Report on the Deliberation Results

December 10, 2013

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

[Brand name]	Suglat Tablets 25 mg and 50 mg
[Non-proprietary name]	Ipragliflozin L-Proline (JAN*)
[Name of applicant]	Astellas Pharma Inc.
[Date of application]	March 13, 2013

[Results of deliberation]
In the meeting held on November 29, 2013, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

**Japanese Accepted Name (modified INN)*

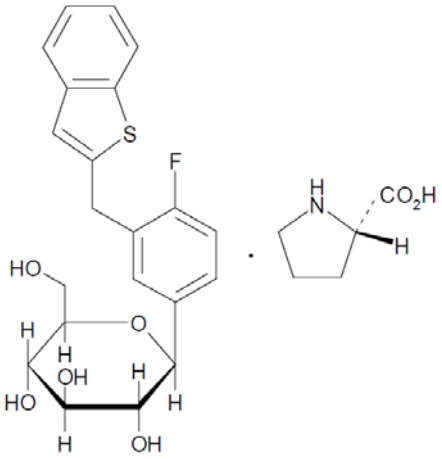
Review Report

November 8, 2013
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]	Suglat Tablets 25 mg and 50 mg
[Non-proprietary name]	Ipragliflozin L-Proline
[Name of applicant]	Astellas Pharma Inc.
[Date of application]	March 13, 2013
[Dosage form/Strength]	Each tablet contains ipragliflozin L-proline equivalent to 25 mg or 50 mg of ipragliflozin
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula:	$C_{21}H_{21}FO_5S \cdot C_5H_9NO_2$
Molecular weight:	519.58
Chemical name:	(1*S*)-1,5-Anhydro-1-*C*-{3-[(1-benzothiophen-2-yl)methyl]-4-fluorophenyl}-D-glucitol-(2*S*)-pyrrolidine-2-carboxylic acid (1:1)
[Items warranting special mention]	Product subjected to prior assessment consultation
[Reviewing office]	Office of New Drug I

Review Results

November 8, 2013

[Brand name]	Suglat Tablets 25 mg and 50 mg
[Non-proprietary name]	Ipragliflozin L-Proline
[Name of applicant]	Astellas Pharma Inc.
[Date of application]	March 13, 2013

[Results of review]
Based on the submitted data, the efficacy of the product in patients with type 2 diabetes mellitus has been demonstrated and the safety of the product is acceptable in view of its observed benefits. The following issues should be further investigated via post-marketing surveillance: whether or not the product can be used in patients with moderate to severe renal impairment; impact of the dosage and type of concomitant oral hypoglycaemic agents on the safety; impact on hypoglycaemia, urinary tract infections, genital infections, pollakiuria, polyuria, body weight (body fluid volume), and electrolytes; adverse events associated with urine ketone body; impact on bone metabolism, cardiovascular risk, and malignant tumour; and safety in patients with renal or hepatic impairment and in elderly patients.

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
[Dosage and administration]	The usual adult dosage is 50 mg of ipragliflozin orally administered once daily before or after breakfast. The dose may be increased up to 100 mg once daily with careful monitoring of the patient's clinical course in the case of inadequate efficacy.

Review Report (1)

September 5, 2013

I. Product Submitted for Registration

[Brand name]	Suglat Tablets 25 mg and 50 mg
[Non-proprietary name]	Ipragliflozin L-Proline
[Name of applicant]	Astellas Pharma Inc.
[Date of application]	March 13, 2013
[Dosage form/Strength]	Each tablet contains ipragliflozin L-proline equivalent to 25 mg or 50 mg of ipragliflozin
[Proposed indication]	Type 2 diabetes mellitus
[Proposed dosage and administration]	The usual adult dosage is 50 mg of ipragliflozin orally administered once daily. The dose may be increased up to 100 mg once daily with careful monitoring of the patient's clinical course in the case of inadequate efficacy.

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

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

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

The active ingredient of the proposed product, Ipragliflozin L-Proline (hereinafter referred to as ipragliflozin), is a selective human sodium glucose cotransporter 2 (SGLT2) inhibitor developed through collaboration of Astellas Pharma Inc. and Kotobuki Pharmaceutical Co., Ltd. SGLT is a transporter that uses sodium concentration gradient serving as the driving force for the active transport of glucose into cells. The functions of SGLT1 and SGLT2 have been elucidated in humans; glucose absorption in the gastrointestinal tract and glucose reabsorption in the proximal renal tubules are mainly mediated by SGLT1 and SGLT2, respectively (Wright EM et al., *J Intern Med.* 2007;261:32-43). In animal models of diabetes, selective SGLT2 inhibitors have been reported to improve hyperglycaemia and insulin resistance and prevent exhaustion of the pancreas and progression of diabetic nephropathy by promoting urinary glucose excretion.[1] Selective SGLT2 inhibitors are unlikely to cause hypoglycaemia because they exert hypoglycaemic activity in an insulin-independent manner.

The applicant has now filed a marketing application for ipragliflozin, claiming that the efficacy and safety of ipragliflozin have been confirmed in patients with type 2 diabetes mellitus.

As of August 2013, ipragliflozin has not been approved in any foreign country or region. The product is currently being developed in Taiwan and Korea.

[1] Blondel O et al., *Metabolism.* 1990;39:787-93, Khan A et al., *Am J Physiol.* 1995;269:E623-626, Krook A et al., *Diabetes.* 1997;46:2110-2114

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white crystal and has been determined for description, melting point, acid dissociation constant, optical rotation, distribution coefficient, solubility, hygroscopicity, crystalline polymorphism, and particle size distribution. [redacted].

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

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

[redacted].

Related substances (Related Substance 1, Related Substance 2) have been identified as critical quality attributes (CQAs) by employing the quality by design (QbD) approach, and identification of critical process parameters (CPPs) and establishment of the control strategy based on quality risk assessments and design of experiments have also been undertaken.

The reaction step and purification step have been defined as critical steps. [redacted].

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

The proposed specifications for the drug substance include content, description, identification (UV, IR), optical rotation, purity (1, heavy metals; 2, related substances [high performance liquid chromatography (HPLC)]; 3, residual solvents [gas chromatography (GC)]), water content, residue on ignition, L-proline content (HPLC), and assay (HPLC).

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

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

Table 1. Stability studies for drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	Pilot 3 batches	25°C	60% RH	Polyethylene bag (double) + fiber drum	12 months
Accelerated testing	Pilot 3 batches	40°C	75% RH		6 months

Based on the above, a retest period of 24 months has been proposed for the drug substance when stored in double polyethylene bags within fiber drums at room temperature, in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003; ICH Q1E Guideline). Long-term testing will be continued up to [redacted] months (Study data at [redacted] months will dictate decision on continuation).

[2] [redacted]
[3] [redacted]
[4] [redacted]

2.A.(2) Drug product

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

The drug product is immediate-release tablets (film-coated tablets) containing 32.15 mg or 64.3 mg of the drug substance (25 mg or 50 mg as ipragliflozin, respectively) per tablet. [redacted].

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

[redacted].

[redacted].

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

[redacted].

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

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

Table 2. Stability studies for drug product

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

Based on the above, a shelf life of 36 months has been proposed for the drug product when packaged in PTP (polyvinyl chloride films/aluminum foils) and stored at room temperature, in accordance with the ICH Q1E Guideline. Long-term testing will be continued up to [redacted] months.

2.B Outline of the review by PMDA

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

2.B.(1) Justification for control strategy for drug substance

PMDA asked the applicant to explain a justification for the starting materials.

The applicant responded as follows:

[redacted]

[redacted].

PMDA asked the applicant to explain a justification for attributes/parameters not determined as CQAs or CPPs.

The applicant responded as follows:
Organic impurities other than the Related Substance 1 and Related Substance 2 were not determined as CQAs because a spike test showed the adequate capability of the manufacturing process to remove such impurities. [redacted].

PMDA accepted the response.

2.B.(2) Justification for control strategy for drug product

[redacted].

The applicant responded as follows:

[redacted].

[redacted].

The applicant responded as follows:

[redacted].

PMDA accepted the response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

As primary pharmacodynamic studies, *in vitro* studies on mechanism of action, and *in vivo* studies on urinary glucose excretion promoting activity and hypoglycaemic activity in normal animals and animal models of diabetes were conducted. As secondary pharmacodynamic studies, studies on effects on glucose absorption in the gastrointestinal tract etc. were conducted. As safety pharmacology studies, studies on the impact on central nervous, cardiovascular, and respiratory

systems were conducted in compliance with GLP standards. As pharmacodynamic drug interaction studies, studies on combination effect with various oral hypoglycaemic agents were conducted. Dose levels of oral hypoglycaemic agents used in the pharmacodynamic drug interaction studies and of ipragliflozin L-proline (hereinafter referred to as ipragliflozin) are expressed as free base.

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

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

(a) Inhibitory effect on human SGLT2 and SGLT1 (4.2.1.1-1)

The inhibitory effect of ipragliflozin on SGLT2 and SGLT1 as measured by sodium-dependent ^{14}C-methyl-α-D-glucopyranoside (^{14}C-AMG) uptake was evaluated in human SGLT2- or SGLT1-expressing CHO cells. As a result, IC_{50} values (geometric mean and its 95% confidence interval [CI]) were 7.38 [6.75, 8.07] and 1880 [1570, 2240] nmol/L, respectively.

(b) Inhibitory effect on human GLUT (4.2.1.1-2)

Caco-2 cells derived from human colon cancer have been found to express glucose transporter 1 (GLUT1), GLUT2, and GLUT3, and HepG2 cells derived from human liver cancer to express GLUT1 and GLUT2.[5] Therefore, the inhibitory effect of ipragliflozin (0.3, 1, 3 μmol/L) on GLUT as measured by ^{14}C-2-deoxy-D-glucose (2DG; a substrate of GLUT) uptake was evaluated in these cells. As a result, decrease in uptake of 2DG was not observed in either cell type.

(c) Inhibitory effect on various receptors, ion channels, transporters, and enzymes (4.2.1.1-3, 4.2.1.1-4)

An evaluation on the inhibitory effect of ipragliflozin (10 μmol/L) on 54 types of receptors, ion channels, and transporters, and 3 types of enzymes showed that the inhibition rates for specific ligand binding were 71.35% for the dopamine transporter, 57.97% for the serotonin 5-HT_{2B} receptor, and <50% for the others. IC_{50} values of ipragliflozin against the dopamine transporter and serotonin 5-HT_{2B} receptor were 5.54 μmol/L and 9.21 μmol/L, respectively.[6]

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

(a) Antihyperglycemic activity in normal mice (single-dose) (4.2.1.1-5)

A single oral dose of ipragliflozin (0.03, 0.1, 0.3, 1, 3, 10, 30, 100 mg/kg) or vehicle[7] was administered to fasted male mice (n = 4/group), and oral glucose tolerance test (OGTT) was performed with glucose solution (2 g/kg) at 0.5 hours post-dose. As a result, the blood glucose AUC up to 6 hours after OGTT decreased in a dose-dependent manner and significantly decreased at ≥0.1 mg/kg compared with vehicle. When ipragliflozin was administered in the same manner to fasted animals without OGTT, the blood glucose AUC during the first 6 hours post-dose decreased in a dose-dependent manner and significantly decreased at ≥10 mg/kg compared with vehicle. In addition, ipragliflozin was administered in the same manner to fed animals. The urine volume[8] measured from 0 to 12 hours post-dose and from 12 to 24 hours post-dose increased in a dose-dependent manner and significantly increased at ≥3 mg/kg and ≥10 mg/kg, respectively, compared with vehicle. Similarly, the urinary glucose excretion[9] increased in a dose-dependent manner, and the increases observed from 0 to 12 hours post-dose and from 12 to 24 hours post-dose were significant at ≥1 mg/kg and ≥10 mg/kg, respectively, compared with vehicle.

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5 Harris DS et al., *Proc Natl Acad Sci USA.* 1992;89:7556-7560, Hah J et al., *J Cell Physiol.* 1992;152:56-63, Pessin JE et al., *Annu Rev Physiol.* 1992;54:911-930

6 This represents 21- to 31-fold C_{max} (2030 ng/mL) at the maximum recommended clinical dose (100 mg/day) observed in the study on circadian variation of blood glucose in Japanese patients with type 2 diabetes mellitus (Study CL-0070), or 34- to 51-fold C_{max} of plasma unbound ipragliflozin (0.18-0.27 μmol/L) calculated from the plasma protein binding (94.6%-96.5%) in humans.

7 0.5% methylcellulose solution

8 Calculated from weight assuming the urine specific gravity as 1

9 The product of urinary glucose concentration and urine volume

(b) Urinary glucose excretion promoting activity in normal and diabetes model mice (single-dose) (4.2.1.1-6)

A single oral dose of ipragliflozin (0.01, 0.03, 0.1, 0.3, 1, 3, 10 mg/kg) or vehicle was administered to fed male normal mice (n = 4/group), nicotinamide/streptozotocin-treated mice[10] (NA/STZ mice) (8 weeks of age, n = 4/group), and KK-A^y mice (11 weeks of age, n = 4/group). As a result, the urine volume[8] during the first 24 hours post-dose increased in normal and NA/STZ mice in a dose-dependent manner, with the increase being significant at ≥3 mg/kg compared with vehicle, but no significant increase was observed in KK-A^y mice. Urine volume was measured at 6-hour intervals for 24 hours post-dose. The maximum urine volume tended to be observed between 6 and 12 hours post-dose in normal and NA/STZ mice and between 12 and 18 hours post-dose in KK-A^y mice. Urine volume measured in normal and NA/STZ mice treated with ≥1 mg/kg between 6 and 12 hours post-dose was significantly higher than that in the control group. Urine volume measured in KK-A^y mice between 12 and 18 hours post-dose was not significantly different from that in the control group. In addition, urine volume tended to be minimized between 18 and 24 hours post-dose in all mice, and no significant difference from the control group was observed in urine volume during this interval. A dose-dependent increase in urinary glucose excretion[9] during the first 24 hours post-dose was observed in all mice, with the increase being significant at ≥0.3 mg/kg compared with vehicle. Urinary glucose excretion[9] was measured at 6-hour intervals for 24 hours post-dose. The maximum and minimum excretions tended to be observed in all mice between 6 and 12 hours post-dose and between 18 and 24 hours post-dose, respectively. Urinary glucose excretion observed between 6 and 12 hours post-dose significantly increased in normal and NA/STZ mice at ≥0.3 mg/kg and KK-A^y mice at ≥1 mg/kg compared with vehicle. In addition, urinary glucose excretion observed between 18 and 24 hours post-dose significantly increased in normal, NA/STZ, and KK-A^y mice at ≥3 mg/kg, ≥3 mg/kg, and ≥10 mg/kg, respectively, compared with vehicle.

(c) Hypoglycaemic activity in KK-A^y mice (single-dose) (4.2.1.1-7)

Following a single oral dose of ipragliflozin (0.1, 0.3, 1 mg/kg) or vehicle[7] in male KK-A^y mice (8 weeks of age, n = 6/group), the fasting blood glucose AUC during the first 8 hours post-dose of ipragliflozin decreased in a dose-dependent manner, with the decrease being significant in all dose groups compared with the control group. One week later, ipragliflozin or vehicle[7] was administered in the same manner and, after 12 hours of fasting, OGTT was performed. As a result, the gain in blood glucose AUC[11] up to 2 hours after OGTT decreased in a dose-dependent manner, with the decrease being significant in all dose groups compared with the control group.

(d) Hypoglycaemic activity in STZ treated rats (single-dose) (4.2.1.1-8)

A single oral dose of ipragliflozin (0.1, 0.3, 1 mg/kg) or vehicle[7] was administered to male rats (10 weeks of age, n = 6/group) 8 days after intravenous administration of STZ (50 mg/kg). As a result, the fasting blood glucose AUC during the first 8 hours post-dose of ipragliflozin decreased in a dose-dependent manner, with the decrease being significant in all dose groups compared with the control group. Six days later, ipragliflozin or vehicle[7] was administered in the same manner and, after 12 hours of fasting, OGTT was performed. As a result, the gain in blood glucose AUC[11] up to 2 hours after OGTT decreased in a dose-dependent manner, with the decrease being significant at ≥0.3 mg/kg compared with vehicle.

(e) Antihyperglycemic activity in normal and diabetes model mice (single-dose) (4.2.1.1-9)

A single oral dose of ipragliflozin (0.1, 0.3, 1 mg/kg) or vehicle[7] was administered to fasted normal male mice (n = 4/group), NA/STZ mice[10] (8 weeks of age, n = 4/group), and KK-A^y mice

[10] These mice had received an intraperitoneal administration of nicotinamide (1000 mg/10 mL/kg) after an overnight fast and, 90 minutes later, an intraperitoneal administration of streptozotocin (150 mg/10 mL/kg, pH 4.5) 7 days before being used in the study.

[11] Increment from the value before glucose or liquid nutrient loading

(11 weeks of age, n = 4/group) and, 0.5, 6, and 12 hours later, liquid nutrient[12] was administered orally. As a result, the gain in blood glucose AUC[11] during the first 2 hours post-load of liquid nutrient decreased in a dose-dependent manner in each of these models at any timepoint of liquid nutrient loading, with the decrease being significant in all ipragliflozin dose groups compared with the control group.

(f) HbA1c-decreasing activity in KK-A^y mice (repeat-dose) (4.2.1.1-10)

Ipragliflozin (0.3, 1 mg/kg) or vehicle[7] was orally administered once daily for 30 days to male KK-A^y mice (8 weeks of age, n = 7/group). As a result, fed blood glucose at 12 hours post-dose on Day 28 significantly decreased in the 1 mg/kg group compared with the control group, and HbA1c significantly decreased in the two dose groups compared with the control group. No significant difference was observed in plasma insulin levels. No significant difference in urine volume[8] during the first 24 hours post-dose on Day 30 was observed compared with the control group, but urinary glucose excretion[9] significantly increased in the 1 mg/kg group compared with the control group. No significant differences were observed in body weight, body weight gain, and food consumption over time compared with the control group based on weekly measurements of body weight and food consumption.

(g) Effects on the pancreas in KK-A^y mice (repeat-dose) (4.2.1.1-14, Reference data)

Ipragliflozin (0.03, 0.1, 0.3, 1, 3 mg/kg) or vehicle[7] was orally administered once daily for 21 days to male KK-A^y mice (7 weeks of age, n = 6/group). As a result, HbA1c and plasma insulin values significantly decreased at ≥0.3 mg/kg compared with vehicle. In addition, a significant increase in pancreatic insulin content was observed at ≥1 mg/kg compared with vehicle.

(h) Effects on the pancreas in db/db mice (repeat-dose) (4.2.1.1-11)

Ipragliflozin (0.1, 0.3, 1 mg/kg) or vehicle[7] was orally administered once daily for 28 days to male db/db mice (7 weeks of age, n = 7-8/group). As a result, the pancreatic insulin content significantly increased at 1 mg/kg compared with vehicle. In addition, based on a blinded evaluation (scored on a 5-point scale[13]) of pancreatic tissue sections immunostained for insulin, a decrease in insulin-positive granules that was observed in the control group was found to be ameliorated, and the median score significantly decreased in all dose groups compared with the control group. HbA1c decreased in a dose-dependent manner and significantly decreased in all dose groups compared with the control group (mean ± standard error was 7.1% ± 0.2%, 6.3% ± 0.4%, 6.1% ± 0.1%, and 5.5% ± 0.1% in the control, 0.1, 0.3, and 1 mg/kg groups, respectively). The plasma insulin value significantly increased in the 1 mg/kg group compared with the control group, and feeding blood glucose significantly decreased in all dose groups compared with the control group. No significant differences were observed in body weight gain and food consumption compared with the control group.

3.(i).A.(1).3) Pharmacological activity of human metabolite (4.2.1.1-12, 4.2.1.1-13)

The inhibitory effect of human metabolites[14] of ipragliflozin (M1, M2, M3, M4, M5, M6) on SGLT2 and SGLT1 as measured by sodium-dependent ^{14}C-AMG uptake was evaluated with human SGLT2- or SGLT1-expressing CHO cells. As a result, IC_{50} against SGLT2 (geometric mean and its 95% CI) were 686 [167, 2820], 1870 [179, 19,600], 7110 [1280, 39,500], 3690 [532, 25,700], 392 [166, 926], and 399 [303, 525] nmol/L, respectively, representing approximately 53- to 963-fold that of ipragliflozin (7.38 nmol/L). IC_{50} against SGLT1 was ≥47,500 nmol/L for all the metabolites. In addition, an evaluation of inhibition of 54 types of receptors, ion channels, and transporters, and 3 types of enzymes by the major metabolite in human plasma (M2) showed that

[12] Ensure-H 20 mL/kg

[13] 0, Negative; 1, Minimal; 2+, Mild; 3+, Moderate; 4, Severe

[14] 6-hydroxylated benzothiophene ring and 2'-O-β-glucuronide conjugate of glucose ring (M1), 2'-*O*-β-glucuronide conjugate of glucose ring (M2), 6'-*O*-β-glucuronide conjugate of glucose ring (M3), 3'-*O*-β-glucuronide conjugate of glucose ring (M4), 6-*O*-β-glucuronide conjugate of benzothiophene ring (M5), and 6-O-sulfate conjugate of benzothiophene ring (M6)

the inhibition rate at the concentration of 10 μmol/L was <50% for all the molecules.

