and Day 10 using an E_{max} model, there were no differences between Day 1 and Day 10 and the EC_{50} was estimated to be about 25 nM. With once-daily dosing, post-prandial active GLP-1 levels at 4 and 24 hours post-dose on Day 10 were higher than the baseline levels. It was determined that in healthy adult subjects, there are no clinically meaningful effects on fasting or post-prandial blood glucose, insulin, C-peptide, or glucagon.

Regarding safety, 3 clinical adverse events occurred in 3 subjects (myalgia, headache, post procedural complication) and 5 laboratory adverse events occurred in 5 subjects (ALT increased, TG increased, CPK increased [1 event each], eosinophil count increased [2 events]). Of which, only eosinophil count increased (1 subject) in the 100 mg group was classified as an adverse drug reaction. There were no deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation and hypoglycaemia was not reported. With respect to vital signs and ECG, there were no clinically relevant changes or treatment-related changes.

(c) Phase I multiple oral dose study (5.3.3.1.3, Study Number A112 [■■■ to ■■■ 20■■■])

A randomized, placebo-controlled, double-blind study in Japanese healthy adult male subjects (target number of cases of 10) was conducted to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple oral doses of 400 mg of Sitagliptin once daily for 10 days.

Placebo or Sitagliptin 400 mg was to be orally administered once daily in the morning in the fasted state for 10 days.

All of the 10 treated subjects (2 subjects in the placebo group, 8 subjects in the Sitagliptin group) were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

Pharmacokinetic analysis showed that plasma Sitagliptin trough concentrations reached a steady-state by Day 2 of repeated administration and the AUC_{0-24} ratio (Day 10/Day 1) was 1.05. The mean fraction of dose excreted unchanged in urine was 0.73 and the mean Cl_R was 355 mL/min.

Pharmacodynamic analysis indicated that plasma DPP-4 inhibition was comparable between Day 1

and Day 10. There were no clinically meaningful effects on fasting blood glucose in healthy adult subjects.

Regarding safety, a clinical adverse event was observed in the Sitagliptin 400 mg group only (1 subject, 1 event of limb injury), but its causal relationship to the study drug was denied. There were no deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation and hypoglycaemia was not reported. With respect to clinical laboratory values, vital signs, ECG, body weight, and physical findings, there were no clinically relevant changes or treatment-related changes.

(d) Oral ADME study (5.3.3.1.6, Study Number P009 [■■■ 20■■■ to ■■■ 20■■■], Reference data)

An open-label study in foreign healthy adult male subjects was conducted to investigate the elimination pathway, mass balance, and safety of Sitagliptin after a single dose of ¹⁴C-labeled Sitagliptin.

A single oral dose of 83.04 mg of ¹⁴C-labeled Sitagliptin was to be administered and blood, urine, and feces were collected for 1 week post-dose.

All of the 6 treated subjects were included in the safety analysis, of which 1 subject with a low recovery of radioactivity was excluded from the primary pharmacokinetic analysis. However, as the recovery rate following readministration of 100 mg of Sitagliptin in this subject was similar to those in the other 5 subjects, it was inferred that there had been a problem when collecting samples.

According to pharmacokinetic analysis, the parent compound accounted for 74% of the radioactivity in plasma, as determined by the ratio of Sitagliptin AUC_{0-last} (AUC up to the last measured concentration) and radioactivity AUC_{0-last}. Approximately 87% of the oral radioactivity dose was recovered in urine and approximately 13% in feces. Approximately 79% of the oral radioactivity dose was recovered unchanged in urine and approximately 16% of the oral radioactivity dose was recovered as metabolites (13% of the dose in urine, 3% of the dose in feces), indicating that the major pathway of elimination of Sitagliptin is via urinary excretion. Six metabolites were detected and the most abundant metabolites in plasma were M5 and M2 (4%-7% and 1%-6%, respectively, of radioactivity in plasma) and other metabolites included M6, M1, M4, and M3.

Regarding safety, no adverse events (including laboratory test abnormalities) were reported.

(e) Study assessing the effect on QTc interval (5.3.4.1.1, Study Number P032 [■■■ to ■■■ 20■■■], Reference data)

A randomized, double-blind, placebo-controlled, 4-period, crossover study in foreign healthy adult

male and female subjects was conducted to assess the potential effect of single doses of Sitagliptin on QTc interval.

Each period consisted of a single oral dose of either 400 mg moxifloxacin (positive control), 100 mg Sitagliptin, 800 mg Sitagliptin, or placebo and there was a 7-day washout interval between periods.

All of the 86 treated subjects were included in the pharmacokinetic and safety analyses, of which 79 subjects excluding 7 subjects who completed < 2 periods of the clinical study were included in the pharmacodynamic analysis.

Pharmacokinetic analysis showed that the $t_{\max}$ (median) and $C_{\max}$ (mean $\pm$ SD) were 3 hours and 882.8 $\pm$ 207.7 nM, respectively, at a dose of 100 mg of Sitagliptin and 2 hours and 10 026 $\pm$ 2440 nM, respectively, at a dose of 800 mg of Sitagliptin.

According to pharmacodynamic analysis, following a dose of 100 mg of Sitagliptin, there was no increase in QTcF observed at any time point, while following a dose of 800 mg, the maximum mean increase in the placebo-corrected change in QTcF from baseline at 3 hours post-dose was 8.0 ms. At the prespecified time point (1 hour post-dose), the mean change in QTcF from baseline was 3.7 ms, supporting the primary hypothesis that it will be less than 10 ms. There were not any differences in maximum QTcF, nor any differences in the maximum QTcF change from baseline across the 2 doses of Sitagliptin and placebo. The sensitivity of the assay to detect modest increases in QTc interval was established with the positive control moxifloxacin.

Regarding safety, 77 clinical adverse events occurred in 42 subjects, of which 40 events were classified as adverse drug reactions. Two laboratory adverse events occurred in 1 subject (ALT increased and AST increased), which were classified as adverse drug reactions. No serious clinical adverse events were reported.

4.(ii).A.(2).2) Pharmacokinetics in patients with type 2 diabetes mellitus

(a) Phase II clinical studies (5.3.5.1.1-3, Study Numbers A201 [REDACTED] 20 [REDACTED] to [REDACTED] 20 [REDACTED]], A202 [REDACTED] 20 [REDACTED] to [REDACTED] 20 [REDACTED]], A203 [REDACTED] 20 [REDACTED] to [REDACTED] 20 [REDACTED]])

Randomized, double-blind, placebo-controlled, parallel-group, comparative studies in Japanese patients with type 2 diabetes mellitus were conducted to evaluate the efficacy and safety of Sitagliptin 100 mg or placebo orally administered once daily for 12 weeks (A201); Sitagliptin 25, 50, 100, and 200 mg or placebo orally administered once daily for 12 weeks (A202); and Sitagliptin 100 mg once-daily, Sitagliptin 50 mg twice-daily, or placebo orally administered for 4 weeks (A203) [see “4.(iii).A.(2) Phase II clinical studies” for the study design and safety data].

Plasma Sitagliptin concentrations in patients who received study drug and had plasma concentrations measured in Study A202 are as shown in Table 5. Plasma Sitagliptin concentrations following a 100 mg dose in Study A201 were similar to those in Study A202.

Table 5. Plasma Sitagliptin concentrations in Study A202

Dose	Treatment Week 2	Treatment Week 12				
	Pre-dose	Pre-dose	0.5 hours post-dose	1 hour post-dose	1.5 hours post-dose	2.5 hours post-dose
25 mg	29.8 [26.9, 32.9] (n = 77)	33.0 [29.0, 37.4] (n = 77)	71.8 [61.1, 84.2] (n = 77)	191.6 [169.1, 217.0] (n = 77)	217.9 [200.1, 237.3] (n = 77)	219.9 [207.9, 232.7] (n = 77)
50 mg	53.9 [48.2, 60.4] (n = 70)	51.0 [45.3, 57.4] (n = 66)	151.1 [123.8, 184.2] (n = 69)	443.1 [386.5, 508.0] (n = 68)	492.4 [452.0, 536.5] (n = 68)	446.0 [419.1, 474.6] (n = 68)
100 mg	84.1 [74.3, 95.2] (n = 69)	81.9 [71.2, 94.1] (n = 64)	387.4 [305.3, 491.7] (n = 67)	1098.8 [953.1, 1266.7] (n = 66)	1149.9 [1051.6, 1257.4] (n = 67)	980.8 [915.9, 1050.2] (n = 67)
200 mg	148.8 [128.3, 172.7] (n = 66)	132.1 [113.5, 153.7] (n = 65)	894.7 [683.3, 1171.6] (n = 65)	2732.3 [2303.2, 3241.3] (n = 66)	2507.0 [2199.1, 2857.9] (n = 66)	2058.1 [1898.0, 2231.7] (n = 66)

Geometric mean (nM) [95% CI]

In Study A203, the geometric mean of plasma Sitagliptin concentration at pre-dose at Treatment Week 4 with its 95% confidence interval and the number of cases were 75.8 nM [54.0, 106.3] and 23, respectively, following 100 mg once daily administration and 155.7 nM [136.7, 177.3] and 23, respectively, following 50 mg twice daily administration.

According to pharmacodynamic analysis, in Study A202, the percent inhibition of DPP-4 activity at pre-dose was similar between Treatment Week 2 and Treatment Week 12 and increased with increasing dose over the dose range of 25 to 200 mg. The geometric mean of the percent inhibition of DPP-4 activity at pre-dose at Treatment Week 12 with its 95% confidence interval were 67.3% [64.3, 70.1] in the 50 mg group and 77.3% [74.6, 79.7] in the 100 mg group. Blood was collected over time from patients who underwent a meal tolerance test at Treatment Week 12 and Sitagliptin at ≥ 50 mg almost completely inhibited plasma DPP-4 activity by 1 hour post-dose. The percent inhibition of plasma DPP-4 activity was dependent on plasma Sitagliptin concentration, which is consistent with the relationship seen in healthy adult subjects in phase I clinical studies. The percent inhibition of plasma DPP-4 activity in Study A201 was similar to that in the 100 mg group of Study A202. In Study A203, the geometric mean of the percent inhibition of DPP-4 activity at 24 hours post-dose at Treatment Week 4 with its 95% confidence interval were 79.7% [76.8, 82.2] in the 100 mg once daily group and 87.9% [86.4, 89.1] in the 50 mg twice daily group.

(b) Population pharmacokinetic analysis of foreign phase II and phase I clinical studies (5.3.3.5.2, Study Numbers P010, P014, P001-008, P012, P013, P017, P027, P029, P033, Reference data)

Using the plasma Sitagliptin concentration data obtained from 18- to 80-year-old healthy subjects or patients with type 2 diabetes mellitus (1059 subjects/patients, 10 119 sampling points [about 20% were sparse sampling data]) in a total of 16 foreign studies including 2 phase II and 14 phase I clinical

studies, a population pharmacokinetic (PPK) analysis was performed using non-linear mixed effect modeling (software, NONMEM [version V, level 1.1]). The basic model was a 2-compartment model. Age, BMI, creatinine clearance (C_{CR}), diabetic status, fed status, formulations, height, obesity status, race, degree of renal insufficiency, serum creatinine, body weight, concomitant medications, gender, and dose were examined as covariates and the background factors other than renal function were considered to have no clinically meaningful effect on the pharmacokinetics of Sitagliptin. In addition, 83 medications coadministered in ≥ 5 patients with a Sitagliptin dose were screened for drug interactions. As a result, none of these medications were identified to have a clinically meaningful effect on the pharmacokinetics of Sitagliptin.

Based on the above, the applicant explained that the results of the PPK analysis are consistent with the results of a study in patients with renal insufficiency and of drug interaction studies.

4.(ii).A.(2).3) Pharmacokinetics in special populations

(a) Foreign pharmacokinetic study in patients with renal insufficiency (5.3.3.2.2, Study Number P008 [■ 20■ to ■ 20■], Reference data)

An open-label study in foreign adult male and female patients with varying degrees of renal insufficiency (renal insufficiency classified on the basis of 24-hour C_{CR} as normal [$> 80 \text{ mL/min/1.73 m}^2$], mild [$50 \text{ to } < 80 \text{ mL/min/1.73 m}^2$], moderate [$30 \text{ to } < 50 \text{ mL/min/1.73 m}^2$], and severe [$< 30 \text{ mL/min/1.73 m}^2$] and end-stage renal disease [ESRD] requiring hemodialysis) and foreign healthy adult male and female subjects was conducted to evaluate the pharmacokinetics, safety, and tolerability of Sitagliptin.

Patients with renal insufficiency excluding ESRD patients were to receive a single 50 mg dose of Sitagliptin and ESRD patients were to receive 2 doses separated by at least a 1-week washout interval.

All of the 30 treated subjects (24 patients with renal insufficiency, 6 healthy subjects) were included in the pharmacokinetic and safety analyses.

Pharmacokinetic parameters are shown in Table 6.

Table 6. Sitagliptin pharmacokinetic parameters following single oral doses of Sitagliptin by degree of renal insufficiency (foreigners)

Parameter	Normal (n = 82*)	Mild renal insufficiency (n = 6)		Moderate renal insufficiency (n = 6)		Severe renal insufficiency (n = 6)		ESRD (n = 6)	
	Mean	Mean	Mean ratio** [90% CI]	Mean	Mean ratio** [90% CI]	Mean	Mean ratio** [90% CI]	Mean	Mean ratio** [90% CI]
AUC _{0-∞} (μM·h)***	4.40	7.09	1.61 [1.43, 1.81]	9.96	2.26 [2.02, 2.53]	16.6	3.77 [3.37, 4.22]	19.8	4.50 [4.03, 5.03]
C _{max} (nM)	391	527	1.35 [1.15, 1.58]	560	1.43 [1.23, 1.67]	684	1.75 [1.51, 2.03]	556	1.42 [1.22, 1.65]
C _{24h} (nM)	43.7	83.3	1.91 [1.60, 2.28]	129	2.96 [2.50, 3.50]	228	5.22 [4.42, 6.16]	260	5.95 [5.04, 7.02]
t _{max} (h)	3.0	3.0	P = 0.303	3.0	P = 0.771	3.5	P = 0.696	5.0	P = 0.027
t _{1/2} (h)	13.1	16.1	P = 0.011	19.1	P < 0.001	22.5	P < 0.001	28.4	P < 0.001
f _{e,0-∞}	0.76	0.84	0.09 [0.01, 0.16]	0.64	-0.12 [-0.18, -0.05]	0.52	-0.24 [-0.30, -0.17]	NA	NA
Cl _R (mL/min)	339	242	0.71 [0.63, 0.81]	126	0.37 [0.33, 0.42]	60.2	0.18 [0.16, 0.20]	NA	NA

Geometric least-squares mean for AUC_{0-∞}, C_{max}, C_{24h}, and Cl_R; median for t_{max}; harmonic mean for t_{1/2}; arithmetic least-squares mean of fraction of dose excreted unchanged in urine extrapolated to infinity for f_{e,0-∞}

ESRD: Patients with hemodialysis at 48 hours post-dose, t_{1/2}: terminal phase elimination half-life, NA: not applicable; urine was not collected for ESRD patients on hemodialysis

* Including the data from Studies P001, P002, P003, P006, P008, P013, P017, P027, P029, P033, and P037. Sample size for AUC_{0-∞} was 151 and 58 for f_{e,0-∞} and Cl_R.

** Geometric mean ratio (renal insufficiency/normal); arithmetic mean difference reported for f_{e,0-∞}; CI = confidence interval

*** Dose-adjusted to 50 mg (single oral doses of 1.5-600 mg) for historical controls.

With decreasing renal function, the AUC_{0-∞} increased and the Cl_R decreased. While the t_{max} was not altered markedly in patients with renal insufficiency, the t_{1/2} was prolonged with decreasing renal function. As compared to subjects with normal renal function, an approximately 1.6-fold increase in the AUC_{0-∞} was observed in patients with mild renal insufficiency, an approximately 2.3-fold increase was observed in patients with moderate renal insufficiency, an approximately 3.8-fold increase was observed in patients with severe renal insufficiency, and an approximately 4.5-fold increase was observed in ESRD patients requiring hemodialysis.

Analysis was performed using an analysis of covariance (ANCOVA) model with C_{CR} as a continuous variable. As a result, the AUC_{0-∞}, C_{max}, and C_{24h} are correlated with C_{CR} (P < 0.050) and the AUC_{0-∞} geometric mean in subjects with C_{CR} ≥ 50 mL/min was largely ≤ 2-fold the AUC_{0-∞} geometric mean in healthy subjects. Hemodialysis removed Sitagliptin by only a modest extent and the percent of plasma protein binding in patients with renal insufficiency was similar to that in healthy subjects.

Regarding safety, 26 clinical adverse events occurred in 14 subjects. One type 1 diabetes mellitus patient receiving insulin pump therapy had a hypoglycemic symptom, which was classified as an adverse drug reaction. Four other events (1 event of stomach upset, 3 events of headache) were also classified as adverse drug reactions, which were all mild or moderate, transient events. There were no laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(b) Foreign pharmacokinetic study in patients with hepatic insufficiency (5.3.3.2.5, Study Number P017 [■ to ■ 20■], Reference data)

An open-label study in foreign adult male and female patients with moderate hepatic insufficiency (a score of 7-9 on the Child-Pugh's scale) and foreign healthy adult male and female subjects was conducted to evaluate the pharmacokinetics and safety of Sitagliptin.

A single dose of 100 mg of Sitagliptin was to be administered.

All of the 20 treated subjects (10 patients with hepatic insufficiency, 10 healthy subjects) were included in the pharmacokinetic and safety analyses.

Pharmacokinetic parameters are shown in Table 7.

Table 7. Single-dose pharmacokinetic parameters of Sitagliptin in patients with moderate hepatic insufficiency and healthy subjects (control) (foreigners)

Parameter	Moderate hepatic insufficiency patients (n = 10)	Healthy subjects (control) (n = 10)	Mean ratio* [90% CI]
AUC _{0-∞} (μM·h)	11.51	9.49	1.21 [1.01, 1.46]
C _{max} (nM)	1186	1046	1.13 [0.91, 1.42]
t _{max} (h)	1.8	1.5	P = 0.726
t _{1/2} (h)	14.4	13.9	P = 0.691
f _{e,0-∞}	0.689	0.681	0.01 [-0.05, 0.07]
Cl _R (mL/min)	243	292	0.83 [0.68, 1.02]

Least-squares mean for AUC_{0-∞}, C_{max}, and Cl_R; median for t_{max}; harmonic least-squares mean for t_{1/2}; arithmetic least-squares mean of fraction of dose excreted unchanged in urine extrapolated to infinity for f_{e,0-∞}

* Ratio of geometric least-squares means (moderate hepatic insufficiency patients/healthy subjects [control]), difference of arithmetic least-squares means (moderate hepatic insufficiency patients - healthy subjects [control]) for f_{e,0-∞}

The C_{max} and AUC_{0-∞} of Sitagliptin were higher in patients with moderate hepatic insufficiency than in healthy subjects, but without significant difference, which were not considered to be clinically meaningful effects.

Regarding safety, clinical adverse events of mild headache occurred in 1 patient with hepatic insufficiency and 3 healthy subjects, which were all classified as adverse drug reactions. There were no hypoglycaemia, laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(c) Foreign single dose study in elderly males and females/adult females/obese adult males (5.3.3.3.1, Study Number P003 [■ to ■ 20■], Reference data)

A randomized, double-blind, placebo-controlled study in foreign healthy elderly male and female subjects (65-80 years, 10 subjects each), healthy adult female subjects (18-45 years, 8 subjects), and obese adult male subjects (18-45 years, BMI 30-40 kg/m², 10 subjects) was conducted to evaluate the safety, tolerability, and pharmacokinetics of a single dose of Sitagliptin.

A single dose of 50 mg Sitagliptin or placebo was to be administered.

All of the 38 treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analyses.

According to pharmacokinetic analysis, the $AUC_{0-\infty}$ and C_{max} ratios (female/male) with corresponding 90% confidence intervals were 1.07 [0.97, 1.17] and 1.46 [1.23, 1.73], respectively, and female subjects exhibited modestly higher C_{max} values. The $AUC_{0-\infty}$ and C_{max} ratios (elderly/adult) with corresponding 90% confidence intervals were 1.31 [1.19, 1.43] and 1.23 [1.04, 1.46], respectively, and the Cl_R ratio was 0.69 [0.63, 0.77]. Thus, one of the factors contributing to higher plasma concentrations in the elderly was considered to be reduced renal function.

Pharmacodynamic analysis showed that the percent inhibition of plasma DPP-4 activity over time following a single dose was similar across the healthy elderly males and females, healthy adult females, and obese adult males.

Regarding safety, 8 clinical adverse events occurred in 8 subjects following the administration of Sitagliptin, of which 6 events in 6 subjects (1 event of abdominal discomfort, 2 events of somnolence, 3 events of headache) were classified as adverse drug reactions. There were no laboratory adverse events, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

4.(ii).A.(2).4) Drug interaction studies

(a) Drug interaction study with voglibose (5.3.3.4.1, Study Number P046 [■■■ to ■■■ 20■■■])

A randomized, open-label, 3-period, crossover study in Japanese patients with type 2 diabetes mellitus² (target number of cases of 12) was conducted to evaluate the effect of voglibose on the pharmacokinetics and pharmacodynamics of Sitagliptin after multiple co-administration of Sitagliptin and voglibose.

Sitagliptin 100 mg was to be orally administered once daily in the morning in the fasted state for 4 days (“Sitagliptin alone group”), Sitagliptin 100 mg was to be orally administered once daily in the morning in the fasted state and voglibose 0.2 mg was to be orally administered three times daily just before each meal for 4 days (“co-administration group”), or voglibose 0.2 mg was to be orally administered three times daily just before each meal for 4 days (“voglibose alone group”) and a 7-day washout interval was included between periods.

² Patients on diet and exercise therapy who had not received an antidiabetic agent within the previous 3 months, with $HbA_{1C} \geq 6.5\%$ and $< 10.0\%$, fasting blood glucose ≤ 270 mg/dL, and fasting serum C-peptide > 0.7 ng/mL

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

According to pharmacokinetic analysis, the plasma AUC_{0-24} and C_{max} geometric mean ratios (co-administration/Sitagliptin alone) on Treatment Day 3 with corresponding 90% confidence intervals were 0.83 [0.77, 0.89] and 0.66 [0.56, 0.77], respectively, and following co-administration, the exposure was decreased and the median t_{max} (2 hours) was shortened by 1 hour.

According to pharmacodynamic analysis, the percent inhibition of plasma DPP-4 activity over time on Treatment Day 3 was similar between Sitagliptin alone and co-administration and there was a trend towards lower blood glucose levels in a meal tolerance test following coadministration compared to Sitagliptin or voglibose alone.

Regarding safety, clinical adverse events occurred in 2 subjects of the Sitagliptin alone group (2 events) (constipation, pain in extremity), 1 subject of the co-administration group (1 event) (feeling abnormal), and 2 subjects of the voglibose alone group (2 events) (herpes zoster, pharyngitis), but a causal relationship to the study drug was denied for all events. Two laboratory adverse events were reported by 1 subject of the voglibose alone group (AST increased and blood CK increased), but a causal relationship to the study drug was denied for both events. There were no deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(b) Drug interaction study (5.3.3.2.4, Study Number P012 [■■■■ to ■■■■ 20■■■], Reference data)

A randomized, double-blind, placebo-controlled, 3-period, crossover study in foreign patients with type 2 diabetes mellitus was conducted to investigate drug interactions following concomitant administration of multiple doses of Sitagliptin and metformin.

Sitagliptin 50 mg + metformin 1000 mg, Sitagliptin 50 mg + placebo to metformin, and placebo to Sitagliptin + metformin 1000 mg were to be orally administered twice daily for 7 days.

Due to poor placebo compliance in 1 patient, one more patient was additionally enrolled and all of the 13 treated subjects were included in the pharmacokinetic and safety analyses.

According to pharmacokinetic analysis, the plasma metformin AUC_{0-12} and C_{max} geometric mean ratios (metformin + Sitagliptin/metformin) on Treatment Day 7 with corresponding 90% confidence intervals were 1.02 [0.95, 1.09] and 0.97 [0.89, 1.05], respectively, and the plasma Sitagliptin AUC_{0-12} and C_{max} geometric mean ratios (metformin + Sitagliptin/Sitagliptin) with corresponding 90%

confidence intervals were 1.02 [0.97, 1.08] and 1.05 [0.95, 1.15], respectively, indicating that Sitagliptin does not interact with metformin pharmacokinetically.