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

3.(i).A.(2).1) Effects on body weight and fat mass in rats on high-fat diet (repeat-dose) (4.2.1.2-1)

Male rats (n = 7-8/group) were fed a high-fat diet (containing 45% fat) for 22 days and subsequently received ipragliflozin (1, 3, 10 mg/kg) or vehicle[7] orally once daily for 30 days with a high-fat diet. In addition, to a group of rats (n = 8) fed a normal diet instead of the high-fat diet, vehicle[7] was administered in the same manner. As a result, body weight gain and fat mass around the epididymis significantly increased in the control rats on a high-fat diet compared with the rats on a normal diet and significantly decreased in the 10 mg/kg group compared with the control group. In addition, urine volume, [8] urinary glucose excretion, [9] and urinary 3-hydroxybutyric acid over 24 hours at 3 weeks post-dose significantly increased in all ipragliflozin groups compared with the control group. There were no changes in blood glucose, plasma 3-hydroxybutyric acid, and plasma free fatty acids under fed conditions, but under fasted conditions, these parameters increased at ≥10 mg/kg, ≥10 mg/kg, and ≥3 mg/kg, respectively, compared with vehicle. Plasma insulin levels decreased in all dose groups under both fasted and fed conditions.

3.(i).A.(2).2) Effects on glucose absorption in the gastrointestinal tract in normal mice (single-dose) (4.2.1.2-2)

A single oral dose of ipragliflozin (0.3, 1, 3, 10, 30 mg/kg) or vehicle[7] was administered to fasted male mice (n = 12/group) and, 15 minutes later, liquid nutrient[12] was loaded. The gastrointestinal tracts (stomach, duodenum + jejunum, ileum, cecum, colon + rectum) were resected at 0.5, 1, and 2 hours after the liquid nutrient load (n = 4/group/timepoint) and saccharide content (glucose, fructose, maltose, sucrose) in the organs was measured. A significant increase in glucose content was observed in the 30 mg/kg group at 0.5 and 1 hour after the liquid nutrient load compared with the control group. There were no significant changes in the content of the other saccharides. In addition, blood glucose decreased in a dose-dependent manner, with the decrease being significant up to 1 hour post-load of the liquid nutrient in all dose groups compared with the control group.

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

3.(i).A.(3).1) Effects on central nervous system (4.2.1.3-1)

A single oral dose of ipragliflozin (10, 100, 1000 mg/kg) or vehicle[7] was administered to male rats (n = 6/group), and general symptoms and behavior were assessed by a modified Irwin test up to 24 hours post-dose. No effect was observed in any dose group. Maximum plasma concentration (C_{max}) at a dose of 1000 mg/kg was 73,300 ng/mL,[15] representing approximately 36 times (26-56 times if based on C_{max} of unbound ipragliflozin) the C_{max} (2030 ng/mL)[16] at the maximum recommended clinical dose (100 mg/day).

3.(i).A.(3).2) Effects on cardiovascular and respiratory systems

(a) Effects on hERG currents (4.2.1.3-2)

Effects of ipragliflozin (0.1, 1, 10 μM) or vehicle[17] on hERG potassium current were evaluated using HEK293 cells expressing hERG channels. As a result, the inhibition rate (mean ± standard deviation [SD]) of hERG current by ipragliflozin 0.1, 1, and 10 μM treatment was 9.1% ± 4.3%, 18.8% ± 7.0%, and 17.4% ± 3.0%, respectively, or -0.6% ± 4.8%, 10.1% ± 7.7%, and 8.5% ± 3.4% after adjustment for the inhibition rate by vehicle treatment (9.7% ± 3.8%). Although a significant increase in the adjusted inhibition rate was observed after 1 μM treatment compared with after vehicle treatment (0.0% ± 4.2%), there were no significant changes after 10 μM

[15] The results from a 2-week oral toxicity study in rats (4.2.3.2-2)
[16] The results from the study on circadian variation of the blood glucose in Japanese patients with type 2 diabetes mellitus (Study CL-0070)
[17] 0.1% dimethyl sulfoxide

treatment, showing no dose-dependency. The concentration of 10 μM was approximately 37- to 56-fold the C_{max} of unbound ipragliflozin (71-110 ng/mL)[15] at the maximum recommended clinical dose (100 mg/day).

(b) Effects on cardiac action potential (4.2.1.3-3)

Papillary muscle preparations from guinea pigs were perfused with vehicle[17] or different concentrations of ipragliflozin (0.1, 1, 10 μM) in a sequential manner to evaluate effects on cardiac action potential. As a result, no effects were observed on action potential duration (APD_{30}, APD_{90}), action potential amplitude, maximum rate of rise, or resting membrane potential.

(c) Effects on cardiovascular and respiratory systems (4.2.1.3-4)

Single oral doses of ipragliflozin (10, 100, 1000 mg/kg) or vehicle[7] were administered at 7-day intervals to unanesthetized male monkeys (n = 4) using a Latin square design, and effects on cardiovascular and respiratory systems were evaluated over time using telemetry. As a result, no apparent effects were observed on blood pressure, heart rate, electrocardiogram (PR, QRS, RR, QT, QTc[18]), respiratory rate, or blood gas at up to 1000 mg/kg. QRS interval before dosing and at 2 and 4 hours post-dose (mean ± SD) was 36.0 ± 1.8, 34.5 ± 1.9, and 34.5 ± 2.5 msec, respectively, in the control group; 35.0 ± 2.4, 35.5 ± 1.9, and 36.5 ± 3.4 msec, respectively, in the 10 mg/kg group; and 35.3 ± 2.4, 36.0 ± 3.3, and 37.5 ± 2.5 msec, respectively, in the 1000 mg/kg group. QRS prolongation was significant in the 10 mg/kg group at 4 hours post-dose and in the 1000 mg/kg group at 2 and 4 hours post-dose[19] compared with the control group. A significant increase in respiratory rate was observed at 0.5 hours post-dose in the 10 mg/kg group compared with the control group, with no dose-dependency. In the evaluation of clinical signs, discoloration of stools (white)[20] was observed in all animals at 24 hours post-dose and 2 animals at 48 hours post-dose in the 1000 mg/kg group, but no other signs were observed. C_{max} values of ipragliflozin at doses of 10, 100, and 1000 mg/kg were 3990 ± 730, 36,900 ± 4000, and 75, 100 ± 13,200 ng/mL, respectively, representing approximately 2, 18, and 37 times the C_{max} (2030 ng/mL) of ipragliflozin,[16] respectively, at the maximum recommended clinical dose (100 mg/day) (approximately 1.7-3.8, 16-35, and 32-72 times, respectively, if based on the C_{max} of unbound ipragliflozin).

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

3.(i).A.(4).1) Effect of ipragliflozin in combination with voglibose in KK-A^y mice (single-dose) (4.2.1.4-1)

Fasted male KK-A^y mice (7 weeks of age, n = 8/group) were treated with a single oral dose of ipragliflozin (0.3 mg/kg) either alone or in combination with voglibose (0.3 mg/kg), voglibose (0.3 mg/kg) alone, or vehicle,[7] followed 0.5 hours later by the liquid nutrient load.[12] As a result, the gain in blood glucose AUC[11] during the first 2 hours post-load of liquid nutrient significantly decreased in each of the monotherapy groups compared with the control group, and in the combination therapy group compared with each of the monotherapy groups.

3.(i).A.(4).2) Effect of ipragliflozin in combination with sitagliptin in normal mice (single-dose) (4.2.1.4-2)

Fasted male mice (n = 10/group) were treated with a single oral dose of ipragliflozin (0.3 mg/kg) either alone or in combination with sitagliptin[21] (1 mg/kg), sitagliptin[21] (1 mg/kg) alone, or vehicle[7] followed 0.5 hours later by the liquid nutrient load.[12] As a result, blood glucose AUC during the first 2 hours post-load of liquid nutrient significantly decreased in each of the monotherapy groups compared with the control group, and in the combination therapy group

[18] Corrected QT interval using Fridericia's correction formula

[19] The applicant discusses that this alteration is not related to ipragliflozin because the change from baseline was minor and within the variability and no dose dependency was observed.

[20] The applicant considers that the discoloration of stools was caused by contamination by ipragliflozin.

[21] Purchased from Merck Ltd. and used after extraction.

compared with each of the monotherapy groups.

3.(i).A.(4).3) Effect of ipragliflozin in combination with nateglinide in normal mice (single-dose) (4.2.1.4-3)

Fasted male mice (n = 8/group) were treated with a single oral dose of ipragliflozin (0.3 mg/kg) either alone or in combination with nateglinide (25 mg/kg), nateglinide (25 mg/kg) alone, or vehicle[7] followed 0.5 hours later by OGTT. As a result, blood glucose AUC up to 2 hours after OGTT significantly decreased in each of the monotherapy groups compared with the control group, and in the combination therapy group compared with each of the monotherapy groups.

3.(i).A.(4).4) Effect of ipragliflozin in combination with metformin in KK-A^y mice (repeat-dose) (4.2.1.4-4)

Male KK-A^y mice (8 weeks of age, n = 8/group) were treated orally with ipragliflozin (0.3 mg/kg, once daily) either alone or in combination with metformin hydrochloride (100 mg/kg/dose, twice daily), metformin hydrochloride (100 mg/kg/dose, twice daily) alone, or vehicle[7] for 28 days. As a result, HbA1c significantly decreased in each of the monotherapy groups compared with the control group, and in the combination therapy group compared with each of the monotherapy groups. No difference was observed in fed blood glucose between the combination therapy and each of the monotherapy groups.

3.(i).A.(4).5) Effect of ipragliflozin in combination with pioglitazone in KK-A^y mice (repeat-dose) (4.2.1.4-5)

Male KK-A^y mice (8 weeks of age, n = 8/group) were treated orally with ipragliflozin (0.3 mg/kg) either alone or in combination with pioglitazone hydrochloride (10 mg/kg), pioglitazone hydrochloride (10 mg/kg) alone, or vehicle[7] for 28 days. As a result, HbA1c significantly decreased in each of the monotherapy groups compared with the control group, and in the combination therapy group compared with each of the monotherapy groups. Fed blood glucose significantly decreased in the combination therapy group compared with the ipragliflozin alone group, but no difference was observed between the combination therapy and pioglitazone hydrochloride alone groups.

3.(i).A.(4).6) Effect of ipragliflozin in combination with glibenclamide in normal mice (single-dose) (4.2.1.4-6, 7)

Male mice (n = 4/group) were treated with a single oral dose of ipragliflozin (0.3 mg/kg) either alone or in combination with glibenclamide (0.3, 1, 3, 10, 30 mg/kg), or vehicle,[7] followed 0.5 hours later by OGTT. As a result, blood glucose AUC up to 6 hours after OGTT in the combination therapy groups decreased glibenclamide-dose-dependently, and a significant decrease in blood glucose AUC was observed at ≥1 mg/kg compared with ipragliflozin alone. In addition, animals were treated under fasted conditions in the same manner without OGTT. Blood glucose AUC during the first 6 hours post-dose decreased glibenclamide-dose-dependently, and a significant decrease in blood glucose AUC was observed at ≥3 mg/kg compared with ipragliflozin alone.

Male mice (n = 4/group) were treated with a single oral dose of glibenclamide (3 mg/kg) either alone or in combination with ipragliflozin (0.03, 0.1, 0.3, 1, 3, 10, 30 mg/kg), or vehicle,[7] followed by OGTT in the same manner. As a result, blood glucose AUC up to 6 hours after OGTT in the combination therapy groups decreased ipragliflozin-dose-dependently, and a significant decreased in blood glucose AUC was observed at ≥0.1 mg/kg compared with glibenclamide alone. In addition, animals were treated under fasted conditions in the same manner without OGTT. Blood glucose AUC during the first 6 hours post-dose decreased ipragliflozin-dose-dependently, and a significant decrease in blood glucose AUC was observed at ≥10 mg/kg compared with glibenclamide alone.

3.(i).A.(4).7) Effect of ipragliflozin in combination with metformin on fasting blood glucose in KK-A^y mice (single- or repeat-dose) (4.2.1.4-8)

Male KK-A^y mice (11 weeks of age, n = 4-5/group) received single or repeated oral doses for 28 days of ipragliflozin (0.3, 1, 3, 10, 30 mg/kg, once daily) either alone or in combination with metformin hydrochloride (200 mg/kg/dose, twice daily), metformin hydrochloride (200 mg/kg/dose, twice daily) alone, or vehicle,[7] and fasting blood glucose during the first 6 hours post-dose was evaluated. As a result, in the combination therapy groups, blood glucose levels after a single dose or repeated doses decreased compared with the metformin hydrochloride alone group, and the number of animals with blood glucose of ≤70 mg/dL was higher than those in the ipragliflozin alone groups. In addition, 1 animal (repeated dose of 10 mg/kg of ipragliflozin alone) had blood glucose of ≤40 mg/dL in the ipragliflozin alone groups while 5 animals (2 animals in a single dose of concomitant use with ipragliflozin 10 mg/kg, 3 animals in repeat-dose of concomitant use with ipragliflozin 30 mg/kg) did in the combination therapy groups. All animals including those with decreased blood glucose levels showed no hypoglycaemic symptoms (convulsion, coma).

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

3.(i).B.(1) Mechanism of action

The applicant explained the mechanism of action of ipragliflozin. Ipragliflozin inhibits SGLT2 in the renal tubules which is responsible for glucose reabsorption, resulting in the promotion of urinary glucose excretion leading to a decrease in blood glucose levels.

PMDA asked the applicant to explain the biological distribution, functions, and homology with SGLT2 of each SGLT isoform as well as selectivity of ipragliflozin for SGLT2, and then discuss the pharmacological activity of ipragliflozin in humans in view of species differences between humans and animal species used in non-clinical studies.

The applicant responded as follows:
SGLT2 has been reported to be expressed specifically in the proximal renal tubules in humans, rats, and mice.[22] In addition, analyses on SGLT2 mutations found in patients with renal glycosuria (Santer R et al., *J Am Soc Nephrol.* 2003;14(11):2873-2882) and on SGLT2-knockout mice (Vallon V et al., *J Am Soc Nephrol.* 2011;22(1):104-112) suggests that SGLT2 plays a role in glucose reabsorption in the tubules and shows no species differences in its functions or distribution among humans, rats, and mice. IC_{50} values of ipragliflozin against SGLT2 in humans, rats, and mice (geometric mean and its 95% CI) are 7.38 [6.75, 8.07], 6.73 [4.07, 11.1], and 5.64 [3.76, 8.47] nmol/L, respectively, indicating comparable inhibition potencies among these species (4.2.1.1-1, Tahara A et al., *Naunyn-Schmiedeberg's Arch Pharmacol.* 2012;385(4):423-436).

Regarding isoforms other than SGLT2, SGLT1 has the main functions of glucose absorption in the small intestine and glucose reabsorption in the renal tubules, and exhibits 59% homology with SGLT2. A study using SGLT2- or SGLT1-expressing CHO cells showed that ipragliflozin was 254 times more selective for SGLT2 than for SGLT1 (4.2.1.1-1). Human SGLT3 has been reported to be able to mediate intracellular sodium uptake but is unable to transport glucose (Kothinti RK et al., *Eur J Pharmacol.* 2012;690(1-3):77-83). SGLT5 has been reported to enhance monosaccharide uptake in human embryonic kidney (HEK293) cells overexpressing human SGLT5 (Grempler R et al., *FEBS Lett.* 2012;586(3):248-253) and represent a major transporter responsible for renal fructose reabsorption (Fukuzawa T et al., *PLoS One.* 2013;8(2):e56681). The applicant considers that the functions of SGLT4 and SGLT6 are not yet fully understood in detail today. The homology between SGLT2 and each of SGLT3 to SGLT6 has been reported to

[22] Kanai Y et al., *J Clin Invest.* 1994;93:397-404, You G et al., *J Biol Chem.* 1995;270:29365-29371, Chen J et al., *Diabetes Ther.* 2010;1:57-92, Vallon V et al., *J Am Soc Nephrol.* 2011;22:104-112

be 49% to 58%.[23] In addition, although not all isoforms have been investigated, a preliminary study on inhibitory effect of ipragliflozin on SGLT4 and SGLT5 showed that IC_{50} values against the isoforms (geometric mean and its 95% CI) were 3790 [217, 66,200] and 3110 [565, 17,100] nmol/L, respectively, and ipragliflozin was 514 and 421 times more selective for SGLT2 than for SGLT4 and SGLT5, respectively.

Based on the above, ipragliflozin is considered to exhibit hypoglycaemic activity also in humans through urinary glucose excretion promoting activity by selectively inhibiting SGLT2, a transporter which is expressed specifically in the renal tubules in humans, rats, and mice and responsible for glucose reabsorption.

PMDA accepted the response because ipragliflozin has been confirmed to be selective for SGLT2 based on the available results of the studied isoforms, although functions and other characteristics of some SGLT isoforms are not unknown at present and ipragliflozin has not been investigated for all SGLT isoforms.

3.(i).B.(2) Persistence of effects

PMDA asked the applicant to explain the persistence of the effects of ipragliflozin.

The applicant responded as follows:

The effects of ipragliflozin on urinary glucose excretion were investigated in the study where urine samples were collected every 6 hours through 24 hours post-dose from normal, NA/STZ, and KK-A^y mice (4.2.1.1-6). Urine volume peaked between 6 and 12 hours post-dose in normal and NA/STZ mice, and significantly increased at ≥1 mg/kg compared with vehicle. In KK-A^y mice, urine volume peaked between 12 and 18 hours post-dose, and no significant increase was observed as compared with the control group. Minimum urine volume was observed between 18 and 24 hours post-dose in all mice tested, and no significant differences were observed as compared with the control group. Urinary glucose excretion between 18 and 24 hours post-dose was significantly increased by ipragliflozin at ≥3 mg/kg for normal and NA/STZ mice, and at 10 mg/kg for KK-A^y mice compared with vehicle. The plasma ipragliflozin concentrations at 24 hours after oral dose of 3 mg/kg in normal, NA/STZ, and KK-A^y mice were calculated to be within the range from 0.15 to 1.26 ng/mL as plasma unbound ipragliflozin concentrations.[24] On the other hand, IC_{50} of ipragliflozin for SGLT2 inhibition was 2.28 ng/mL in normal and KK-A^y mice (Tahara A et al., *Naunyn-Schmiedeberg's Arch Pharmacol*. 2012;385:423-436). These results suggest that ipragliflozin at doses of 3 to 10 mg/kg may maintain an increase in urinary glucose excretion induced by the inhibition of SGLT2 and the resultant hypoglycaemic activity even from 18 to 24 hours after administration. Regarding the effects of ipragliflozin on blood glucose, antihyperglycemic activity of ipragliflozin was evaluated in normal, NA/STZ, and KK-A^y mice. Significantly potent hypoglycaemic activity was observed at ≥0.1 mg/kg even at 12 hours after a single oral dose compared with vehicle (4.2.1.1-9). In addition, for rodents, in consideration of the necessity for investigation on glycemic control during the nighttime (dark period) as the main period of feeding behavior, effects of once-daily evening dosing of ipragliflozin has been evaluated in the repeated oral dose studies in KK-A^y and db/db mice. As a result, casual blood glucose and HbA1c levels in KK-A^y mice at 12 hours post-dose on Day 28 significantly decreased in the 1 mg/kg group and in the ≥0.3 mg/kg groups, respectively, compared with the control group (4.2.1.1-10, 4.2.1.1-11). In the studies in db/db mice, repeated doses of ipragliflozin at any dose of 0.1, 0.3, and 1 mg/kg for 28 days significantly decreased casual blood glucose and HbA1c levels compared with vehicle (4.2.1.1-11, 4.2.1.1-14). Based on

[23] Wright EM et al., *Pflugers Arch.* 2004;447(5):510-518, Chen J et al., *Diabetes Ther.* 2010;1(2):57-92, Mather A et al., *Kidney Int.* 2011;79(Suppl 120):S1-6

[24] Calculated from the results of preliminary investigation on blood levels 24 hours after an oral dose of 3 mg/kg of ipragliflozin in normal, NA/STZ, and KK-A^y mice (blood levels at 24 hours after an oral dose of 3 mg/kg of ipragliflozin were within 3.2-18.5 ng/mL) and the plasma protein binding in mice (93.2%-95.4%, 4.2.2.3-6).

the above, the applicant has determined that once-daily administration of ipragliflozin can be expected to show an adequate effect.

PMDA accepted the response [for persistence of the effects in humans, see "4.(iii).B.(5).1) Dosage regimen"].

3.(i).B.(3) Activities other than urinary glucose excretion promoting activity

PMDA asked the applicant to explain possible activities of ipragliflozin, including those resulting from SGLT1 inhibition except the urinary glucose excretion promoting activity, based on the mechanism of action of ipragliflozin.

The applicant responded as follows:

Based on findings in SGLT2- and SGLT1-knockout mice[25] and non-clinical data, increase in urine volume, decreased body fluid volume, and variation in blood electrolytes that are associated with the increase in urinary glucose excretion, as well as urinary tract and genital infections, impact on renal function, bone metabolism, and ketone body metabolism are discussed as possible effects resulting from SGLT2 inhibition. In addition, as a possible effect resulting from SGLT1 inhibition, diarrhea is discussed.

As for increase in urine volume, decreased body fluid volume, and variation in blood electrolytes, approximately 90% of the glucose filtered through the glomerulus is reabsorbed by SGLT2, primarily located in S1 and S2 of the proximal tubules, and the remaining 10% is reabsorbed by SGLT1, primarily located in S3 (Mather A et al., *Kidney Int.* 2011;79[Suppl 120]:S1-6). SGLT2 is a sodium glucose cotransporter, and its inhibition causes an elevation of urinary glucose and sodium concentrations leading to increase in urine volume associated with osmotic diuresis, possibly resulting in a decrease in body fluid volume, increase in excretion of electrolytes such as potassium and chloride, and the resultant decrease in plasma electrolyte concentrations. The results of an investigation on effects of ipragliflozin on urinary glucose excretion and urine volume in ICR, NA/STZ, and KK-A^y mice showed that urinary glucose excretion significantly increased at ≥0.3 mg/kg compared with vehicle. In addition, all animals treated with ipragliflozin at ≥3 mg/kg showed a significant increase in urine volume or a trend toward it compared with the control animals (4.2.1.1-6). However, no results suggesting decreased body fluid volume or variation in plasma electrolytes were obtained in non-clinical studies. As for urinary tract and genital infections, an increase in urogenital lesions was observed in the 104-week carcinogenicity study in mice (4.2.3.4.1-3), but the applicant considered that it was a secondary effect due to deteriorated hygiene caused by contamination of the rearing cage floors with highly-viscous glucose-containing urine excreted due to the urinary glucose excretion promoting activity of ipragliflozin. As for impact on renal function, in the repeat-dose toxicity studies in rats and monkeys, urinary N-acetyl-β-D-glucosaminidase (NAG) excretion and urinary β2-microglobulin excretion increased (4.2.3.2-4, 4.2.3.2-8). These changes have also been observed in other SGLT2 inhibitors with urinary glucose excretion promoting activity (4.2.3.7.7-1 to 4.2.3.7.7-4), suggesting that the changes resulted primarily from exposure of tubular epithelial cells to the high concentration sugar-containing urine induced by a SGLT2 inhibitor. It has been confirmed that no exacerbation due to a long-term exposure to ipragliflozin is observed, and that these are reversible changes ameliorable after withdrawal of the drug and not associated with dysfunctional changes in the kidney. In addition, because no noteworthy findings other than an increase in renal calcification were observed in the 104-week carcinogenicity study in rats (4.2.3.4.1-6), concerns about the impact of a long-term exposure to ipragliflozin on renal function is considered small. As for impact on bone metabolism, in the 13-week oral dose study (dose-ranging study) in rats, elevation of blood phosphorus and increases in the trabeculae of the sternum and femur were

[25] Gorboulev V et al., *Diabetes.* 2012;61:187-196, Jurczak MJ et al., *Diabetes.* 2011;60:890-898, Ly JP et al., *J Am Soc Nephrol.* 2011;22:113-123

observed at ≥250 mg/kg/day, and elevation of blood calcium was observed at ≥500 mg/kg/day (4.2.3.4.1-5). In the 104-week carcinogenicity study in rats, mineralization (calcification) of the arterial wall of the heart, tongue, and lung, and of the kidney and cornea, etc., as well as hyperostosis of the sternum and femur were observed at ≥12.5 mg/kg/day as non-neoplastic changes (4.2.3.4.1-6). These systemic metastatic calcification and hyperostosis are likely to have been caused by overintake of phosphorus and calcium associated with an increase in food consumption as a change in compensation for the urinary glucose excretion promoting activity of ipragliflozin. As for impact on ketone body metabolism, in the study where ipragliflozin was administered to high-fat diet fed obese rats for 3 weeks, urinary glucose excretion significantly increased in rats treated with ipragliflozin compared with the control rats, and body weight gain and fat mass around the epididymis significantly decreased in the 10 mg/kg group compared with the control group. In addition, administration of ipragliflozin increased fasting plasma free fatty acid and 3-hydroxybutyric acid levels which are markers of fatty acid oxidation (4.2.1.2-1). The elevation of these parameters suggests an enhancement of *in vivo* fat utilization. As for diarrhea, because glucose absorption in the gastrointestinal tract is mainly mediated by SGLT1, humans with genetic aberrations in SGLT1 experience serious diarrhea from birth.[26] SGLT1 knockout mice, which can survive on a diet containing neither glucose nor galactose after weaning, have been recently generated. It has been reported that the SGLT1 knockout mice show diarrhea symptoms similar to those in humans with congenital glucose-galactose malabsorption syndrome and die due to weight loss and weakening within 7 to 12 days after switching to a standard diet at 2 months of age (Gorboulev V et al., *Diabetes*. 2012;61:187-196). Normal mice treated with a single oral dose of 30 mg/kg of ipragliflozin had higher glucose content in the gastrointestinal tract than the control mice (4.2.1.2-2). Since this finding was obtained only in the 30 mg/kg group, this dose of ipragliflozin is considered to inhibit glucose absorption through SGLT1 inhibition. Although stool abnormalities such as loose or watery stools were found in more than half of the animals orally treated with 1000 mg/kg of ipragliflozin in the repeat-dose toxicity study in monkeys, no noteworthy gastrointestinal symptoms were found in other studies (4.2.3.2-6). In humans, the analysis results of the pooled comparative studies[27] showed a similar incidence of diarrhea in the 50 mg group (2.9%) to that in the placebo group (3.0%) (5.3.5.3-4). Based on the above, concerns about safety associated with diarrhea due to SGLT1 inhibition by ipragliflozin are considered small.

PMDA accepted the response [for effects in humans, see "4.(iii).B.(3). Safety"].

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics of ipragliflozin or ^{14}C-ipragliflozin in rats and monkeys following intravenous or oral administration was evaluated. In addition, pharmacokinetics following repeated oral administration was evaluated based on toxicokinetics observed in toxicity studies. Unchanged ipragliflozin and metabolites of ipragliflozin in plasma (M1, M2, M3, M4, M6) were measured by high performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) with a lower limit of quantitation of 1 ng/mL[28] for unchanged ipragliflozin and metabolites in rat and monkey plasma. Radioactivity in biological samples was measured using liquid scintillation counting, radio-high performance liquid chromatography, and whole-body autoradiography. Metabolites were identified by LC-MS. Primary study results are shown below. Dose levels of ipragliflozin are expressed as free base.

[26] Wright EM et al., *J Intern Med*. 2007;261:32-43, Turk E et al., *Nature*. 1991;350:354-356

[27] Pooled analysis of the following 6 studies: Japanese phase II dose-finding study (Study CL-0103), Japanese phase III monotherapy study (Study CL-0105), metformin combination therapy study (Study CL-0106), pioglitazone combination therapy study (Study CL-0107), sulfonylurea combination therapy study (Study CL-0109), and study in patients with renal impairment (Study CL-0072).

[28] The lower limit of quantitation for plasma unchanged ipragliflozin in F344 rats was 5 ng/mL.

3.(ii).A.(1) Absorption (4.2.2.2-1, 4.2.2.2-2, 4.2.2.4-6, 4.2.2.4-7)

Pharmacokinetic parameters of unchanged ipragliflozin following a single intravenous dose and a single oral dose of ipragliflozin to male rats and monkeys were as shown in Table 3.

Table 3. Pharmacokinetic parameters following a single dose of unchanged ipragliflozin

Species (n)	Route of administration	Dose (mg/kg)	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{inf} (ng·h/mL)	CL_{tot} (L/h/kg)	V_{ss} (L/kg)	BA (%)
Rat[a] (n = 3)	i.v.	0.3	—	—	3.85	692	0.433	1.68	—
	p.o.	0.3	0.500	114	4.43	541	—	—	78.2
		1	1.00	331	3.61	1654	—	—	71.7
		3	0.500	832	3.93	6277	—	—	90.7
Monkey[b] (n = 4)	i.v.	0.3	—	—	9.45 ± 2.02	1271 ± 367	0.252 ± 0.072	2.32 ± 0.76	—
	p.o.	0.3	2.00 ± 0.00	133 ± 12	8.65 ± 0.65	952 ± 343	—	—	74.5 ± 8.5
		1	1.75 ± 0.50	444 ± 144	10.1 ± 1.1	3231 ± 1204	—	—	75.3 ± 7.1
		3	1.75 ± 0.50	1358 ± 380	9.56 ± 1.23	9564 ± 3184	—	—	74.8 ± 5.0

i.v., Intravenous administration; p.o., Oral administration; t_{max}, Time to reach the maximum plasma concentration; C_{max}, Maximum plasma concentration; $t_{1/2}$, Half-life; AUC_{inf}, Area under the plasma concentration-time curve (extrapolated to infinity); CL_{tot}, Total body clearance; V_{ss}, Steady-state volume of distribution; BA, Bioavailability; -, Not calculated

a) Mean

b) Mean ± SD

Pharmacokinetic parameters of unchanged ipragliflozin following once daily oral doses of ipragliflozin to male and female rats and monkeys for 14 days were as shown in Table 4.

Table 4. Pharmacokinetic parameters of unchanged ipragliflozin following repeated oral doses of ipragliflozin

Species		Dose (mg/kg)	C_{max} (ng/mL)			$AUC_{24\,h}$ (ng·h/mL)		
			Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
Rat[a]	Male (n = 3)	10	2070	1810	1270	18,300	13,800	7870
		100	14,500	12,300	8500	157,000	147,000	77,600
		1000	53,200	73,300	53,500	936,000	1,050,000	805,000
	Female (n = 3)	10	3690	3250	3000	26,100	26,200	15,300
		100	21,700	29,000	16,100	265,000	258,000	179,000
		1000	92,200	94,600	75,400	1,930,000	1,590,000	1,170,000
Monkey[b]	Male (n = 3)	10	3260 ± 220	3750 ± 650	3160 ± 660	27,400 ± 2500	32,900 ± 900	27,400 ± 200
		100	19,000 ± 3500	24,300 ± 7400	22,300 ± 5500	219,000 ± 38,000	276,000 ± 24,000	255,000 ± 23,000
		300	35,800 ± 17,400	33,400 ± 15,300	21,900 ± 5100	453,000 ± 302,000	446,000 ± 331,000	280,000 ± 48,000
		1000	44,400 ± 13,000	71,900 ± 12,600	61,100 ± 29,300	736,000 ± 263,000	981,000 ± 375,000	804,000 ± 673,000
	Female (n = 3)	10	3910 ± 820	3960 ± 460	3690 ± 1380	32,800 ± 6000	36,400 ± 6200	33,300 ± 12,400
		100	21,500 ± 4300	29,200 ± 8700	25,500 ± 7400	258,000 ± 59,000	339,000 ± 146,000	318,000 ± 113,000
		300	41,900 ± 6300	38,900 ± 9400	40,700 ± 16,400	597,000 ± 12,000	414,000 ± 150,000	422,000 ± 229,000
		1000	63,300 ± 8200	63,600 ± 21,400	67,100 ± 16,200	972,000 ± 224,000	903,000 ± 328,000	795,000 ± 241,000

C_{max}, Maximum plasma concentration; AUC_{24h}, Area under the plasma concentration-time curve from 0 to 24 hours

a) Mean

b) Mean ± SD

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

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in male albino rats (n = 3/timepoint), radioactivity levels in the small intestine, thymus, Harderian gland, and testis peaked at 4 hours post-dose, while in other tissues the peak levels were observed within 1 hour post-dose. Except for the gastrointestinal tract, the radioactivity level at 1 hour post-dose was highest in the kidney

(9.49 times the plasma radioactivity level), followed in descending order by the liver, adrenal gland, heart, submaxillary gland, pancreas, lung, pituitary gland, Harderian gland, spleen, and bone marrow, all of which tissues showed higher radioactivity levels than that in plasma (6.17-1.16 times). In most tissues, the radioactivity levels declined over time after reaching the peak, to <10% of the peak level at 24 hours post-dose, excluding that in the testis (21% of its peak). Radioactivity levels following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in male pigmented rats (n = 1/timepoint) were similar to those observed in albino rats, excluding that in the eyeball where the radioactivity declined to approximately 2% of the peak at 168 hours post-dose and was subsequently eliminated with a half-life of 602 hours, falling below the detection limit at 672 hours post-dose. Radioactivity levels in the non-pigmented and pigmented skins at 1 hour post-dose were 0.52- and 0.56-fold, respectively, the plasma radioactivity level and those at 24 hours post-dose were 1.12- and 2.54-fold, respectively, the plasma radioactivity level. A whole-body autoradiography evaluation on localization of radioactivity in the eyeball following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in pigmented rats showed that the radioactivity distributed specifically to the iris, ciliary body, retina, and choroid, which are melanin-rich. Following once daily oral doses of 1 mg/kg of ^{14}C-ipragliflozin in male albino rats (n = 3/timepoint) for 21 days, radioactivity levels on Day 14 were similar to those on Day 21. At 168 hours after the last dose, radioactivity of ≤5% of the highest level was detected, in descending order, in the kidney, submaxillary gland, liver, skin, Harderian gland, blood, eyeball, spleen, lung, and large intestine.

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in pregnant rats (Gestation Day 14, n = 3/timepoint), maternal radioactivity levels in the blood, plasma, lung, heart, liver, kidney, spleen, pancreas, ovary, and uterus peaked at 0.5 hours post-dose, and maternal radioactivity levels in the brain, mammary gland, amnionic fluid, and placenta as well as fetal radioactivity levels peaked at 4 hours post-dose. In most maternal tissues, the radioactivity levels were higher than that in plasma, excluding the brain, amnionic fluid, and fetuses where lower levels were observed than that in plasma. The radioactivity levels in the placenta and fetuses at 4 hours post-dose were 1.22- and 0.36-fold, respectively, the plasma radioactivity level and declined to 3% and 2%, respectively, of the peak levels at 48 hours post-dose.

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in lactating rats (Lactation Day 13, n = 3/timepoint), radioactivity level in milk peaked at 4 hours post-dose, and declined to <2% of the peak level at 48 hours post-dose. Radioactivity was detected in the blood, plasma, and tissues (brain, lung, heart, liver, and kidney) of the feeding pups at 4, 24, and 48 hours post-dose, and the radioactivity levels in the kidney of the feeding pups at 24 and 48 hours post-dose were 16- and 88-fold, respectively, the maternal plasma radioactivity level.

The plasma protein binding (mean, ultrafiltration method) of ^{14}C-ipragliflozin (0.05-200 μg/mL) in mice, rats, rabbits, dogs, and monkeys was 93.2% to 95.4%, 94.6% to 96.1%, 92.2% to 94.0%, 93.8% to 95.7%, and 93.2% to 95.3%, respectively. The distribution in blood cells (mean) of ^{14}C-ipragliflozin (0.02-200 μg/mL) in mice, rats, and monkeys was 32.2% to 38.7%, 41.7% to 44.5%, and 24.3% to 27.5%, respectively.

3.(ii).A.(3) Metabolism (4.2.2.4-1, 4.2.2.4-3, 4.2.2.4-5 to 4.2.2.4-7)

Liver microsomes of mice, rats, dogs, and monkeys were incubated with ipragliflozin (0.05 μmol/L) in the presence of NADPH. The metabolic rates ($CL_{int,\ in\ vitro}$) were 0.0046, 0.0142, 0.0033, and 0.0062 mL/min/mg protein, respectively.

As metabolites of ipragliflozin, 6-hydroxylated benzothiophene ring and 2'-*O*-β-glucuronide conjugate of glucose ring (M1), 2'-*O*-β-glucuronide conjugate of glucose ring (M2), 6'-*O*-β-glucuronide conjugate of glucose ring (M3), 3'-*O*-β-glucuronide conjugate of glucose ring (M4), 6-*O*-β-glucuronide conjugate of benzothiophene ring (M5), 6-*O*-sulfate conjugate of

benzothiophene ring (M6), *S*-oxide form of benzothiophene ring (M7), *O*-sulfate conjugate of benzothiophene ring (M8), and *O*-sulfate conjugate of glucose ring (M9) were detected.

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in male rats (n = 3/timepoint), unchanged ipragliflozin, M2, M3, and M7 accounted for 82.6%, 1.5%, 4.1%, and 0.9%, respectively, of the plasma radioactivity at 0.25 hours post-dose and 82.2%, 0.4%, 1.0%, and 1.9%, respectively, of the plasma radioactivity at 4 hours post-dose. Unchanged ipragliflozin, M2, M3, and M7 accounted for 35.7%, 0.8%, 0.5%, and 55.3%, respectively, of the total radioactivity in urine during the first 6 hours post-dose and 47.8%, 0.8%, 0.4%, and 40.3%, respectively, of the total radioactivity in urine from 6 to 24 hours post-dose. Unchanged ipragliflozin, M2, M3, M4, M5, and M7 accounted for 1.9%, 58.0%, 7.6%, 3.5%, 7.5%, and 9.5%, respectively, of the total radioactivity in bile during the first 6 hours post-dose and 4.7%, 55.4%, 5.5%, 4.3%, 9.3%, and 4.0%, respectively, of the total radioactivity in bile from 6 to 24 hours post-dose.

Following once daily oral doses of 10, 100, or 1000 mg/kg of ipragliflozin in male and female rats (n = 3/sex/timepoint) for 14 days, the AUC_{24h} of unchanged ipragliflozin was the highest among those of the substances detected on Day 1, Day 7, and Day 14; the AUC_{24h} in males and females accounted for 82.3% to 92.9% and 90.3% to 96.7%, respectively, of the total AUC_{24h} of unchanged ipragliflozin and the metabolites. The metabolite that showed the highest AUC_{24h} was M2, which accounted for 3.1% to 10.9% in males and 1.3% to 5.1% in females, followed by M3, which accounted for 3.2% to 5.6% and 1.7% to 4.1%, respectively (M1 in males and females accounted for 0.0%-0.1% and 0.0%, respectively; M4 accounted for 0.4%-0.8% and 0.2%-0.5%, respectively; and M6 accounted for 0.1%-0.9% and 0.0%, respectively).[29]

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in male monkeys (n = 3/timepoint), unchanged ipragliflozin accounted for 47.6% to 69.5% of the plasma radioactivity from 0.5 to 24 hours post-dose, and M2, M3, M4, M6, and M7 accounted for 2.3% to 7.9%, 0.9% to 3.3%, 6.2% to 16.9%, 0.5% to 1.5%, and 1.8% to 3.4%, respectively. Unchanged ipragliflozin, M2, M3, M4, M6, and M7 accounted for 1.8% to 2.7%, 42.9% to 48.7%, 4.4% to 6.2%, 11.1% to 14.6%, 1.4% to 1.9%, and 14.7% to 19.7%, respectively, of the total radioactivity in urine.[30] Unchanged ipragliflozin, M2, M3, M4, M5, M6, and M7 accounted for 8.7% to 67.8%, 2.7% to 36.1%, 0.7% to 0.9%, 6.0% to 33.3%, 0.3% to 0.4%, 7.0% to 8.5%, and 1.5% to 2.2%, respectively, of the total radioactivity in bile.[30]

Following once daily oral doses of 10, 100, 300, or 1000 mg/kg of ipragliflozin in male and female monkeys (n = 3/sex/timepoint) for 14 days, the AUC_{24h} of unchanged ipragliflozin was the highest among those of the substances detected on Day 1, Day 7, and Day 14; the AUC_{24h} in males and females accounted for 71.5% to 80.2% and 75.5% to 83.2%, respectively, of the total AUC_{24h} of unchanged ipragliflozin and the metabolites. The metabolite that showed the highest AUC_{24h} was M2, which accounted for 7.6% to 15.0% in males and 5.0% to 12.6% in females, followed by M4, which accounted for 6.9% to 11.6% and 5.7% to 11.2%, respectively (M1 and M3 accounted for 0.1% and 1.3% to 3.0%, respectively, in both sexes, and M6 accounted for 0.8% to 1.5% in males and 0.7% to 1.6% in females).