Regarding safety, 11 clinical adverse events occurred in 2 subjects (gastrointestinal disorders, 1 mild event and 10 moderate events), of which 3 events in 1 subject (all occurred following concomitant administration and 1 of these 3 events was mild in severity) and 1 event in 1 subject (following administration of metformin alone) were classified as adverse drug reactions. There were no hypoglycaemia, laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(c) Drug interaction study with glibenclamide (5.3.3.4.7, Study Number P031 [■■■ to ■■■ 20■■], Reference data)

A randomized, open-label, 2-period, crossover study in foreign healthy adult male and female subjects was conducted to investigate the effect of multiple-dose administration of Sitagliptin on the single-dose pharmacokinetics of glibenclamide.

Subjects were to receive Sitagliptin 200 mg once daily on Days 1 to 6 with a single 1.25-mg dose of glibenclamide co-administered with Sitagliptin on Day 5 or receive a single 1.25-mg dose of glibenclamide on Day 1.

All of the 9 treated subjects were included in the safety analysis, of which 8 subjects excluding 1 subject who discontinued due to consent withdrawal were included in the pharmacokinetic analysis.

According to pharmacokinetic analysis, the glibenclamide $AUC_{0-\infty}$ and C_{max} geometric mean ratios (glibenclamide + Sitagliptin/glibenclamide) with corresponding 90% confidence intervals were 1.09 [0.96, 1.24] and 1.01 [0.84, 1.23], respectively, indicating that Sitagliptin does not affect the pharmacokinetics of glibenclamide.

Regarding safety, 3 clinical adverse events (anxiety and upper respiratory tract infection; light headedness) were noted and the anxiety was classified as an adverse drug reaction, but all events were mild in severity. There were no hypoglycaemia, laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(d) Drug interaction study with simvastatin (5.3.3.4.5, Study Number P025 [■■■ to ■■■ 20■■], Reference data)

A randomized, open-label, 2-period, crossover study in foreign healthy adult male and female subjects was conducted to investigate the effect of multiple-dose administration of Sitagliptin on the

single-dose pharmacokinetics of simvastatin.

Subjects were to receive a single dose of simvastatin 20 mg or Sitagliptin 200 mg once daily on Days 1 to 5 co-administered with a single dose of simvastatin 20 mg on Day 5.

All of the 12 treated subjects were included in the pharmacokinetic and safety analyses.

Pharmacokinetic analysis showed that the AUC_{0-last} and C_{max} geometric mean ratios (simvastatin + Sitagliptin/simvastatin) with corresponding 90% confidence intervals were 1.06 [0.88, 1.26] and 0.94 [0.66, 1.34], respectively, for active HMG-CoA reductase inhibitors, 1.01 [0.80, 1.28] and 0.88 [0.59, 1.31], respectively, for total HMG-CoA reductase inhibitors, 1.12 [0.93, 1.35] and 1.06 [0.86, 1.32], respectively, for simvastatin acid, and 0.85 [0.60, 1.22] and 0.80 [0.51, 1.26], respectively, for simvastatin.

Regarding safety, 29 clinical adverse events occurred in 10 subjects (events with at least 3 occurrences, 10 events of headache and 3 events of sore throat), of which 8 events in 4 subjects (5 events of headache, 1 event of gastric pain, 1 event of stomach heaviness, 1 event of vomiting) were classified as adverse drug reactions, but were all mild or moderate in severity and resolved. As a serious clinical adverse event, pneumonia developed in 1 subject, which persisted for about 2 months and required hospitalization, but the event was judged unlikely related to the study drug. Twenty-two laboratory adverse events occurred in 2 subjects, of which 21 events were those associated with the above-mentioned pneumonia and no serious laboratory adverse events were reported. There were no deaths or adverse events (including laboratory test abnormalities) leading to discontinuation.

(e) Drug interaction study with rosiglitazone (5.3.3.4.8, Study Number P034 [■■■ to ■■■ 20■■], Reference data)

A randomized, open-label, 2-period, crossover study in foreign healthy adult male and female subjects was conducted to investigate the effect of multiple-dose administration of Sitagliptin on the single-dose pharmacokinetics of rosiglitazone.

Subjects were to receive a single dose of rosiglitazone 4 mg in the fasted state or Sitagliptin 200 mg once daily on Days 1 to 5 coadministered with a single dose of rosiglitazone 4 mg on Day 5.

All of the 12 treated subjects were included in the pharmacokinetic and safety analyses.

According to pharmacokinetic analysis, the rosiglitazone $AUC_{0-\infty}$ and C_{max} geometric mean ratios (rosiglitazone + Sitagliptin/rosiglitazone) with corresponding 90% confidence intervals were 0.98 [0.93, 1.02] and 0.99 [0.88, 1.12], respectively, indicating that Sitagliptin does not affect the

pharmacokinetics of rosiglitazone.

Regarding safety, 19 clinical adverse events occurred in 7 subjects (events with at least 3 occurrences, 6 events of headache), of which 10 events in 4 subjects (6 events of headache, 2 events of nausea, 1 event of vomiting, 1 event of warmth) were classified as adverse drug reactions, but were all mild in severity. There were no laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(f) Drug interaction study with digoxin (5.3.3.4.3, Study Number P018 [] to [] 20[]), Reference data)

A randomized, double-blind, placebo-controlled, 2-period, crossover study in foreign healthy adult male and female subjects was conducted to investigate drug interactions following concomitant administration of multiple doses of Sitagliptin and digoxin.

In Part I, 0.25-mg doses of digoxin were to be given concomitantly with 100-mg doses of Sitagliptin or placebo once daily for 10 days. In Part II, 0.25-mg doses of digoxin were to be given concomitantly with 200-mg doses of Sitagliptin or placebo once daily for 10 days.

All of the 36 treated subjects (Part I, 15 subjects; Part II, 21 subjects) were included in the safety analysis, of which 32 subjects (Part I, 12 subjects; Part II, 20 subjects) excluding 3 subjects who discontinued Part I of the clinical study (2 subjects due to consent withdrawal, 1 subject due to pregnancy) and 1 subject who discontinued Part II of the clinical study due to moving out of the area were included in the pharmacokinetic analysis.

Pharmacokinetic analysis showed that the plasma digoxin AUC_{0-24} and C_{max} geometric mean ratios (digoxin + Sitagliptin/digoxin) with corresponding 90% confidence intervals were 1.11 [1.01, 1.21] and 1.18 [1.05, 1.33], respectively, with Sitagliptin 100 mg, and 1.18 [1.08, 1.29] and 1.24 [1.12, 1.36], respectively, with Sitagliptin 200 mg, but the Cl_R of digoxin was not altered.

Regarding safety, in Part I, 44 clinical adverse events occurred in 8 subjects (events with at least 3 occurrences, 15 events of headache, 5 events of dyspnoea, 4 events of dizziness, 4 events of palpitations, 3 events of dysmenorrhoea), of which 10 events in 5 subjects (5 events of headache, 2 events of fatigue, 2 events of dizziness, 1 event of lethargy) were classified as adverse drug reactions, but were all transient and mild or moderate in severity except for 1 severe adverse drug reaction of headache noted in 1 subject treated with digoxin alone. In Part II, 24 clinical adverse events occurred in 11 subjects (events with at least 3 occurrences, 9 events of headache, 5 events of dizziness), of which 15 events in 8 subjects (9 events of headache, 3 events of dizziness, 1 event of nausea, 1 event

of photophobia, 1 event of vomiting) were classified as adverse drug reactions, but were all transient and mild in severity. There were no laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(g) Drug interaction study with warfarin (5.3.3.4.4, Study Number P022 [■■■ to ■■■ 20■■], Reference data)

A randomized, open-label, 2-period, crossover study in foreign healthy adult male and female subjects was conducted to investigate the effect of multiple-dose administration of Sitagliptin on the single-dose pharmacokinetics of warfarin.

A single dose of warfarin 30 mg was to be given on Day 5 during 11 days of once-daily dosing with Sitagliptin 200 mg or a single dose of warfarin 30 mg was to be given on Day 1.

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

Pharmacokinetic analysis showed that the S(-) warfarin $AUC_{0-\infty}$ and C_{max} geometric mean ratios (warfarin + Sitagliptin/warfarin) with corresponding 90% confidence intervals were 0.95 [0.90, 1.02] and 0.89 [0.86, 0.92], respectively, and the R(+) warfarin $AUC_{0-\infty}$ and C_{max} geometric mean ratios with corresponding 90% confidence intervals were 0.99 [0.95, 1.03] and 0.89 [0.86, 0.93], respectively. Pharmacodynamic analysis indicated that the prothrombin time (INR: International Normalized Ratio) AUC_{0-168} and INR_{max} geometric mean ratios (warfarin + Sitagliptin/warfarin) with corresponding 95% confidence intervals were 1.01 [0.96, 1.06] and 1.08 [1.00, 1.17], respectively. Based on the above, Sitagliptin was considered to have no clinically relevant effect on the pharmacokinetics or pharmacodynamics of warfarin.

Regarding safety, 25 clinical adverse events occurred in 8 subjects (events with at least 3 occurrences, 10 events of headache), of which 17 events in 7 subjects (10 events of headache, 2 events of pruritus, 1 event of numbness in right hand, 1 event of numbness in left hand, 1 event of paraesthesia of fingers, 1 event of fatigue, 1 event of nausea) were classified as adverse drug reactions, but were all mild or moderate in severity. There was no treatment discontinuation except 1 subject who discontinued from the clinical study due to a non-serious adverse event (motor vehicle accident). There were no laboratory adverse events, deaths, or serious adverse events (including laboratory test abnormalities).

(h) Drug interaction study with an oral contraceptive (5.3.3.4.6, Study Number P026 [■■■ to ■■■ 20■■], Reference data)

A randomized, placebo-controlled, 2-period, crossover study in foreign healthy adult female subjects was conducted to investigate drug interactions following multiple coadministration of Sitagliptin and an oral contraceptive (ethinyl estradiol [EE₂]/norethisterone [NET]).

The oral contraceptive once daily for 28 days (Days 1-28, oral contraceptive placebo on Days 22-28) was to be coadministered with 200-mg doses of Sitagliptin or matching placebo once daily for 21 days (Days 1-21).

All of the 18 treated subjects were included in the pharmacokinetic and safety analyses.

Pharmacokinetic analysis showed that the plasma EE₂ AUC₀₋₂₄ and C_{max} geometric mean ratios (oral contraceptive + Sitagliptin/oral contraceptive) with corresponding 90% confidence intervals were 0.99 [0.93, 1.06] and 0.97 [0.86, 1.10], respectively, and the plasma NET AUC₀₋₂₄ and C_{max} geometric mean ratios with corresponding 90% confidence intervals were 1.03 [0.97, 1.09] and 0.98 [0.89, 1.07], respectively, indicating that the concomitant administration of Sitagliptin does not affect the pharmacokinetics of the oral contraceptive.

Regarding safety, 38 clinical adverse events occurred in 14 subjects (events with at least 3 occurrences, 10 events of headache, 8 events of drowsiness, 4 events of dizziness, 4 events of nausea, 3 events of diarrhoea), of which 21 events in 11 subjects were observed with co-administration of Sitagliptin and the oral contraceptive. All of the clinical adverse events were classified as adverse drug reactions, but were all mild and transient. There were no laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

(i) Drug interaction study with cyclosporine (5.3.3.4.9, Study Number P037 [■■■ to ■■■ 20■■], Reference data)

A randomized, open-label, 2-period, crossover study in foreign healthy adult male subjects was conducted to investigate the effect of a single dose of cyclosporine on the single-dose pharmacokinetics of Sitagliptin.

A single dose of Sitagliptin 100 mg was to be coadministered with a single dose of cyclosporine 600 mg or a single dose of Sitagliptin 100 mg was to be administered.

All of the 8 treated subjects were included in the pharmacokinetic and safety analyses.

Pharmacokinetic analysis showed that the Sitagliptin $AUC_{0-\infty}$ and C_{max} geometric mean ratios (Sitagliptin + cyclosporine/Sitagliptin) with corresponding 90% confidence intervals were 1.29 [1.24, 1.34] and 1.68 [1.36, 2.08], respectively.

Regarding safety, 2 clinical adverse events occurred in 1 subject (nausea and vomiting), both of which were classified as adverse drug reactions, but were mild and transient. There were no laboratory adverse events, deaths, serious adverse events (including laboratory test abnormalities), or adverse events (including laboratory test abnormalities) leading to discontinuation.

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

4.(ii).B.(1) Use in patients with renal insufficiency

PMDA asked the applicant to investigate factors leading to pharmacokinetic variability, focusing on renal function, in Japanese patients from Japanese phase II clinical studies (A201-203) and then explain the use of Sitagliptin in patients with moderate or severe renal insufficiency.

The applicant responded as follows:

In the phase II clinical studies in Japanese type 2 diabetic patients (A201-203), plasma trough concentrations were measured in 45 patients with mild renal insufficiency ($C_{CR} > 50$ and ≤ 80 mL/min) and 1 patient with moderate renal insufficiency ($C_{CR} > 30$ and ≤ 50 mL/min) and the trough concentrations in Japanese and foreign subjects with normal renal function/patients with mild or moderate renal insufficiency were compared by dosage and dose regimen. As a result, the trough concentrations were comparable and though the Japanese data on moderate renal insufficiency are limited, the value was similar to those reported from the foreign patients. In Study P008 involving foreign patients with renal insufficiency, the Sitagliptin $AUC_{0-\infty}$ in patients with mild renal insufficiency was about 1.6-fold higher than that in subjects with normal renal function. PPK analysis of foreign clinical studies was performed using the data from phase I and phase II clinical studies containing 176 patients with mild renal insufficiency, 8 patients with moderate renal insufficiency, and diabetes mellitus patients, and the effect of renal function on the AUC of Sitagliptin was evaluated. As a result, the Sitagliptin AUC increased 1.09-fold in patients with mild renal insufficiency. Based on Study P008 data and the PPK analysis, it was decided to recommend no dose adjustment for patients with mild renal insufficiency. In Study P008, $AUC_{0-\infty}$ increased 2.3-fold in patients with moderate renal insufficiency and the results of this study, the PPK analysis, and a clinical study in diabetic patients with renal insufficiency (P028) were used as the basis for recommending dose adjustment for patients with moderate renal insufficiency. Therefore, it should be appropriate to establish a dose adjustment recommendation for Japanese patients with renal insufficiency, referring to the dose adjustment recommendation for patients with renal insufficiency overseas.

Concerning the use of Sitagliptin in patients with renal insufficiency, PMDA considers as follows,

from a pharmacokinetic point of view:

Although there is no problem with referring to the results of Foreign Study P008 as a guide for evaluating the effect of renal function on Sitagliptin AUC, the usual dosage is different between Japan and overseas (the approved dosage overseas, 100 mg once daily; the proposed dosage in Japan, 50 mg once daily). If the dose recommended by the applicant (25 mg) is administered to patients with severe renal insufficiency including those requiring hemodialysis, the exposure will be similar to that at the Japanese clinical dose (maximum 100 mg/day) in patients with normal renal function. Although the applicant used the results of Study P008, the PPK analysis of foreign clinical studies, and Study P028 as the basis for determining whether dose adjustment is required for patients with renal insufficiency, the final PPK model presented includes many factors, e.g. factors that are considered correlated with each other (serum creatinine and C_{CR} , body weight and BMI, etc.) as covariates, etc. and modeling of covariates for a PPK model needs more consideration. There are no safety data from Japanese patients with severe renal insufficiency who may also be taking a number of concomitant medications when treated with Sitagliptin over a long period of time at exposures corresponding to the Japanese clinical dose (maximum 100 mg/day) and there is a safety concern about long-term treatment with Sitagliptin. Therefore, at present, the use of Sitagliptin in patients with moderate or severe renal insufficiency should be avoided [see “4.(iii).B.(4).1) Patients with renal insufficiency”].

4.(ii).B.(2) Drug interactions

4.(ii).B.(2).1) Drug interaction studies with voglibose, digoxin, and cyclosporine

(a) While the mean C_{max} ratio of Sitagliptin (Sitagliptin + voglibose/Sitagliptin) was 0.66, the blood glucose-lowering effect of coadministration was greater compared to Sitagliptin alone, (b) the pharmacokinetic changes observed with coadministration of Sitagliptin and digoxin fell outside the pre-specified bounds, and (c) coadministration with cyclosporine resulted in a 1.68-fold increase in the C_{max} of Sitagliptin. Thus, PMDA asked the applicant to explain the necessity of dose adjustment for Sitagliptin when coadministered with these drugs and of including a caution statement in the package insert.³

The applicant responded as follows:

(a) α -glucosidase inhibitory action affected the digestion and absorption of carbohydrates, altering the bacterial spectrum in the gastrointestinal tract, which may have affected the absorption of Sitagliptin. However, there were no major changes in the AUC_{0-24} , indicating that the amount absorbed following

³ The applicant explained that the most relevant pharmacokinetic parameter to assess a clinically meaningful change is AUC based on the mode of action, PK/PD analyses, and clinical efficacy/safety profile of Sitagliptin and the applicant had specified the range for Sitagliptin pharmacokinetic studies for lack of a clinically meaningful change for the AUC geometric mean ratio as 0.5-2. Meanwhile, in some drug interaction studies etc., other bounds that are different from the pre-specified range for Sitagliptin pharmacokinetic studies or the bioequivalence acceptance ranges (as specified in the “Guideline for Bioequivalence Testing of Generic Drugs” [PFSB/ELD Notification No. 1124004 dated November 24, 2006] and the “Methods of Drug Interaction Studies” [PFSB/ELD Notification No. 813 dated June 4, 2001]) were set for assessment. PMDA checked the rationale for these ranges specified by the applicant. In evaluating drug interaction, PMDA assessed the data based on the bioequivalence acceptance ranges as specified in the notification “Methods of Drug Interaction Studies”, and made inquiries about individual deviations of the parameter values, taking into account the efficacy and safety information from the relevant study and other clinical studies, etc.

coadministration was also similar. Based on the data on the percent inhibition of plasma DPP-4 activity on Treatment Day 3 etc., coadministration with voglibose has no clinically meaningful effect on the pharmacokinetics of Sitagliptin. In this study (P046), adverse events of hypoglycaemia etc. were not reported despite that a dose higher than the usual dose of 50 mg was administered. Therefore, there is no need to recommend dose reduction or advise how to manage hypoglycaemia, etc. in the package insert.

(b) The maximum change in digoxin $C_{\max}$ was a 24% increase when coadministered with 200 mg Sitagliptin. The median $t_{\max}$ following coadministration with Sitagliptin was ≤ 1.4 hours post-dose and in view of general sampling points for plasma digoxin concentration monitoring, the increase in $C_{\max}$ following coadministration seems a transient change before the completion of distribution. However, the use of digoxin with a narrow therapeutic window needs to be monitored appropriately when coadministered with Sitagliptin.

(c) In Japan, the safety of Sitagliptin up to 200 mg has been confirmed. Sitagliptin does not inhibit the activities of CYP isoforms. Although Sitagliptin is a substrate for P-gp, taking account of the results of the drug interaction study with digoxin, Sitagliptin is unlikely to have a marked effect on cyclosporine concentrations. Therefore, no dose adjustment for Sitagliptin is required.

PMDA accepted the applicant's response that the changes in the pharmacokinetics of Sitagliptin observed in the drug interaction studies are not clinically relevant problems, taking account of the efficacy and safety information.

4.(ii).B.(2).2 Drug interactions involving OAT3

PMDA asked the applicant to explain the reason for not conducting a drug interaction study with OAT inhibitors such as probenecid, taking account of the *in vitro* study results.

The applicant responded as follows:

Drug interactions with substrates for hOAT1 and hOAT3 were evaluated in *in vitro* experiments. As a result, Sitagliptin did not inhibit ^3H -cidofovir uptake over a concentration range of 0.1 to 500 μM , but it showed weak inhibition of ^3H -cimetidine uptake. The IC_{50} values of Sitagliptin for hOAT1 and hOAT3 were $> 500 \mu\text{M}$ and 160 μM , respectively, which were higher than the $C_{\max}$ after a Sitagliptin 100 mg dose (about 1 μM). The effects of various drugs on hOAT3-mediated Sitagliptin uptake were investigated using CHO-K1 cells expressing hOAT3. As a result, the IC_{50} values of these drugs except for probenecid were higher than their $C_{\max}$ or unbound concentrations and Sitagliptin is unlikely to cause clinically meaningful interactions with these drugs. Since Sitagliptin has a wide safety margin; the PPK analysis of clinical studies showed no meaningful increases in Sitagliptin plasma concentrations despite that about half of the concomitant medications were predominantly renally eliminated drugs; and literature reports indicate that probenecid had no effect on the AUC of a concomitant drug or caused an up to 78% increase in the AUC of a concomitant drug, Sitagliptin is

unlikely to cause clinically meaningful drug interactions with OAT3 inhibitors. According to the post-marketing reports from the product launch in August 2006 until February 2009, there were 2 reports of concomitant use of an OAT inhibitor, but they did not support its clinically meaningful effect on the elimination of Sitagliptin.

PMDA considers as follows:

Based on the submitted *in vitro* study data, clinical study data, overseas post-marketing reports, and literature information, at present, the applicant's response concerning the investigation of drug interactions with OAT inhibitors is acceptable. However, Sitagliptin has a novel mode of action and is expected to be used concomitantly with a number of drugs, e.g. existing oral antihyperglycemic agents and drugs for treatment of underlying diseases, and especially when Sitagliptin is concomitantly used with drugs with similar pharmacokinetic profiles or narrow therapeutic range drugs, careful monitoring is needed. Thus, it is necessary to collect post-marketing information on concomitant medications, especially renally excreted drugs.

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, the results from 5 Japanese phase I clinical studies (P013, A111, A112, P046, P076), 3 Japanese phase II clinical studies (A201-A203), and 5 Japanese phase III clinical studies (P054, P055, ONO-5435-08 to -10) were submitted. As the reference data, the results from the following foreign studies were submitted: 24 phase I clinical studies including a pharmacokinetic study in patients with renal insufficiency (P008) and a pharmacokinetic study in patients with hepatic insufficiency (P017), 4 phase II clinical studies, and 6 phase III clinical studies including a study in patients with type 2 diabetes mellitus and renal insufficiency (P028).

4.(iii).A.(1) Phase I clinical studies

See “4. Clinical data (i) Summary of biopharmaceutic studies and associated analytical methods and (ii) Summary of clinical pharmacology studies” for the results from phase I clinical studies.

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

4.(iii).A.(2).1 Early phase II clinical study (5.3.5.1.1, Study Number A201 [■■■ 20■■■ to ■■■ 20■■■])

A randomized, placebo-controlled, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus⁴ (target number of cases of 126, 63 cases per group) was conducted to evaluate the efficacy and safety of Sitagliptin.

After a 2-week oral administration of placebo once daily before breakfast, placebo or Sitagliptin 100

⁴ Patients on diet and exercise therapy with $HbA_{1C} \geq 6.5\%$ and $< 10.0\%$ who had not received an oral antihyperglycemic agent within the previous 8 weeks or those with $HbA_{1C} \geq 6.0\%$ and $\leq 9.0\%$ who had received a single oral antihyperglycemic agent (an insulin secretagogue, an α -glucosidase inhibitor [α -GI], or a biguanide) within the previous 8 weeks

mg was to be orally administered once daily before breakfast for 12 weeks. A 6-week washout was required for patients on prior oral antihyperglycemic therapy.

All of the 151 treated subjects (76 subjects in the placebo group, 75 subjects in the Sitagliptin 100 mg group) were included in the safety analysis, of which 150 subjects (75 subjects in the placebo group, 75 subjects in the Sitagliptin 100 mg group) excluding 1 subject with no on-treatment data in the placebo group were included in the FAS (Full Analysis Set) for efficacy. Eleven subjects were discontinued from the study (9 subjects in the placebo group, adverse events [including laboratory test abnormalities] [3 subjects], consent withdrawal [1 subject], other reasons [5 subjects]; 2 subjects in the Sitagliptin 100 mg group, other reasons [2 subjects]).

The primary efficacy endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (missing values at Treatment Week 12 were imputed via last observation carried forward [LOCF]) is shown in Table 8. The between-treatment difference in the change with corresponding 95% confidence interval was -1.05 [-1.27, -0.84], showing a significant difference between the groups ($P < 0.001$, analysis of covariance [ANCOVA] including treatment group as a factor and baseline HbA_{1C} as a covariate).