3.(ii).A.(4) Excretion (4.2.2.3-1, 4.2.2.5-1)

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in male rats (n = 4/timepoint), the cumulative urinary excretion up to 24 hours and 168 hours post-dose (mean ± SD) was 12.5% ± 0.7% and 13.2% ± 0.7%, respectively, of the administered radioactivity and the cumulative fecal excretion was 82.8% ± 3.2% and 86.9% ± 2.6%, respectively.

[29] Values <0.05% are expressed as 0.0%.

[30] Percentages of radioactivity recovered in the urine or bile from 0 to 8, 8 to 24, 24 to 48, and 48 to 72 hours post-dose

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in male monkeys (n = 3/timepoint), the cumulative urinary excretion up to 24 hours and 168 hours post-dose (mean ± SD) was 36.7% ± 5.8% and 44.7% ± 8.2%, respectively, of the administered radioactivity and the cumulative fecal excretion was 22.1% ± 10.4% and 48.4% ± 11.6%, respectively.

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in bile duct cannulated male rats (n = 4/timepoint), the cumulative urinary and biliary excretion up to 72 hours post-dose (mean ± SD) was 13.7% ± 4.6% and 83.6% ± 7.4%, respectively, of the administered radioactivity.

Following a single oral dose of 1 mg/kg of ^{14}C-ipragliflozin in bile duct cannulated male monkeys (n = 3/timepoint), the 72-hour cumulative urinary and biliary excretion (mean ± SD) accounted for 45.6% ± 8.8% and 32.3% ± 14.2%, respectively, of the administered radioactivity.

Following an oral dose of 1 mg/kg of ^{14}C-ipragliflozin in bile duct cannulated male rats (n = 4/timepoint), bile (0.5 mL) recovered up to 6 hours post-dose was intraduodenally administered to other male rats (n = 4/timepoint), the cumulative urinary and biliary excretion (mean ± SD) up to 72 hours post-dose was 6.5% ± 1.2% and 55.3% ± 8.5%, respectively, of the administered radioactivity.

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

Taking into account that the tissue distribution studies in pigmented rats have shown melanin affinity of ipragliflozin as evidenced by the slower elimination of ipragliflozin from the eyeball than from other tissues and high radioactivity levels in melanin containing tissues (iris, ciliary body, retina, choroid), PMDA asked the applicant to explain the safety of ipragliflozin in humans (especially, ocular and skin safety of long-term treatment in the Japanese population).

The applicant responded as follows:

Although ipragliflozin has shown melanin affinity, this is not directly associated with toxicological significance; binding capacity of drugs to intraocular melanin has been reported to have no direct relationship to ocular toxicity.[31] In addition, no changes suggesting phototoxicity have been identified in previous toxicity studies of ipragliflozin.

On the other hand, regarding safety in humans, an investigation was performed on the profile of adverse events included in the System Organ Classes (SOC) “eye disorders” and “skin and subcutaneous tissue disorders,” and eye- and skin-related adverse events included in SOC “neoplasms benign, malignant and unspecified (incl cysts and polyps)” using data from the pooled comparative studies.[27] As a result, no apparent differences were observed between the placebo and each of the ipragliflozin groups.

Regarding long-term safety, adverse events reported in ≥2% of subjects in the 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled 52-week studies[32] were eczema (3.3%, 34 of 1017 subjects) and diabetic retinopathy (2.2%, 22 of 1017 subjects).

As described above, the applicant determined that there were no major problems with ocular and skin safety of long-term treatment with ipragliflozin up to 52 weeks in Japanese patients with type 2 diabetes mellitus.

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[31] Leblanc B et al., *Regul Toxicol Pharmacol.* 1998;28:124-132, Rubin LF et al., *Manual of oculotoxicity.* 1992;177-191

[32] Pooled analysis of the following eight 52-week studies: Japanese long-term monotherapy study (Study CL-0121), metformin combination therapy study (Study CL-0106), pioglitazone combination therapy study (Study CL-0107), sulfonylurea combination therapy study (Study CL-0109), α-glucosidase inhibitor combination therapy study (Study CL-0108), dipeptidyl peptidase-4 inhibitor combination therapy study (Study CL-0110), nateglinide combination therapy study (Study CL-0111), and study in patients with renal impairment (Study CL-0072).

PMDA accepted the response.

3.(iii) Summary of toxicology studies

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

The results from single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicity studies were submitted. Some studies were non-GLP studies and were handled by PMDA as reference data. Dose levels of metformin hydrochloride used in the concomitant oral dose toxicity study and of ipragliflozin are expressed as free base.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1-1 to 4.2.3.1-2, 4.2.3.1-4)

Single-dose toxicity was evaluated in oral toxicity studies in male and female SD rats and cynomolgus monkeys. For the results in rats, females at ≥1000 mg/kg died (1000 mg/kg, 1 of 5 rats; 2000 mg/kg, 2 of 5 rats), and a decrease in locomotor activity, bradypnea, side-lying position, emaciation, atrophy of the spleen, erosion of the gastric fundus and pylorus, ulcer of the forestomach, and necrosis of the gastric fundic mucosa, etc. were observed in the dead animals. Loose stools, unkept coat, and reduced body weight gain, etc. were found in survived animals in the 1000 and 2000 mg/kg groups. In cynomolgus monkeys, no deaths were observed in both males and females at up to 2000 mg/kg, and vomiting, loose stools, and a decrease in food consumption were observed at 1000 and 2000 mg/kg. The approximate lethal doses were determined to be >2000 mg/kg (males) or 1000 mg/kg (females) in rats, and >2000 mg/kg in cynomolgus monkeys.

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

Repeat-dose toxicity was evaluated in oral toxicity studies in SD rats (2-week, 13-week, 26-week) and cynomolgus monkeys (2-week, 13-week, 52-week). The primary target organs were the kidneys (increases in blood urea nitrogen [BUN] and in urinary N-Acetylglucosaminidase [NAG] excretion; renal tubular disorder), liver (increases in aspartate aminotransferase [AST] and alanine aminotransferase [ALT] in plasma), and gastrointestinal tract (erosion). The exposure at the no observed adverse effect level (NOAEL) in rats (26-week) and cynomolgus monkeys (52-week) (rats, 0.1 mg/kg/day; cynomolgus monkeys, 10 mg/kg/day [males] or 1 mg/kg/day [females]) was estimated to be approximately 0.02- or 0.05-fold (males and females, respectively) and 5- or 0.4-fold (males and females, respectively) the exposure (AUC_{24h}, 9213 ng·h/mL)[16] at the maximum recommended clinical dose (100 mg/day), respectively.

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

Male and female SD rats orally received ipragliflozin at 0 (vehicle[7]), 1, 10, 100, or 1000 mg/kg/day once daily for 2 weeks. One death occurred in males at 1000 mg/kg/day (1 of 18 rats). Findings observed were deposition of glycogen in Henle's loop and distal tubules at ≥1 mg/kg/day; increases in urine volume and water consumption, a decrease in urine osmolarity, increases in plasma AST and BUN, an increase in kidney weight, hypertrophy of tubular epithelial cells in thick ascending limb of Henle's loop, dilatation of distal tubules and collecting tubules, erosion and haemorrhage of gastric fundus and pylorus, and a decrease in pancreatic zymogen granules at ≥10 mg/kg/day; an increase in plasma ALT, hypertrophy of collecting tubular epithelial cells, hyperplasia of renal pelvic transitional epithelium, and erosion and thickening of the duodenum, etc. at ≥100 mg/kg/day; reduced body weight gain, an increase in plasma alkaline phosphatase (ALP), dilatation of proximal tubules, hypertrophy and necrosis of proximal tubular epithelial cells, necrosis of collecting tubular epithelial cells and renal papillae, cellular infiltration into the ureteral serosa, an increase in liver weight, hypertrophy of hepatocytes, necrosis of epithelial cells of the gastric fundus and pylorus, calcification of the lamina propria of the gastric fundus, mucosal thickening of the jejunum, ileum and caecum, etc. at 1000 mg/kg/day. All findings were reversible after a 2-week recovery period. Hypertrophy of the adrenal cortex was observed at ≥1 mg/kg/day, but its toxicological significance was considered limited, because this

change is considered to be caused by osmotic diuresis associated with increased urinary glucose concentration and glucose excretion due to the pharmacological activity of ipragliflozin and was not observed in the 13- and 26-week oral dose studies in rats described below. The NOAEL of ipragliflozin was determined to be 1 mg/kg/day.

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

Male and female SD rats orally received ipragliflozin at 0 (vehicle[7]), 0.1, 1, 10, or 100 mg/kg/day once daily for 13 weeks. Findings observed were an increase in water consumption, and increases in urinary NAG and electrolyte excretion at ≥1 mg/kg/day; reduced body weight gain, an increase in urine volume, a decrease in urine osmolarity, increases in urinary β2-microglobulin excretion and creatinine clearance, an increase in BUN, an increase in kidney weight, dilatation of proximal tubules and thick ascending limb of Henle's loop at ≥10 mg/kg/day; decreases in erythrocyte parameters (red blood cell count, haematocrit value, haemoglobin levels), increases in plasma AST and ALT, dilatation of distal tubules and collecting tubules, hypertrophy of proximal tubular epithelial cells, necrosis of mucosal epithelial cells and congestion or haemorrhage of the lamina propria in the glandular stomach, etc. at 100 mg/kg/day. All findings were reversible after a 4-week recovery period. The NOAEL of ipragliflozin was determined to be 0.1 mg/kg/day.

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

Male and female SD rats orally received ipragliflozin at 0 (vehicle[7]), 0.1, 1, 10, or 100 mg/kg/day once daily for 26 weeks. Findings observed were an increase in urine volume at ≥0.1 mg/kg/day; increases in urinary NAG and β2-microglobulin excretion, an increase in urinary electrolyte excretion, an increase in kidney weight, and a decrease in pancreatic zymogen granules at ≥1 mg/kg/day; an increase in water consumption, a decrease in urine osmolarity, an increase in creatinine clearance, increases in plasma ALT and BUN, dilatation of proximal tubules, thick ascending limb of Henle's loop, distal tubules, and collecting tubules, necrosis of mucosal epithelial cells of duodenum at ≥10 mg/kg/day; reduced body weight gain, decreases in erythrocyte parameters (red blood cell count, haematocrit value, haemoglobin levels), dilatation of the fundic gland, necrosis of mucosal epithelial cells and congestion or haemorrhage of the lamina propria in the glandular stomach, infiltration of inflammatory cells into the glandular stomach mucosa, etc. at 100 mg/kg/day. The NOAEL of ipragliflozin was determined to be 0.1 mg/kg/day.

3.(iii).A.(2).4) Two-week oral dose study in monkeys (4.2.3.2-6)

Male and female cynomolgus monkeys orally received ipragliflozin at 0 (vehicle[7]), 10, 100, or 1000 mg/kg/day once daily for 2 weeks. One death occurred in females at 1000 mg/kg/day (1 of 6 monkeys), and perforation of the stomach, white and red lesions in the gastric mucosa, and generalised oedema of subcutaneous tissues were observed in the dead animal. Vomiting, loose or watery stools, a decrease in food consumption, emaciation, increases in erythrocyte parameters (red blood cell count, haematocrit value, haemoglobin levels), an increase in BUN, etc. were observed in survived animals in the 1000 mg/kg/day groups, but all findings were reversible after a 2-week recovery period. The NOAEL of ipragliflozin was determined to be 100 mg/kg/day.

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

Male and female cynomolgus monkeys orally received ipragliflozin at 0 (vehicle[7]), 10, 100, or 300 mg/kg/day once daily for 13 weeks. An increase in urinary NAG excretion was observed at ≥100 mg/kg/day, but was reversible after a 4-week recovery period. No histopathologic changes in response to ipragliflozin were found in tissue of any organs including the kidney, liver, and gastrointestinal tract. The NOAEL of ipragliflozin was determined to be 10 mg/kg/day.

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

Male and female cynomolgus monkeys orally received ipragliflozin at 0 (vehicle[7]), 1, 10, or 300 mg/kg/day once daily for 52 weeks. An increase in urinary NAG excretion was observed in

females at ≥10 mg/kg/day and an increase in urinary NAG excretion and increases in plasma AST, ALT, and BUN were observed at 300 mg/kg/day. No histopathologic changes in response to ipragliflozin were found in tissue of any organs including the kidney, liver, and gastrointestinal tract. The NOAEL of ipragliflozin was determined to be 10 mg/kg/day for males and 1 mg/kg/day for females.

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

Genotoxicity was evaluated in *in vitro* studies including a bacterial reverse mutation assay and a chromosomal aberration assay using Chinese hamster lung fibroblast (CHL/IU cells), and *in vivo* studies including a rat bone marrow micronucleus assay and an unscheduled DNA synthesis assay in rat hepatocytes. In the chromosomal aberration assay using CHL/IU cells, the frequency of cells with structural chromosomal aberrations increased in ipragliflozin at concentrations of 210 µg/mL (cell proliferation rate, 51.6%) and 240 µg/mL (cell proliferation rate, 39.9%) in the absence of metabolic activation system (S9) as well as at a concentration of 270 µg/mL (cell proliferation rate, 34.9%) in the presence of S9. However, the results of the bacterial reverse mutation assay and of the *in vivo* studies (rat bone marrow micronucleus assay, unscheduled DNA synthesis assay in rat hepatocytes) were negative, and the exposure at the maximum dose used in the *in vivo* studies (2000 mg/kg) was estimated to be approximately 340- to 475-fold the exposure (AUC_{24h}, 9213 ng·h/mL)[16] at the maximum recommended clinical dose (100 mg/day). Therefore, ipragliflozin was determined to have no *in vivo* genotoxicity.

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

In 104-week oral dose studies in mice and rats, adrenal medullary phaeochromocytomas were observed in rats. The non-carcinogenic dose was determined to be 12.5 mg/kg/day for males and 40 mg/kg/day for females.

3.(iii).A.(4).1) Thirteen-week oral dose study in mice (dose-ranging study) (4.2.3.4.1-2)

Male and female B6C3F1 mice orally received ipragliflozin at 0 (vehicle[7]), 250, 500, or 1000 mg/kg/day once daily for 13 weeks. Findings observed were increases in plasma AST and ALT, increases in liver and kidney weight, and dilatation of distal tubules and collecting tubules at ≥250 mg/kg/day; an increase in plasma ALP, a decrease in thymus weight, and an increase in BUN at ≥500 mg/kg/day; increase in body weight, decreases in spleen and thymus weight, an increase in the trabeculae (femur), etc. at 1000 mg/kg/day.

3.(iii).A.(4).2) Carcinogenicity study in mice (4.2.3.4.1-1)

Male and female B6C3F1 mice orally received ipragliflozin at 0 (vehicle[7]), 50, 150, or 500 mg/kg/day once daily for 104 weeks. Due to a decrease in the survival rate, males in the 500 mg/kg/day group were excluded from the study at Week 49, and treatment was discontinued in all males in the 150 mg/kg/day group at Week 91. All animals tested were necropsied at Week 97. Increased incidence of neoplastic lesions in response to ipragliflozin was not observed, and no findings suggesting carcinogenicity were observed. As non-neoplastic lesions, dilatation of the renal pelvis, pyelonephritis, and inflammation of the prostate in males and peripheral nerve fiber lesions (degeneration of lingual, sciatic, and vagus nerves) in females were found. Among these non-neoplastic lesions, findings observed in males were considered to be a secondary effect related to urinary tract infection and those in females to be accelerated form of change commonly occurring in aged mice.

3.(iii).A.(4).3) Thirteen-week oral dose study in rats (dose-ranging study) (4.2.3.4.1-5)

Male and female F344 rats orally received ipragliflozin at 0 (vehicle[7]), 250, 500, or 1000 mg/kg/day once daily for 13 weeks. Nine of 11 males and 4 of 11 females in the 1000 mg/kg/day group died or were sacrificed moribund due to deterioration of the general condition. Findings observed were reduced body weight gain, increases in plasma AST, ALT, ALP, and BUN, increases in liver and kidney weight, erosion of the glandular stomach and duodenum,

vacuolization of hepatocytes, dilatation of renal tubules, vacuolization and necrosis of tubular epithelial cells, renal pelvic calculi hyperplasia of renal pelvic transitional epithelium, increase in trabeculae (sternum, femur) at ≥250 mg/kg/day; hyperplasia of caecal epithelium at 500 mg/kg/day.

3.(iii).A.(4).4) Carcinogenicity study in rats (4.2.3.4.1-6)

Male and female F344 rats orally received ipragliflozin at 0 (vehicle[7]), 12.5, 40, 125, and 250 mg/kg/day[33] once daily for 104 weeks. Due to a decrease in the survival rate, treatment was discontinued at Week 99 and observation was continued until Week 104 in the 250 mg/kg/day group. The incidence of adrenal medullary phaeochromocytomas increased in males at ≥40 mg/kg/day and in females at ≥125 mg/kg/day (male, 9 of 55 rats [control], 17 of 55 rats [12.5 mg/kg/day], 22 of 55 rats [40 mg/kg/day], 36 of 55 rats [125 mg/kg/day]; female, 4 of 55 rats [control], 3 of 55 rats [12.5 mg/kg/day], 5 of 55 rats [40 mg/kg/day], 24 of 55 rats [125 mg/kg/day], 29 of 55 rats [250 mg/kg/day]). As non-neoplastic lesions, vacuolization of proximal tubules, cystic dilatation of distal tubules, dilatation of collecting tubules, hyperplasia of vesical transitional epithelium, erosion of the glandular stomach, hyperkeratosis of esophagus, an increase in granulocytic haematopoiesis in the bone marrow, hyperostosis, and other findings including systemic calcification involving the arterial wall of the heart, tongue, and lung, as well as the kidney and eyeball (cornea) were observed.

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

Reproductive and developmental toxicity was evaluated in a study of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a study on prenatal and postnatal development including maternal function in rats. In the embryo-fetal development study, changes related to delay of embryo-fetal development (such as decreases in fetal body weight and placenta weight) were observed in rats, but teratogenicity or embryo-fetal lethality was not observed. The exposure (AUC_{24h}) at the NOAEL for embryo-fetal development (300 mg/kg/day in rats and rabbits) was estimated to be approximately 142-fold and 254-fold the exposure (AUC_{24h}, 9213 ng·h/mL)[16] at the maximum recommended clinical dose (100 mg/day) in rats and rabbits, respectively. In addition, placental transfer and excretion in milk (4.2.2.3-5) were observed in rats.

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

Ipragliflozin at 0 (vehicle[7]), 100, 300, or 1000 mg/kg/day was orally administered once daily to male SD rats from 2 weeks before mating until the day before necropsy and to female SD rats from 2 weeks before mating until Gestation Day 7. In the 1000 mg/kg/day group, dead and moribund animals were observed before mating (12 of 20 males, 16 of 20 females) and all the remaining animals were necropsied on Day 8; therefore the effects on reproductive functions or early embryonic development were not evaluated. Deaths occurred in males at 100 mg/kg/day and in females at 300 mg/kg/day (1 of 20 male rats and 1 of 20 female rats), and reduced body weight gain in males at ≥100 mg/kg/day were observed, but no effects on male and female reproductive functions (estrous cycle, copulation index, fertility index, number of days until mating, corpora lutea count, number of implantation sites) or early embryonic development (number of live fetuses, preimplantation loss, postimplantation loss) were observed. The NOAEL of ipragliflozin was determined to be <100 mg/kg/day (males) or 100 mg/kg/day (females) for general toxicity in parent animals, and 300 mg/kg/day for reproductive functions and early embryonic development.

[33] The 250 mg/kg/day group was evaluated in female F344 rats only.

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

Pregnant SD rats orally received ipragliflozin at 0 (vehicle[7]), 100, 300, or 600 mg/kg/day once daily from Gestation Day 7 until Gestation Day 17. As maternal effects, deaths (3 of 18 rats) in the 600 mg/kg/day group and reduced body weight gain in the ≥300 mg/kg/day groups were observed. As fetal effects, changes related to developmental delay (such as decrease in fetal body weight and placenta weight) were found in the 600 mg/kg/day group, but teratogenicity or embryo-fetal lethality was not found. The NOAEL of ipragliflozin was determined to be 100 mg/kg/day for maternal animals, and 300 mg/kg/day for embryo-fetal development.