Table 8. Change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) (FAS)

Treatment group	N	Mean (SD) (%)		Change from baseline (Treatment Week 0) (%)	
		Treatment Week 0	Treatment Week 12	Least squares mean	95% CI
Placebo	75	7.69 (0.86)	8.09 (1.04)	0.41	[0.26, 0.56]
Sitagliptin 100 mg	75	7.54 (0.85)	6.90 (1.00)	-0.65	[-0.80, -0.50]
Between treatment comparison		Least squares mean difference		95% CI	P-value
Sitagliptin 100 mg vs. Placebo		-1.05		[-1.27, -0.84]	$P < 0.001$

ANCOVA including treatment group as a factor and baseline HbA_{1C} as a covariate

As to secondary endpoints, the change in fasting blood glucose from baseline to Treatment Week 12 (LOCF) (least squares mean [95% CI]) was -22.5 mg/dL [-28.0, -17.0] in the Sitagliptin 100 mg group and 9.4 mg/dL [3.9, 14.9] in the placebo group and the between-treatment difference with corresponding 95% confidence interval was -31.9 mg/dL [-39.7, -24.1]. The change in body weight from baseline to Treatment Week 12 (LOCF) was -0.1 kg [-0.4, 0.3] in the Sitagliptin 100 mg group and -0.7 kg [-1.0, -0.4] in the placebo group and the between-treatment difference with corresponding 95% confidence interval was 0.7 kg [0.2, 1.1].

Regarding safety, the incidence of clinical adverse events was 64.5% (49 of 76 subjects) in the placebo group and 58.7% (44 of 75 subjects) in the Sitagliptin 100 mg group and the incidence of clinical adverse drug reactions was 3.9% (3 of 76 subjects) and 2.7% (2 of 75 subjects), respectively. Clinical adverse events reported by at least 2 subjects in either group were as shown in Table 9.

Table 9. Clinical adverse events reported by at least 2 subjects in either group (Safety analysis population)

Name of adverse event	Placebo group (n = 76)	Sitagliptin 100 mg group (n = 75)
Nasopharyngitis	35.5 (27)	30.7 (23)
Headache	6.6 (5)	5.3 (4)
Gingivitis	2.6 (2)	4.0 (3)
Diarrhoea	0.0 (0)	2.7 (2)
Gastritis	1.3 (1)	2.7 (2)
Stomach discomfort	1.3 (1)	2.7 (2)
Toothache	2.6 (2)	2.7 (2)
Hordeolum	0.0 (0)	2.7 (2)
Hypoaesthesia	0.0 (0)	2.7 (2)
Upper respiratory tract inflammation	2.6 (2)	2.7 (2)
Constipation	3.9 (3)	1.3 (1)
Back pain	2.6 (2)	1.3 (1)
Periarthritis	2.6 (2)	1.3 (1)
Atrial fibrillation	2.6 (2)	0.0 (0)
Dental caries	2.6 (2)	0.0 (0)
Allergic rhinitis	2.6 (2)	0.0 (0)

Incidence % (N), MedDRA/J ver.7.0

The incidence of laboratory adverse events⁵ was 20.0% (15 of 75 subjects) in the placebo group and 12.0% (9 of 75 subjects) in the Sitagliptin 100 mg group and the incidence of laboratory adverse drug reactions was 2.7% (2 of 75 subjects) in both groups. Laboratory adverse events reported by at least 2 subjects in either group were as shown in Table 10.

Table 10. Laboratory adverse events reported by at least 2 subjects in either group (Safety analysis population)

Name of adverse event	Placebo group (n = 75)	Sitagliptin 100 mg group (n = 75)
Blood potassium increased	0.0 (0)	2.7 (2)
Blood uric acid increased	2.7 (2)	2.7 (2)
White blood cell count increased	1.3 (1)	2.7 (2)
ALT increased	2.7 (2)	1.3 (1)
γGTP increased	4.0 (3)	1.3 (1)
Glucose urine present	2.7 (2)	0.0 (0)
Glycosylated haemoglobin increased	2.7 (2)	0.0 (0)

Incidence % (N),

The number of cases in each treatment group refers to the number of cases with pretreatment and posttreatment laboratory data

MedDRA/J ver.7.0

No deaths were reported. Serious adverse events (including laboratory test abnormalities) were reported in 3 subjects of the placebo group (4 events) (overdose; myocardial infarction; exfoliative dermatitis and cellulitis) and 1 subject of the Sitagliptin 100 mg group (1 event) (overdose), of which exfoliative dermatitis and cellulitis observed in 1 subject of the placebo group were classified as adverse drug reactions. Adverse events (including laboratory test abnormalities) leading to discontinuation were reported in 3 subjects of the placebo group (exfoliative dermatitis and cellulitis [relisted]; headache; glycosylated haemoglobin increased). Hypoglycaemia did not occur in either group. As gastrointestinal symptoms, gastrointestinal disorder occurred in 17.1% of the placebo group (13 of 76 subjects) and 21.3% of the Sitagliptin 100 mg group (16 of 75 subjects), of which 1 case in the Sitagliptin 100 mg group (gastritis) was classified as an adverse drug reaction.

⁵ The denominator is the number of cases with pretreatment and posttreatment laboratory data and the numerator is the number of cases with abnormal changes as judged by the investigator.

4.(iii).A.(2).2) Late phase II clinical study (5.3.5.1.2, Study Number A202 [■■■ 20■■■ to ■■■ 20■■■])

A randomized, placebo-controlled, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus⁶ (target number of cases of 350, 70 cases per group) was conducted to evaluate the dose-response, efficacy, and safety of Sitagliptin 25 mg, 50 mg, 100 mg, and 200 mg once daily.

After a 2-week oral administration of placebo once daily before breakfast, placebo or Sitagliptin 25 mg, 50 mg, 100 mg, or 200 mg was to be orally administered once daily before breakfast for 12 weeks. A 6-week washout was required for patients on prior oral antihyperglycemic therapy.

All of the 363 treated subjects (73 subjects in the placebo group, 80 subjects in the Sitagliptin 25 mg group, 72 subjects in the Sitagliptin 50 mg group, 70 subjects in the Sitagliptin 100 mg group, 68 subjects in the Sitagliptin 200 mg group) were included in the safety analysis and the FAS for efficacy. Twelve subjects were discontinued from the study (5 subjects in the placebo group, lack of efficacy [2 subjects], consent withdrawal [3 subjects]; 3 subjects in the Sitagliptin 25 mg group, lack of efficacy [2 subjects], other reasons [1 subject]; 1 subject in the Sitagliptin 50 mg group, laboratory adverse events; 2 subjects in the Sitagliptin 100 mg group, a laboratory adverse event [1 subject], consent withdrawal [1 subject]; 1 subject in the Sitagliptin 200 mg group, a clinical adverse event).

The primary efficacy endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) is shown in Table 11. Sitagliptin at all doses provided significant reductions in HbA_{1C} compared to placebo, while comparisons among the Sitagliptin dose groups indicated that the reductions in HbA_{1C} at the doses of ≥ 50 mg were similar.

⁶ Patients on diet and exercise therapy with HbA_{1C} $\geq 6.5\%$ and $< 10.0\%$ who had not received an oral antihyperglycemic agent within the previous 8 weeks or those with HbA_{1C} $\geq 6.0\%$ and $\leq 9.0\%$ who had received a single oral antihyperglycemic agent (an insulin secretagogue, α -GI, or a biguanide) within the previous 8 weeks

Table 11. Change in HbA_{1c} from baseline to Treatment Week 12 (LOCF) (FAS)

Treatment group	N	Mean (SD) (%)		Change from baseline (Treatment Week 0) (%)	Sitagliptin groups vs. Placebo group
		Treatment Week 0	Treatment Week 12	Least-squares mean [95% CI]	Least-squares mean difference [95% CI]
Placebo	73	7.74 (0.93)	8.04 (1.24)	0.28 [0.16, 0.40]	—
Sitagliptin 25 mg	80	7.49 (0.82)	7.11 (0.94)	-0.41 [-0.52, -0.29]	-0.69 [-0.85, -0.52]
Sitagliptin 50 mg	72	7.57 (0.84)	6.87 (0.82)	-0.71 [-0.83, -0.59]	-0.99 [-1.16, -0.82]
Sitagliptin 100 mg	70	7.56 (0.80)	6.85 (0.90)	-0.69 [-0.81, -0.56]	-0.96 [-1.14, -0.79]
Sitagliptin 200 mg	68	7.65 (0.82)	6.88 (0.80)	-0.76 [-0.89, -0.64]	-1.04 [-1.21, -0.86]
Dose response analysis*					
Stepwise Linear Contrast Test (Doses included in the current step)				Coefficients of the linear contrast	P-value (one-sided)
Placebo to Sitagliptin 200 mg				-2 -1 0 1 2	<i>P</i> < 0.001
Placebo to Sitagliptin 100 mg				-3 -1 1 3	<i>P</i> < 0.001
Placebo to Sitagliptin 50 mg				-1 0 1	<i>P</i> < 0.001
Placebo to Sitagliptin 25 mg				-1 1	<i>P</i> < 0.001

ANCOVA including dose group and prior therapy (diabetes) status as factors and baseline HbA_{1c} as a covariate

* A stepwise linear contrast test (a closed testing procedure) based on the above ANCOVA model was to be performed. First, a linear contrast test including all 5 groups was performed and if there was a significant difference, it would be determined that there was a difference between the placebo and highest dose groups and a linear contrast test excluding the highest dose group was to be repeated. This procedure was to be repeated until no significant difference was observed and the lowest dose with a significant difference was to be identified as the minimum effective dose.

Regarding safety, the incidence of clinical adverse events was 53.4% (39 of 73 subjects) in the placebo group, 57.5% (46 of 80 subjects) in the Sitagliptin 25 mg group, 65.3% (47 of 72 subjects) in the Sitagliptin 50 mg group, 65.7% (46 of 70 subjects) in the Sitagliptin 100 mg group, and 73.5% (50 of 68 subjects) in the Sitagliptin 200 mg group and the incidence of clinical adverse drug reactions was 4.1% (3 of 73 subjects), 7.5% (6 of 80 subjects), 4.2% (3 of 72 subjects), 7.1% (5 of 70 subjects), and 1.5% (1 of 68 subjects), respectively. Clinical adverse events reported by at least 3% of subjects in any group were as shown in Table 12.

Table 12. Clinical adverse events reported by at least 3% of subjects in any group (safety analysis population)

Name of adverse event	Placebo group (n = 73)	Sitagliptin 25 mg group (n = 80)	Sitagliptin 50 mg group (n = 72)	Sitagliptin 100 mg group (n = 70)	Sitagliptin 200 mg group (n = 68)
Nasopharyngitis	23.3 (17)	20.0 (16)	22.2 (16)	32.9 (23)	17.6 (12)
Upper respiratory tract inflammation	4.1 (3)	3.8 (3)	4.2 (3)	2.9 (2)	5.9 (4)
Hypoglycaemia	2.7 (2)	1.3 (1)	4.2 (3)	4.3 (3)	4.4 (3)
Allergic rhinitis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	4.4 (3)
Eczema	0.0 (0)	0.0 (0)	4.2 (3)	1.4 (1)	4.4 (3)
Feeling abnormal	1.4 (1)	3.8 (3)	0.0 (0)	0.0 (0)	2.9 (2)
Pharyngitis	0.0 (0)	0.0 (0)	2.8 (2)	5.7 (4)	2.9 (2)
Hypertension	1.4 (1)	2.5 (2)	1.4 (1)	4.3 (3)	2.9 (2)
Constipation	4.1 (3)	7.5 (6)	2.8 (2)	4.3 (3)	1.5 (1)
Headache	6.8 (5)	0.0 (0)	1.4 (1)	0.0 (0)	1.5 (1)
Abdominal pain upper	1.4 (1)	3.8 (3)	0.0 (0)	2.9 (2)	0.0 (0)

Incidence % (N), MedDRA/J ver.8.0

The incidence of laboratory adverse events was 11.0% (8 of 73 subjects) in the placebo group, 18.8% (15 of 80 subjects) in the Sitagliptin 25 mg group, 19.4% (14 of 72 subjects) in the Sitagliptin 50 mg group, 17.1% (12 of 70 subjects) in the Sitagliptin 100 mg group, and 11.8% (8 of 68 subjects) in the

Sitagliptin 200 mg group and the incidence of laboratory adverse drug reactions was 2.7% (2 of 73 subjects), 3.8% (3 of 80 subjects), 8.3% (6 of 72 subjects), 1.4% (1 of 70 subjects), and 2.9% (2 of 68 subjects), respectively. Laboratory adverse events reported by at least 3% of subjects in any group were as shown in Table 13.

Table 13. Laboratory adverse events reported by at least 3% of subjects in any group (Safety analysis population)

Name of adverse event	Placebo group (n = 73)	Sitagliptin 25 mg group (n = 80)	Sitagliptin 50 mg group (n = 72)	Sitagliptin 100 mg group (n = 70)	Sitagliptin 200 mg group (n = 68)
Protein urine present	0.0 (0)	2.5 (2)	0.0 (0)	4.3 (3)	4.4 (3)
Blood CK increased	2.7 (2)	8.8 (7)	2.8 (2)	1.4 (1)	1.5 (1)
ALT increased	1.4 (1)	0.0 (0)	5.6 (4)	0.0 (0)	0.0 (0)
AST increased	1.4 (1)	0.0 (0)	4.2 (3)	0.0 (0)	0.0 (0)

Incidence % (N), MedDRA/J ver.8.0

No deaths were reported. Serious adverse events (including laboratory test abnormalities) were reported in 1 subject of the Sitagliptin 50 mg group (1 event) (angina pectoris) and 2 subjects of the Sitagliptin 200 mg group (4 events) (chronic cardiac failure, hypertensive heart disease, and myocardial ischaemia; overdose), but none of these events required special treatment and their causal relationship to the study drug was denied. Adverse events (including laboratory test abnormalities) leading to discontinuation were observed in 1 subject of the Sitagliptin 50 mg group (AST increased, ALT increased, γ GTP increased), 1 subject of the Sitagliptin 100 mg group (protein urine present), and 1 subject of the Sitagliptin 200 mg group (myocardial ischaemia, which was also reported as a serious adverse event), all of which resolved after study drug discontinuation. The incidence of hypoglycaemia was 2.7% (2 of 73 subjects) in the placebo group, 1.3% (1 of 80 subjects) in the Sitagliptin 25 mg group, 4.2% (3 of 72 subjects) in the Sitagliptin 50 mg group, 4.3% (3 of 70 subjects) in the Sitagliptin 100 mg group, and 4.4% (3 of 68 subjects) in the Sitagliptin 200 mg group, of which 6 cases (1 case in the placebo group, 1 case in the Sitagliptin 50 mg group, 3 cases in the Sitagliptin 100 mg group, 1 case in the Sitagliptin 200 mg group) were classified as adverse drug reactions, but all resolved without discontinuing the study drug. The incidence of gastrointestinal symptoms (nausea, vomiting, diarrhoea) was 1.4% in the placebo group (diarrhoea [1 of 73 subjects]), 3.8% in the Sitagliptin 25 mg group (vomiting [1 of 80 subjects], diarrhoea [2 of 80 subjects]), 0.0% in the Sitagliptin 50 mg group (0 of 72 subjects), 0.0% in the Sitagliptin 100 mg group (0 of 70 subjects), and 4.4% in the Sitagliptin 200 mg group (nausea [1 of 80 subjects], diarrhoea [2 of 68 subjects]), but a causal relationship to the study drug was denied for all cases.

4.(iii).A.(2).3) Phase II clinical study -Evaluation of glucose-lowering effect- (5.3.5.1.3, Study Number A203 [■ 20■ to ■ 20■])

A randomized, placebo-controlled, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus⁷ (target number of cases of 60, 20 cases per group) was

⁷ Patients on diet and exercise therapy with HbA_{1c} $\geq$ 6.5% and < 10.0% who had not received an oral antihyperglycemic agent within the previous 8 weeks or those with HbA_{1c} $\geq$ 6.0% and $\leq$ 9.0% who had received a single oral antihyperglycemic agent (an insulin secretagogue, α -GI, or a biguanide) within the previous 8 weeks

conducted to evaluate the blood glucose-lowering effect of Sitagliptin.

After a 2-week oral administration of placebo twice daily before meal (3 tablets before breakfast, 1 tablet before evening meal), subjects were randomized to receive placebo, Sitagliptin 100 mg once daily (“Sitagliptin 100 mg q.d. group”), or Sitagliptin 50 mg twice daily (“Sitagliptin 50 mg b.i.d. group”) and study drug was to be orally administered twice daily before meal (3 tablets before breakfast, 1 tablet before evening meal) for 4 weeks. A 6-week washout was required for patients on prior oral antihyperglycemic therapy.

All of the 80 treated subjects (28 subjects in the placebo group, 27 subjects in the Sitagliptin 100 mg q.d. group, 25 subjects in the Sitagliptin 50 mg b.i.d. group) were included in the safety analysis, of which 76 subjects (27 subjects in the placebo group, 25 subjects in the Sitagliptin 100 mg q.d. group, 24 subjects in the Sitagliptin 50 mg b.i.d. group) excluding 2 subjects who discontinued the study (1 subject in the placebo group due to lack of efficacy; 1 subject in the Sitagliptin 100 mg q.d. group who could not continue to take study drug due to spoiled study drugs) and 2 subjects who took incorrect study drug (1 subject each in the Sitagliptin 100 mg q.d. group and Sitagliptin 50 mg b.i.d. group) were included in the PPS (Per Protocol Set) for primary efficacy analysis.

The primary efficacy endpoint of the change in 24-hour weighted mean glucose from baseline to Treatment Week 4 is shown in Table 14. Both the Sitagliptin 100 mg q.d. group and the Sitagliptin 50 mg b.i.d. group had significant reductions compared to the placebo group ($P < 0.001$ for both, ANCOVA including treatment group as a factor and baseline 24-hour weighted mean glucose as a covariate), but there was no significant difference between the Sitagliptin groups ($P = 0.146$).

Table 14. Change in 24-hour weighted mean glucose from baseline to Treatment Week 4 (PPS)

Treatment group	N	Mean (SD) (mg/dL)		Change from baseline (Treatment Week 0) (mg/dL)		
		Treatment Week 0	Treatment Week 4	Mean (SD)	Least-squares mean	95% CI for least-squares mean
Placebo	27	191.3 (41.6)	182.8 (37.4)	-8.5 (19.7)	-9.0	[-14.8, -3.2]
Sitagliptin 100 mg q.d.	25	197.6 (57.0)	161.1 (33.8)	-36.5 (29.1)	-34.9	[-40.9, -28.9]
Sitagliptin 50 mg b.i.d.	24	189.6 (47.4)	162.1 (36.7)	-27.5 (14.8)	-28.6	[-34.7, -22.4]
Between group comparisons		Least-squares mean difference		95% CI		P-value
Sitagliptin 100 mg q.d. vs. Placebo		-25.9		[-34.2, -17.5]		$P < 0.001$
Sitagliptin 50 mg b.i.d. vs. Placebo		-19.5		[-28.0, -11.1]		$P < 0.001$
Sitagliptin 100 mg q.d. vs. Sitagliptin 50 mg b.i.d.		-6.4		[-15.0, 2.3]		$P = 0.146$

q.d.: once daily, b.i.d.: twice daily

ANCOVA including treatment group as a factor and baseline 24-hour weighted mean glucose as a covariate

No adjustment for multiplicity of comparisons between groups was performed.

As to the secondary endpoints of the change in fasting blood glucose from baseline to Treatment Week

4 (Table 15) and the change in 2-hour post-prandial blood glucose (breakfast, lunch, evening meal) from baseline to Treatment Week 4 (Table 16), both the Sitagliptin 100 mg q.d. group and the Sitagliptin 50 mg b.i.d. group had significant reductions compared to the placebo group, but there was no significant difference between the Sitagliptin groups (the same ANCOVA model as in the primary efficacy analysis).

Table 15. Change in fasting blood glucose from baseline to Treatment Week 4 (PPS)

Treatment group	N	Mean (SD) (mg/dL)		Change from baseline (Treatment Week 0) (mg/dL)		
		Treatment Week 0	Treatment Week 4	Mean (SD)	Least-squares mean	95% CI for least-squares mean
Placebo	27	159.8 (29.8)	156.5 (29.9)	-3.3 (14.5)	-3.1	[-8.2, 2.0]
Sitagliptin 100 mg q.d.	25	160.7 (41.9)	137.8 (27.1)	-22.9 (22.2)	-22.3	[-27.7, -17.0]
Sitagliptin 50 mg b.i.d.	24	156.5 (42.1)	141.4 (29.5)	-15.2 (17.3)	-16.0	[-21.4, -10.6]
Between group comparisons		Least-squares mean difference		95% CI		P-value
Sitagliptin 100 mg q.d. vs. Placebo		-19.3		[-26.6, -11.9]		$P < 0.001$
Sitagliptin 50 mg b.i.d. vs. Placebo		-12.9		[-20.4, -5.4]		$P < 0.001$
Sitagliptin 100 mg q.d. vs. Sitagliptin 50 mg b.i.d.		-6.3		[-13.9, 1.3]		$P = 0.101$

ANCOVA including treatment group as a factor and baseline fasting blood glucose as a covariate
No adjustment for multiplicity of comparisons between groups was performed.

Table 16. Change in 2-hour post-prandial blood glucose from baseline to Treatment Week 4 (PPS)

Treatment group	After breakfast			After lunch			After evening meal		
	N	Least-squares mean [95% CI]		N	Least-squares mean [95% CI]		N	Least-squares mean [95% CI]	
Placebo	27	-8.2 [-19.6, 3.1]		27	-14.8 [-24.6, -5.1]		27	-12.7 [-23.6, -1.8]	
Sitagliptin 100 mg q.d.	25	-54.5 [-66.3, -42.7]		25	-43.9 [-54.0, -33.7]		25	-33.2 [-44.6, -21.9]	
Sitagliptin 50 mg b.i.d.	24	-42.6 [-54.6, -30.6]		24	-31.0 [-41.4, -20.6]		24	-34.1 [-45.7, -22.5]	
Between group comparisons		Least-squares mean difference [95% CI]	P-value		Least-squares mean difference [95% CI]	P-value		Least-squares mean difference [95% CI]	P-value
Sitagliptin 100 mg q.d. vs. Placebo		-46.3 [-62.7, -29.9]	$P < 0.001$		-29.1 [-43.1, -15.0]	$P < 0.001$		-20.5 [-36.3, -4.7]	$P = 0.012$
Sitagliptin 50 mg b.i.d. vs. Placebo		-34.4 [-50.9, -17.9]	$P < 0.001$		-16.2 [-30.4, -1.9]	$P = 0.027$		-21.4 [-37.3, -5.5]	$P = 0.009$
Sitagliptin 100 mg q.d. vs. Sitagliptin 50 mg b.i.d.		-11.9 [-28.7, 4.9]	$P = 0.163$		-12.9 [-27.5, 1.7]	$P = 0.083$		0.9 [-15.4, 17.1]	$P = 0.915$

ANCOVA including treatment group as a factor and baseline 2-hour post-prandial blood glucose as a covariate
No adjustment for multiplicity of comparisons between groups was performed.

Regarding safety, the incidence of clinical adverse events was 14.3% (4 of 28 subjects) in the placebo group, 14.8% (4 of 27 subjects) in the Sitagliptin 100 mg q.d. group, and 16.0% (4 of 25 subjects) in the Sitagliptin 50 mg b.i.d. group and a causal relationship to the study drug was denied for all events. Clinical adverse events reported by at least 2 subjects in any group were as shown in Table 17.

Table 17. Clinical adverse events reported by at least 2 subjects in any group (Safety analysis population)

Name of adverse event	Placebo group (n = 28)	Sitagliptin 100 mg q.d. group (n = 27)	Sitagliptin 50 mg b.i.d. group (n = 25)
Nasopharyngitis	7.1 (2)	3.7 (1)	4.0 (1)
Overdose	0.0 (0)	3.7 (1)	8.0 (2)

Incidence % (N), MedDRA/J ver:8.0

The incidence of laboratory adverse events was 10.7% (3 of 28 subjects) in the placebo group, 3.7% (1 of 27 subjects) in the Sitagliptin 100 mg q.d. group, and 8.0% (2 of 25 subjects) in the Sitagliptin 50 mg b.i.d. group and the incidence of laboratory adverse drug reactions was 7.1% (2 of 28 subjects), 3.7% (1 of 27 subjects), and 4.0% (1 of 25 subjects), respectively. Laboratory adverse events were as shown in Table 18. Four events in 2 subjects of the placebo group (blood uric acid increased; haematocrit decreased, haemoglobin decreased, and red blood cell count decreased), 1 event in the Sitagliptin 100 mg q.d. group (red blood cell count decreased), and 1 event in the Sitagliptin 50 mg b.i.d. group (blood uric acid increased) were classified as adverse drug reactions.

Table 18. Laboratory adverse events (Safety analysis population)

Name of adverse event	Placebo group (n = 28)	Sitagliptin 100 mg q.d. group (n = 27)	Sitagliptin 50 mg b.i.d. group (n = 25)
Red blood cell count decreased	3.6 (1)	3.7 (1)	0.0 (0)
Blood uric acid increased	3.6 (1)	0.0 (0)	4.0 (1)
Haematocrit decreased	3.6 (1)	0.0 (0)	0.0 (0)
Haemoglobin decreased	3.6 (1)	0.0 (0)	0.0 (0)
White blood cell count increased	0.0 (0)	0.0 (0)	4.0 (1)
Urine ketone body present	3.6 (1)	0.0 (0)	0.0 (0)

Incidence % (N), MedDRA/J ver:8.0

No deaths were reported. Serious adverse events (including laboratory test abnormalities) were observed in 1 subject of the Sitagliptin 100 mg q.d. group (1 event) and 2 subjects of the Sitagliptin 50 mg b.i.d. group (2 events) and all of these cases were reported as overdose due to a suspected mix-up of study drug, but unblinding revealed that only the 1 subject in the Sitagliptin 50 mg b.i.d. group had taken a dose exceeding the maximum dose of Sitagliptin as specified by the protocol. There were no adverse events (including laboratory test abnormalities) leading to discontinuation. Hypoglycaemia was reported in 1 subject of the placebo group. Gastrointestinal symptoms (nausea, vomiting, diarrhoea) were not reported in any group.

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

4.(iii).A.(3).1) Phase III double-blind comparative study (5.3.5.1.4, Study Number P054 [■■■■] 20■■■ to ■■■■ 20■■■))

A randomized, double-blind, parallel-group, voglibose-controlled, comparative study in Japanese patients with type 2 diabetes mellitus⁸ (target number of cases of 310, 155 cases per group) was conducted to compare the efficacy between Sitagliptin and voglibose and evaluate the safety and tolerability of Sitagliptin.

After a 2-week oral administration of placebo, Sitagliptin 50 mg once daily before breakfast (Sitagliptin group) or voglibose 0.2 mg three times daily just before each meal (voglibose group) was to be orally administered for 12 weeks. A 6-week washout was required for patients on prior oral antihyperglycemic therapy.

All of the 319 treated subjects (163 subjects in the Sitagliptin group, 156 subjects in the voglibose group) were included in the safety analysis. Of which 318 subjects (163 subjects in the Sitagliptin group, 155 subjects in the voglibose group) excluding 1 subject with no on-treatment data in the voglibose group were included in the FAS and after excluding a further 17 subjects (8 subjects in the Sitagliptin group — no evaluable data at Treatment Week 12 [6 subjects], non-compliance with study treatment [2 subjects]; 9 subjects in the voglibose group — no evaluable data at Treatment Week 12 [8 subjects], non-compliance with exercise therapy [1 subject]), 301 subjects (155 subjects in the Sitagliptin group, 146 subjects in the voglibose group) were included in the PPS for primary efficacy analysis. Seventeen subjects were discontinued from the study (8 subjects in the Sitagliptin group — clinical adverse events [2 subjects], lack of efficacy [2 subjects], moving out of the area [1 subject], consent withdrawal [3 subjects]; 9 subjects in the voglibose group — clinical adverse events [4 subjects], lack of efficacy [5 subjects]).

The primary efficacy endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 is shown in Table 19. The between-treatment difference in the change with corresponding 95% confidence interval was 0.39% [0.28, 0.51] and as the lower limit of the 95% confidence interval fell above the pre-defined non-inferiority margin (-0.2%), the non-inferiority of Sitagliptin to voglibose has been confirmed. Analysis based on the FAS (LOCF) indicated that the between-treatment difference in the change with corresponding 95% confidence interval was 0.44% [0.30, 0.57] and the results based on the FAS were consistent with those based on the PPS.

⁸ Patients on diet and exercise therapy with HbA_{1C} ≥ 6.5% and < 10.0% who had not received an oral antihyperglycemic agent within the previous 8 weeks or those with HbA_{1C} ≥ 6.0% and ≤ 9.0% who had received a single oral antihyperglycemic agent (an insulin secretagogue or a biguanide) within the previous 8 weeks

Table 19. Change in HbA_{1C} from baseline to Treatment Week 12 (PPS)

Treatment group	N	Mean (SD) (%)		Change from baseline (Treatment Week 0) (%)		
		Treatment Week 0	Treatment Week 12	Mean (SD)	Least-squares mean	95% CI for least-squares mean
Sitagliptin	155	7.74 (0.90)	7.03 (0.78)	-0.71 (0.56)	-0.70	[-0.78, -0.62]
Voglibose	146	7.78 (0.84)	7.45 (0.89)	-0.34 (0.53)	-0.30	[-0.39, -0.22]
Between treatment comparison				Least-squares mean difference		95% CI
Voglibose vs. Sitagliptin				0.39		[0.28, 0.51]

ANCOVA including treatment group and prior antidiabetic agent status as factors and baseline HbA_{1C} as a covariate

The secondary endpoints of the changes in fasting blood glucose and in 2-hour post-prandial blood glucose from baseline to Treatment Week 12 (least-squares mean [95% CI]) were -19.6 mg/dL [-22.8, -16.4] and -51.0 mg/dL [-56.5, -45.4], respectively, in the Sitagliptin group and -8.9 mg/dL [-12.2, -5.5] and -32.2 mg/dL [-37.9, -26.5], respectively, in the voglibose group. The between-treatment difference with corresponding 95% confidence interval was 10.7 mg/dL [6.2, 15.3] and 18.8 mg/dL [10.9, 26.7], respectively.

Regarding safety, the incidence of clinical adverse events was 48.5% (79 of 163 subjects) in the Sitagliptin group and 64.7% (101 of 156 subjects) in the voglibose group and the incidence of clinical adverse drug reactions was 10.4% (17 of 163 subjects) and 26.3% (41 of 156 subjects), respectively. Clinical adverse events reported by at least 3% of subjects in either group were as shown in Table 20.

Table 20. Clinical adverse events reported by at least 3% of subjects in either group (Safety analysis population)

Name of adverse event	Sitagliptin group (n = 163)	Voglibose group (n = 156)
Nasopharyngitis	13.5 (22)	15.4 (24)
Abdominal distension	4.3 (7)	9.0 (14)
Flatulence	4.3 (7)	10.9 (17)
Constipation	3.1 (5)	2.6 (4)
Diarrhoea	2.5 (4)	7.7 (12)
Upper respiratory tract inflammation	1.2 (2)	3.2 (5)

Incidence % (N) , MedDRA/J ver.9.1

The incidence of laboratory adverse events was 6.7% (11 of 163 subjects) in the Sitagliptin group and 16.8% (26 of 155 subjects) in the voglibose group and the incidence of laboratory adverse drug reactions was 2.5% (4 of 163 subjects) and 9.0% (14 of 155 subjects), respectively. Laboratory adverse events reported by at least 2 subjects were blood TG increased (1.8% [3 of 163 subjects]), blood CK increased (1.2% [2 of 163 subjects]), LDL cholesterol increased (1.2% [2 of 163 subjects]), and white blood cell count increased (1.2% [2 of 163 subjects]) in the Sitagliptin group and ALT increased (7.1% [11 of 155 subjects]), blood CK increased (3.9% [6 of 155 subjects]), AST increased (2.6% [4 of 155 subjects]), γ GTP increased (2.6% [4 of 155 subjects]), LDL cholesterol increased (1.9% [3 of 155 subjects]), blood ALP increased (1.9% [3 of 155 subjects]), blood TG increased (1.3%

[2 of 155 subjects]), and urine ketone body present (1.3% [2 of 155 subjects]) in the voglibose group. No deaths were reported. Serious adverse events (including laboratory test abnormalities) were reported in 1 subject of the Sitagliptin group (1 event) (cellulitis) and 2 subjects of the voglibose group (2 events) (foot fracture; Crohn's disease), but a causal relationship to the study drug was denied for all events. Adverse events (including laboratory test abnormalities) leading to discontinuation were observed in 2 subjects of the Sitagliptin group (abdominal distension; dizziness) and 4 subjects of the voglibose group (foot fracture [relisted]; Crohn's disease [relisted]; abdominal pain upper; diarrhoea), all of which resolved after treatment discontinuation. Of these cases, 2 cases in the Sitagliptin group and 2 cases in the voglibose group (abdominal pain upper; diarrhoea) were classified as adverse drug reactions, but were moderate or mild in severity. The incidence of hypoglycemic adverse events was 1.8% (3 of 163 subjects) in the Sitagliptin group and 2.6% (4 of 156 subjects) in the voglibose group and the incidence of adverse drug reactions was 1.2% (2 of 163 subjects) and 1.3% (2 of 156 subjects), respectively. There was no hypoglycaemia leading to discontinuation or clinically relevant hypoglycaemia. The change in body weight from baseline to Treatment Week 12 (mean $\pm$ SD) was -0.27 ± 1.26 kg in the Sitagliptin group and -0.96 ± 1.17 kg in the voglibose group.

4.(iii).A.(3).2 Pioglitazone combination study (5.3.5.1.5, Study Number P055 [■ 20■ to ■ 20■])

A combination study of Sitagliptin with pioglitazone, consisting of a 12-week, randomized, placebo-controlled, double-blind, parallel-group, comparative phase and a 40-week open-label phase, was conducted in Japanese patients with type 2 diabetes mellitus⁹ (target number of cases of 130, 65 cases per group) to evaluate the efficacy and safety of Sitagliptin in combination with pioglitazone and the long-term safety of the combination therapy.

Placebo or Sitagliptin 50 mg during the double-blind phase (12 weeks) and Sitagliptin 50 mg during the open-label phase (40 weeks) were to be orally administered once daily before breakfast. If HbA_{1C} was $\geq 7.0\%$ at or after Treatment Week 24 or fasting blood glucose was ≥ 140 mg/dL at or after Treatment Week 16 and there was no safety problem, the dose of Sitagliptin was to be increased from 50 mg to 100 mg at the next scheduled visit. Subjects were to continue pioglitazone throughout the study period at the same dose as taken at ≥ 16 weeks prior to the start of the double-blind phase (no changes in pioglitazone dose were permitted).

For the double-blind phase (12 weeks), all of the 134 treated subjects (68 subjects in the placebo group, 66 subjects in the Sitagliptin 50 mg group) were included in the safety analysis and the FAS for efficacy. Four subjects were discontinued from the study (1 subject in the placebo group, lack of efficacy; 3 subjects in the Sitagliptin 50 mg group, clinical adverse events [2 subjects], other reasons [1 subjects]).

⁹ Patients with HbA_{1C} $\geq 6.5\%$ and $< 10.0\%$ on pioglitazone at a stable dosage for ≥ 14 weeks and not on any other oral antihyperglycemic agents (insulin secretagogues, α -GI, or biguanides) within the previous 8 weeks or patients with HbA_{1C} $\geq 6.0\%$ and $\leq 9.0\%$ on pioglitazone at a stable dosage for ≥ 8 weeks and on another single oral antihyperglycemic agent within the previous 8 weeks

For the long-term treatment phase (52 weeks), 133 subjects (67 subjects treated with placebo during the double-blind phase [P/S group], 66 subjects treated with Sitagliptin 50 mg during the double-blind phase [S/S group])¹⁰ were included in the safety analysis and the FAS for efficacy. Twenty-five subjects were discontinued from the study (8 subjects in the P/S group, lack of efficacy [8 subjects]; 17 subjects in the S/S group, clinical adverse events [5 subjects], lack of efficacy [9 subjects], consent withdrawal [2 subjects], other reasons [1 subject]). The dose of Sitagliptin was increased to 100 mg by Treatment Week 40 in 83 subjects (41 subjects in the P/S group, 42 subjects in the S/S group).

Efficacy and safety analyses were performed separately for the double-blind phase (Treatment Week 12) and the long-term treatment phase (Treatment Week 52).

The primary efficacy endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) is shown in Table 21 and the Sitagliptin 50 mg group had a significant reduction compared to the placebo group ($P < 0.001$, ANCOVA including treatment group and prior antidiabetic agent status as factors and baseline HbA_{1C} as a covariate).

Table 21. Change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) (FAS)

Treatment group	N	Mean (SD) (%)		Change from baseline (Treatment Week 0) (%)	
		Treatment Week 0	Treatment Week 12	Least-squares mean	95% CI
Placebo	68	7.62 (0.78)	8.03 (1.16)	0.40	[0.26, 0.53]
Sitagliptin 50 mg	66	7.73 (0.89)	7.34 (1.03)	-0.41	[-0.55, -0.27]
Between treatment comparison		Least-squares mean difference		95% CI	P-value
Sitagliptin 50 mg vs. Placebo		-0.81		[-1.00, -0.61]	$P < 0.001$

ANCOVA including treatment group and prior antidiabetic agent (except for pioglitazone) status as factors and baseline HbA_{1C} as a covariate

The changes in HbA_{1C} over time from baseline (Treatment Week 12 for the P/S group; Treatment Week 0 for the S/S group) to Treatment Week 52 in the P/S and S/S groups are presented in Figure 1 and significant reductions from baseline were observed in both groups ($P < 0.001$, a paired t-test) and the effect was maintained until Treatment Week 52. Among the subjects who had their dose increased from 50 mg to 100 mg, the proportion of subjects with an even lower HbA_{1C} value at 12 weeks after their dose increase was 70.0% (56 of 80 subjects, including 31 of 40 subjects in the P/S group and 25 of 40 subjects in the S/S group) and the proportion of subjects achieving an HbA_{1C} $< 7.0\%$ was 35.0% (28 of 80 subjects, including 15 of 40 subjects in the P/S group and 13 of 40 subjects in the S/S group).

¹⁰ Sixty-seven subjects in the P/S group were double-blind phase completers, 66 subjects in the S/S group included 63 double-blind phase completers and 3 double-blind phase withdrawals.

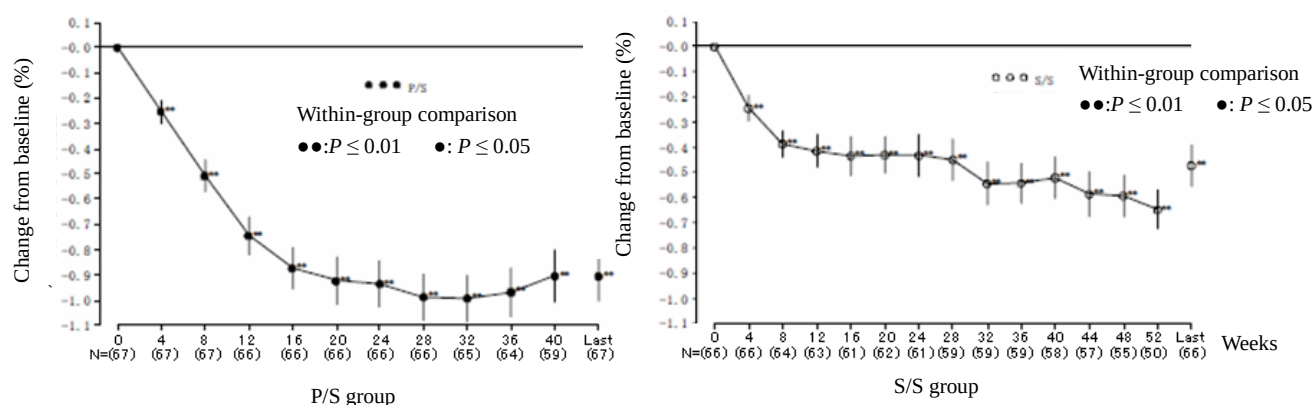


Figure 1. Change in HbA_{1c} (%) over time (FAS) (without LOCF imputation) (Mean ± SE)

Regarding safety in the double-blind phase, the incidence of clinical adverse events was 57.4% (39 of 68 subjects) in the placebo group and 57.6% (38 of 66 subjects) in the Sitagliptin 50 mg group and the incidence of clinical adverse drug reactions was 7.4% (5 of 68 subjects) and 6.1% (4 of 66 subjects), respectively. Clinical adverse events reported by at least 2 subjects in either group were as shown in Table 22.

Table 22. Clinical adverse events reported by at least 2 subjects in either group (Double-blind phase) (Safety analysis population)

Name of adverse event	Placebo group (n = 68)	Sitagliptin group (n = 66)
Nasopharyngitis	25.0 (17)	16.7 (11)
Upper respiratory tract inflammation	4.4 (3)	13.6 (9)
Gastroenteritis	2.9 (2)	4.5 (3)
Hypertension	0.0 (0)	4.5 (3)
Laryngopharyngitis	0.0 (0)	3.0 (2)
Weight increased	0.0 (0)	3.0 (2)
Hypoglycaemia	2.9 (2)	3.0 (2)
Cystitis	2.9 (2)	1.5 (1)
Gastritis	2.9 (2)	0.0 (0)
Hyperglycaemia	2.9 (2)	0.0 (0)
Hypoaesthesia	2.9 (2)	0.0 (0)

Incidence % (N), MedDRA/J ver.9.0

The incidence of laboratory adverse events was 7.4% (5 of 68 subjects) in the placebo group and 7.6% (5 of 66 subjects) in the Sitagliptin 50 mg group and a causal relationship to the study drug was denied for all cases. Laboratory adverse events reported by at least 2 subjects were CK increased in the placebo group (2 subjects, 2.9%) only. No deaths were reported. Serious adverse events (including laboratory test abnormalities) were observed in 1 subject of the placebo group (2 events) (lower limb fracture and ligament injury) and 3 subjects of the Sitagliptin 50 mg group (3 events) (coronary artery stenosis; cerebral infarction; hypertension), but a causal relationship to the study drug was denied for all cases. Treatment was discontinued in the 2 subjects of the Sitagliptin 50 mg group (coronary artery stenosis; cerebral infarction). The incidence of hypoglycemic adverse events was 2.9% (2 of 68 subjects) in the placebo group and 3.0% (2 of 66 subjects) in the Sitagliptin 50 mg group and the 2

cases in the Sitagliptin group were mild in severity. The incidence of adverse events of gastrointestinal symptoms (nausea, vomiting, diarrhoea) was 1.5% in the placebo group (diarrhoea [1 of 68 subjects]) and 1.5% in the Sitagliptin group (diarrhoea [1 of 66 subjects]) and both were not serious. The change in body weight from baseline to Treatment Week 12 (mean $\pm$ SD) was -0.44 ± 1.54 kg in the placebo group and 0.40 ± 1.39 kg in the Sitagliptin 50 mg group.

Regarding safety in the long-term treatment phase, the incidence of clinical adverse events was 80.6% (54 of 67 subjects) in the P/S group and 90.9% (60 of 66 subjects) in the S/S group and the incidence of clinical adverse drug reactions was 4.5% (3 of 67 subjects) and 15.2% (10 of 66 subjects), respectively. Clinical adverse events reported by at least 5% of subjects in either group were as shown in Table 23.

Table 23. Clinical adverse events reported by at least 5% of subjects in either group (Safety analysis population)

Name of adverse event	P/S group* (n = 67)	S/S group (n = 66)	Total (n = 133)
Nasopharyngitis	38.8 (26)	33.3 (22)	36.1 (48)
Upper respiratory tract inflammation	6.0 (4)	22.7 (15)	14.3 (19)
Weight increased	4.5 (3)	10.6 (7)	7.5 (10)
Osteoarthritis	4.5 (3)	7.6 (5)	6.0 (8)
Periodontitis	7.5 (5)	3.0 (2)	5.3 (7)
Hypoaesthesia	6.0 (4)	4.5 (3)	5.3 (7)
Gastritis	7.5 (5)	1.5 (5)	4.5 (6)
Rash (including eczema)	3.0 (2)	6.1 (4)	4.5 (6)
Joint sprain	0.0 (0)	7.6 (5)	3.8 (5)
Contusion	1.5 (1)	6.1 (4)	3.8 (5)
Headache	1.5 (1)	6.1 (4)	3.8 (5)
Hypertension	0.0 (0)	6.1 (4)	3.0 (4)

Incidence % (N), MedDRA/J ver.9.0

* Data from 40-week treatment with Sitagliptin (Treatment Weeks 12-52)

The overall incidences of laboratory adverse events and adverse drug reactions¹¹ for the both groups combined were 26.3% (35 of 133 subjects) and 3.0% (4 of 133 subjects), respectively, and long-term treatment was not associated with increased incidences. Laboratory adverse events with an incidence of at least 5% were CK increased (12.8%) (17 of 133 subjects), blood urine present (100%) (2 of 2 subjects), white blood cells urine positive (100%) (1 of 1 subject), and nitrite urine present (100%) (1 of 1 subject) and laboratory adverse drug reactions reported by at least 2 subjects were ALT increased (1.5%) (2 of 133 subjects). No deaths were reported. Eight serious adverse events (including laboratory test abnormalities) occurred in 7 subjects, of which 4 new serious adverse events were detected during Treatment Weeks 12 to 52 in 3 subjects (pneumothorax traumatic and rib fracture; patella fracture; and enteritis infectious) of the P/S group and 1 new serious adverse event in 1 subject (hepatic neoplasm malignant) of the S/S group, but a causal relationship to the study drug was denied

¹¹ The denominator is the number of cases with pretreatment and posttreatment laboratory data available and the numerator is the number of cases with abnormal changes as judged by the investigator.

for all events. Three new adverse events (including laboratory test abnormalities) leading to discontinuation occurred during Treatment Weeks 12 to 52 in 3 subjects (hepatic neoplasm malignant [relisted]; rash; and sciatica) of the S/S group, of which rash was classified as an adverse drug reaction. The incidence of hypoglycemic adverse events was 3.0% (4 of 133 subjects) and the incidences of adverse events of gastrointestinal symptoms (nausea, vomiting, diarrhoea) were all 0.8% (1 of 133 subjects) and all of these events were mild or moderate in severity. The change in body weight from baseline to Treatment Week 52 (mean $\pm$ SD) was 1.24 ± 1.91 kg in the P/S group and 0.76 ± 2.06 kg in the S/S group.

4.(iii).A.(3).3) Metformin combination study (5.3.5.1.6, Study Number ONO-5435-08 [■■■ 20■■■ to ■■■ 20■■■])

A combination study of Sitagliptin with metformin, consisting of a 12-week, randomized, placebo-controlled, double-blind, parallel-group, comparative phase and a 40-week open-label phase, was conducted in Japanese patients with type 2 diabetes mellitus¹² (target number of cases of 130, 65 cases per group) to evaluate the efficacy and safety of Sitagliptin in combination with metformin and the long-term safety of the combination therapy.

Placebo or Sitagliptin 50 mg during the double-blind phase (12 weeks) and Sitagliptin 50 mg during the open-label phase (40 weeks) were to be orally administered once daily before breakfast. If HbA_{1C} was $\geq 7.0\%$ at or after Treatment Week 24 or fasting blood glucose was ≥ 140 mg/dL at or after Treatment Week 16 and there was no safety problem, the dose of Sitagliptin was to be increased from 50 mg to 100 mg at the next scheduled visit. Subjects were to continue metformin throughout the study period at the same dose as taken at ≥ 12 weeks prior to the start of the double-blind phase (no changes in metformin dose were permitted).

For the double-blind phase (12 weeks), all of the 149 treated subjects (72 subjects in the placebo group, 77 subjects in the Sitagliptin 50 mg group) were included in the safety analysis, of which 147 subjects (71 subjects in the placebo group, 76 subjects in the Sitagliptin 50 mg group) excluding 2 subjects with no data after the start of the study (1 subject each in the placebo group and the Sitagliptin 50 mg group) were included in the FAS for efficacy. Five subjects were discontinued from the study (4 subjects in the placebo group, consent withdrawal [3 subjects], lack of efficacy [1 subject]; 1 subject in the Sitagliptin 50 mg group, deteriorated glycemic control found on the start day of treatment).

For the long-term treatment phase (52 weeks), 145 subjects (68 subjects treated with placebo during the double-blind phase [P/S group], 77 subjects treated with Sitagliptin 50 mg during the double-blind

¹² Patients with HbA_{1C} $\geq 6.5\%$ and $< 10.0\%$ on metformin at a stable dosage for ≥ 10 weeks and not on any other oral antihyperglycemic agents within the previous 8 weeks or patients with HbA_{1C} $\geq 6.0\%$ and $\leq 9.0\%$ on metformin at a stable dosage for ≥ 4 weeks and on another single oral antihyperglycemic agent (excluding pioglitazone) within the previous 8 weeks

phase [S/S group])¹³ were included in the safety analysis, of which 144 subjects (68 subjects in the P/S group, 76 subjects in the S/S group) excluding 1 subject with no on-treatment data in the S/S group were included in the FAS for efficacy. Twenty-three subjects were discontinued from the study (10 subjects in the P/S group, adverse events [including laboratory test abnormalities] [3 subjects], consent withdrawal [3 subjects], lack of efficacy [4 subjects]; 13 subjects in the S/S group, adverse events [including laboratory test abnormalities] [4 subjects], lack of efficacy [6 subjects], moving out of the area [1 subject], other reasons [2 subjects]). The dose of Sitagliptin was increased to 100 mg by Treatment Week 40 in 97 subjects (49 subjects in the P/S group, 48 subjects in the S/S group).