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

Pregnant NZW rabbits orally received ipragliflozin at 0 (vehicle[7]), 30, 100, or 300 mg/kg/day once daily from Gestation Day 6 until Gestation Day 18. As maternal effects, deaths (3 of 22 rabbits) and abortions (5 of 22 rabbits) in the 300 mg/kg/day group as well as a decrease in food consumption and reduced body weight gain were observed. Effects on embryo-fetal development or teratogenicity were not found. The NOAEL of ipragliflozin was determined to be 100 mg/kg/day for maternal animals, and 300 mg/kg/day for embryo-fetal development.

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

Pregnant SD rats orally received ipragliflozin at 0 (vehicle[7]), 30, 100, or 300 mg/kg/day once daily from Gestation Day 7 until 7 days after parturition. As a result, deaths (2 of 20 rats) and deaths of all fetuses were observed in the 300 mg/kg/day group, and a decrease in locomotor activity, emaciation, and decreases in body weight and food consumption were found a few days before the deaths. In addition, a trend towards decreases in birth rate and survival rate on the day of birth was observed in the litters in the 300 mg/kg/day group, but effects on physical development, sensory functions, reflexes, behavior, or reproductive functions were not observed. The NOAEL of ipragliflozin was determined to be 100 mg/kg/day for maternal general toxicity and reproductive functions as well as litters.

3.(iii).A.(6) Local tolerance

3.(iii).A.(6).1) Eye irritation study in rabbits (4.2.3.6-1, Reference data)

A single dose of 100 mg of ipragliflozin[34] was administered to the conjunctival sac of male JW rabbits. Corneal epithelial defect, redness and/or oedema of the conjunctiva, etc. were observed following administration of ipragliflozin; therefore, ipragliflozin was considered to be a weak irritant to the ocular mucosa of rabbits.

3.(iii).A.(6).2) Local vascular tolerance study in rabbit (4.2.3.6-2)

Male JW rabbits received ipragliflozin (0.05 mg/mL) intravenously (10 mL/kg) or perivenously (0.2 mL/site). No changes related to ipragliflozin were found at any injection sites or surrounding tissues; therefore, ipragliflozin was not considered to be a local irritant to blood vessels.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Skin sensitization study in guinea pigs (4.2.3.7.1-1, Reference data)

Male Hartley guinea pigs were sensitized by intracutaneous injection of ipragliflozin along with Freund's complete adjuvant in the induction phase, and then ipragliflozin was applied to the animals using the occluded patch in the elicitation phase. As a result, no cutaneous reactions were observed in the sensitised group; therefore, ipragliflozin was not considered to be a skin sensitizer.

3.(iii).A.(7).2) Study investigating the effects of SGLT2 inhibitors on urinalysis parameters (4.2.3.7.7-1, 4.2.3.7.7-2; Reference data)

[34] Powder was used.

Male SD rats orally received ipragliflozin at 0 (vehicle[7]) or 10 mg/kg/day, Compound 1 at 30 mg/kg/day, or Compound 2 at 1 mg/kg/day, both of which are SGLT2 inhibitors, once daily for 1 week. An increase in urine volume, a decrease in urine osmolarity, increases in urinary glucose concentration and excretion, and increases in urinary NAG and β2-microglobulin excretion were observed with any of these drugs, but no histopathologic changes were found in the kidney.

3.(iii).A.(7).3) Four-week oral toxicity study of ipragliflozin versus Compound 2 (4.2.3.7.7-3, 4.2.3.7.7-4; Reference data)

Male SD rats orally received ipragliflozin at 0 (vehicle[7]), 1, 10, or 100 mg/kg/day or Compound 2 at 0.1, 1, 10, or 100 mg/kg/day once daily for 4 weeks. Changes including reduced body weight gain, an increase in urine volume, a decrease in urine osmolarity, increases in urinary electrolytes and uric acid excretion, increases in urinary NAG and β2-microglobulin excretion, increases in plasma AST, ALT, and BUN, an increase in kidney weight, dilatation of renal tubules, hypertrophy of collecting tubular epithelial cells, and erosion of the stomach were observed both in the ipragliflozin and Compound 2 groups; therefore, the toxicological profile of ipragliflozin was considered to be similar to that of Compound 2.

3.(iii).A.(7).4) Thirteen-week oral dose toxicity study of concomitant use with metformin hydrochloride (4.2.3.7.7-5, 4.2.3.7.7-6; Reference data)

Male and female SD rats orally received ipragliflozin/metformin hydrochloride concomitantly at doses of 0/0 (vehicle[7]), 0/100, 100/0, 0.1/100, 1/100, 10/100, and 100/100 mg/kg/day once daily for 13 weeks. Toxicological concerns associated with concomitant use of ipragliflozin with metformin were considered limited because toxicological findings observed in the concomitant treatment groups were also observed in the ipragliflozin alone group and there were no major differences in the severity of toxicity.

3.(iii).A.(7).5) *In vitro* hemolysis study with human blood (4.2.3.7.7-7)

Hemolytic profile of ipragliflozin was investigated using human peripheral blood. As a result, ipragliflozin (0.05 mg/mL) was not considered to induce hemolysis of human blood.

3.(iii).A.(7).6) Investigation on the adrenal medulla in rats (4.2.3.7.7-9)

Since adrenal medullary phaeochromocytomas were observed in the carcinogenicity study in rats, ipragliflozin at 0 (vehicle) or 125 mg/kg/day was orally administered once daily for 13 weeks to male F344 rats fed a standard diet or a diet containing high amounts of calcium and vitamin D_3 (calcium/vitamin D_3 rich diet) to investigate the mechanism by which adrenal medullary phaeochromocytomas occur. Findings observed in both animals fed the standard diet and those fed the calcium/vitamin D_3 rich diet in the ipragliflozin groups included an increase in food consumption; reduced body weight gain; increases in urinary excretion of calcium, inorganic phosphorus and catecholamine metabolites (metanephrine, normetanephrine, vanilmandelic acid); an increase in adrenal gland weight; and an increase in PCNA-positive cell counts in the adrenal medulla. Among these findings, PCNA-positive cell counts in the adrenal medulla significantly increased in the animals on the calcium/vitamin D_3 rich diet compared with those on the standard diet. Therefore, the proliferative changes in the adrenal medulla in response to ipragliflozin were considered to be secondary changes associated with calcium elevation. Based on these results, the increase in the incidence of adrenal medullary phaeochromocytomas in the carcinogenicity study observed in rats was considered to be caused by an increase in calcium intake.

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

PMDA accepted the applicant's response based on toxicological reviews in 3.(iii).B.(1) to 3.(iii).B.(6) described below. However, nephrotoxicity of ipragliflozin as well as urinary tract and genital infections will be further reviewed in the clinical sections [See "4.(iii).B.(3).2). Adverse

events related to urinary tract and genital infections" and "4.(iii).B.(6).1). Patients with renal impairment"].

3.(iii).B.(1) Effects on the kidney

PMDA asked the applicant to explain the toxicological significance of the increases in urinary NAG and β2-microglobulin excretion observed in the repeat-dose toxicity studies.

The applicant responded as follows:

The increases in urinary NAG and β2-microglobulin excretion following ipragliflozin treatment are commonly caused by SGLT2 inhibitors that promote urinary glucose excretion, and this results primarily from exposure of tubular epithelial cells to the high concentration glucose-containing urine induced by SGLT2 inhibitors. In rats, necrosis of proximal tubules was observed in 1 female at 1000 mg/kg/day in the 2-week oral dose study, but in the 13-week and 26-week oral dose studies, despite the increases in urinary NAG and β2-microglobulin excretion and an increase in BUN at ≥1 mg/kg/day, no histopathologic changes were found in tubular epithelial cells. In addition, although increases in urinary NAG and β2-microglobulin excretion were observed at ≥10 mg/kg/day in the repeat-dose toxicity study in cynomolgus monkeys, no histopathologic changes in the kidney were found at the highest dose of 300 mg/kg/day in the 52-week oral dose study. Based on the above, the observed increases in urinary NAG and β2-microglobulin excretion following ipragliflozin treatment are findings of little toxicological significance.

PMDA asked the applicant to discuss the toxicological effect of ipragliflozin on the kidney and to explain the safety in human.

The applicant responded as follows:

The toxicological effect of ipragliflozin on the kidney seems to depend on increases in urinary glucose excretion and urine volume. Specifically, in rats, ipragliflozin enhanced urinary glucose excretion, leading to increased renal load; thus, the NOAEL for the kidney was as low as 0.1 mg/kg/day (a 26-week oral study in rats). However, in cynomolgus monkeys, no toxicological effect on the kidney was observed after 52 weeks of oral dose of 300 mg/kg/day because ipragliflozin relatively weakly induced urinary glucose excretion, ensuring a safety margin corresponding to approximately 87-fold the human exposure (AUC_{24h}, 9213 ng·h/mL)[16] observed at the maximum recommended clinical dose (100 mg/day). Considering that daily urinary glucose excretion in humans observed at clinical doses of ipragliflozin (approximately 1-2.38 g/kg/day for 50 kg body weight) was similar to that in cynomolgus monkeys, nephrotoxicity risk of ipragliflozin in humans is considered to be low. In addition, although an increase in urinary β2-microglobulin excretion and adverse events related to renal impairment have been reported in clinical studies of ipragliflozin, reversibility has been confirmed for serious renal impairment, and decrease in estimated glomerular filtration rate (eGFR) was also mild and transient. Thus, administration of ipragliflozin is unlikely to cause irreversible damage to the kidney in humans.

3.(iii).B.(2) Calcification and hyperostosis

PMDA asked the applicant to explain the human safety regarding the systemic calcification and hyperostosis observed in the carcinogenicity study in rats.

The applicant responded as follows:

The carcinogenicity study in rats was conducted using F344 rats which are susceptible to the development of calcification and hyperostosis, and therefore, overintake of calcium and inorganic phosphorus associated with an increase in food consumption as a change in compensation for SGLT2 inhibition was likely to have induced the systemic calcification and hyperostosis. Other SGLT2 inhibitors (dapagliflozin, canagliflozin) have been reported to decrease intestinal glucose absorption by inhibiting intestinal SGLT1 in rats, and as a result, to increase intestinal calcium

absorption through decreased intestinal pH due to activation of intestinal flora.[35] Since selectivity for rat SGLT2 versus SGLT1 is not substantially different among ipragliflozin, dapagliflozin, and canagliflozin, ipragliflozin may also have induced a decrease in intestinal glucose absorption by inhibiting intestinal SGLT1 and increased intestinal calcium absorption, resulting in the observed systemic calcification and hyperostosis in the carcinogenicity study in F344 rats. On the other hand, in mice and cynomolgus monkeys, none of increased blood calcium, increased inorganic phosphorus, systemic calcification, or systemic hyperostosis were observed following ipragliflozin treatment. As in mice and cynomolgus monkeys, no clinically relevant effects on blood calcium and inorganic phosphorus concentrations were observed in humans following ipragliflozin treatment, and no apparent effects were observed on bone metabolic markers. The incidence of fracture was similar between the placebo and ipragliflozin groups. Based on the above, safety concerns in humans associated with calcification and bone are limited.

3.(iii).B.(3) Hyperplasia of vesical transitional epithelium

PMDA asked the applicant to explain the safety in humans regarding the hyperplasia of vesical transitional epithelium observed in the carcinogenicity study in rats.

The applicant responded as follows:

Based on the finding of calculus formation in the renal pelvic at ≥250 mg/kg/day in the 13-week oral dose study in rats (dose-ranging study), the hyperplasia of vesical transitional epithelium observed in the carcinogenicity study in rats may be a secondary change associated with physical irritation by calculus or crystals. However, because the carcinogenicity study in rats was conducted using F344 rats, calculus formation in the renal pelvic may be enhanced by the same mechanism as in the case of the systemic calcification and hyperostosis. Based on the fact that no clinically relevant effects on blood calcium and inorganic phosphorus concentrations were observed in humans, the calculus formation in the renal pelvic observed in F344 rats is a change considered to be of low clinical relevance. Other mechanisms may include reactive changes of the vesical mucosa due to osmotic diuretic action of ipragliflozin, leading to hyperplasia of transitional epithelium. However, the exposure (AUC_{24h}) at 125 mg/kg/day, which did not cause hyperplasia of vesical transitional epithelium in the carcinogenicity study in rats, provides a safety margin corresponding to approximately 62-fold the exposure (AUC_{24h}, 9213 ng·h/mL)[16] in the Japanese population at the maximum recommended clinical dose (100 mg/day), and bladder cancer has not been observed in non-clinical and clinical studies of ipragliflozin. Based on the above, the hyperplasia of vesical transitional epithelium observed in the carcinogenicity study in rats is unlikely to become relevant in humans.

3.(iii).B.(4) Adrenal medullary phaeochromocytoma

The applicant explained the increase in the frequency of adrenal medullary phaeochromocytomas observed in the carcinogenicity study in rats as follows:

In the study investigating the adrenal medulla in rats, cell proliferation activity in the adrenal medulla increased with increasing blood calcium and inorganic phosphorus caused by an increase in food consumption. Thus, the proliferative changes in rat adrenal medulla following ipragliflozin treatment can be secondary changes mediated by blood calcium elevation rather than direct effects of ipragliflozin. In rats treated with vitamin D, polyols, or lactose, proliferative changes in the adrenal medulla are caused by increased intestinal calcium absorption. However, long-term exposure to these compounds do not cause adrenal medullary phaeochromocytoma in mice, dogs, and humans, and therefore, proliferative changes in the adrenal medulla mediated by alteration of calcium homeostasis have been considered to be a specific finding in rats.[36] Based on the above, although ipragliflozin causes an increase in the frequency of adrenal medullary

[35] Foxiga: EPAR-Public assessment report (EMEA/H/C/002322), FDA Briefing Document Briefing Information for the January 10, 2013 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

[36] Roe FJC, *Human Toxicol.* 1989;8:87-98, WHO Technical Report Series. Toxicological significance of proliferative lesions of the adrenal medula in rats fed on polyols and other poorly digestible carbohydrates 1997;868:8-12.

phaeochromocytomas in rats, this finding is probably specific to rat adrenal medulla and due to an overintake of calcium, and therefore not relevant to humans.

PMDA asked the applicant to explain the safety in humans regarding the adrenal medullary phaeochromocytoma.

The applicant responded as follows:
Adrenal medullary phaeochromocytoma has not been noted in clinical studies. Also, urinary metanephrine and normetanephrine were tested (n = 589 and 592, respectively) as a screening test for human phaeochromocytoma in some phase III clinical studies,[37] and no abnormalities exceeding the screening criteria (creatinine-corrected value > 3-fold the upper limit of normal) were noted in those studies. Based on the above, safety concerns in humans associated with adrenal medullary phaeochromocytoma are likely to be limited.

3.(iii).B.(5) Urinary tract and genital infections

PMDA asked the applicant to explain the safety in humans regarding the increase in urogenital lesions observed in the carcinogenicity study in mice.

The applicant responded as follows:
Although an increase in urogenital lesions was observed in males at ≥50 mg/kg/day in the carcinogenicity study in mice, this is a secondary effect due to contact of mouse penis with the rearing cage floor contaminated with glucose-containing urine excreted due to the urinary glucose excretion promoting activity of ipragliflozin. In addition, this finding is probably unique to male mice, given the absence of such findings in female mice, male and female rats, and cynomolgus monkeys. Patients with diabetes mellitus have been reported to be susceptible to infectious diseases including urinary tract and skin infections, and a trend towards increased incidences of urinary tract and genital infections has been reported in clinical studies of other SGLT2 inhibitors (dapagliflozin, canagliflozin).[38] However, in clinical studies of ipragliflozin, there has been neither an apparent difference in incidence of adverse events related to urinary tract infections between the placebo and ipragliflozin groups nor a trend toward increasing incidence with increasing treatment duration. The incidence of adverse events related to genital infections was higher in the ipragliflozin group than in the placebo group, but all events were mild. Based on the above, concerns about the occurrence of urinary tract and genital infections in humans due to the urinary glucose excretion promoting activity of ipragliflozin are likely to be limited.

3.(iii).B.(6) Gastrointestinal toxicity

PMDA asked the applicant to explain the safety in humans regarding the gastrointestinal toxicity observed in the repeat-dose toxicity studies in rats.

The applicant responded as follows:
Given the irritant effect of ipragliflozin on the mucosa observed in the eye irritation study in rabbits, the gastrointestinal toxicity observed in rats is attributable to local irritant effects. However, there was no trend toward worsening with increasing treatment duration and, additionally, the changes were reversible. Furthermore, no gastrointestinal toxicities were observed in the long-term toxicity studies in mice and cynomolgus monkeys, and serious effects on the gastrointestinal tract have not been found in clinical studies. Based on the above, the gastrointestinal toxicity observed in the repeat-dose toxicity studies in rats is unlikely to become

[37] While the 7 studies (Studies CL-0122, CL-0107, CL-0109, CL-0108, CL-0110, CL-0111, and CL-0072) excluding the Japanese phase II dose-finding study (Study CL-0103), Japanese phase III monotherapy study (Study CL-0105), Japanese long-term monotherapy study (Study CL-0121), and metformin combination therapy study (Study CL-0106) were being conducted, metanephrine and normetanephrine were newly included in the laboratory tests.

[38] FDA Briefing Document. NDA 202293, Dapagliflozin Tablets, 5 and 10 mg. Sponsor: Bristol-Myers Squibb. Advisory Committee Meeting, July 19, 2011, Nyirjesy P et al., *Curr Med Res Opin.* 2012;28(7):1173-1178.

relevant in humans.

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 ipragliflozin, 6 types of the formulations (1 mg tablet, 10 mg tablet, 12.5 mg tablet, 50 mg tablet [2 types including the proposed commercial formulation], 100 mg tablet) were used and a breakdown of the formulations used in Japanese clinical studies is as shown in Table 5.

Table 5. Formulations used in Japanese clinical studies

Formulation	Study (No.)
1 mg tablet, 10 mg tablet, 100 mg tablet	Japanese phase I study (Study CL-0101)
12.5 mg tablet, 50 mg tablet	Japanese phase II dose-finding study (Study CL-0103) Drug interaction study with miglitol (Study CL-0062) Study on circadian variation of blood glucose (Study CL-0070) PK/PD study in patients with renal impairment (Study CL-0073)
50 mg tablet (proposed commercial formulation)	Japanese phase III monotherapy study (Study CL-0105) Japanese long-term monotherapy studies (Studies CL-0121 and CL-0122) Metformin combination therapy study (Study CL-0106) Pioglitazone combination therapy study (Study CL-0107) α-glucosidase inhibitor combination therapy study (Study CL-0108) Sulfonylurea combination therapy study (Study CL-0109) Dipeptidyl peptidase-4 inhibitor combination therapy study (Study CL-0110) Nateglinide combination therapy study (Study CL-0111) Food effect study (Study CL-0071) Study in patients with renal impairment (Study CL-0072) Drug interaction study with mitiglinide (Study CL-0074)

Quantitation in human biomaterials was performed using high performance liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limits of quantitation were 0.2,[39] 1, 2, or 5 ng/mL for plasma concentrations of unchanged ipragliflozin; 1 ng/mL for plasma concentrations of M1, M3, M4, and M6; 1 or 5 ng/mL for plasma concentrations of M2; 2 or 25 ng/mL for urine concentrations of unchanged ipragliflozin; 25 ng/mL for urine concentrations of M1 and M6; and 50 ng/mL for urine concentrations of M2, M3, and M4.

As the biopharmaceutic evaluation data, the results from a Japanese phase I study (Study CL-0101), a foreign phase I study (Study CL-0001), a food effect study with the Japanese finished product formulation (Study CL-0071), and a foreign absolute bioavailability study (Study CL-0057) were submitted [for summary of the phase I study (Study CL-0101), see "4.(ii).A. Summary of the submitted data"].

4.(i).A.(1) Food effect study (5.3.1.1-1, Study CL-0071 [October to November 2010])

A randomized, open-label, six-treatment, three-regimen, three-period cross-over study in Japanese healthy adult male subjects (target sample size, 30) was conducted to evaluate the food effect after a single dose of ipragliflozin on pharmacokinetics and pharmacodynamic effects.

Ipragliflozin 50 mg was to be orally administered under fasted conditions, before a meal (breakfast should be started 5 minutes after the administration and completed within 20 minutes),

[39] Measured substance, concentration of unbound ipragliflozin; Relevant studies, Studies CL-0058, CL-0063, and CL-0064.

and after a meal (administered within 10 minutes after breakfast) in Periods 1 to 3. A washout period of ≥6 days was included between the treatment periods.

All of the 30 treated subjects (n = 5 per group) were included in the pharmacokinetic, pharmacodynamic effect, and safety analysis sets.

Regarding the pharmacokinetics, the geometric mean ratios (preprandial/fasted) and the 90% CIs for C_{max} and AUC_{last} were 1.23 [1.14, 1.33] and 1.04 [1.01, 1.07], respectively. The geometric mean ratios (postprandial/fasted) and the 90% CIs for C_{max} and AUC_{last} were 0.82 [0.76, 0.89] and 1.00 [0.97, 1.03], respectively. The least squares mean changes in t_{max} (preprandial or postprandial state minus fasted state) and the 90% CIs were -0.48 [-0.66, -0.30] for the preprandial state and 0.73 [0.55, 0.91] for the postprandial state.

Regarding the pharmacodynamic effects, the 24-hour cumulative urinary glucose excretions (mean ± SD) after fasted, preprandial, and postprandial administration were 44,016 ± 8703, 51,908 ± 9010, and 49,248 ± 9172 mg, respectively. The 72-hour cumulative urinary glucose excretions (mean ± SD) were 58,930 ± 13,799, 69,083 ± 16,132, and 67,245 ± 15,522 mg, respectively.

Regarding safety, no adverse events were reported.

4.(i)A.(2) Absolute bioavailability study (5.3.1.1-2, Study CL-0057 [June to July 2011])
A randomized, open-label, two-period cross-over study in foreign healthy adult subjects (target sample size, 14; n = ≥5 per sex) was conducted to evaluate absolute bioavailability after a single dose of ipragliflozin.

A single oral dose of ipragliflozin 100 mg[40] or a single intravenous infusion of ipragliflozin 25 mg was to be administered under fasted conditions in Treatment Periods 1 and 2. A washout period of ≥7 days was included between the treatment periods.

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

The pharmacokinetic parameters of unchanged ipragliflozin following a single oral dose or single intravenous infusion were as shown in Table 6. The absolute bioavailability (mean ± SD) of ipragliflozin after oral administration was 90.2% ± 5.3%.

[40] The 50 mg tablets were used.

Table 6. Pharmacokinetic parameters of unchanged ipragliflozin following a single oral dose or single intravenous infusion

Parameter	100 mg oral administration (n = 14)	25 mg intravenous infusion (n = 14)
C_{max} (ng/mL)	1406 ± 338	612 ± 90[a)]
AUC_{inf} (ng·h/mL)	8457 ± 1320	2374 ± 429
t_{max} (h)	1.50 ± 0.88	0.97 ± 0.004
$t_{1/2}$ (h)	16.3 ± 5.5	16.8 ± 5.0
CL[b)] (L/h)	12.1 ± 2.0	10.9 ± 2.0
Ae_{last} (% dose)	1.13 ± 0.28	1.32 ± 0.30
CL_r (L/h)	0.14 ± 0.03	0.15 ± 0.03

Mean ± SD

C_{max}, Maximum plasma concentration; AUC_{inf}, Area under the plasma concentration-time curve extrapolated to infinity; t_{max}, Time to reach the maximum plasma concentration; $t_{1/2}$, Half-life; CL, Clearance; Ae_{last}, Urinary excretion rate; CL_r, Renal clearance

a) n = 13

b) Total body clearance (CL_{tot}) for intravenous infusion; oral clearance (CL/F) for oral administration

Regarding safety, 8 adverse events were reported by 3 of 14 subjects after oral administration of ipragliflozin and 15 adverse events were reported by 7 of 14 subjects after intravenous infusion of ipragliflozin. Among these, adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were reported by 1 of 14 subjects after the oral administration (5 events) and by 4 of 14 subjects after the intravenous infusion (8 events). No deaths, serious adverse events, or treatment discontinuations due to adverse events were reported.

4.(ii) Summary of clinical pharmacology studies

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

As evaluation data, results from Japanese clinical studies (Studies CL-0101, CL-0070, and CL-0073) and foreign clinical studies (Studies CL-0001, CL-0002, CL-0050, CL-0052, CL-0054, CL-0055, CL-0056, CL-0058, CL-0059, CL-0060, CL-0062, CL-0063, CL-0064, CL-0066, and CL-0074) were submitted. In addition, results from studies using human biomaterials were submitted. Results of main studies are shown below.

4.(ii).A.(1) Studies using human biomaterials (4.2.2.3-6, 4.2.2.3-7, 4.2.2.4-1, 5.3.2.2-1, 5.3.2.2-3 to 5.3.2.2-10, 5.3.2.3-1 to 5.3.2.3-10)

The plasma protein binding (mean, ultrafiltration method) of ^{14}C-ipragliflozin (0.05-200 μg/mL) in humans was 94.6% to 96.5%.

The binding (mean, ultrafiltration method) of ^{14}C-ipragliflozin (2 μg/mL) to human serum albumin (40 mg/mL), α_1-acid glycoprotein (1 mg/mL), high-density lipoprotein (3 mg/mL), low-density lipoprotein (3 mg/mL), and γ-globulin (10 mg/mL) were 89.8%, 48.3%, 75.7%, 56.9%, and 7.8%, respectively.

The distribution in blood cells (mean) of ^{14}C-ipragliflozin (0.02-200 μg/mL) in humans was 16.9% to 19.1%.

Human liver microsomes were incubated with ipragliflozin (0.05 μmol/L) in the presence of NADPH. The metabolic rate ($CL_{int,\ in\ vitro}$) was 0.0067 mL/min/mg protein.

Metabolic activities of ipragliflozin (0.05 μmol/L) in human liver microsomes in the presence of NADPH were evaluated. No significant correlations with marker activities of each CYP isoform (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A11) or flavin-containing monooxygenase (FMO) were observed (R^2 = 0.000497-0.0882, P = 0.3026-0.9397). Based on the

evaluation results of formation of M2 (major metabolite) from ipragliflozin (2, 100 μg/mL) using human uridine diphosphate-glucuronosyltransferase (UGT) expression system (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, 2B17), metabolization of ipragliflozin was considered to be mediated mainly by UGT2B7, and contribution of UGT2B4, 1A8, and 1A9 was also suggested.

Human liver, kidney, or small intestine microsomes were incubated with ipragliflozin (2, 20 μmol/L) and the rates of formation of the glucuronide conjugate metabolites M2, M3, and M4 were determined. As a result, the rates of formation were found to be in the descending order of M2, M4, and M3 in any of the microsomes.[41] As for M2 and M4, the highest rate of formation was observed in kidney microsomes, representing 1.3- to 1.4-fold and 2.7- to 2.9-fold the rates in liver microsomes, respectively. For M3, the highest rate of formation was observed in liver microsomes, representing 3.8-fold the rates in kidney microsomes.

In an evaluation of inhibition of each CYP isoform (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11) by ipragliflozin (1.03-250 μmol/L) using human liver microsomes, IC_{50} of ipragliflozin against CYP2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 activities was found to be 58.4, 129, 218, 183, 206, and 116 μmol/L, respectively, and those against activity of the other isoforms were found to be >250 μmol/L. Time-dependent inhibitions of the evaluated CYP isoforms by ipragliflozin were barely observed.

An evaluation of induction of CYP1A2 and 3A4 by ipragliflozin (0.1-100 μmol/L) using human primary cultured hepatocytes suggested that drug interaction due to CYP induction activity is unlikely.[42]

In an evaluation of inhibition of UGT isoforms (UGT1A1, 1A4, 1A6, 1A9, 2B7) by ipragliflozin (0.1-100 μmol/L) using human liver microsomes, inhibitions of these isoforms were barely observed (IC_{50} >100 μmol/L).

In an evaluation on transcellular transport of ^{14}C-ipragliflozin (1, 10 μmol/L) using canine tubular epithelium-derived MDCKII cells expressing human P-glycoprotein (P-gp), the permeability coefficient ratio adjusted with the data of control cells (B→A [from basolateral surface to apicolateral surface]/A→B [from apicolateral surface to basolateral surface]) was found to be 3.2 and 3.6 for 1 and 10 μmol/L, respectively, and the ratio (B→A/A→B) was found to be decreased to 1.3 and 1.2, respectively, by addition of P-gp inhibitors verapamil and ketoconazole; therefore, ipragliflozin was considered to be a substrate of P-gp. ^{3}H-digoxin transport was not inhibited by ipragliflozin (0.412-100 μmol/L) in canine tubular epithelium-derived MDCKII cells expressing human P-gp (IC_{50} >100 μmol/L).

An evaluation of substrate specificity of ^{14}C-ipragliflozin (1 μmol/L) for human breast cancer resistance protein (BCRP) and multidrug resistance-associated protein (MRP) 2 using membrane vesicles expressing each of these proteins suggested that ipragliflozin is not a substrate of BCRP or MRP2.[43] In the membrane vesicles expressing human BCRP or MRP2, ipragliflozin (0.3-100

[41] The rates of formation of metabolites M2, M3, and M4 in the presence of ipragliflozin 20 μmol/L were 49.40, 2.28, and 11.45 pmol/min/mg protein in liver microsomes, 67.93, 0.60, and 33.18 pmol/min/mg protein in kidney microsomes, 3.77, NA (lower than the detection limit of 0.21 pmol/min/mg protein), and 1.61 pmol/min/mg protein in small intestine microsomes, respectively.

[42] The fold induction values of enzyme activity and mRNA expression were 0.866 to 1.87 and 0.822 to 1.65 for CYP1A2 and 0.943 to 2.39 and 0.970 to 8.36 for CYP3A4, and induction of CYP1A2 and CYP3A4 by ipragliflozin 100 μmol/L was ≤1% of that by the positive control β-naphthoflavone and ≤12% of that by the positive control rifampicin, respectively.

[43] When membrane vesicles expressing human BCRP were incubated with ^{14}C-ipragliflozin for 1, 2, 5, and 10 minutes, the ATP-dependent intravesicular uptake of ^{14}C-ipragliflozin was 72.3, 84.1, 88.5, and 82.6 μL/mg protein, respectively, and the ATP-independent uptake was 69.4, 90.2, 94.8, and 93.3 μL/mg protein, respectively. When membrane vesicles expressing human MRP2 were incubated with ^{14}C-ipragliflozin for 1, 2, 5, and 10 minutes, the ATP-dependent intravesicular uptake of ^{14}C-ipragliflozin was

μmol/L) showed no effect on ATP-dependent intravesicular uptake of ^{3}H-labeled methotrexate and estradiol 17β-D-glucuronide (IC_{50} >100 μmol/L).

Using human embryonic kidney-derived HEK293 cells expressing human multidrug and toxin extrusion transporter (MATE) 1 or MATE2-K, effects of ipragliflozin (0.3-100 μmol/L) on intracellular uptake of metformin (10 μmol/L), a typical substrate of these transporters, were evaluated. The results suggested that drug interaction between ipragliflozin and concomitant drugs associated with transport inhibition mediated by MATE1 and MATE2-K is unlikely (IC_{50} >100 μmol/L).

Intracellular uptake of ^{14}C-ipragliflozin (1 μmol/L) was investigated using human embryonic kidney-derived HEK293 cells expressing human organic anion transporting polypeptide (OATP) 1B1 or OATP1B3. As a result, ipragliflozin was not considered to be a substrate of OATP1B1 or 1B3.[44] In an evaluation of inhibition of ^{3}H-estradiol 17β-D-glucuronide by ipragliflozin (0.3-100 μmol/L) using the above cells, IC_{50} against OATP1B1 and 1B3 was found to be 23.2 and 96.1 μmol/L, respectively. In an evaluation of inhibition of ^{3}H-labeled para-aminohippuric acid and estrone sulfate by ipragliflozin (0.3-100 μmol/L) using mouse proximal renal tubule-derived S2 cells expressing human organic anion transporter (OAT) 1 and OAT3, IC_{50} against OAT1 and OAT3 was found to be >100 and 28.5 μmol/L, respectively. In an evaluation of inhibition of ^{14}C-metformin by ipragliflozin (10-500 μmol/L) using human embryonic kidney-derived HEK293 cells expressing human organic cation transporter (OCT) 1 and OCT2, IC_{50} against OCT1 and OCT2 was found to be 70.9 and >500 μmol/L, respectively.

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

4.(ii).A.(2).1) Japanese phase I study (5.3.3.1-1, Study CL-0101 [December 2006 to July 2007])

A placebo-controlled, randomized, single-blind study in Japanese healthy adult male subjects (target sample size; 48 subjects in Part I, 36 subjects in Part II) was conducted to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamic effects after single and multiple oral doses of ipragliflozin as well as the food effect after a single oral dose of 100 mg of ipragliflozin.

In Part I, a single oral dose of 1, 3, 10, 30, 100, or 300 mg of ipragliflozin or placebo was to be administered under fasted conditions. Subjects in the ipragliflozin 100 mg group received a single oral dose 30 minutes after breakfast following 7 to 10 days of follow-up after investigation on the administration under fasted conditions. In Part II, a single oral dose of 20, 50, or 100 mg of ipragliflozin or placebo was to be administered 30 minutes after breakfast, followed by a 1-day washout period, and the same dose was to be orally administered once daily for 7 days at 30 minutes after breakfast. Of 8 subjects included in each dose group in Part I, 2 subjects were allocated to the placebo group and 6 subjects to the ipragliflozin groups in a randomized manner. Of 12 subjects included in each dose group in Part II, 4 subjects were allocated to the placebo group and 8 subjects to the ipragliflozin groups in a randomized manner.

All of the 48 treated subjects in Part I were included in the pharmacodynamic effects and safety analysis sets, and 36 subjects who received ipragliflozin were included in the pharmacokinetics analysis set.[45] One subject in the 300 mg group in Part I discontinued the study for personal

29.1, 29.7, 46.9, and 60.5 μL/mg protein, respectively, and the ATP-independent uptake was 30.4, 22.4, 48.7, and 68.5 μL/mg protein, respectively.

[44] When human OATP1B1- or OATP1B3-expressing cells and control cells were incubated with ^{14}C-ipragliflozin for 1, 2, 5, and 10 minutes, the intracellular uptake of ^{14}C-ipragliflozin by human OATP1B1-expressing cells was 55.0, 103.6, 176.6, and 249.7 μL/mg protein, respectively; that of human OATP1B3-expressing cells was 60.7, 94.0, 191.0, and 217.7 μL/mg protein, repectively; and that of the control cells was 54.1, 95.8, 161.6, and 212.4 μL/mg protein, respectively.

[45] Of 36 subjects who received ipragliflozin, 1 subject in the 300 mg group discontinued the study due to consent withdrawal, thus pharmacokinetic parameters were calculated in 35 subjects. Pharmacodynamic parameters from 6 hours after administration of ipragliflozin were calculated in 5 subjects excluding this subject.

reasons.

The pharmacokinetic parameters of unchanged ipragliflozin following a single dose were as shown in Table 7. The geometric mean ratios (fed/fasted) and the two-sided 90% CIs for C_{max} and AUC_{last} of unchanged ipragliflozin in plasma after fasted or fed administration of 100 mg of ipragliflozin were 1.162 [0.867, 1.557] and 0.975 [0.727, 1.308], respectively.

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

Parameter	1 mg (n = 6)	3 mg (n = 6)	10 mg (n = 6)	30 mg (n = 6)	100 mg[a] (n = 6)	100 mg[b] (n = 6)	300 mg (n = 5)
C_{max} (ng/mL)	17.89 ± 4.00	53.72 ± 15.55	174.34 ± 14.26	523.63 ± 103.36	1392.39 ± 422.99	1593.68 ± 379.98	3421.41 ± 690.45
AUC_{last} (ng·h/mL)	50.81 ± 9.91	212.48 ± 25.76	826.43 ± 162.18	2848.77 ± 373.41	9569.73 ± 2169.51	9355.89 ± 2164.68	27,121.21 ± 4494.74
t_{max} (h)	0.75 ± 0.27	0.92 ± 0.20	0.92 ± 0.20	1.58 ± 1.11	2.33 ± 1.21	1.58 ± 0.20	2.60 ± 1.34
$t_{1/2}$ (h)	4.35 ± 1.05	10.01 ± 2.28	13.34 ± 4.99	12.43 ± 5.05	11.71 ± 2.00	16.81 ± 7.97	10.34 ± 1.59
CL/F (L/h)	17.45 ± 3.05	12.49 ± 1.92	12.14 ± 2.80	10.49 ± 1.27	11.00 ± 3.64	11.09 ± 4.04	11.26 ± 2.00
Ae_{last} (% dose)	0.65 ± 0.19	0.75 ± 0.07	0.75 ± 0.14	1.18 ± 0.21	1.11 ± 0.24	1.16 ± 0.26	1.11 ± 0.09
CL_r (L/h)	NA	0.10 ± 0.01	0.09 ± 0.02	0.12 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01

Mean ± SD, NA: Not applicable

C_{max}, Maximum plasma concentration; AUC_{last}, Area under the concentration-time curve up to the last measurable concentration; t_{max}, Time to reach the maximum plasma concentration; $t_{1/2}$, Half-life; CL/F, Oral clearance; Ae_{last}, Urinary excretion to the last measurable concentration; CL_r, Renal clearance

a) Administered under fasted conditions
b) Administered 30 minutes after breakfast

The pharmacokinetic parameters of unchanged ipragliflozin following single and multiple oral doses in Part II were as shown in Table 8.

Table 8. Pharmacokinetic parameters of unchanged ipragliflozin following single and multiple oral doses

Parameter	Dosage regimen	20 mg (n = 8)	50 mg (n = 8)	100 mg (n = 8)
C_{max} (ng/mL)	Single-dose	338.99 ± 58.04	878.84 ± 132.00	1419.93 ± 326.13
	Multiple-dose	398.05 ± 60.14	975.53 ± 187.54	1731.61 ± 229.83
AUC_{last} (ng·h/mL)	Single-dose	1749.03 ± 443.25	4400.26 ± 1057.35	8476.24 ± 1741.27
$AUC_{24\,h}$ (ng·h/mL)	Multiple-dose	1894.04 ± 323.89	4693.11 ± 1074.39	9113.99 ± 1326.31
t_{max} (h)	Single-dose	1.25 ± 0.27	1.25 ± 0.27	1.81 ± 0.80
	Multiple-dose	1.25 ± 0.27	1.25 ± 0.38	1.38 ± 0.44
$t_{1/2}$ (h)	Single-dose	13.43 ± 2.95	9.81 ± 1.63	12.55 ± 4.12
	Multiple-dose	13.93 ± 3.52	11.24 ± 3.34	15.36 ± 5.03
CL/F (L/h)	Single-dose	11.32 ± 2.63	11.50 ± 2.28	11.68 ± 2.66
	Multiple-dose	10.82 ± 1.75	11.05 ± 2.04	11.17 ± 1.56
Ae_{last} (% dose)	Single-dose	1.24 ± 0.17	1.02 ± 0.26	0.98 ± 0.21
Ae_{24} (% dose)	Multiple-dose	1.44 ± 0.23	1.35 ± 0.28	1.29 ± 0.25
CL_r (L/h)	Single-dose	0.15 ± 0.02	0.12 ± 0.01	0.12 ± 0.01
	Multiple-dose	0.15 ± 0.02	0.15 ± 0.03	0.14 ± 0.02

Mean ± SD

C_{max}, Maximum plasma concentration; AUC_{last}, Area under the concentration-time curve up to the last measurable concentration; AUC_{24h}, Area under the concentration-time curve up to 24 hours post-dose; t_{max}, Time to reach the maximum plasma concentration; $t_{1/2}$, Half-life; CL/F, Oral clearance; Ae_{last}, Urinary excretion up to the last measurable concentration; Ae_{24} (% dose), Urinary excretion up to 24 hours post-dose; CL_r, Renal clearance

Regarding the pharmacodynamic effects, the 24-hour cumulative urinary glucose excretions (mean ± SD) observed in Part I after administration of placebo or ipragliflozin at doses of 1, 3, 10, 30, 100, and 300 mg were 79 ± 221, 547 ± 420, 4261 ± 1353, 19,569 ± 3778, 38,259 ± 8241, 55,737 ± 8777, and 70,803 ± 7853 mg, respectively, and the 72-hour cumulative urinary glucose excretions were 138 ± 306, 547 ± 420, 4474 ± 1562, 21,014 ± 4124, 49,416 ± 11,497, 107,233 ± 26,666, and 143,053 ± 20,523 mg, respectively. The 48-hour cumulative urinary glucose excretions observed in Part II after a single dose of placebo or ipragliflozin at doses of 20, 50, and 100 mg were 183 ± 274, 43,542 ± 9719, 66,937 ± 21,927, and 87,756 ± 20,773 mg, respectively, and those after 7 oral doses were 136 ± 311, 42,865 ± 11,054, 64,026 ± 23,676, and 73,497 ± 22,015 mg, respectively.