Efficacy and safety analyses were performed separately for the double-blind phase (Treatment Week 12) and the long-term treatment phase (Treatment Week 52).

The primary efficacy endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) is shown in Table 24 and the Sitagliptin 50 mg group had a significant reduction compared to the placebo group ($P < 0.001$, ANCOVA including treatment group and prior antidiabetic agent status as factors and baseline HbA_{1C} as a covariate).

Table 24. Change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) (FAS)

Treatment group	N	Mean (SD) (%)		Change from baseline (Treatment Week 0) (%)	
		Treatment Week 0	Treatment Week 12	Least-squares mean	95% CI
Placebo	71	7.93 (0.94)	8.06 (1.21)	0.30	[0.14, 0.46]
Sitagliptin 50 mg	76	7.72 (0.85)	7.15 (0.85)	-0.39	[-0.56, -0.23]
Between treatment comparison			Least-squares mean difference	95% CI	P-value
Sitagliptin 50 mg vs. Placebo			-0.69	[-0.88, -0.51]	$P < 0.001$

ANCOVA including treatment group and prior antidiabetic agent (except for metformin) status as factors and baseline HbA_{1C} as a covariate

The changes in HbA_{1C} over time from baseline (Treatment Week 12 for the P/S group; Treatment Week 0 for the S/S group) to Treatment Week 52 in the P/S and S/S groups are presented in Figure 2 and significant reductions from baseline were observed in both groups ($P < 0.001$, a paired t-test) and the effect was maintained until Treatment Week 52. Among the subjects who had their dose increased from 50 mg to 100 mg, the proportion of subjects with an even lower HbA_{1C} value at 12 weeks after their dose increase was 66.7% (62 of 93 subjects, including 33 of 45 subjects in the P/S group and 29 of 48 subjects in the S/S group) and the proportion of subjects achieving an HbA_{1C} < 7.0% was 39.8% (37 of 93 subjects, including 16 of 45 subjects in the P/S group and 21 of 48 subjects in the S/S group).

¹³ Sixty-eight subjects in the P/S group were double-blind phase completers, 77 subjects in the S/S group included 76 double-blind phase completers and 1 double-blind phase withdrawal

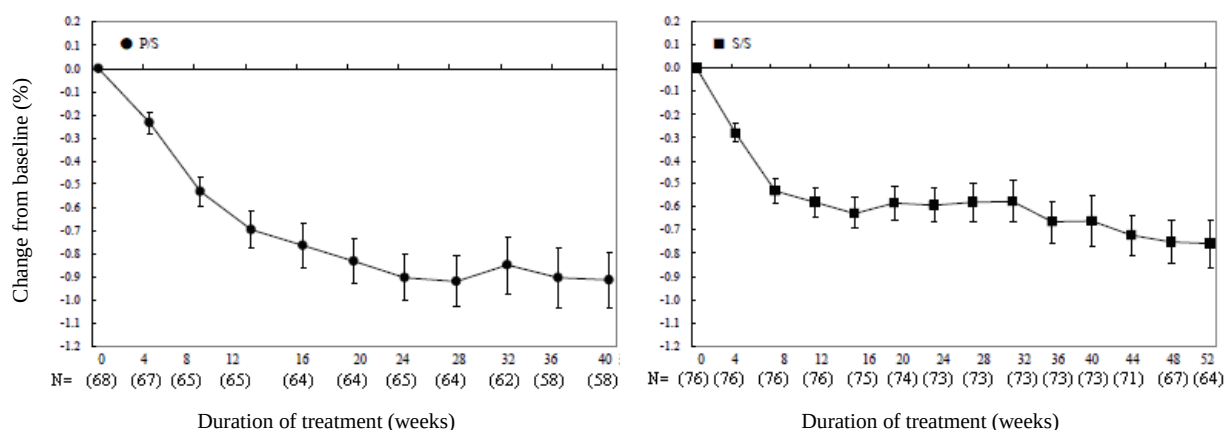


Figure 2. Change in HbA_{1c} (%) over time (FAS) (without LOCF imputation) (Mean ± SE)

Regarding safety in the double-blind phase, the incidence of clinical adverse events was 37.5% (27 of 72 subjects) in the placebo group and 36.4% (28 of 77 subjects) in the Sitagliptin 50 mg group and the incidence of clinical adverse drug reactions was 6.9% (5 of 72 subjects) and 1.3% (1 of 77 subjects), respectively. Clinical adverse events reported in at least 2 subjects of the Sitagliptin 50 mg group and more commonly than in the placebo group were arthralgia (2.6%) (2 of 77 subjects), upper respiratory tract inflammation (3.9%) (3 of 77 subjects), and eczema (2.6%) (2 of 77 subjects). None of the clinical adverse drug reactions in the Sitagliptin 50 mg group occurred in ≥ 2 subjects. The incidence of laboratory adverse events was 6.9% (5 of 72 subjects) in the placebo group and 9.2% (7 of 76 subjects) in the Sitagliptin 50 mg group and the incidence of laboratory adverse drug reactions was 4.2% (3 of 72 subjects) and 5.3% (4 of 76 subjects), respectively. Laboratory adverse events reported in at least 2 subjects of the Sitagliptin 50 mg group and more commonly than in the placebo group were ALT increased, blood TG increased, and γ GTP increased (2.6% [2 of 76 subjects] each). None of the laboratory adverse drug reactions in the Sitagliptin 50 mg group occurred in ≥ 2 subjects. No deaths were reported. Serious adverse events (including laboratory test abnormalities) were reported by 1 subject of the placebo group (1 event) (pneumonia) and 1 subject of the Sitagliptin 50 mg group (1 event) (pneumonia), but a causal relationship to the study drug was denied for both cases. There were no adverse events (including laboratory test abnormalities) leading to discontinuation. Hypoglycaemia was not reported in either group. The incidence of gastrointestinal symptoms (diarrhoea) was 2.8% (2 of 72 subjects) in the placebo group and 1.3% (1 of 77 subjects) in the Sitagliptin 50 mg group and the 1 case in the placebo group only was classified as an adverse drug reaction. The change in body weight from baseline to Treatment Week 12 (mean $\pm$ SD) was -0.29 ± 1.24 kg in the placebo group and 0.42 ± 1.28 kg in the Sitagliptin 50 mg group.

Regarding safety in the long-term treatment phase (52 weeks), the incidence of clinical adverse events was 72.1% (49 of 68 subjects) in the P/S group and 81.8% (63 of 77 subjects) in the S/S group and the incidence of clinical adverse drug reactions was 4.4% (3 of 68 subjects) and 5.2% (4 of 77 subjects), respectively. The incidence of laboratory adverse events was 10.3% (7 of 68 subjects) in the P/S group

and 19.7% (15 of 76 subjects) in the S/S group and the incidence of laboratory adverse drug reactions was 4.4% (3 of 68 subjects) and 7.9% (6 of 76 subjects), respectively. Adverse events (including laboratory adverse events) reported by at least 5% of subjects in either group were as shown in Table 25.

Table 25. Adverse events (including laboratory adverse events) reported by at least 5% of subjects in either group (Safety analysis population)

Name of adverse event	P/S group* (n = 68)	S/S group (n = 77**)	Total (n = 145**)
Nasopharyngitis	27.9 (19)	27.3 (21)	27.6 (40)
γGTP increased	4.4 (3)	7.9 (6)	6.3 (9)
Upper respiratory tract inflammation	5.9 (4)	6.5 (5)	6.2 (9)
ALT increased	4.4 (3)	6.6 (5)	5.6 (8)
Eczema	4.4 (3)	6.5 (5)	5.5 (8)
Back pain	4.4 (3)	5.2 (4)	4.8 (7)
Blood TG increased	0.0 (0)	7.9 (6)	4.2 (6)
Diarrhoea	1.5 (1)	6.5 (5)	4.1 (6)
Rash (including rash papular)	2.9 (2)	5.2 (4)	4.1 (6)
Diabetic retinopathy	1.5 (1)	5.2 (4)	3.4 (5)

Incidence % (N), MedDRA /J ver.9.0

* Data from 40-week treatment with Sitagliptin (Treatment Weeks 12-52)

** For laboratory adverse events, n = 76 in the S/S group and n = 144 in total

One death occurred in the S/S group (aortic dissection), but its causal relationship to the study drug was denied. Ten serious adverse events (including laboratory test abnormalities) occurred in 9 subjects, of which 2 new serious adverse events were detected during Treatment Weeks 12 to 52 in 2 subjects (overdose [200 mg/day]; and loss of consciousness) of the P/S group and 7 new serious adverse events in 6 subjects (pneumonia; lumbar spinal stenosis; colon cancer; aortic dissection [relisted]; prostate cancer; and angina pectoris and duodenal ulcer haemorrhage) of the S/S group, but a causal relationship to the study drug was denied for all events. Adverse events (including laboratory test abnormalities) leading to discontinuation detected during Treatment Weeks 12 to 52 were chest pain; muscular weakness (lower limb); and ALT increased in 3 subjects of the P/S group and aortic dissection (relisted); rash; colon cancer (relisted); and blood creatinine increased in 4 subjects of the S/S group. Of which, chest pain, rash, and ALT increased were classified as adverse drug reactions. Muscular weakness (lower limb) and blood creatinine increased did not resolve even after treatment discontinuation. The incidence of hypoglycemic adverse events was 0.7% (1 of 145 subjects) and the incidence of adverse events of gastrointestinal symptoms was 2.8% (4 of 145 subjects) for nausea, 0.7% (1 of 145 subjects) for vomiting, and 4.1% (6 of 145 subjects) for diarrhoea and all of these events were mild or moderate in severity. The change in body weight from baseline to Treatment Week 52 (mean ± SD) was -0.23 ± 1.86 kg in the P/S group and -0.48 ± 2.11 kg in the S/S group.

4.(iii).A.(3).4 Glimepiride combination study (5.3.5.1.7, Study Number ONO-5435-09 [20 to 20])

A combination study of Sitagliptin with glimepiride, consisting of a 12-week, randomized, placebo-controlled, double-blind, parallel-group, comparative phase and a 40-week open-label phase, was conducted in Japanese patients with type 2 diabetes mellitus¹⁴ (target number of cases of 130, 65 cases per group) to evaluate the efficacy and safety of Sitagliptin in combination with glimepiride and the long-term safety of the combination therapy.

Placebo or Sitagliptin 50 mg during the double-blind phase (12 weeks) and Sitagliptin 50 mg during the open-label phase (40 weeks) were to be orally administered once daily before breakfast. If HbA_{1C} was $\geq 7.0\%$ at or after Treatment Week 24 or fasting blood glucose was ≥ 140 mg/dL at or after Treatment Week 16 and there was no safety problem, the dose of Sitagliptin was to be increased from 50 mg to 100 mg at the next scheduled visit. Subjects were to continue glimepiride throughout the study period at the same dose as taken at ≥ 12 weeks prior to the start of the double-blind phase (no changes in glimepiride dose were permitted).

For the double-blind phase (12 weeks), all of the 138 treated subjects (67 subjects in the placebo group, 71 subjects in the Sitagliptin 50 mg group) were included in the safety analysis, of which 134 subjects (64 subjects in the placebo group, 70 subjects in the Sitagliptin 50 mg group) excluding 4 subjects with no efficacy data (3 subjects in the placebo group, 1 subject in the Sitagliptin 50 mg group) were included in the FAS for efficacy. Nine subjects were discontinued from the study (7 subjects in the placebo group, consent withdrawal [5 subjects], clinical adverse events [2 subjects]; 2 subjects in the Sitagliptin 50 mg group, consent withdrawal [2 subjects]).

For the long-term treatment phase (52 weeks), 131 subjects (60 subjects treated with placebo during the double-blind phase [P/S group], 71 subjects treated with Sitagliptin 50 mg during the double-blind phase [S/S group])¹⁵ were included in the safety analysis, of which 130 subjects (60 subjects in the P/S group, 70 subjects in the S/S group) excluding 1 subject with no on-treatment data in the S/S group were included in the FAS for efficacy. Twenty-three subjects were discontinued from the study (8 subjects in the P/S group, a clinical adverse event [1 subject], lack of efficacy [7 subjects]; 15 subjects in the S/S group, consent withdrawal [3 subjects], moving out of the area [1 subject], lack of efficacy [10 subjects], other reasons [1 subject]). The dose of Sitagliptin was increased to 100 mg by Treatment Week 40 in 110 subjects (49 subjects in the P/S group, 61 subjects in the S/S group).

Efficacy and safety analyses were performed separately for the double-blind phase (Treatment Week

¹⁴ Patients with HbA_{1C} $\geq 7.0\%$ and $< 10.0\%$ on glimepiride at a stable dosage for ≥ 10 weeks and not on any other oral antihyperglycemic agents within the previous 8 weeks or patients with HbA_{1C} $\geq 6.5\%$ and $\leq 9.0\%$ on glimepiride at a stable dosage for ≥ 4 weeks and on other oral antihyperglycemic agents (excluding pioglitazone) within the previous 8 weeks

¹⁵ Sixty subjects in the P/S group were double-blind phase completers, 71 subjects in the S/S group included 69 double-blind phase completers and 2 double-blind phase withdrawals

12) and the long-term treatment phase (Treatment Week 52).

The primary efficacy endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) is presented in Table 26 and the Sitagliptin 50 mg group had a significant reduction compared to the placebo group ($P < 0.001$, ANCOVA including treatment group and prior antidiabetic agent status as factors and baseline HbA_{1C} as a covariate).

Table 26. Change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) (FAS)

Treatment group	N	Mean (SD) (%)		Change from baseline (Treatment Week 0) (%)	
		Treatment Week 0	Treatment Week 12	Least-squares mean	95% CI
Placebo	64	7.90 (0.79)	8.13 (0.80)	0.29	[0.11, 0.47]
Sitagliptin 50 mg	70	8.14 (0.73)	7.54 (0.87)	-0.47	[-0.65, -0.29]
Between treatment comparison		Least-squares mean difference		95% CI	P-value
Sitagliptin 50 mg vs. Placebo		-0.76		[-0.98, -0.55]	$P < 0.001$

ANCOVA including treatment group and prior antidiabetic agent (except for glimepiride) status as factors and baseline HbA_{1C} as a covariate

The changes in HbA_{1C} over time from baseline (Treatment Week 12 for the P/S group, Treatment Week 0 for the S/S group) to Treatment Week 52 in the P/S and S/S groups are presented in Figure 3 and significant reductions from baseline were observed in both groups ($P < 0.001$, a paired t-test) and the effect was maintained until Treatment Week 52. The percentage of discontinuations due to lack of efficacy was 13.1% (17 of 130 subjects). Among the subjects who had their dose increased from 50 mg to 100 mg, the proportion of subjects with an even lower HbA_{1C} value at 12 weeks after their dose increase was 57.8% (63 of 109 subjects, including 30 of 49 subjects in the P/S group and 33 of 60 subjects in the S/S group) and the proportion of subjects achieving an HbA_{1C} $< 7.0\%$ was 24.8% (27 of 109 subjects, including 14 of 49 subjects in the P/S group and 13 of 60 subjects in the S/S group).

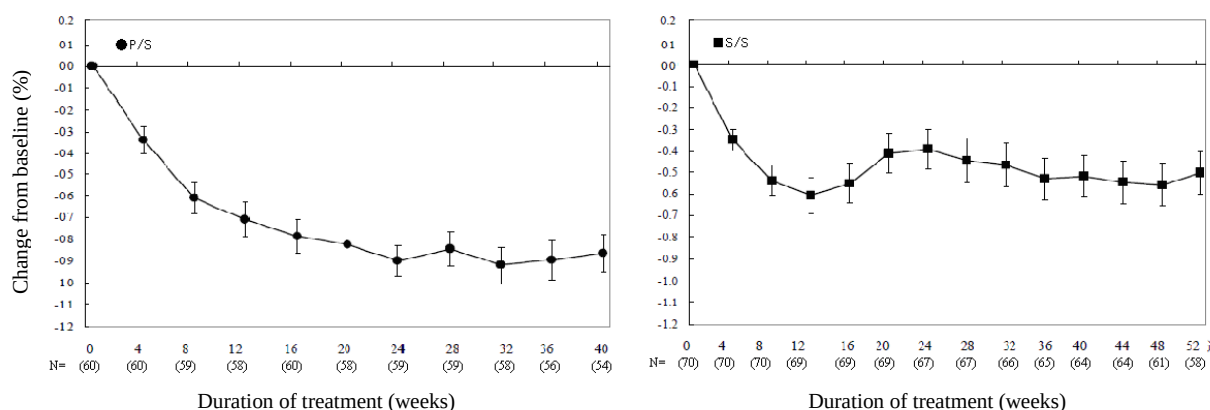


Figure 3. Change in HbA_{1C} (%) over time (FAS) (without LOCF imputation) (Mean $\pm$ SE)

Regarding safety in the double-blind phase, the incidence of clinical adverse events was 50.7% (34 of

67 subjects) in the placebo group and 52.1% (37 of 71 subjects) in the Sitagliptin 50 mg group and the incidence of clinical adverse drug reactions was 6.0% (4 of 67 subjects) and 12.7% (9 of 71 subjects), respectively. Clinical adverse events reported by at least 2 subjects in either group were as shown in Table 27.

Table 27. Clinical adverse events reported by at least 2 subjects in either group (Double-blind phase) (Safety analysis population)

Name of adverse event	Placebo group (n = 67)	Sitagliptin 50 mg group (n = 71)
Nasopharyngitis	23.9 (16)	9.9 (7)
Upper respiratory tract inflammation	6.0 (4)	7.0 (5)
Hypoglycaemia	0.0 (0)	5.6 (4)
Diabetic retinopathy	0.0 (0)	2.8 (2)
Diarrhoea	6.0 (4)	2.8 (2)
Periodontitis	3.0 (2)	2.8 (2)
Electrocardiogram QT prolonged	0.0 (0)	2.8 (2)
Back pain	0.0 (0)	2.8 (2)
Diabetic neuropathy	1.5 (1)	2.8 (2)
Dizziness	3.0 (2)	2.8 (2)
Arteriosclerosis	0.0 (0)	2.8 (2)

Incidence % (N), MedDRA/J ver.9.0

The incidence of laboratory adverse events was 7.6% (5 of 66 subjects) in the placebo group and 8.5% (6 of 71 subjects) in the Sitagliptin 50 mg group and the incidence of laboratory adverse drug reactions was 3.0% (2 of 66 subjects) and 4.2% (3 of 71 subjects), respectively. Laboratory adverse events reported in at least 2 subjects of the Sitagliptin 50 mg group and more commonly than in the placebo group were blood CK increased (4.2%) (3 of 71 subjects). No deaths were reported. Serious adverse events (including laboratory test abnormalities) were reported by 2 subjects of the placebo group (2 events) (acute myocardial infarction; coronary artery stenosis) and 1 subject of the Sitagliptin 50 mg group (1 event) (gastroenteritis), and the 1 case in the Sitagliptin 50 mg group resolved with just drug interruption. The incidence of hypoglycaemia was 5.6% (4 of 71 subjects) in the Sitagliptin 50 mg group, of which 2 cases were classified as adverse drug reactions, but did not lead to study drug discontinuation. The incidence of adverse events of gastrointestinal symptoms (nausea, vomiting, diarrhoea) was 7.5% (vomiting [1 of 67 subjects], diarrhoea [4 of 67 subjects]) in the placebo group and 5.6% (nausea [1 of 71 subjects], vomiting [1 of 71 subjects], diarrhoea [2 of 71 subjects]) in the Sitagliptin 50 mg group. The change in body weight from baseline to Treatment Week 12 (mean $\pm$ SD) was 0.03 ± 1.06 kg in the placebo group and 0.50 ± 0.99 kg in the Sitagliptin 50 mg group.

Regarding safety in the long-term treatment phase, the incidence of clinical adverse events was 73.3% (44 of 60 subjects) in the P/S group and 93.0% (66 of 71 subjects) in the S/S group and the incidence of clinical adverse drug reactions was 18.3% (11 of 60 subjects) and 18.3% (13 of 71 subjects), respectively. The incidence of laboratory adverse events was 18.3% (11 of 60 subjects) in the P/S group and 23.9% (17 of 71 subjects) in the S/S group and the incidence of laboratory adverse drug reactions was 6.7% (4 of 60 subjects) and 11.3% (8 of 71 subjects), respectively. Adverse events

(including laboratory adverse events) reported by at least 5% of subjects in either group were as shown in Table 28.

Table 28. Adverse events (including laboratory adverse events) reported by at least 5% of subjects in either group (Safety analysis population)

Name of adverse event	P/S group* (n = 60)	S/S group (n = 71)	Total (n = 131)
Nasopharyngitis	23.3 (14)	36.6 (26)	30.5 (40)
Hypoglycaemia	11.7 (7)	11.3 (8)	11.5 (15)
Upper respiratory tract inflammation	11.7 (7)	11.3 (8)	11.5 (15)
Blood CK increased	8.3 (5)	7.0 (5)	7.6 (10)
Constipation	11.7 (7)	1.4 (1)	6.1 (8)
Back pain	3.3 (2)	8.5 (6)	6.1 (8)
Dizziness	5.0 (3)	7.0 (5)	6.1 (8)
ALT increased	6.7 (4)	5.6 (4)	6.1 (8)
Vertigo	3.3 (2)	5.6 (4)	4.6 (6)
Diabetic neuropathy	5.0 (3)	4.2 (3)	4.6 (6)
Eczema	5.0 (3)	4.2 (3)	4.6 (6)
Arteriosclerosis	3.3 (2)	5.6 (4)	4.6 (6)
Urinary tract infection (including cystitis and pyuria)	5.0 (3)	4.2 (3)	4.6 (6)
Diarrhoea	1.7 (1)	5.6 (4)	3.8 (5)
Contusion	1.7 (1)	5.6 (4)	3.8 (5)
Diabetic retinopathy	0.0 (0)	5.6 (4)	3.1 (4)
Spinal osteoarthritis	0.0 (0)	5.6 (4)	3.1 (4)
Hypoaesthesia	5.0 (3)	0.0 (0)	2.3 (3)

Incidence % (N), MedDRA/J ver.9.0

* Data from 40-week treatment with Sitagliptin (Treatment Weeks 12-52)

No deaths were reported. Two serious adverse events (including laboratory test abnormalities) were reported in 2 subjects and new serious adverse events detected during Treatment Weeks 12 to 52 were vertigo in 1 subject of the S/S group, but its causal relationship to the study drug was denied. New adverse events (including laboratory test abnormalities) leading to discontinuation detected during Treatment Weeks 12 to 52 were rash in 1 subject of the P/S group, which resolved after treatment discontinuation. The incidence of hypoglycemic adverse events was 11.5% (15 of 131 subjects) and the incidence of adverse events of gastrointestinal symptoms was 3.8% (5 of 131 subjects) for diarrhoea, 2.3% (3 of 131 subjects) for nausea, and 1.5% (2 of 131 subjects) for vomiting and all of these events were mild or moderate in severity. The change in body weight from baseline to Treatment Week 52 (mean $\pm$ SD) was 0.36 ± 1.70 kg in the P/S group and 0.28 ± 2.07 kg in the S/S group.

4.(iii).A.(3).5 Long-term treatment study (5.3.5.2.1, Study Number ONO-5435-10 [REDACTED] 20 [REDACTED] to [REDACTED] 20 [REDACTED])

An open-label, long-term treatment study in Japanese patients with type 2 diabetes mellitus¹⁶ (target

¹⁶ Patients on diet and exercise therapy with HbA_{1c} $\geq$ 6.5% and < 10.0% who had not received an oral antihyperglycemic agent within the previous 8 weeks or those with HbA_{1c} $\geq$ 6.0% and $\leq$ 9.0% who had received a single oral antihyperglycemic agent (an insulin secretagogue, α -GI, or a biguanide) within the previous 8 weeks

number of cases of 150) was conducted to evaluate the safety and tolerability of Sitagliptin 50 mg or 100 mg (if the dose was increased) once daily.

Sitagliptin 50 mg was to be orally administered once daily before breakfast for 52 weeks. If HbA_{1C} was $\geq 7.0\%$ or fasting blood glucose was ≥ 140 mg/dL at or after Treatment Week 12 and there was no safety problem, the dose of Sitagliptin was to be increased from 50 mg to 100 mg at the next scheduled visit.

All of the 177 treated subjects were included in the safety analysis, of which 175 subjects excluding 2 subjects with no on-treatment data were included in the FAS for efficacy. Treatment was discontinued in 38 subjects (consent withdrawal [7 subjects], clinical adverse events [12 subjects], study closure at the relevant site [4 subjects], lack of efficacy [13 subjects], moving out of the area [1 subject], other reasons [Due to a suspected tumor, treatment was discontinued in consideration of the subject's safety] [1 subject]). The dose of Sitagliptin was increased to 100 mg by Treatment Week 52 in 112 subjects.