Regarding safety, in Part I, 4 adverse events were reported by 4 of 12 subjects in the placebo group, 1 adverse event was reported by 1 of 6 subjects in the 1 mg group, 4 adverse events were reported by 3 of 6 subjects in the 3 mg group, 8 adverse events were reported by 5 of 6 subjects in the 10 mg group, 1 adverse event was reported by 1 of 6 subjects in the 30 mg group, 3 adverse events were reported by 3 of 6 subjects in the 100 mg group, and 3 adverse events were reported by 3 of 6 subjects in the 300 mg group; and in the 100 mg group (postpradial administration), 3 adverse events were reported by 2 of 6 subjects. Among these events, those classified as adverse drug reactions were as follows: 3 events reported by 2 of 6 subjects in the 3 mg group, 8 events reported by 5 of 6 subjects in the 10 mg group, 2 events reported by 2 of 6 subjects in the 100 mg group, and 3 events reported by 3 of 6 subjects in the 300 mg group; and in the 100 mg group (postprandial administration), 3 events were reported by 2 of 6 subjects. In Part II, 1 event was reported by 1 of 12 subjects in the placebo group, 11 adverse events were reported by 5 of 8 subjects in the 20 mg group, 11 adverse events were reported by 8 of 8 subjects in the 50 mg group, and 3 adverse events were reported by 3 of 8 subjects in the 100 mg group. Among these events, those classified as adverse drug reactions were as follows: 10 events reported by 5 of 8 subjects in the 20 mg group, 10 events reported by 8 of 8 subjects in the 50 mg group, and 3 events reported by 3 of 8 subjects in the 100 mg group. No deaths, serious adverse events, or discontinuations due to adverse events were reported in either part.

4.(ii).A.(2).2) Mass balance study (5.3.3.1-4, Study CL-0055 [May to October 2008])

An open-label, uncontrolled study in foreign healthy adult male subjects (target sample size, 6) was conducted to evaluate the disposition of ^{14}C-ipragliflozin after a single dose.

A single oral dose of 100 mg of ^{14}C-ipragliflozin was to be administered under fasted conditions.

All of the 6 treated subjects were included in the pharmacokinetics and safety analysis sets.

Regarding the pharmacokinetics, C_{max} (mean ± SD) was 2724 ± 133, 1863 ± 58.4 ng eq/mL, and 1688 ± 185 ng/mL for radioactivity in plasma, radioactivity in whole-blood, and unchanged ipragliflozin in plasma, respectively; AUC_{last} was 14,880 ± 1654, 8313 ± 795 ng eq·h/mL, and 7229 ± 1365 ng·h/mL, respectively; t_{max} was 1.00 ± 0.00, 1.00 ± 0.00, and 0.75 ± 0.27 h, respectively; and $t_{1/2}$ was 12.6 ± 4.55, 10.0 ± 2.81, and 11.1 ± 3.57 h, respectively. The AUC_{last} value of unchanged ipragliflozin in plasma accounted for 48.5% of that of radioactivity in plasma, and the C_{max} value of unchanged ipragliflozin in plasma accounted for 61.9% of that of radioactivity in plasma. The cumulative urinary and fecal radioactivity excretions up to 144 hours post-dose accounted for 67.9% and 32.7% of the administered radioactivity, respectively, and no radioactivity was detected in expired air. The urinary excretion of unchanged ipragliflozin up to 144 hours post-dose was 1.0% ± 0.3%, and CL_r was 0.133 ± 0.0293 L/h.

Regarding safety, 11 adverse events were reported by 5 of 6 subjects, and among these event, those classified as adverse drug reactions were 8 events reported by 4 of 6 subjects. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

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

4.(ii).A.(3).1) Study on circadian variation of blood glucose (5.3.4.2-1, Study CL-0070 [November 2009 to March 2010])

A placebo-controlled, randomized, double-blind study in Japanese patients with type 2 diabetes mellitus (target sample size, 24; n = 8 per group) was conducted to evaluate pharmacodynamic effects, pharmacokinetics, and safety after multiple oral doses of ipragliflozin.

Following a single oral dose of placebo during the run-in (baseline) period in a single-blind fashion, multiple oral doses of 50 or 100 mg of ipragliflozin or placebo were to be administered once daily before breakfast for 14 days in a double-blind fashion.

All of the 30 treated subjects were included in the safety analysis set. Of these subjects, 28 subjects were included in the pharmacodynamic effects and pharmacokinetics analysis sets, except for 2 subjects who discontinued the study due to adverse events (toxic skin eruption, rash).

Regarding the pharmacokinetics, after the last dose of 50 and 100 mg of ipragliflozin, C_{max} (mean ± SD) was 1225.35 ± 255.05 and 2030.44 ± 654.37 ng/mL, respectively; AUC_{last} was 4806.00 ± 1460.75 and 9210.37 ± 3939.28 ng·h/mL, respectively; t_{max} was 0.7 ± 0.3 and 0.9 ± 0.3 h, respectively; $t_{1/2}$ was 11.3 ± 3.3 and 10.5 ± 2.6 h, respectively; CL/F was 11.26 ± 3.29 and 12.14 ± 3.64 L/h, respectively; Ae_{24h} was 1.24 ± 0.21 and 1.22 ± 0.52% dose, respectively; and CL_r was 0.14 ± 0.04 and 0.13 ± 0.02 L/h, respectively.

Regarding the pharmacodynamic effects, the changes from baseline[46] in the pharmacodynamic parameters after the last dose of 50 or 100 mg of ipragliflozin or placebo were as shown in Table 9.

Table 9. Changes from baseline in the pharmacodynamic parameters

Parameter	Placebo (n = 10)	50 mg (n = 9)	100 mg (n = 9)
24-hour cumulative urinary glucose excretion (mg)	5282.9 ± 19,323.06	80,614.9 ± 22,202.41	89,660.7 ± 12,309.47
24-hour cumulative urine volume (mL)	-61.0 ± 688.37	224.4 ± 656.79	203.3 ± 1059.53
24-hour water intake (mL)	43.0 ± 471.81	156.7 ± 607.66	81.1 ± 763.04
Blood glucose AUC_{3h} (mg·h/dL)	2.33 ± 99.514	-172.63 ± 106.603	-174.58 ± 92.041
Blood glucose AUC_{24h} (mg·h/dL)	63.81 ± 732.486	-1103.68 ± 693.903	-919.91 ± 636.034
Fasting blood glucose (mg/dL)	0.3 ± 20.54	-31.6 ± 24.29	-35.8 ± 29.12
Fasting insulin (μU/mL)	0.54 ± 2.076[a)]	-1.31 ± 1.213	-2.38 ± 1.876

Mean ± SD

Blood glucose AUC_{th}, AUC up to t hours after the last administration of placebo or 50 or 100 mg of ipragliflozin

a) n = 9

Regarding safety, 7 adverse events were reported by 5 of 10 subjects in the 50 mg group and 3 adverse events were reported by 3 of 10 subjects in the 100 mg group. Among these events, those classified as adverse drug reactions were 5 events reported by 4 of 10 subjects in the 50 mg group

[46] The baseline values (mean ± SD) for cumulative urinary glucose excretion, cumulative urine volume, and water intake during the first 24 hours after the last dose were 26,977.3 ± 35,157.28 mg, 2177.0 ± 817.65 mL, and 2038.0 ± 738.12 mL in the placebo group, 29,102.1 ± 33,154.66 mg, 2034.4 ± 800.99 mL, and 1790.0 ± 846.91 mL in the ipragliflozin 50 mg group, and 23,536.3 ± 29,372.16 mg, 2557.2 ± 1422.54 mL, and 2362.2 ± 1310.38 mL in the ipragliflozin 100 mg group, respectively. The baseline values for AUC up to 3 and 24 hours after the last dose were 877.84 ± 162.053 and 5787.42 ± 1594.371 mg·h/dL in the placebo group, 838.03 ± 132.522 and 5532.06 ± 834.910 mg·h/dL in the 50 mg group, and 781.86 ± 155.051 and 5180.82 ± 1290.698 mg·h/dL in the 100 mg group, respectively. The baseline values for fasting blood glucose and fasting insulin after the last dose were 177.5 ± 33.80 mg/dL and 7.23 ± 4.074 μU/mL in the placebo group, 172.9 ± 25.47 mg/dL and 5.48 ± 2.229 μU/mL in the 50 mg group, and 165.3 ± 35.09 mg/dL and 7.27 ± 3.826 μU/mL in the 100 mg group, respectively.

and 2 events reported by 2 of 10 subjects in the 100 mg group. Two subjects discontinued the study due to adverse events (toxic skin eruption in the 50 mg group, rash in the 100 mg group). No deaths were reported. No serious adverse events were reported during study treatment, but myocardial infarction in 1 subject in the 50 mg group met the criteria for serious adverse events after completion of the study.[47]

4.(ii).A.(3).2) Population pharmacokinetic analysis (5.3.3.5-1, 5.3.3.5-2; Studies PK-0001 and PK-0006)

In order to explore sources of variation and quantify the effects on pharmacokinetics of ipragliflozin using plasma drug concentrations obtained at 534 sampling points in Studies CL-0070 and CL-0073 in Japanese patients with type 2 diabetes mellitus (108 sampling points for 50 mg and 108 sampling points for 100 mg in Study CL-0070, 318 sampling points for 50 mg in Study CL-0073), a population pharmacokinetic (PPK analysis) model was established using nonlinear mixed effects modeling (NONMEM software [version 7.1.0]) based on a 2-compartment model. In addition, this model was modified by adding plasma drug (trough) concentrations obtained at 3714 sampling points in Studies CL-0103, CL-0105, CL-0121, and CL-0072 (271 sampling points for 12.5 mg, 280 sampling points for 25 mg, 269 sampling points for 50 mg, 274 sampling points for 100 mg in Study CL-0103, 229 sampling points for 50 mg in Study CL-0105, 1246 sampling points for 50/50 mg, 818 sampling points for 50/100 mg in Study CL-0121, 327 sampling points for 50 mg in Study CL-0072) and used to perform PPK analysis. In the modified model considering the trough levels, inter-individual variability was analyzed as random effects on CL/F. The analysis data set included 683 subjects. Based on the results of stepwise analysis of covariates on oral clearance (CL/F), the final model included body-surface area (BSA), glomerular filtration rate (GFR; eGFR × BSA/1.73), total protein (TPRO), and total bilirubin (TBIL). The population average of CL/F was estimated to be 9.47 L/h based on the typical covariate values (BSA = 1.73 m^2, GFR = 90 mL/min, TPRO = 7 g/dL, TBIL = 0.8 mg/dL). The inter-individual coefficient of variation (CV [%]) of CL/F was 23.4%. The final model suggested that decrease in BSA by 10% would lead to decrease in CL/F by approximately 6%. In addition, the model suggested that patients with GFR of 45 mL/min (moderate renal impairment) would have approximately 15% lower CL/F than patients with GFR of 90 mL/min (normal renal function). Variabilities in TPRO and TBIL within normal ranges (TPRO = 6.7-8.3 g/dL, TBIL = 0.2-1.2 mg/dL) as compared with typical patients (TPRO = 7 g/dL, TBIL = 0.8 mg/dL) were both expected to lead to variability in CL/F of $\leq \pm$ 10%.

4.(ii).A.(3).3) PPK/pharmacodynamic analysis (5.3.3.5-3, Study PK-0005)

In order to evaluate the relationship between exposure to ipragliflozin and urinary glucose excretion using values of AUC_{24h} and changes from baseline in 24-hour urinary glucose excretion (ΔUGE_{24h}) obtained at 155 sampling points in Studies CL-0070, CL-0073, and CL-0101 in Japanese healthy adult subjects and patients with type 2 diabetes mellitus (21 sampling points in Study CL-0070, 25 sampling points in Study CL-0073, 109 sampling points in Study CL-0101), a PPK/pharmacodynamic analysis (PPK/PD analysis) was performed using a nonlinear mixed effects modeling (NONMEM software [version 7.1.0]) based on the E_{max} model. Because the ΔUGE_{24h} values were obtained only at 1 to 2 points from each subject, the inter-individual variability of E_{max} or EC_{50} was not estimated. The analysis data set included 111 subjects (65 healthy adult subjects, 46 patients with type 2 diabetes mellitus). Because fasting plasma glucose (FPG) and GFR were considered to have substantial effects on the ΔUGE_{24h} values, these effects were included in the pre-dose E_{max} values in advance. In addition, based on an expectation that the correlation between exposure to ipragliflozin and urinary glucose excretion would change at

[47] The subject had chest symptoms on Day 6, and visited a cardiologist on Day 17 as an abnormal electrocardiogram was observed on Day 15 (study treatment was continued up to Day 14). The study was terminated with a follow-up on Day 21. Subsequently, the event was considered as a serious adverse event because the subject was hospitalized on Day 25. Based on the results of coronary arteriography on Day 26, a percutaneous coronary intervention was performed. The subject was discharged from the hospital on Day 27, and considered as improved as of Day 51.

the point where the FAC[48] value reaches around 16,000 to 18,000, E_{max} was modeled separately for different FAC values, and the final model was established as ΔUGE_{24h} (mg) = E_{max} × $AUC_{24h}/(EC_{50} + AUC_{24h})$.[49] Based on the PPK/PD analysis using the final model, the population average of E_{max} was estimated to be 72.3 g for FAC ≤18,000 (assuming FPG as 100 mg/dL and GFR as 90 mL/min) or 107 g for FAC >18,000. EC_{50} was estimated to be 1590 ng·h/mL.

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

4.(ii).A.(4).1) Study investigating elderly subjects and gender-related differences (5.3.3.3-1, Study CL-0052 [November 2007 to January 2008])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in foreign healthy adult subjects (target sample size, 64; 16 non-elderly males and 16 non-elderly females, 16 elderly males and 16 elderly females) was conducted to evaluate effects of age and sex on the pharmacokinetics, pharmacodynamic effects, and safety after single or multiple oral doses of ipragliflozin.

A single oral dose of 100 mg of ipragliflozin or placebo was to be administered 5 minutes before breakfast in non-elderly (aged ≥18 and ≤45 years) and elderly (aged ≥65 years) males and females, and after an interval of a 3-day washout period, multiple oral doses of 100 mg of ipragliflozin or placebo were to be administered once daily 5 minutes before breakfast for 14 days.

All of the 65 treated subjects[50] (32 non-elderly subjects [16 males, 16 females], 33 elderly subjects [16 males, 17 females]) were included in the pharmacodynamic effects and safety analysis sets, and of which 49 subjects who received ipragliflozin were included in the pharmacokinetics analysis set. Four subjects discontinued the study, including 2 non-elderly subjects (lost to follow-up and adverse events, 1 subject each) and 2 elderly subjects (lost to follow-up and other reasons, 1 subject each).

Regarding the pharmacokinetics, the geometric mean ratios (female/male) and the 90% CIs for C_{max} and AUC[51] of unchanged ipragliflozin in plasma were 1.31 [1.07, 1.60] and 1.13 [0.99, 1.30] after a single dose in non-elderly subjects, 1.06 [0.89, 1.25] and 1.16 [1.01, 1.33] after multiple doses in non-elderly subjects, 1.32 [1.09, 1.61] and 1.34 [1.17, 1.53] after a single dose in elderly subjects, and 1.35 [1.15, 1.58] and 1.39 [1.22, 1.59] after multiple doses in elderly subjects, respectively. The geometric mean ratios (elderly/non-elderly) and the 90% CIs for C_{max} and AUC[51] of unchanged ipragliflozin in plasma were 1.20 [0.98, 1.46] and 1.20 [1.05, 1.38] after a single dose in male subjects, 0.99 [0.84, 1.16] and 1.21 [1.06, 1.38] after multiple doses in male subjects, 1.21 [1.00, 1.47] and 1.42 [1.24, 1.63] after a single dose in female subjects, and 1.25 [1.06, 1.49] and 1.45 [1.27, 1.67] after multiple doses in female subjects, respectively.

Regarding the pharmacodynamic effects, the geometric mean ratios (female/male) and the 90% CIs for 24-hour cumulative urinary glucose excretion were 0.75 [0.68, 0.82] after a single dose and 0.71 [0.61, 0.82] after multiple doses; and the geometric mean ratios (elderly/non-elderly) and the 90% CIs for 24-hour cumulative urinary glucose excretion were 0.73 [0.66, 0.80] and 0.69 [0.59, 0.80] after single and multiple doses, respectively.

Regarding safety, 1 adverse events were reported by 1 of 16 subjects in the placebo group and 14 adverse events were reported by 9 of 49 subjects in the ipragliflozin group. Among these events, those classified as adverse drug reactions were 1 event reported by 1 of 16 subjects in the placebo

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[48] FPG × GFR

[49] For FAC ≤8000, $E_{max,i}$ (mg) = 72,300 × $(FPG/100)^{1.37}$ × $(GFR/90)^{0.623}$; for FAC >18,000, $E_{max,i}$ (mg) = 107,000

[50] Sixteen non-elderly male subjects (12 subjects in the ipragliflozin group, 4 subjects in the placebo group), 16 non-elderly female subjects (12 subjects in the ipragliflozin group, 4 subjects in the placebo group), 16 elderly male subjects (12 subjects in the ipragliflozin group, 4 subjects in the placebo group), and 17 elderly female subjects (13 subjects in the ipragliflozin group, 4 subjects in the placebo group)

[51] AUC_{last}, after a single dose; AUC_{24h}, after multiple doses

group (non-elderly male) and 8 events reported by 6 of 49 subjects in the ipragliflozin group (1 event in non-elderly males, 2 events in elderly females, 4 events in non-elderly females, and 1 event in non-elderly males). One non-elderly female subject who experienced rash generalised/pruritus/periorbital oedema discontinued the study. No deaths or serious adverse events were reported.

4.(ii).A.(4).2) PK/PD study in patients with renal impairment (5.3.3.3-2, Study CL-0073 [February to June 2010])

An open-label study in Japanese patients with type 2 diabetes mellitus (target sample size, 18; n = 6 for each severity category of renal impairment) was conducted to evaluate the effects of renal function on pharmacokinetics, pharmacodynamic effects, and safety after a single dose of ipragliflozin.

A single oral dose of 50 mg of ipragliflozin was to be administered within 10 minutes before breakfast in patients with normal renal function (eGFR[52] ≥90 mL/min/1.73 m^2), mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2), and moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2).

All of the 25 treated subjects (8 patients with normal renal function, 9 patients with mild renal impairment, and 8 patients with moderate renal impairment) were included in the pharmacokinetics, pharmacodynamic effects, and safety analysis sets.

Regarding the pharmacokinetics, the pharmacokinetic parameters of unchanged ipragliflozin following a single oral dose of ipragliflozin 50 mg were as shown in Table 10.

Table 10. Pharmacokinetic parameters of unchanged ipragliflozin following a single oral dose of ipragliflozin 50 mg

Parameter	Patients with normal renal function (n = 8)	Patients with mild renal impairment (n = 9)		Patients with moderate renal impairment (n = 8)	
	Mean ± SD	Mean ± SD	Geometric mean ratio [90% CI][a)]	Mean ± SD	Geometric mean ratio [90% CI][a)]
C_{max} (ng/mL)	1044.74 ± 347.55	1088.77 ± 223.40	1.122 [0.827, 1.522]	1160.97 ± 357.94	1.168 [0.853, 1.599]
AUC_{inf} (ng·h/mL)	4821.35 ± 1558.49	4482.28 ± 1587.80	0.936 [0.694, 1.261]	5947.60 ± 2461.76	1.213 [0.892, 1.649]
t_{max} (h)	1.43 ± 1.86	0.84 ± 0.26	—	0.95 ± 0.32	—
$t_{1/2}$ (h)	14.97 ± 4.58	15.37 ± 8.46	0.955 [0.671, 1.360]	17.08 ± 7.79	1.096 [0.762, 1.576]
CL/F (L/h)	11.65 ± 4.85	12.16 ± 3.35	1.069 [0.793, 1.441]	9.64 ± 3.63	0.825 [0.606, 1.121]
Ae_{last} (% dose)	1.05 ± 0.25	0.86 ± 0.15	—	0.84 ± 0.40	—
CL_r (L/h)	0.12 ± 0.03	0.10 ± 0.02	0.885 [0.712, 1.099]	0.07 ± 0.02	0.623 [0.498, 0.778]

C_{max}, Maximum plasma concentration; AUC_{inf}, Area under the plasma concentration-time curve (extrapolated to infinity); t_{max}, Time to reach the maximum plasma concentration; $t_{1/2}$, Half-life; CL/F, Oral clearance; Ae_{last}, Urinary excretion up to the last measurable concentration; CL_r, Renal clearance;
-, Not calculated
a) Ratio of geometric means compared with patients with normal renal function (patients with renal impairment/patients with normal renal function), CI = Confidence interval

[52] Severity of renal impairment was classified according to glomerular filtration rate estimation equation for Japanese subjects based on screening serum creatinine (eGFR [mL/min/1.73 m^2] = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ [for female subjects, 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739]).