Concerning efficacy, the change in HbA_{1C} over time from baseline to different timepoints is presented in Figure 4. There were consistent, significant reductions in HbA_{1C} from baseline to Treatment Week 4 and thereafter ($P < 0.001$, a paired t-test) and the effect was maintained until Treatment Week 52.

There was a significant reduction in 2-hour post-prandial blood glucose from baseline to Treatment Week 52 ($P < 0.001$). Among the subjects who had their dose increased from 50 mg to 100 mg, the proportion of subjects with an even lower HbA_{1C} value at 12 weeks after their dose increase was 54.3% (57 of 105 subjects) and the proportion of subjects achieving HbA_{1C} $< 7.0\%$ was 41.0% (43 of 105 subjects).

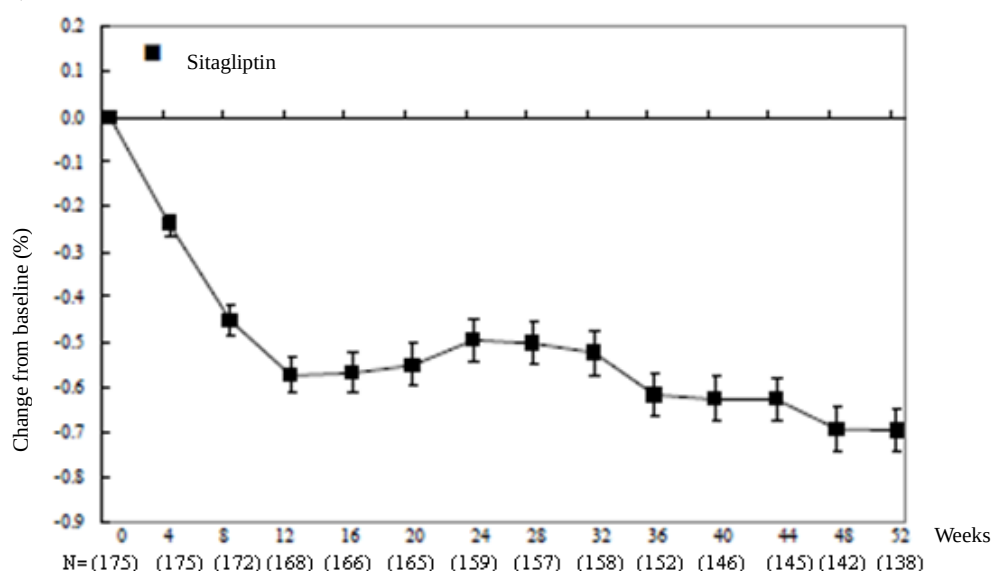


Figure 4. Change in HbA_{1C} (%) over time (FAS) (without LOCF imputation) (Mean ± SE)

Regarding safety, the incidence of clinical adverse events was 78.5% (139 of 177 subjects) and the

incidence of clinical adverse drug reactions was 10.2% (18 of 177 subjects). The incidence of laboratory adverse events was 15.3% (27 of 176 subjects) and the incidence of laboratory adverse drug reactions was 2.3% (4 of 176 subjects). Clinical adverse events with an incidence of $\geq 5\%$ were nasopharyngitis (35.0%) (62 of 177 subjects), constipation (8.5%) (15 of 177 subjects), back pain (5.1%) (9 of 177 subjects), and upper respiratory tract inflammation (5.1%) (9 of 177 subjects). The incidences of specific laboratory adverse events were as shown in Table 29.

Table 29. Laboratory adverse events (Safety analysis population)

Name of adverse event	Sitagliptin group
ALT increased	4.5 (8/176)
γ GTP increased	4.5 (8/176)
AST increased	4.0 (7/176)
Blood bilirubin increased	1.7 (3/176)
Blood uric acid increased	1.7 (3/176)
Blood CK increased	1.1 (2/176)
Blood creatinine increased	0.6 (1/176)
Blood glucose decreased	0.6 (1/176)
Free fatty acids increased	0.6 (1/176)
Haematocrit decreased	0.6 (1/176)
Haemoglobin decreased	0.6 (1/176)
Platelet count decreased	0.6 (1/176)
Red blood cell count decreased	0.6 (1/176)
White blood cell count increased	0.6 (1/176)
Urine human chorionic gonadotropin increased	20.0 (1/5)
Occult blood positive	100 (2/2)

Incidence %, MedDRA/J ver.9.0

The denominator in parenthesis is the number of cases with pretreatment and posttreatment laboratory data available and the numerator in parentheses is the number of cases with abnormal changes as judged by the investigator

One death occurred (acute cardiac failure), but its causal relationship to the study drug was denied. Nineteen serious adverse events (including laboratory test abnormalities) occurred in 18 subjects (large intestine carcinoma [2 subjects]; acute myocardial infarction; myocardial infarction; colonic polyp; gastric cancer; optic ischaemic neuropathy; dehydration; loss of consciousness; cerebral infarction; acute cardiac failure (relisted); neuroma; abdominal pain; hypoaesthesia and vertigo; dizziness; cataract; spinal compression fracture; ischaemic colitis), of which loss of consciousness was classified as an adverse drug reaction. The incidence of adverse events (including laboratory test abnormalities) leading to discontinuation was 6.8% (12 of 177 subjects) (acute cardiac failure; large intestine carcinoma [2 subjects]; optic ischaemic neuropathy; dehydration; loss of consciousness; acute myocardial infarction; myocardial infarction; cerebral infarction; neuroma (all relisted); iron deficiency anaemia; hepatitis C). Of which, loss of consciousness and iron deficiency anaemia were classified as adverse drug reactions. The incidence of hypoglycemic adverse events was 1.7% (3 of 177 subjects) and the incidences of adverse events of gastrointestinal symptoms (nausea, vomiting, diarrhoea) were all 0.6% (1 of 177 subjects). The change in body weight from baseline to Treatment

Week 52 (mean $\pm$ SD) was -0.24 ± 2.14 kg.

4.(iii).A.(3).6 Placebo-controlled comparative study in patients with renal insufficiency [Foreign study] (5.3.5.1.16, Study Number P028 [■ 20■ to ■ 20■ (Phase A), ■ 20■ (Phase B)], Reference data)

A randomized, double-blind study in patients with type 2 diabetes mellitus and chronic renal insufficiency¹⁷ was conducted to evaluate the tolerability and safety of Sitagliptin. The study included 2 periods, i.e. the 12-week, placebo-controlled Phase A and the 42-week, active-controlled Phase B. In Phase A, subjects were stratified by renal function into 2 strata (Stratum 1 and Stratum 2) and randomized in a 1:2 ratio to placebo or Sitagliptin.

Subjects in Stratum 1 ($C_{CR} \geq 30$ to < 50 mL/min) were to be orally administered placebo or Sitagliptin 50 mg once daily before breakfast. Subjects in Stratum 2 ($C_{CR} < 30$ mL/min or end-stage renal disease [on hemodialysis or on peritoneal dialysis]) were to be orally administered placebo or Sitagliptin 25 mg once daily before breakfast. If fasting blood glucose exceeded the reference range on 2 consecutive measurements, an increased dose of insulin or open-label sulfonylurea (SU agent) was to be administered as rescue therapy. In Phase B, if fasting blood glucose at the end of Phase A was ≥ 130 mg/dL, one 5-mg tablet of glipizide was to be added for subjects treated with placebo in Phase A (placebo/glipizide group) and dose increase of up to four 5-mg tablets of glipizide was allowed. However, glipizide was not given to those who had been on insulin at baseline or who had received insulin or SU agent as rescue therapy.

Fifty-six of the 58 subjects in the Sitagliptin group who had completed Phase A, excluding 1 subject with a clinical adverse event and 1 subject who withdrew consent, and 25 subjects in the placebo group excluding 1 subject who discontinued due to an adverse event (glaucoma) before randomization entered Phase B.

In Phase A, 1 subject in the placebo group (due to a preexisting adverse event before randomization) and 7 subjects in the Sitagliptin group (an adverse event [1 subject] [loss of consciousness], other reasons [3 subjects] [1 subject died; 2 subjects used prohibited concomitant medications], consent withdrawal [3 subjects]) were discontinued from the study. After the completion of Phase A, 1 subject with an adverse event (cerebrovascular accident) and 1 subject who withdrew consent in the Sitagliptin group were discontinued from the study. Rescue therapy with glipizide was initiated in 2 subjects in the Sitagliptin group on Day 48 and Day 63, respectively.

¹⁷ Adult type 2 diabetes mellitus patients with moderate renal insufficiency ($C_{CR} \geq 30$ to < 50 mL/min, according to Cockcroft-Gault formula), severe renal insufficiency ($C_{CR} < 30$ mL/min), or end-stage renal disease (on hemodialysis or on peritoneal dialysis) were eligible if they had not been on an oral antihyperglycemic agent for ≥ 6 or 8 weeks with $HbA_{1C} \geq 6.5\%$ and $\leq 10\%$ or they had been on stable insulin monotherapy with $HbA_{1C} \geq 7.5\%$ and $\leq 10\%$ and fasting blood glucose > 130 mg/dL.

In Phase B, 5 subjects in the placebo/glipizide group (adverse events [2 subjects] [prostate cancer; bacteraemia], other reasons [2 subjects] [renal transplant; death], consent withdrawal [1 subject]) and 10 subjects in the Sitagliptin group (adverse events [2 subjects] [pancreatic carcinoma; hyperglycaemia], other reasons [4 subjects] [1 subject used prohibited concomitant medications; 3 subjects died], consent withdrawal [2 subjects], moving out of the area [1 subject], lost to follow-up [1 subject]) were discontinued from the study. The percentage of subjects who did not receive rescue therapy throughout 54 weeks was 84.6% (22 of 26 subjects) in the placebo/glipizide group and 80.0% (52 of 65 subjects) in the Sitagliptin group.

In the primary safety analysis, adverse events occurring before the initiation of rescue therapy were assessed and deaths and non-fatal serious adverse events were all documented. The incidence of clinical adverse events through 54 weeks was 84.6% (22 of 26 subjects) in the placebo/glipizide group and 76.9% (50 of 65 subjects) in the Sitagliptin group. In Phase A, 1 subject in the Sitagliptin group died (sudden death). In Phase B, 1 subject in the placebo/glipizide group (sepsis) and 4 subjects in the Sitagliptin group (death during hemodialysis; myocardial ischaemia; myocardial infarction; pancreatic carcinoma) died. In the placebo/glipizide group, 22 serious adverse events occurred in 10 subjects (abdominal pain upper; prostate cancer; retinopathy; polytraumatism; colon cancer; hypertension; hypertension, pericarditis, renal artery stenosis, hypertension, and thalamic infarction; anaemia, large intestinal haemorrhage, diabetic foot, and urinary tract infection; staphylococcal infection, arteriovenous graft site infection, anaemia, arterial and venous thrombosis, and bacteraemia; coronary artery stenosis and staphylococcal infection). In the Sitagliptin group, 29 serious adverse events occurred in 17 subjects (bronchitis; squamous cell carcinoma of skin; myocardial infarction, myocardial infarction, and cardiac failure congestive; cardiac failure; metastases to liver; pneumonia and gastroenteritis; gastroduodenitis and cerebrovascular accident; hydronephrosis; transient ischaemic attack; cardiac failure; renal failure chronic, acute pulmonary oedema, and hypertensive crisis; urinary tract infection and gastroenteritis; squamous cell carcinoma of skin, supraventricular tachycardia, and acute myocardial infarction; cardiac failure congestive and loss of consciousness; cellulitis; gastroenteritis and hyperglycaemia; pneumonia and pneumonia). Of these serious adverse events, only loss of consciousness in 1 subject of the Sitagliptin group was classified as an adverse drug reaction. Due to serious adverse events, 1 subject in the Sitagliptin group (loss of consciousness) during Phase A and 1 subject in the Sitagliptin group (cerebrovascular accident) after the completion of Phase A were discontinued from the study. In Phase B, 2 subjects in the placebo/glipizide group (prostate cancer; bacteraemia) and 1 subject in the Sitagliptin group (hyperglycaemia) were discontinued from the study. The subject with a serious adverse event of metastases to liver was definitely diagnosed with pancreatic carcinoma later and discontinued from the study and then died. The above-mentioned serious adverse events in 3 subjects (supraventricular tachycardia and acute myocardial infarction; transient ischaemic attack; gastroenteritis and hyperglycaemia) in the Sitagliptin group developed after the initiation of rescue therapy. Clinical adverse events reported by at

least 5% of subjects in the Sitagliptin group were diarrhoea (15.4% [4 of 26 subjects] in the placebo/glipizide group and 9.2% [6 of 65 subjects] in the Sitagliptin group), gastroenteritis (0.0% [0 of 26 subjects] and 6.2% [4 of 65 subjects], respectively), nasopharyngitis (3.8% [1 of 26 subjects] and 6.2% [4 of 65 subjects], respectively), upper respiratory inflammation (19.2% [5 of 26 subjects] and 7.7% [5 of 65 subjects], respectively), urinary tract infection (11.5% [3 of 26 subjects] and 9.2% [6 of 65 subjects], respectively), dizziness (3.8% [1 of 26 subjects] and 6.2% [4 of 65 subjects], respectively), and cough (3.8% [1 of 26 subjects] and 6.2% [4 of 65 subjects], respectively). The incidence of hypoglycemic adverse events was 23.1% (6 of 26 subjects) in the placebo/glipizide group and 4.6% (3 of 65 subjects) in the Sitagliptin group.

Table 30. Clinical adverse events throughout the entire study period*

	Placebo/glipizide group (n = 26)	Sitagliptin group (n = 65)
Adverse events	84.6 (22)	76.9 (50)
Adverse drug reactions	19.2 (5)	12.3 (8)
Deaths	3.8 (1)	7.7 (5)
Serious adverse events	38.5 (10)	27.7 (18)
Serious adverse drug reactions	0.0 (0)	1.5 (1)
Adverse events leading to discontinuation	7.7 (2)	4.6** (3)
Adverse drug reactions leading to discontinuation	0.0 (0)	1.5 (1)
Serious adverse events leading to discontinuation	7.7 (2)	4.6 (3)
Serious adverse drug reactions leading to discontinuation	0.0 (0)	1.5 (1)

Incidence % (N)

* Excluding adverse events occurring after the initiation of rescue therapy

** Excluding 1 subject who discontinued due to the use of prohibited concomitant medications for the treatment of cardiac failure that had developed after the start of study drug administration

Table 31. Laboratory adverse events throughout the entire study period*

	Placebo/glipizide group (n = 26)	Sitagliptin group (n = 65)
Adverse events	30.8 (8)	23.1 (15)
Adverse drug reactions	0.0 (0)	3.1 (2)
Serious adverse events	0.0 (0)	0.0 (0)
Serious adverse drug reactions	0.0 (0)	0.0 (0)
Adverse events leading to discontinuation	0.0 (0)	0.0 (0)
Adverse drug reactions leading to discontinuation	0.0 (0)	0.0 (0)
Serious adverse events leading to discontinuation	0.0 (0)	0.0 (0)
Serious adverse drug reactions leading to discontinuation	0.0 (0)	0.0 (0)

Incidence % (N)

* Excluding adverse events occurring after the initiation of rescue therapy

There were no major differences in the trend of occurrence of adverse events, even when analysis was performed including adverse events occurring after the initiation of rescue therapy.

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

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

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

The applicant responded as follows:

Sitagliptin is an oral antihyperglycemic agent with a new mode of action that selectively inhibits DPP-4 and prevents the inactivation of GLP-1 and GIP. The prevention of the inactivation of these gastrointestinal hormones potentiates glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion, resulting in the improvement of glycemic control, especially, the improvement of post-prandial hyperglycemia, in patients with type 2 diabetes mellitus. Based on its mode of action, Sitagliptin is positioned as a drug that is expected to increase insulin secretion, reduce glucagon release, and improve post-prandial hyperglycemia and is useful for patients with non-insulin-dependent (type 2) diabetes mellitus when used as an initial monotherapy or at an increased dose or in combination with other oral antihyperglycemic agents.

Since Sitagliptin has a novel mode of action and Japanese clinical studies have evaluated the efficacy and safety of Sitagliptin as a monotherapy and in combination with existing oral antihyperglycemic agents with different mode of actions (pioglitazone, metformin, glimepiride) [see “4.(iii).B.(2) Efficacy” and “4.(iii).B.(3) Safety”], PMDA accepted the response, concluding that like existing oral antihyperglycemic agents, Sitagliptin can be chosen as a drug that may be used alone or in combination with other oral antihyperglycemic agents.

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

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

PMDA considers as follows:

A voglibose-controlled, phase III, double-blind comparative study (P054) was conducted. For the primary endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (double-blind phase), the difference between the Sitagliptin (50 mg/day) and voglibose groups with its 95% confidence interval was 0.39% [0.28, 0.51] and as the lower limit of the 95% confidence interval fell above the pre-defined non-inferiority margin (-0.2%), the non-inferiority of Sitagliptin to voglibose has been confirmed. Also in a long-term treatment study (ONO-5435-10), the efficacy of Sitagliptin (50-100 mg/day) was maintained until Treatment Week 52. Therefore, the efficacy of Sitagliptin in monotherapy has been demonstrated. In the case where there is no approved drug with the same mode of action as Sitagliptin in Japan, placebo should be chosen as the control group for a comparative study. However, since voglibose has been commonly used as an oral antihyperglycemic agent in Japan and both Sitagliptin and voglibose are expected to improve post-prandial hyperglycemia etc., there are no particular problems with the choice of voglibose as a control drug for the phase III double-blind comparative study (P054).

4.(iii).B.(2).2 Efficacy in combination therapy with pioglitazone

PMDA asked the applicant to discuss the efficacy by gender and by the dose of pioglitazone in a pioglitazone combination study (P055).

The applicant responded as follows:

Subgroup analyses of Study P055 were performed according to gender and the dose of pioglitazone. For the subgroup analysis according to the dose of pioglitazone, patients treated with 45 mg/day were combined with those treated with 30 mg/day because the number of patients treated with 45 mg/day was small (1 subject in the placebo group, 2 subjects in the Sitagliptin group). For fasting blood glucose and 2-hour post-prandial blood glucose, there were slight differences between the subgroups for the least-squares mean differences between the Sitagliptin and placebo groups in the changes from baseline to Treatment Week 12 (double-blind phase). However, for all efficacy endpoints including HbA_{1C} (Table 32), the 95% confidence intervals for the least-squares mean differences between the Sitagliptin and placebo groups for each subgroup were wide and the interaction between treatment group and each variable (gender, the dose of pioglitazone) was not significant.

Table 32. Change in HbA_{1C} from baseline to Treatment Week 12 (LOCF) (FAS)

	N (Sitagliptin 50 mg group/Placebo group)	Sitagliptin 50 mg group – Placebo group Least-squares mean difference [95% CI]*	P-value Interaction**
Dose of pioglitazone			
15 mg	35/30	-0.8 [-1.1, -0.5]	0.914
30 mg + 45 mg	31/38	-0.8 [-1.1, -0.6]	
Gender			
Females	28/19	-0.8 [-1.1, -0.5]	0.927
Males	38/49	-0.8 [-1.1, -0.5]	

* ANCOVA including treatment group and prior another antidiabetic agent status as factors and baseline HbA_{1C} as a covariate for each subgroup

** ANCOVA including treatment group, prior another antidiabetic agent status, subgroup variable, and treatment-by-subgroup variable interaction as factors and baseline HbA_{1C} as a covariate

As described in the above, the subgroup analyses of Study P055 showed no major differences in the efficacy of Sitagliptin combination therapy with pioglitazone according to gender or the dose of pioglitazone.

PMDA considers as follows:

The pioglitazone combination study (P055) was conducted and for the primary endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (double-blind phase), the difference between the Sitagliptin (50 mg/day) and placebo groups with its 95% confidence interval was -0.81% [-1.00, -0.61], showing a significant reduction in the Sitagliptin group compared to the placebo group and the efficacy of Sitagliptin (50-100 mg/day) was maintained until Treatment Week 52. Therefore, the efficacy of Sitagliptin combination therapy with pioglitazone was demonstrated.

As the applicant explained that there are no major differences in the efficacy of the combination therapy according to gender or the dose of pioglitazone, PMDA accepted the response.

4.(iii).B.(2).3) Efficacy in combination therapy with metformin

PMDA considers as follows:

A metformin combination study (ONO-5435-08) was conducted and for the primary endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (double-blind phase), the difference between the Sitagliptin (50 mg/day) and placebo groups with its 95% confidence interval was -0.69% [-0.88, -0.51], showing a significant reduction in the Sitagliptin group compared to the placebo group and the efficacy of Sitagliptin (50-100 mg/day) was maintained until Treatment Week 52. Therefore, the efficacy of Sitagliptin combination therapy with metformin was demonstrated.

4.(iii).B.(2).4) Efficacy in combination therapy with glimepiride

PMDA considers as follows:

A glimepiride combination study (ONO-5435-09) was conducted and for the primary endpoint of the change in HbA_{1C} from baseline to Treatment Week 12 (double-blind phase), the difference between the Sitagliptin (50 mg/day) and placebo groups with its 95% confidence interval was -0.76% [-0.98, -0.55], showing a significant reduction in the Sitagliptin group compared to the placebo group and the efficacy of Sitagliptin (50-100 mg/day) was maintained until Treatment Week 52. Therefore, the efficacy of Sitagliptin combination therapy with glimepiride was demonstrated.

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

4.(iii).B.(3).1) Risk of hypoglycaemia

Since the risk of hypoglycaemia may differ between monotherapy and combination therapy and among other oral antihyperglycemic agents to be combined with Sitagliptin, PMDA determined that the risk of hypoglycaemia should be assessed by indicated therapy [see “4.(iii).B.(3) Safety” 4)-7)].

4.(iii).B.(3).2) Relationship to tumor development

Since an increased incidence of hepatocellular carcinomas and of hepatocellular adenomas has been observed in a rat 106-week oral carcinogenicity study (4.2.3.4.1.3) and the development of malignant tumors has been reported in Japanese long-term treatment studies of Sitagliptin, PMDA asked the applicant to discuss whether there is a consistent trend in the development of benign, malignant and unspecified neoplasms (including cysts and polyps).

The applicant responded as follows:

Based on pooled data on benign, malignant and unspecified neoplasms (including cysts and polyps) (hereinafter referred to as “tumors etc.”) from 4 Japanese long-term treatment studies (P055, ONO-5435-08 to -10), 10 cases of tumors etc. reported were examined in detail. The 10 cases included

hepatic neoplasm malignant; colon cancer; prostate cancer; seborrhoeic keratosis; uterine leiomyoma; gastric cancer; neuroma; skin papilloma and haemangioma of liver; and large intestine carcinoma (2 cases). Seven serious adverse events were reported in 7 subjects, of which 5 events in 5 subjects led to discontinuation, but a causal relationship to the study drug was denied for all cases. Pooled analysis of foreign clinical studies (12 phase II and phase III studies) was performed based on 6,139 patients with type 2 diabetes mellitus exposed for 18 to 106 weeks. In these studies, the total observation period was 2,994 patient-years for the Sitagliptin group and 2,270 patient-years for the non-Sitagliptin group. The incidence of tumors etc. by treatment group was slightly higher in the Sitagliptin group than in the non-Sitagliptin group (2.2% vs. 1.6%; between-treatment difference with its 95% CI, 0.6 [-0.1, 1.3]). The mean number of days to onset of malignant tumors was 241 days after randomization in the Sitagliptin group and 230 days after randomization in the non-Sitagliptin group. The above results indicate that there is no consistent trend in the development of tumors etc.

PMDA understands that there was no consistent trend in the development of tumors etc. in the Japanese long-term treatment studies, but considers that it is necessary to continue to collect information on the development of tumors etc. after the market launch.

4.(iii).B.(3).3 Relationship to musculoskeletal and connective tissue disorders or cardiac disorders

PMDA asked the applicant to discuss the relationship of increased creatine phosphokinase (CK) observed in Japanese long-term treatment studies with musculoskeletal and connective tissue disorders or cardiac disorders.

The applicant responded as follows:

An adverse event of CK increased occurred in 32 subjects during treatment with Sitagliptin. The cause of CK increased was discussed based on the patient background, test results on safety parameters (ECG and other laboratory parameters, etc.), and the investigators' comments. As a result, an adverse event of CK increased was determined by the investigator to be associated with exercise or physical labor for 22 subjects (28 events). For other 2 subjects, CK increased was determined to be associated with concomitant medications (HMG-CoA reductase inhibitor). For the remaining 10 subjects (including 2 subjects with an adverse event of CK increased during treatment with placebo in the double-blind phase), the cause of CK increased could not be identified, but there were no adverse events categorized as musculoskeletal and connective tissue disorders or cardiac disorders. As the protocol did not require CK isozyme determination, at present, there is no evidence suggesting that CK increased was a sign of cardiovascular disease.

PMDA considers as follows:

The applicant's response is acceptable. However, taking into account that Sitagliptin is likely to be

used concomitantly with drugs known to be associated with musculoskeletal adverse reactions, e.g. HMG-CoA reductase inhibitors, in patients with type 2 diabetes mellitus, it is necessary to collect information on musculoskeletal and connective tissue disorders and cardiac disorders after the market launch.

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

PMDA considers as follows:

In a phase III, double-blind comparative study (P054), no serious adverse drug reactions were reported in the Sitagliptin group, as in the voglibose group and there was also no clinically relevant hypoglycaemia. In a long-term treatment study (ONO-5435-10), of the 19 serious adverse events in 18 subjects, loss of consciousness (1 event) was classified as an adverse drug reaction (causality was determined as “unassessable”), but a causal relationship to Sitagliptin was denied for all other serious adverse events and the incidence of hypoglycaemia was similar to that in Study P054, etc. Therefore, there are no major safety problems with Sitagliptin monotherapy.

4.(iii).B.(3).5) Safety in combination therapy with pioglitazone

It has been reported that the action of elevated GIP on adipocytes is associated with increased insulin resistance (Flatt PR, *Diabetic Med*, 2008; 25: 759-764) and the possible development of oedema should be noted during the use of pioglitazone. Thus, PMDA asked the applicant to discuss the potential for Sitagliptin to increase the cardiovascular risk, when used concomitantly with pioglitazone, by antagonizing the action of pioglitazone on adipocytes.

The applicant responded as follows:

Based on the data from 2 Sitagliptin studies in type 2 diabetic patients who had inadequate glycemic control on pioglitazone monotherapy (Japanese Study P055, Foreign Study P019), adverse events of oedema, cardiovascular disease, or fluid retention (including deterioration of complications) reported during the double-blind phase were examined in detail. In Study P055, adverse events of hypertension, oedema, and weight increased were reported in the Sitagliptin 50 mg group and their incidences were 4.5% (3 of 66 subjects), 1.5% (1 of 66 subjects), and 3.0% (2 of 66 subjects), respectively. All events resolved without study drug discontinuation. Among the 3 subjects with hypertension, 1 subject required hospitalization, which was classified as a serious adverse event and the other 2 cases were reported as hypertension aggravated. As the subjects with hypertension did not experience increased weight or oedema, these cases were not considered to be deterioration of hypertensive complication due to fluid retention. In Study P019, no adverse events of cardiac failure or myocardial ischaemia were reported in the Sitagliptin 100 mg group (175 patients) among the 353 patients with type 2 diabetes mellitus. Oedema occurred in 2 subjects of the Sitagliptin group (1.1%) and 1 subject of the placebo group (0.6%) and peripheral oedema occurred in 7 subjects of the Sitagliptin group (4.0%) and 5 subjects of the placebo group (2.8%). Weight increased was observed in both groups and the

change in body weight was 1.8 kg in the Sitagliptin group and 1.5 kg in the placebo group. The above results indicate that Sitagliptin combination therapy with pioglitazone is unlikely to cause an increased incidence of cardiovascular adverse events or deterioration of cardiovascular complications.

PMDA asked the applicant to discuss the safety by gender and by the dose of pioglitazone in the pioglitazone combination study (P055).

The applicant responded as follows:

Subgroup analyses of Study P055 showed no increases in adverse drug reactions characteristic of pioglitazone with Sitagliptin combination therapy with pioglitazone, etc. as presented in Table 33. Thus, there were no major differences in the safety of the combination therapy according to gender or the dose of pioglitazone.

Table 33. Clinical adverse events and adverse drug reactions (Study P055)

	Pioglitazone 15 mg		Pioglitazone 30 mg + 45 mg	
Treatment group	Placebo	Sitagliptin	Placebo	Sitagliptin
Adverse events	53.3 (16/30)	57.1 (20/35)	60.5 (23/38)	58.1 (18/31)
Adverse drug reactions	3.3 (1/30)	5.7 (2/35)	10.5 (4/38)	6.5 (2/31)
Specific adverse event				
Oedema	0.0 (0/30)	0.0 (0/35)	0.0 (0/38)	3.2 (1/31)
Weight increased	0.0 (0/30)	5.7 (2/35)	0.0 (0/38)	0.0 (0/31)
	Females		Males	
Adverse events	68.4 (13/19)	60.7 (17/28)	53.1 (26/49)	55.3 (21/38)
Adverse drug reactions	5.3 (1/19)	7.1 (2/28)	8.2 (4/49)	5.3 (2/38)
Specific adverse event				
Oedema	0.0 (0/19)	3.6 (1/28)	0.0 (0/49)	0.0 (0/38)
Weight increased	0.0 (0/19)	0.0 (0/28)	0.0 (0/49)	5.3 (2/38)

Incidence % (No. of cases with events/No. of cases included in safety analysis)

PMDA considers that the safety of Sitagliptin combination therapy with pioglitazone was demonstrated because in the pioglitazone combination study (P055), there were no major differences in the occurrence of serious adverse events or adverse drug reactions between the Sitagliptin and placebo groups in the double-blind phase (Treatment Week 12), there was also no clinically relevant hypoglycaemia, and no major differences were seen in the safety profile between the double-blind phase (Treatment Week 12) and Treatment Week 52. As the applicant explained that there are no major differences in the safety of the combination therapy according to gender or the dose of pioglitazone, PMDA accepted the response.

4.(iii).B.(3).6 Safety in combination therapy with metformin

PMDA considers that the safety of Sitagliptin combination therapy with metformin was demonstrated because in a metformin combination study (ONO-5435-08), the safety profile in the double-blind

phase (Treatment Week 12) was similar between the Sitagliptin and placebo groups and there were no particular problems with the safety profile up to Treatment Week 52, including hypoglycaemia and gastrointestinal symptoms.

4.(iii).B.(3).7) Safety in combination therapy with glimepiride

The incidence of hypoglycaemic adverse events in the Sitagliptin group tended to be higher in a glimepiride combination study (ONO-5435-09) than in other combination studies (12-week double-blind phase in the phase III clinical studies, 0%-3% with monotherapy or other combination therapies, 5.6% with combination therapy with glimepiride; throughout the treatment period in the long-term treatment studies, 0.7%-3% with monotherapy or other combination therapies, 11.5% with combination therapy with glimepiride). Thus, PMDA asked the applicant to discuss the relationship between the dose of glimepiride and the occurrence of hypoglycaemia.

The applicant responded as follows:

In Study ONO-5435-09, the number of subjects with hypoglycaemia was small, i.e. 3 subjects, at the doses of 4 to 6 mg/day of glimepiride, while at the doses of 1 to 3 mg/day of glimepiride, there was a trend towards higher incidence of hypoglycaemia with increasing dose of glimepiride (1 mg/day, 7.0%; 2 mg/day, 8.8%; 3 mg/day, 20.7%). However, there was no clear relationship between the severity of hypoglycaemia, the time to onset, and causality and the dose of glimepiride. The reported events of hypoglycaemia were all mild or moderate in severity and none of the patients were discontinued from the study due to an adverse event of hypoglycaemia. Taking account of the above findings, the following caution statement has been included in the Sitagliptin package insert (draft): “When Sitagliptin is used in combination with a sulfonylurea (SU) agent, start with a lower dose of the SU agent may be considered in order to reduce the risk of hypoglycaemia associated with the SU agent.”

PMDA considers that the safety of Sitagliptin combination therapy with glimepiride was demonstrated because in the glimepiride combination study (ONO-5435-09), the incidences of serious adverse events and adverse drug reactions in the double blind phase (Treatment Week 12) were similar between the Sitagliptin and placebo groups, there was no clinically relevant hypoglycaemia, and no major differences were seen in the safety profile between the double-blind phase (Treatment Week 12) and Treatment Week 52. As with overseas labelings, the Japanese package insert (draft) also contains a caution stating that, when Sitagliptin is used in combination with a SU agent, start with a lower dose of the SU agent may be considered in order to reduce the risk of hypoglycaemia. PMDA concluded that such caution statement is appropriate and accepted the response.

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

4.(iii).B.(4).1 Patients with renal insufficiency

PMDA asked the applicant to explain differences in the safety between patients with and without renal insufficiency in Japanese clinical studies.

The applicant responded as follows:

Subgroup analysis was performed by dividing 1,190 subjects across all Japanese clinical studies in patients with type 2 diabetes mellitus according to the presence ($C_{CR} < 80$ mL/min) or absence ($C_{CR} \geq 80$ mL/min) of renal insufficiency. The incidences of clinical adverse events, adverse drug reactions, and serious adverse events in the patients with renal insufficiency were 71.4% (110 of 154 subjects), 9.1% (14 of 154 subjects), and 4.5% (7 of 154 subjects), respectively, which were similar to those in the patients without renal insufficiency, i.e. 66.4% (688 of 1036 subjects), 7.9% (82 of 1036 subjects), and 3.6% (37 of 1036 subjects), respectively. According to the incidences of clinical adverse events, laboratory adverse events, and adverse drug reactions by the presence or absence of renal insufficiency, there was no trend towards an increased incidence of overall adverse events or adverse drug reactions in the patients with renal insufficiency and there was also no trend towards an increased incidence of specific adverse events or adverse drug reactions in the patients with renal insufficiency. Furthermore, based on the data from 6 studies where Sitagliptin was administered in a double-blind manner (12 weeks) (A201, A202, P054, P055, ONO-5435-08, ONO-5435-09), the incidences of clinical adverse events, laboratory adverse events, and adverse drug reactions by dose level (placebo, 25, 50, 100, 200 mg) and by the presence or absence of renal insufficiency were examined. As a result, there was no relationship between the dose of Sitagliptin and the occurrence of adverse events in the patients with renal insufficiency (Table 34). Due to the limited number of cases evaluated, there was a high variability in incidences among subgroups, but there was no trend towards an increased incidence of specific adverse events or adverse drug reactions with increasing dose of Sitagliptin.

Table 34. Clinical adverse events in double-blind (12 weeks) studies (A201, A202, P054, P055, ONO-5435-08, ONO-5435-09) (by the presence or absence of renal insufficiency) (Safety analysis population)

Treatment group	Placebo group		Sitagliptin 25 mg group		Sitagliptin 50 mg group		Sitagliptin 100 mg group		Sitagliptin 200 mg group	
Presence or absence of renal insufficiency	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
No. of cases included in safety analysis	n = 319	n = 37	n = 71	n = 9	n = 385	n = 64	n = 128	n = 17	n = 63	n = 7
Adverse events	52.4 (167)	56.8 (21)	54.9 (39)	77.8 (7)	50.4 (194)	56.3 (36)	61.7 (79)	64.7 (11)	65.1 (41)	71.4 (5)
Adverse drug reactions	5.6 (18)	5.4 (2)	8.5 (6)	0.0 (0)	7.3 (28)	9.4 (6)	5.5 (7)	0.0 (0)	7.9 (5)	0.0 (0)
Serious adverse events	1.6 (5)	5.4 (2)	0.0 (0)	0.0 (0)	1.6 (6)	1.6 (1)	0.8 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Adverse events leading to discontinuation	0.9 (3)	2.7 (1)	0.0 (0)	0.0 (0)	0.8 (3)	1.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Incidence % (N)

Renal insufficiency: Present ($C_{CR} < 80$ mL/min), Absent ($C_{CR} \geq 80$ mL/min)

As only 3 patients with type 2 diabetes mellitus and moderate renal insufficiency were enrolled into

the Sitagliptin group in Japanese clinical studies, PMDA asked the applicant to explain the safety in type 2 diabetic patients with moderate ($C_{CR} \geq 30$ to < 50 mL/min) or severe ($C_{CR} < 30$ mL/min or end-stage renal disease [on hemodialysis or on peritoneal dialysis]) renal insufficiency in Foreign Study P028.

The applicant responded as follows:

The summary values of the data regarding adverse events reported in patients with moderate or severe renal insufficiency were similar between the Sitagliptin and placebo/glipizide groups (Tables 30, 31) and there were also no differences in the severity of adverse events. Meanwhile, in patients with moderate renal insufficiency (Stratum 1, $C_{CR} \geq 30$ to < 50 mL/min) and those with severe renal insufficiency (Stratum 2, $C_{CR} < 30$ mL/min or end-stage renal disease [on hemodialysis or on peritoneal dialysis]), there was a trend towards higher incidence of serious adverse events of cardiac disorders, including death, in the Sitagliptin group than in the placebo/glipizide group (Table 35). As there were differences in the prevalence of cardiovascular underlying diseases between the two groups (Table 36), the higher severity of cardiac disorders observed in the Sitagliptin group was considered associated with the differences in underlying disease.

Table 35. Deaths and adverse events categorized as cardiac disorders throughout the entire study period of Study P028*
(by severity and by degree of renal insufficiency)

Renal insufficiency	Stratum 1		Stratum 2	
Treatment group	Placebo/glipizide group	Sitagliptin group	Placebo/glipizide group	Sitagliptin group
No. of cases included in safety analysis	15	36	11	29
Death	0.0 (0)	2.8 (1)	9.1 (1)	13.8 (4)
Overall cardiac disorders	0.0 (0)	13.9 (5)	27.3 (3)	10.3 (3)
Mild	0.0 (0)	5.6 (2)	18.2 (2)	3.4 (1)
Moderate	0.0 (0)	8.3 (3)	18.2 (2)	0.0 (0)
Severe	0.0 (0)	0.0 (0)	9.1 (1)	6.9 (2)

Incidence % (N) * Excluding adverse events occurring after the initiation of rescue therapy

Stratum 1: Moderate renal insufficiency ($C_{CR} \geq 30$ to < 50 mL/min)

Stratum 2: Severe renal insufficiency ($C_{CR} < 30$ mL/min) or end-stage renal disease (on hemodialysis or on peritoneal dialysis)

Table 36. Overview of patients diagnosed with a cardiovascular disease category before randomization in Study P028
(by degree of renal insufficiency)

	Placebo/glipizide group			Sitagliptin group		
	Stratum 1	Stratum 2	Overall	Stratum 1	Stratum 2	Overall
No. of cases included in safety analysis	15	11	26	36	29	65
ASVD	40.0 (6)*	45.5 (5)	42.3 (11)	50.0 (18)	55.2 (16)	52.3 (34)
CAD	26.7 (4)*	18.2 (2)	23.1 (6)	38.9 (14)	41.4 (12)	40.0 (26)
Heart failure	13.3 (2)*	0.0 (0)	7.7 (2)	11.1 (4)	17.2 (5)	13.8 (9)

% (N)

ASVD: Atherosclerotic cardiovascular disease (including CAD), CAD: Coronary artery disease

* Including 1 subject who discontinued the study due to an adverse event in the run-in period after randomization

Two studies in type 2 diabetes mellitus patients with [REDACTED] ([REDACTED]) or [REDACTED] ([REDACTED]) (about [REDACTED] cases in total) [REDACTED] and [REDACTED].

PMDA considers as follows:

PMDA understands the applicant's response that there were no differences in the safety between patients with mild renal insufficiency and those with normal renal function in Japanese clinical studies. However, patients with moderate or severe renal insufficiency have not been studied in Japan and moreover, in Foreign Study P028 in patients with moderate or severe renal insufficiency, cardiac disorders occurred in the Sitagliptin group only among the patients with moderate renal insufficiency (Stratum 1) though there were some differences in the prevalence of cardiovascular underlying diseases between the groups. Taking also into account that Sitagliptin is renally eliminated, the information is insufficient to evaluate the safety in Japanese patients with moderate or severe renal insufficiency. As the safety of Sitagliptin in Japanese patients with moderate or severe renal insufficiency has not been confirmed at present, it is appropriate to avoid the use of Sitagliptin in this patient population, but a final conclusion will be made taking account of comments from the Expert Discussion.

4.(iii).B.(4).2) Patients with hepatic insufficiency

As a clinical study in patients with severe hepatic insufficiency of equivalent level to Child-Pugh class C has not been conducted, PMDA asked the applicant to explain the safety of Sitagliptin in patients with severely reduced hepatic function and measures to be taken.

The applicant responded as follows:

As Sitagliptin is minimally metabolized by the liver and is primarily renally eliminated, hepatic insufficiency is unlikely to alter the pharmacokinetic profile of Sitagliptin. In Study P017, the single-dose pharmacokinetics of Sitagliptin in foreign subjects were similar between patients with moderate hepatic insufficiency and healthy subjects (control). Although patients with severe hepatic insufficiency of equivalent level to Child-Pugh class C were not enrolled into Study P017, it is considered that the pharmacokinetics of Sitagliptin in these patients are not essentially different from those in patients with moderate hepatic insufficiency and no dose adjustment is required for Sitagliptin. No additional tests are needed as well when Sitagliptin is used in patients with severe hepatic insufficiency and this can be managed through careful observation of each patient.

When Japanese long-term treatment studies were compared to foreign long-term treatment studies (the pooled safety population), the incidences of AST increased and ALT increased were higher in the Japanese studies using a lower dose of Sitagliptin than in the foreign studies (Japanese studies, AST increased [3.8%], ALT increased [5.1%]; foreign studies, AST increased [1.2%], ALT increased [1.9%]). PMDA asked the applicant to discuss this finding.

The applicant responded as follows:

The patients with adverse events or adverse drug reactions of AST increased or ALT increased in the

Japanese long-term treatment studies were examined. As a result, 35.5% (11 of 31 patients) of these patients had hepatic steatosis and 64.5% (20 of 31 patients) had hyperlipidaemia or hypercholesterolaemia. Thus, it is considered that the higher incidences of adverse events of AST increased and ALT increased observed in the Japanese long-term treatment studies were not associated with exposure to Sitagliptin, but were substantially associated with the concomitant illnesses.

PMDA considers as follows:

PMDA understands the applicant's view that as Sitagliptin is not a hepatically metabolized drug, the effect of hepatic insufficiency on the safety of Sitagliptin is insignificant. However, as there is no clinical experience with Sitagliptin in patients corresponding to Child-Pugh class C, a caution statement should be included in the package insert (draft). Since background factors commonly present in patients with type 2 diabetes mellitus, i.e. hepatic steatosis and hyperlipidaemia were related to the occurrence of adverse events of AST increased and ALT increased in the Japanese long-term treatment studies and it has been reported that GIP (the inactivation of both GIP and GLP-1 is inhibited by Sitagliptin) is correlated with obesity and hepatic steatosis (Musso, G *et al.*, *Am J Clin Nutr*, 2009; 89: 558-567.), it is necessary to collect post-marketing safety information regarding hepatic steatosis.

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

PMDA asked the applicant to explain the safety of an increased dose of 100 mg/day of Sitagliptin in the elderly.

The applicant responded as follows:

In Japanese long-term treatment studies (P055, ONO-5435-08 to -10, up to 52 weeks of treatment), the incidence of clinical adverse events in the subjects aged ≥ 65 years who had their dose increased was almost comparable to that in the overall population (Table 37). Adverse events leading to discontinuation occurred in 5 subjects aged ≥ 65 years who had their dose increased (large intestine carcinoma, gastric cancer, acute cardiac failure, myocardial infarction, dizziness), including 1 death (acute cardiac failure), but a causal relationship to the study drug was denied for all cases. There were also no differences in the incidence of hypoglycaemia between the subjects aged ≥ 65 years who had their dose increased (4.3%, 5 of 116 subjects) and the overall population (3.8%, 21 of 522 subjects). Likewise, there were no major differences in the occurrence of laboratory adverse events between the subjects aged ≥ 65 years who had their dose increased and the overall population. The above results indicate that an increased dose of 100 mg/day of Sitagliptin is well tolerated in patients aged ≥ 65 years.

Table 37. Clinical and laboratory adverse events and adverse drug reactions in long-term treatment studies (P055, ONO-5435-08 to -10)*

	Clinical		Laboratory	
	Subjects ≥ 65 years with dose increase (n = 116)	Overall population (n = 552)	Subjects ≥ 65 years with dose increase (n = 116)	Overall population (n = 552)
Adverse events	83.6 (97)	81.7 (451)	15.5 (18)	19.6 (108)
Adverse drug reactions	12.9 (15)	10.3 (57)	2.6 (3)	5.3 (29)
Deaths	0.9 (1)	0.4 (2)	0.0 (0)	0.0 (0)
Serious adverse events	7.8 (9)	4.7 (26)	0.0 (0)	0.0 (0)
Adverse events leading to discontinuation	4.3 (5)	2.5 (14)	0.0 (0)	0.4 (2)

Incidence % (N)

In Studies P055, ONO-5435-08, and ONO-5435-09, 40 weeks of treatment for the placebo group in the double-blind phase and 52 weeks of treatment for the Sitagliptin 50 mg group in the double-blind phase. In Study ONO-5435-10, 52 weeks of treatment.

* Adapted by PMDA from the applicant's table

As there were no major differences in the safety between the subjects aged ≥ 65 years who had their dose increased and the overall population, PMDA accepted the response.

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

PMDA asked the applicant to explain the proposed indication for Sitagliptin (improvement of post-prandial hyperglycemia in type 2 diabetes mellitus), which is different from the indication in the US/Europe.

The applicant responded as follows:

Referring to the indication for voglibose, which was used as the control drug for a Japanese phase III, double-blind, comparative study (P054), a new drug application for Sitagliptin for the proposed indication of “improvement of post-prandial hyperglycemia in type 2 diabetes mellitus” was filed. On the other hand, the indication in the US/Europe is “improvement of glycemic control in patients with type 2 diabetes mellitus.” The degree of improvement of glycemic control in foreign patients with type 2 diabetes mellitus was similar to the results of Japanese clinical studies. Japanese phase II and phase III clinical studies in patients with type 2 diabetes mellitus have confirmed that Sitagliptin improves not only HbA_{1c} but also fasting blood glucose and 2-hour post-prandial blood glucose and is well tolerated. Based on the above, the appropriate indication would be “type 2 diabetes mellitus” rather than “improvement of post-prandial hyperglycemia in type 2 diabetes mellitus.” Therefore, the proposed indication will be modified as follows.

[After modification]

Type 2 diabetes mellitus;

Sitagliptin should be used only in patients who do not sufficiently respond to any one of the following treatments.

- (a) Dietary therapy and/or exercise therapy only
- (b) Use of sulfonylureas in addition to dietary therapy and/or exercise therapy
- (c) Use of insulin-sensitizing agents in addition to dietary therapy and/or exercise therapy

(d) Use of biguanides in addition to dietary therapy and/or exercise therapy

Taking account of the results of clinical studies of Sitagliptin, PMDA concluded that it is appropriate to modify the proposed indication from “improvement of post-prandial hyperglycemia in type 2 diabetes mellitus” to “type 2 diabetes mellitus” and accepted the response. However, as to the wording of “(c) Use of insulin-sensitizing agents in addition to dietary therapy and/or exercise therapy,” although biguanides and thiazolidinediones have been approved as drugs with insulin-sensitizing action in Japan, as the clinical study data submitted in this application support Sitagliptin combination therapy with pioglitazone, a thiazolidinedione, the appropriate wording in the indication section would be “thiazolidinediones” rather than “insulin-sensitizing agents.” With respect to combination therapy with a biguanide, although the clinical study data submitted in this application support Sitagliptin combination therapy with metformin and there are no data on combination therapy with buformin that is classified as a biguanide as is metformin, taking into account that the use of buformin is very uncommon as compared to metformin in Japan, it is recommended that post-marketing data on combination therapy with buformin should be collected. As to the wording of “(d) Use of biguanides in addition to dietary therapy and/or exercise therapy,” the Japanese term for “biguanides” should be modified.

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

4.(iii).B.(6).1 Dosage regimen

(a) Dosing frequency

The applicant explained the rationale for once-daily dosing of Sitagliptin as follows:

A phase I single oral dose study (P013) and phase I multiple oral dose studies (A111, A112) in healthy adult male subjects showed that the plasma AUC of Sitagliptin increased in a dose-dependent manner up to 400 mg. In these studies, the percent inhibition of plasma DPP-4 activity increased dose-dependently and plasma Sitagliptin concentration-dependently, and the weighted mean percent increase in plasma active GLP-1 concentration was about ≥ 2 -fold higher following ≥ 25 -mg once-daily multiple doses of Sitagliptin compared to placebo. A phase II clinical study in patients with type 2 diabetes mellitus was conducted to evaluate the blood glucose-lowering effect of Sitagliptin 100 mg q.d. and 50 mg b.i.d. (A203). For the primary endpoint of the change in 24-hour weighted mean glucose from baseline to Treatment Week 4, both the Sitagliptin 100 mg q.d. and 50 mg b.i.d. groups had significant reductions compared to the placebo group. On the other hand, there were no significant differences between the two dosage regimens and comparable efficacy was demonstrated. As the above results indicated that there are no major differences between the q.d. and b.i.d. regimens, the q.d. regimen that is more convenient for patients was chosen and phase III clinical studies were conducted.

As the phase II clinical study (A203) demonstrated that not only efficacy but also safety were comparable between the 100 mg q.d. and 50 mg b.i.d. regimens of Sitagliptin etc., PMDA considers

that there is no problem with choosing the once-daily regimen in consideration of patients' convenience.

(b) Timing of dosing

PMDA asked the applicant to provide a justification for recommending once-daily dosing without specifying the timing of dosing relative to meals in the dosage and administration section of the package insert, despite that the improvement of glycemic control by Sitagliptin was evaluated in clinical studies in which Sitagliptin was administered before breakfast.

The applicant responded as follows:

In all Japanese and foreign phase II and phase III clinical studies with Sitagliptin administered once daily, subjects were required to take the study drug before breakfast and its efficacy and safety were evaluated. No phase II or phase III clinical study has been conducted with Sitagliptin administered once daily at other times of the day (after breakfast, before or after lunch or evening meal, in the evening, etc.). However, a clinical pharmacology study assessing the effect of food on the pharmacokinetics of Sitagliptin (P076) indicated that the pharmacokinetics of Sitagliptin is very unlikely to be affected by food. The Sitagliptin pharmacokinetic and pharmacodynamic data from Japanese clinical studies (A111, A112, A202, A203) suggested that the efficacy of Sitagliptin is unlikely to be substantially compromised even when Sitagliptin is administered at lunch or evening meal time. Furthermore, the time of day of dosing does not influence the pharmacokinetics or pharmacodynamics of Sitagliptin and thus has no meaningful effect on its safety or tolerability and given the glucose-dependent pharmacological effects of Sitagliptin, there is also little concern about hypoglycaemia. Therefore, in consideration of patients' convenience and in expectation of long-term maintenance of good compliance, the timing of dosing relative to meals has not been specified in the Japanese package insert (draft).

PMDA considers as follows:

The Japanese clinical study assessing food effect (P076) has shown that food has no clinically meaningful effect on the pharmacokinetics of Sitagliptin and in foreign countries where Sitagliptin is already on the market, Sitagliptin has been taken with or without food. Taking account of these points, there is no major problem with recommending once-daily dosing without specifying the timing of dosing relative to meals in the dosage and administration section. However, whether or not the timing of dosing affects glycemic control has not been investigated. Thus, it is necessary to collect information on the timing of dosing and efficacy via post-marketing surveillance.

4.(iii).B.(6).2) Dose

The applicant explained the dose rationale for Sitagliptin (The dose of Sitagliptin is 50 mg once daily. If the effect is insufficient, the dosage may be increased up to 100 mg once daily) as follows:

A late phase II clinical study in patients with type 2 diabetes mellitus (A202) was conducted where Sitagliptin 25, 50, 100, and 200 mg or placebo was administered once daily for 12 weeks. As a result, for the primary endpoint of the change in HbA_{1C} from baseline to Treatment Week 12, Sitagliptin at the doses of 25 to 200 mg all provided significant reductions compared to placebo, whereas the changes in HbA_{1C} at the doses of ≥ 50 mg were similar (the difference from placebo was about -1%). The incidence of clinical adverse events was significantly higher only in the Sitagliptin 200 mg group than in the placebo group, but there were no specific System Organ Classes (SOCs) or specific adverse events with a particularly higher incidence in the Sitagliptin 200 mg group than in the placebo group. The incidence in each of the other Sitagliptin dose groups were not significantly different from the placebo group and there was also no trend towards a dose-dependent increase in the incidence of clinical adverse events or adverse drug reactions either by SOC or by specific event. There were no significant differences in the incidence of laboratory adverse events or adverse drug reactions between the placebo and Sitagliptin groups and the tolerability and safety of Sitagliptin up to 200 mg were demonstrated. Based on these results, 50 mg/day has been chosen as the recommended clinical dose. In phase III clinical studies (P055, ONO-5435-08, ONO-5435-09) and a long-term treatment study (ONO-5435-10), in order to evaluate the effect of an increased dose of 100 mg once daily in patients responding inadequately to 50 mg once daily, if HbA_{1C} or fasting blood glucose met the criteria for dose increase during treatment with 50 mg once daily, the dose was to be increased to 100 mg once daily. In these 4 studies, 61.5% (238 of 387 patients) of the patients with HbA_{1C} measured at 12 weeks after a dose increase to 100 mg (patients who had their dose increased in the 4 studies combined) had an even lower HbA_{1C} value compared to the values before the dose increase and 16.8% (65 of 387 patients) of the patients with an HbA_{1C} $\geq 7.0\%$ achieved an HbA_{1C} $< 7.0\%$ at 12 weeks after a dose increase to 100 mg. On the other hand, there seems no particular safety problem with an increased dose of 100 mg in terms of clinical or laboratory adverse events or adverse drug reactions.

PMDA considers as follows:

The late phase II clinical study (A202) showed no particular differences in the efficacy (change in HbA_{1C}, fasting blood glucose, 2-hour post-prandial blood glucose, etc.) or safety of Sitagliptin among the 50, 100, and 200 mg doses. Selecting a dose that is slightly more effective numerically is of little clinical significance. Thus, there is no particular problem with choosing 50 mg/day as the usual clinical dose. There is also no major problem with allowing a dose increase up to 100 mg once daily if the effect is insufficient because there were patients who had an even lower HbA_{1C} value or achieved an HbA_{1C} $< 7.0\%$, a goal of glycemic control, after their dose increase in the long-term treatment studies.

4.(iii).B.(7) Post-marketing surveillance plan

PMDA asked the applicant to explain a Sitagliptin post-marketing surveillance plan.

The applicant presented an outline of a post-marketing surveillance protocol (draft) and then responded as follows:

In order to collect post-marketing information on the safety and efficacy of Sitagliptin in patients with type 2 diabetes mellitus under routine drug uses and other proper use information, a drug use-results survey via prospective, central registration system is planned to be conducted. The observation period is 24 weeks from the start of Sitagliptin administration, the planned duration of the survey is 3 years from the initiation of the survey, and the target number of cases is 3000. As a considerable number of type 2 diabetic patients are expected to be elderly or have renal or hepatic insufficiency, the safety and efficacy of Sitagliptin in these patients identified from the use-results survey will be investigated. The long-term treatment can be evaluated in a 24-week use-results survey as phase III clinical studies (P055, ONO-5435-08, ONO-5435-09, ONO-5435-10) showed no differences in the safety or efficacy of Sitagliptin between Week 24 and Week 52. Although the use of Sitagliptin in children and pregnant women/nursing mothers will be extremely rare, if these patients are collected via the use-results survey, the safety and efficacy will be determined.

PMDA considers as follows:

As it is important to accumulate long-term safety data on DPP-4 inhibitors worldwide, it is necessary to evaluate the safety and efficacy of a long-term treatment with Sitagliptin, including the occurrence of hypoglycaemia, musculoskeletal and connective tissue disorders, cardiac disorders, and skin disorders and tumor development, via post-marketing surveillance, taking also account of post-marketing safety information on other drugs of the same class that have been approved overseas.

Based on the above, PMDA is urging the applicant to further consider the details of the survey, including the appropriate number of cases, data items to be collected, and observation period. In the US, cardiovascular risk assessment of a novel antidiabetic agent in diabetic patients is required when filing an application for a drug containing a new active ingredient in the diabetes field. It is necessary to determine what kind of risk assessment should be performed in future, taking into account that the incidence of cardiovascular events is considered to be lower in Japanese patients than in foreign patients.

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 reliability assessment

A document-based inspection and reliability assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted documents on the product.

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.1, 5.3.5.1.2, 5.3.5.1.4, 5.3.5.1.6, 5.3.5.1.7, 5.3.5.2.1). As a result, it was found that at some clinical trial sites, the study drug for the open-label phase, instead of the study drug assigned for the double-blind phase, had mistakenly been dispensed to a subject, but PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

IV. Overall Evaluation

It is concluded that the submitted data have demonstrated the efficacy and safety of Sitagliptin in type 2 diabetes mellitus.

Sitagliptin may be approved for the indication of type 2 diabetes mellitus if it can be concluded that there are no particular problems, taking account of comments from the Expert Discussion.

Review Report (2)

July 8, 2009

I. Product Submitted for Registration

[Brand name]	Januvia Tablets 25 mg, ¹⁾ 50 mg, ¹⁾ 100 mg ¹⁾ Glactiv Tablets 25 mg, ²⁾ 50 mg, ²⁾ 100 mg ²⁾
[Non-proprietary name]	Sitagliptin Phosphate Hydrate
[Applicant]	Banyu Pharmaceutical Co., Ltd. ¹⁾ Ono Pharmaceutical Co., Ltd. ²⁾
[Date of application]	December 10, 2007

II. Content of the Review

The Pharmaceuticals and Medical Devices Agency (PMDA) sought the expert advisors' opinions based on the Review Report (1). The results of the review, taking account of discussions with the expert advisors, are reported below. 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 "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. Use in patients with renal insufficiency

PMDA concluded as follows:

The safety of Sitagliptin in type 2 diabetic patients with moderate or severe renal insufficiency has been little studied in Japan. In Foreign Study P028 in type 2 diabetic patients with renal insufficiency, adverse events of cardiac disorders occurred in the Sitagliptin group only among the patients with moderate renal insufficiency though there were some differences in the prevalence of cardiovascular underlying diseases between the groups. Taking also into account that Sitagliptin is renally eliminated, the information is insufficient to evaluate the safety in Japanese patients with moderate or severe renal insufficiency. As described above, the safety of Sitagliptin in Japanese patients with moderate or severe renal insufficiency has not been confirmed at present. Thus, it is appropriate to avoid the use of Sitagliptin in this patient population.

The expert advisors made the following comments on the above conclusion by PMDA:

Oral antihyperglycemic agents that can be administered to patients with renal insufficiency are limited and it is useful to allow the use of Sitagliptin also in patients with renal insufficiency. As it is difficult to draw a clear line between mild and moderate renal insufficiency based on creatinine clearance to determine whether or not Sitagliptin should be administered to the patient, patients considered to have moderate renal insufficiency based on their serum creatinine levels etc. may be administered a reduced

dose of 25 mg of Sitagliptin while carefully observing their conditions. On the other hand, PMDA's conclusion that the use of Sitagliptin should be avoided in patients with severe renal insufficiency including those requiring hemodialysis or peritoneal dialysis is appropriate, considering that Sitagliptin is primarily renally eliminated and dose adjustment (e.g. further reduce the dose for patients with moderate renal insufficiency [25 mg]) is impossible with the proposed commercial formulation at present.

Taking account of the comments from the Expert Discussion, PMDA concluded as follows:

In view of the utility in the clinical practice, Sitagliptin may be used in patients with type 2 diabetes mellitus with moderate renal insufficiency through careful administration and dose adjustment. However, as only 3 patients with type 2 diabetes mellitus with moderate renal insufficiency were investigated in Japanese clinical studies, it is necessary to conduct a post-marketing specified drug use-results survey to investigate the safety of Sitagliptin in patients with moderate renal insufficiency. On the other hand, since no patients with severe renal insufficiency including those requiring hemodialysis or peritoneal dialysis have been studied in Japan and dose adjustment is impossible with the proposed commercial formulation, Sitagliptin has to be contraindicated in this patient population at present.

Based on the above, PMDA asked for the applicant's view on the possibility of developing a 12.5-mg formulation to allow for dose adjustment also in patients with severe renal insufficiency and asked the applicant to [REDACTED] foreign [REDACTED] study and [REDACTED] study in type 2 diabetic patients with [REDACTED] renal insufficiency.

The applicant explained as follows:

Sitagliptin will be contraindicated in [REDACTED], [REDACTED], and patients with severe renal insufficiency including those requiring hemodialysis or peritoneal dialysis as plasma concentrations may be elevated. [REDACTED] [REDACTED] study and [REDACTED] study [REDACTED].

PMDA accepted the applicant's response on the premise that a post-marketing specified drug use-results survey of patients with renal insufficiency will be conducted to investigate the safety of Sitagliptin in patients with moderate renal insufficiency [see "3. Post-marketing surveillance"].

2. Caution about combination therapy with other antihyperglycemic agents

PMDA concluded that the caution statement included in the package insert (draft) (when Sitagliptin is used in combination with a SU agent, a lower dose of the SU agent may be considered in order to reduce the risk of hypoglycaemia) was appropriate. However, after the Expert Discussion, PMDA considered that the appropriate statement would be "When Sitagliptin is used in combination with a

SU agent, attention should be paid to the possible occurrence of hypoglycaemia” rather than a statement giving an instruction about the dose of a concomitant medication and instructed the applicant to modify the statement. In addition, as the blood glucose-lowering effect may be enhanced also when Sitagliptin is used in combination with other antihyperglycemic agents other than SU agents, PMDA instructed the applicant to include a caution statement in the package insert (draft).

The applicant responded as follows:

The statement in the package insert (draft) will be modified as follows: “When Sitagliptin is used in combination with a SU agent, the risk of hypoglycaemia may be increased. Special attention should be paid to the possible occurrence of hypoglycaemia when used in combination with a SU agent.” Also for combination therapy with other antihyperglycemic agents other than SU agents, a caution statement will be included in the package insert (draft).

PMDA accepted the response.

3. Post-marketing surveillance

PMDA considered that as Sitagliptin is a drug with a novel mode of action and it is important to systematically accumulate long-term safety data on all DPP-4 inhibitors worldwide, it is necessary to evaluate the safety and efficacy of a long-term treatment with Sitagliptin, including the occurrence of hypoglycaemia, musculoskeletal and connective tissue disorders, cardiac disorders, and skin disorders and tumor development, via post-marketing surveillance, taking also account of post-marketing safety information on other drugs of the same class that have been approved overseas. This conclusion by PMDA was supported by the expert advisors. In the US, cardiovascular risk assessment in diabetic patients is required when filing an application of an antidiabetic drug containing a new active ingredient. PMDA considered that it is necessary to determine what kind of risk assessment should be performed for Japanese patients in future, taking into account that the incidence of cardiovascular events is expected to be lower in Japanese patients than in foreign patients, and sought the expert advisors’ opinions on the content of a post-marketing surveillance to be conducted, including its feasibility. The following comments were raised from the expert advisors: Although it is important to include a control group, this will be difficult in terms of feasibility; Thus, a post-marketing surveillance plan should be developed so as to be cross-referenced to overseas post-marketing surveillance programs; A surveillance to confirm that the risk of cardiovascular events in Japanese patients is not higher than that in foreign patients by comparing incidences of cardiovascular events between Japan and overseas is feasible.

Based on the above comments from the Expert Discussion, PMDA asked the applicant to explain whether there are Sitagliptin data that are in accordance with the guidance for evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes, issued by the FDA

(December 2008).

The applicant responded as follows:

As Sitagliptin was approved about 2 years prior to the enforcement of this guidance, cardiovascular risk analysis, as currently required by the FDA for a novel antidiabetic agent, has not been performed. However, in order to assess the overall safety of Sitagliptin (including cardiovascular risk), pooled analysis from 12 foreign phase II and phase III clinical studies of Sitagliptin was performed. In these studies, the duration of treatment was 18 to 106 weeks and of the 6139 patients with type 2 diabetes mellitus, 3415 patients received Sitagliptin (the mean duration of treatment, 307 days; the duration of treatment, 1-792 days) and the other 2724 patients received placebo or active control (Sitagliptin non-exposed group) (the mean duration of treatment, 294 days; the duration of treatment, 1-801 days). The data from the Sitagliptin 100 mg/day group (100 mg once daily or 50 mg twice daily) and the Sitagliptin non-exposed group (the concurrent control group that was treated concurrently over almost the same period of time) in each study were pooled. As a result, 1343 patients in the Sitagliptin group were treated for ≥ 1 year, of which 356 patients were treated for 2 years. The corresponding numbers of patients in the Sitagliptin non-exposed group were 981 and 290, respectively. In these studies, the total observation period was 2994 patient-years for the Sitagliptin group and 2270 patient-years for the non-exposed group. Though the studies included in this analysis were not cardiovascular outcome studies, but were studies evaluating the safety and efficacy of Sitagliptin 100 mg/day, as shown in the table below, there were no meaningful differences in the incidence of adverse events categorized as cardiac disorders including adverse events of ischemic events between the Sitagliptin group and the non-exposed group, indicating that the risk of cardiovascular events is almost comparable between type 2 diabetic patients treated with Sitagliptin and those untreated with Sitagliptin. Sitagliptin [REDACTED] study ([REDACTED] study, [REDACTED] cases, about [REDACTED] years) [REDACTED].

Table. Incidence of adverse events categorized as cardiac disorders

	Sitagliptin 100 mg group (n = 3415)	Sitagliptin non-exposed group (n = 2724)	Difference between Sitagliptin and non-exposed groups (%) [95% CI]
Adverse events of cardiac disorders (SOC)	4.0%	3.9%	0.1 [-0.9, 1.1]
Serious adverse events of cardiac disorders	1.2%	1.5%	-0.3 [-1.0, -0.3]
Adverse events of ischemic events	2.0%	2.3%	-0.2 [-1.0, -0.5]
Serious adverse events of ischemic events	1.1%	1.5%	-0.4 [-1.0, 0.2]

PMDA considered as follows:

The pooled data from 12 foreign studies did not indicate a particular risk of cardiovascular events in type 2 diabetic patients treated with Sitagliptin. However, taking account of the comments from the Expert Discussion, at least 3 years of observation period are needed for assessing cardiovascular events and tumor development so as to be cross-referenced to overseas post-marketing surveillance

programs, and although patients with type 2 diabetes mellitus with moderate renal insufficiency can be managed by careful administration and dose adjustment, it is necessary to conduct a specified drug use-results survey of patients with renal insufficiency to actively collect safety information on patients with moderate renal insufficiency, etc.

Therefore, PMDA asked the applicant to present a post-marketing surveillance protocol (draft) capable of investigating the above.

The applicant presented a post-marketing surveillance protocol (draft) and then explained as follows: A specified use-results survey on the long-term use and a specified use-results survey of patients with renal insufficiency will be conducted. The information on safety, efficacy, cardiovascular events, and tumor development etc. following a long-term treatment with Sitagliptin will be collected via a specified use-results survey with a 3-year observation period and a planned number of cases of 3000. With respect to assessment of survey results on cardiovascular events, direct comparison with overseas post-marketing surveillance programs is difficult due to different practice and procedures etc. and it is also difficult to compare the survey results with the data collected from randomized controlled clinical studies. However, not only by collecting all adverse events, but also by setting the cardiovascular events as survey items including the primary endpoint of [REDACTED] study of [REDACTED], [REDACTED], [REDACTED], and [REDACTED], and by attempting to perform similar assessments, [REDACTED] can be done when [REDACTED] study is [REDACTED] (scheduled for 20[REDACTED]). [REDACTED] study, [REDACTED]. When information on cardiovascular events and tumor development has been collected, relevant laboratory data etc. will be reexamined. The information on actual drug use, safety, and efficacy of Sitagliptin in patients with moderate renal insufficiency will be collected via a specified use-results survey of patients with renal insufficiency with a 1-year observation period and a planned number of cases of 100. Although the duration of this survey will be 3 years, in order to collect information on patients with moderate renal insufficiency early, survey results will be summarized promptly before the completion of the survey period once the data from the target number of cases have been collected. In the end, in addition to the cases collected via this survey, patients with moderate renal insufficiency collected via the above-mentioned specified drug use-results survey on the long-term use (about [REDACTED] cases are expected to be collected) will also be included in analyses.

PMDA concluded that there are no major problems with the post-marketing surveillance protocol (draft) and accepted the response.

III. Overall Evaluation

As a result of the above review, PMDA concluded that the product may be approved after modifying the indication and the dosage and administration as shown below. As the product submitted for registration is a drug with a new active ingredient, the appropriate 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;

Sitagliptin should be used only in patients who do not sufficiently respond to any one of the following treatments.

- (a) Dietary therapy and/or exercise therapy only
- (b) Use of sulfonylureas in addition to dietary therapy and/or exercise therapy
- (c) Use of thiazolidinediones in addition to dietary therapy and/or exercise therapy
- (d) Use of biguanides in addition to dietary therapy and/or exercise therapy

[Dosage and administration]

The usual adult dosage is 50 mg of Sitagliptin orally administered once daily. If the effect is insufficient, the dosage may be increased up to 100 mg once daily while closely observing the clinical course.

The summary of the submitted data and the outline of review by PMDA regarding the Drug Master File (DMF) for Januvia Tablets 25 mg, 50 mg, and 100 mg and Glactiv Tablets 25 mg, 50 mg, and 100 mg (220MF10082)

Summary of the submitted data pertaining to the drug substance

[illegible]

The specifications for the drug substance have been set for description, identification (IR), particle size, optical purity ((*S*)-enantiomer [HPLC]), purity (related substances [HPLC]), water content, residue on ignition, and assay (HPLC). Concerning related substances, specifications for levels of starting

materials [REDACTED]

[REDACTED] and other individual related substances and the total level of related substances have been provided. Though not included in the specifications, the drug substance has also been tested for residual solvents, identity of phosphate, optical rotation, arsenic, and heavy metals.

As the stability studies of the drug substance, long-term testing (30°C/65%RH, 36 months, 1 lot) (25°C/60%RH, 36 months, 3 lots), accelerated testing (40°C/75%RH, 6 months, 4 lots), and photostability testing (cool white fluorescent lamp and near ultraviolet lamp, an overall illumination of not less than 1.2 million lux·h and an integrated near ultraviolet energy of not less than 200 W·h/m²) were performed on samples (pilot scale) stored in double polyethylene bags placed in fiber drums. The attributes tested in these studies include description, water content, total related substances (HPLC), optical purity ((S)-enantiomer [HPLC]), and assay (HPLC), and identification tests (IR) and color of the solution were also performed in photostability testing.

Using the lots produced at a commercial scale, long-term testing (25°C/60%RH, 36 months, 3 lots) and accelerated testing (40°C/75%RH, 6 months, 1 lot) were performed and the attributes tested were description, water content, related substances (HPLC) ([REDACTED], other individual related substances and the total level of related substances), and assay (HPLC). As a result, in the long-term, accelerated, and photostability testings, the samples met the specifications for all attributes and there were no quality changes.

Furthermore, as part of assay method validation, stress testing (acid hydrolysis [REDACTED], alkaline hydrolysis [REDACTED], oxidative degradation [REDACTED], thermal degradation [REDACTED]) was also performed on 1 pilot scale lot and the attribute tested was assay (HPLC). Likewise, related substances (HPLC) were determined for samples after [REDACTED] acid hydrolysis, alkaline hydrolysis, and oxidative degradation and samples after thermal degradation under the same condition as for assay. In the stress testing, assay was performed and as a result, [REDACTED] degradation product was identified after acid and alkaline hydrolysis and [REDACTED] degradation product was identified after oxidative degradation, but thermal degradation product was [REDACTED]. When related substances were determined, [REDACTED] degradation product after acid hydrolysis, [REDACTED] degradation product after alkaline hydrolysis, [REDACTED] degradation product after oxidative degradation, and [REDACTED] degradation product ([REDACTED]) after thermal degradation were identified, but these degradation products have never been found in the drug substances produced so far.

Based on the above results, the proposed re-test period for the drug substance is 36 months when stored in double polyethylene bags placed in fiber drums at room temperature.

Outline of the review by PMDA

As Sitagliptin has an asymmetric carbon, PMDA asked the MF registrant to explain about racemization and a decrease in chirality during the manufacture of the drug substance.

The MF registrant explained as follows:

(S)-enantiomer has been reduced in all lots in [REDACTED] from [REDACTED] to [REDACTED]. Concerning the stability of the drug substance in the dry conditions, when the drug substance was stored for 6 months at 40°C/75%RH in accelerated testing, which was severer than the condition of the drying process ([REDACTED]), all 4 lots were stable and no racemization was observed. Moreover, also in terms of chemical structure, the asymmetric carbon atom that is located in the β position to the aromatic ring and the carbonyl group and is adjacent to the amino group is stable against racemization. Racemization is likely to occur in [REDACTED]. In crystallization of [REDACTED], as Sitagliptin, (R)-enantiomer, is thermodynamically superior to (S)-enantiomer, optical purity is increased. Based on the above, in [REDACTED], there should be no racemization or decreased chirality.

PMDA considers that although the asymmetric carbon of Sitagliptin is stable and racemization is unlikely to occur, taking into account that the chirality is introduced during the manufacturing process etc., optical purity determination is very important. Thus, PMDA instructed the MF registrant to include optical purity in the final drug substance specifications.

The MF registrant responded that optical purity ((S)-enantiomer [HPLC]) will be included in the drug substance specifications.

PMDA accepted the response.

Based on the above, PMDA concluded that there are no particular problems with the specifications, storage, and re-test period established for the drug substance.