Regarding the pharmacodynamic effects, the pharmacodynamic parameters[53] following a single oral dose of ipragliflozin 50 mg were as shown in Table 11.

Table 11. Pharmacodynamic parameters following a single oral dose of ipragliflozin 50 mg

Parameter	Time point	Patients with normal renal function (n = 8)	Patients with mild renal impairment (n = 9)	Patients with moderate renal impairment (n = 8)
Cumulative urinary glucose excretion (mg)	Between 0-24 hours	127,851 ± 85,489	68,069 ± 29,170	43,280 ± 16,951
	Between 0-48 hours	203,064 ± 147,715	96,871 ± 48,674	63,430 ± 32,767
	Between 0-72 hours	253,424 ± 205,428	110,681 ± 61,604	71,139 ± 39,248
Fasting blood glucose[a)] (mg/dL)	After 24 hours	-24.9 ± 22.67	-11.9 ± 11.10	-4.1 ± 10.44
	After 48 hours	-14.6 ± 19.67	-6.7 ± 12.78	-4.1 ± 11.10
	After 72 hours	-14.6 ± 18.47	-5.9 ± 13.18	-7.5 ± 8.12
	Follow-up period[b)]	-4.5 ± 11.74	5.9 ± 8.40	4.3 ± 13.02
Urine volume[a)] (mL)	Between 0-24 hours	475.6 ± 620.34	573.0 ± 541.83	446.4 ± 471.38
	Between 24-48 hours	-193.8 ± 846.76	-179.2 ± 283.60	-116.0 ± 690.07
	Between 48-72 hours	-551.5 ± 661.69	-117.1 ± 499.07	-316.1 ± 708.68

Mean ± SD
a) Change from baseline
b) Days 11 to 18

Regarding safety, 5 adverse events were reported by 3 of 8 patients with normal renal function, 5 adverse events were reported by 3 of 9 patients with mild renal impairment, and 4 adverse events by 3 of 8 patients with moderate renal impairment. Among these events, those classified as adverse drug reactions were 4 events reported by 3 of 8 patients with normal renal function, 2 events reported by 2 of 9 patients with mild renal impairment, and 1 event reported by 1 of 8 patients with moderate renal impairment. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

4.(ii).A.(4).3) Foreign study in patients with renal impairment (5.3.3.3-3, Study CL-0064 [January to June 2010])

An open-label, parallel-group, comparative study in foreign healthy adult subjects and patients with type 2 diabetes mellitus (target sample size, 40; n = 8 per group) was conducted to evaluate the effects of renal function on pharmacokinetics, pharmacodynamic effects, and safety after a single dose of ipragliflozin.

A single oral dose of 100 mg of ipragliflozin was to be administered under fasted conditions in healthy adult subjects and patients with normal renal function (eGFR[54] ≥90 mL/min/1.73 m^2, 8 subjects each), patients with mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2, 8 subjects), patients with moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2, 8 subjects), and patients with severe renal impairment (eGFR ≥15 and <30 mL/min/1.73 m^2, 8 subjects).

All of the 40 treated subjects (8 healthy adult subjects, 8 patients with normal renal function, 8 patients with mild renal impairment, 8 patients with moderate renal impairment, and 8 patients with severe renal impairment) were included in the pharmacokinetics, pharmacodynamic effects,

[53] The cumulative urinary glucose excretion (mean ± SD) from 24 hours pre-dose to the time of dosing of ipragliflozin (baseline) was 56,745 ± 82,414 mg in patients with normal renal function, 6873 ± 7008 mg in patients with mild renal impairment, and 4820 ± 11,252 mg in patients with moderate renal impairment. The fasting plasma glucose (mean ± SD) before administration of ipragliflozin (baseline) was 159.9 ± 57.49 mg/dL in patients with normal renal function, 133.3 ± 29.81 mg/dL in patients with mild renal impairment, and 121.5 ± 29.35 mg/dL in patients with moderate renal impairment. The urine volume (mean ± SD) from 24 hours pre-dose to the time of dosing of ipragliflozin (baseline) was 2677.5 ± 1317.31 mL in patients with normal renal function, 1915.9 ± 794.44 mL in patients with mild renal impairment, and 2183.3 ± 920.66 mL in patients with moderate renal impairment.

[54] Severity of renal impairment was classified according to MDRD equation based on screening serum creatinine (eGFR [mL/min/1.73 m^2] = 32,788 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × [1.210 (black subjects)] × [0.742 (female subjects)]).

and safety analysis sets.

Regarding the pharmacokinetics, the pharmacokinetic parameters of unchanged ipragliflozin and its metabolites[55] following a single oral dose of ipragliflozin 100 mg were as shown in Table 12 and Table 13, respectively. As for the pharmacokinetic parameters of unchanged ipragliflozin in patients with normal renal function and with mild, moderate, and severe renal impairment versus healthy adult subjects, the least squares mean ratios and the 90% CIs for AUC_{inf} were 1.141 [0.873, 1.492], 1.432 [1.095, 1.872], 1.599 [1.212, 2.110], and 1.673 [1.279, 2.186], respectively. The least squares mean ratios and the 90% CIs for C_{max} were 1.174 [0.945, 1.460], 1.281 [1.031, 1.593], 1.126 [0.905, 1.400], and 1.238 [0.996, 1.539], respectively; and the least squares mean ratios and the 90% CIs for CL_r were 0.967 [0.711, 1.316], 0.775 [0.569, 1.054], 0.706 [0.519, 0.960], and 0.432 [0.317, 0.587], respectively.

Table 12. Pharmacokinetic parameters of unchanged ipragliflozin following a single oral dose of ipragliflozin 100 mg

Parameter	Healthy adult subjects	Patients with type 2 diabetes mellitus			
		Patients with normal renal function	Patients with mild renal impairment	Patients with moderate renal impairment	Patients with severe renal impairment
C_{max} (ng/mL)	1277 ± 360	1456 ± 156	1626 ± 417	1448 ± 420	1576 ± 404
AUC_{inf} (ng·h/mL)	7326 ± 2037	8241 ± 1812	10,506 ± 3165	12,104 ± 4906 a)	12,687 ± 4840
t_{max} (h)	1.56 ± 0.68	1.20 ± 0.45	1.06 ± 0.32	1.31 ± 0.70	1.50 ± 0.80
$t_{1/2}$ (h)	15.2 ± 7.7	19.2 ± 6.2	20.6 ± 8.1	20.8 ± 9.8 a)	21.2 ± 9.2
CL/F (L/h)	14.6 ± 3.9	12.6 ± 2.4	10.2 ± 2.6	9.4 ± 3.4 a)	9.1 ± 3.8
Ae_{last} (% dose)	0.92 ± 0.12	1.03 ± 0.26	1.09 ± 0.57	1.05 ± 0.39	0.68 ± 0.21
CL_r (L/h)	0.13 ± 0.02	0.13 ± 0.04	0.11 ± 0.04	0.10 ± 0.03	0.06 ± 0.03
V_Z/F (L)	318.42 ± 196.98	335.46 ± 73.76	289.16 ± 106.06	257.20 ± 104.76 a)	254.23 ± 79.45
$fu_{,2\,h}$	0.030 ± 0.0040	0.028 ± 0.0042	0.028 ± 0.0028	0.034 ± 0.0072	0.030 ± 0.0034
$fu_{,6\,h}$	0.033 ± 0.0031	0.035 ± 0.0033	0.032 ± 0.0044	0.038 ± 0.0054	0.034 ± 0.0028

Mean ± SD, n = 8/group

C_{max}, Maximum plasma concentration; AUC_{inf}, Area under the plasma concentration-time curve (extrapolated to infinity); t_{max}, Time to reach the maximum plasma concentration; $t_{1/2}$, Half-life; CL/F, Oral clearance; Ae_{last}, Urinary excretion up to the last measurable concentration; CL_r, Renal clearance; V_Z/F, Apparent volume of distribution; $fu_{,2h}$, Unbound fraction at 2 hours post-dose; $fu_{,6h}$, Unbound fraction at 6 hours post-dose

a) n = 7

[55] 6-hydroxylated benzothiophene ring and 2'-*O*-β-glucuronide conjugate of glucose ring (M1), 2'-*O*-β-glucuronide conjugate of glucose ring (M2), 6'-*O*-β-glucuronide conjugate of glucose ring (M3), 3'-*O*-β-glucuronide conjugate of glucose ring (M4), and 6-*O*-sulfate conjugate of benzothiophene ring (M6).

Table 13. Pharmacokinetic parameters of metabolites following a single oral dose of ipragliflozin 100 mg

Metabolite	Parameter	Healthy adult subjects	Patients with type 2 diabetes mellitus			
			Patients with normal renal function	Patients with mild renal impairment	Patients with moderate renal impairment	Patients with severe renal impairment
M1	C_{max} (ng/mL)	62.4 ± 17.3	37.3 ± 14.4	53.0 ± 32.5	56.7 ± 23.1	99.4 ± 51.2
	AUC_{inf} (ng·h/mL)	524 ± 184[a)]	354 ± 157[a)]	582 ± 464	1075 ± 585[b)]	2111 ± 1261
	Ae_{last} (% dose)	3.98 ± 0.78	2.08 ± 0.37	3.17 ± 1.88	2.68 ± 1.01	2.29 ± 1.25
	CL_r (L/h)	12.8 ± 4.0	11.1 ± 4.0	9.2 ± 1.9	4.4 ± 1.9	1.9 ± 0.7
M2	C_{max} (ng/mL)	858 ± 263	995 ± 276	1115 ± 328	1258 ± 311	1953 ± 475
	AUC_{inf} (ng·h/mL)	5065 ± 1430	5594 ± 1434	8107 ± 3575	14,993 ± 5335	27,504 ± 9611
	Ae_{last} (% dose)	39.4 ± 5.5	36.2 ± 8.8	44.0 ± 17.4	38.2 ± 11.0	34.7 ± 10.5
	CL_r (L/h)	12.2 ± 3.9	10.1 ± 3.8	8.4 ± 2.2	3.9 ± 0.9	1.9 ± 0.7
M3	C_{max} (ng/mL)	165 ± 46	177 ± 54	179 ± 54	205 ± 54	338 ± 249
	AUC_{inf} (ng·h/mL)	1404 ± 551	1601 ± 574	2016 ± 869	4623 ± 1135[a)]	9095 ± 5174
	Ae_{last} (% dose)	3.66 ± 0.50	3.08 ± 0.86	3.57 ± 1.82	3.61 ± 0.92	3.14 ± 1.26
	CL_r (L/h)	4.27 ± 1.41	3.23 ± 1.30	2.70 ± 0.63	1.25 ± 0.28	0.58 ± 0.23
M4	C_{max} (ng/mL)	168 ± 44	229 ± 77	233 ± 74	279 ± 91	384 ± 125
	AUC_{inf} (ng·h/mL)	1064 ± 53	1423 ± 463	1679 ± 705	2977 ± 1093[a)]	4979 ± 2919
	Ae_{last} (% dose)	10.7 ± 2.2	11.7 ± 3.4	11.3 ± 3.7	8.9 ± 2.4	5.6 ± 2.0
	CL_r (L/h)	14.7 ± 3.2	13.5 ± 7.7	10.8 ± 3.8	5.0 ± 2.0	2.0 ± 1.0
M6	C_{max} (ng/mL)	48.9 ± 25.1	55.3 ± 34.4	66.6 ± 47.0	45.1 ± 33.9	40.9 ± 15.4
	AUC_{inf} (ng·h/mL)	678 ± 265	863 ± 456	1140 ± 745	1133 ± 666[a)]	1080 ± 473
	Ae_{last} (% dose)[c)]	0.94 ± 0.14	1.32 ± NA	1.51 ± NA	NA ± NA	NA ± NA
	CL_r (L/h)[c)]	1.53 ± 0.34	1.41 ± NA	0.80 ± NA	NA ± NA	NA ± NA

Mean ± SD; n = 8/group; NA, Not applicable

C_{max}, Maximum plasma concentration; AUC_{inf}, Area under the plasma concentration-time curve (extrapolated to infinity); Ae_{last}, Urinary excretion up to the last measurable concentration; CL_r, Renal clearance

a) n = 7

b) n = 6

c) Healthy adult subjects, n = 3; patients with normal renal function and patients with mild renal impairment, n = 1; patients with moderate renal impairment and patients with severe renal impairment, n = 0

Regarding the pharmacodynamic effects, the cumulative urinary glucose excretions (mean ± SD) at baseline (from 20 hours pre-dose to the time of dosing) and from 4 to 24 hours post-dose were 157 ± 251 and 43,740 ± 18,000 mg in healthy adult subjects, 1107 ± 2720 and 48,780 ± 19,440 mg in patients with normal renal function, 3564 ± 7848 and 64,980 ± 36,000 mg in patients with mild renal impairment, 1057 ± 1633 and 22,320 ± 16,920 mg in patients with moderate renal impairment, and 1615 ± 2956 and 12,024 ± 8748 mg in patients with severe renal impairment, respectively.

Regarding safety, 3 adverse events were reported by 1 of 8 healthy adult subjects and 4 adverse events were reported by 2 of 8 patients with moderate renal impairment. No adverse drug reactions, deaths, serious adverse events, or discontinuations due to adverse events were reported.

4.(ii).A.(4).4) Foreign study in patients with hepatic impairment (5.3.3.3-4, Study CL-0063 [May to August 2010])

An open-label, parallel-group, comparative study in foreign adult male and female subjects (target sample size, 16; n = 8 per group) was conducted to evaluate the effects of hepatic function on pharmacokinetics, pharmacodynamic effects, and safety after a single dose of ipragliflozin.

A single oral dose of 100 mg of ipragliflozin was to be administered under fasted conditions in

healthy adult subjects and patients with moderate hepatic impairment (Child-Pugh score for classification of hepatic impairment, 7-9).

All of the 16 treated subjects (8 healthy adult subjects, 8 patients with moderate hepatic impairment) were included in the pharmacokinetics, pharmacodynamic effects, and safety analysis sets.

Regarding the pharmacokinetics, the pharmacokinetic parameters of unchanged ipragliflozin and its metabolites[55] following a single oral dose of ipragliflozin 100 mg were as shown in Table 14 and Table 15, respectively. As for the pharmacokinetic parameters of unchanged ipragliflozin in patients with moderate hepatic impairment versus healthy adult subjects, the least-square geometric mean ratios and the 90% CIs for AUC_{inf} and C_{max} were 1.249 [0.938, 1.662] and 1.268 [0.928, 1.732], respectively.

Table 14. Pharmacokinetic parameters of unchanged ipragliflozin following a single oral dose of ipragliflozin 100 mg

Parameter	Healthy adult subjects	Patients with moderate hepatic impairment
C_{max} (ng/mL)	1398 ± 445.0	1761 ± 511.1
AUC_{inf} (ng·h/mL)	9104 ± 2418.8 [a)]	11,814 ± 3529.2
t_{max} (h)	1.94 ± 0.904	1.38 ± 0.354
$t_{1/2}$ (h)	16.2 ± 3.55 [a)]	15.8 ± 10.40
CL/F (L/h)	11.71 ± 3.243 [a)]	9.25 ± 3.099
Ae_{last} (% dose)	0.93 ± 0.216	1.35 ± 0.678
CL_r (L/h)	0.109 ± 0.0369	0.115 ± 0.0397
Vz/F (L)	270.65 ± 91.01 [a)]	203.79 ± 125.35
fu	0.032 ± 0.0036	0.037 ± 0.0028

Mean ± SD, n = 8/group

C_{max}, Maximum plasma concentration; AUC_{inf}, Area under the plasma concentration-time curve (extrapolated to infinity); t_{max}, Time to reach the maximum plasma concentration; $t_{1/2}$, Half-life; CL/F, Oral clearance; Ae_{last}, Urinary excretion up to the last measurable concentration; CL_r, Renal clearance; V_Z/F, Apparent volume of distribution; fu, Unbound fraction

a) n = 7

Table 15. Pharmacokinetic parameters of metabolites following a single oral dose of ipragliflozin 100 mg

Metabolite	Parameter	Healthy adult subjects	Patients with moderate hepatic impairment
M1	C_{max} (ng/mL)	84 ± 41.5	69 ± 45.8
	AUC_{inf} (ng·h/mL)	656 ± 343.8	691 ± 458.4
	Ae_{last} (% dose)	6.04 ± 1.214	6.82 ± 4.248
	CL_r (L/h)	11.83 ± 4.221	11.83 ± 4.067
M2	C_{max} (ng/mL)	966 ± 433.8	907 ± 280.9
	AUC_{inf} (ng·h/mL)	6416 ± 2636.7	6655 ± 2422.3
	Ae_{last} (% dose)	59.45 ± 4.042	64.79 ± 27.710
	CL_r (L/h)	10.43 ± 3.030	9.96 ± 2.766
M3	C_{max} (ng/mL)	159 ± 68.7	177 ± 63.0
	AUC_{inf} (ng·h/mL)	1565 ± 755.5	1943 ± 554.1
	Ae_{last} (% dose)	4.73 ± 1.575	5.88 ± 1.916
	CL_r (L/h)	3.40 ± 1.153	3.16 ± 1.113
M4	C_{max} (ng/mL)	197 ± 96.5	338 ± 129.3
	AUC_{inf} (ng·h/mL)	1476 ± 797.2 [a)]	2922 ± 1562.8
	Ae_{last} (% dose)	16.89 ± 1.364	31.72 ± 13.373
	CL_r (L/h)	14.46 ± 5.176	11.72 ± 3.333
M6	C_{max} (ng/mL)	60 ± 29.9	81 ± 31.1
	AUC_{inf} (ng·h/mL)	865 ± 452.3 [a)]	1377 ± 606.0
	Ae_{last} (% dose)	0.97 ± 0.608	1.08 ± 0.698
	CL_r (L/h)	1.10 ± 0.442	0.83 ± 0.423

Mean ± SD, n = 8/group
C_{max}, Maximum plasma concentration; AUC_{inf}, Area under the plasma concentration-time curve (extrapolated to infinity); Ae_{last}, Urinary excretion up to the last measurable concentration; CL_r, Renal clearance
a) n = 7

Regarding the pharmacodynamic effects, the cumulative urinary glucose excretions up to 24 and 144 hours post-dose (mean ± SD) were 28,080 ± 10,494 and 44,280 ± 17,118 mg in healthy adult subjects, respectively, and 23,580 ± 10,026 and 37,080 ± 17,082 mg in patients with moderate hepatic impairment, respectively.

Regarding safety, 2 adverse events were reported by 1 of 8 healthy adult subjects and 6 adverse events were reported by 3 of 8 patients with moderate hepatic impairment. Among these events, those classified as adverse drug reactions were 2 events reported by 1 of 8 healthy adult subjects and 6 events reported by 3 of 8 patients with moderate hepatic impairment. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

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

4.(ii).A.(5).1) Drug interaction study with metformin (5.3.3.4-1, Study CL-0056 [February to December 2009])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in foreign patients with type 2 diabetes mellitus[56] (target sample size, 36; n = 18 per group) was conducted to evaluate pharmacokinetics, pharmacodynamic interactions, and safety after concomitant use of ipragliflozin with metformin hydrochloride (metformin).

Multiple oral doses of 850, 1000, or 1500 mg/dose of metformin were to be administered twice daily at morning and evening meals for 14 days, followed by multiple oral doses of 850, 1000, or 1500 mg/dose of metformin (twice daily with morning and evening meals) in combination with 300 mg of ipragliflozin (once daily 5 minutes before breakfast) or placebo for 14 days.

[56] Major inclusion criteria: Patients whose disease condition is stable for ≥3 months on metformin monotherapy (1500-3000 mg/day) or combination therapy with metformin (1500-3000 mg/day) and sulfonylureas.

All of the 36 treated subjects were included in the pharmacokinetics, pharmacodynamic effects, and safety analysis sets.

Regarding the pharmacokinetics of metformin, the geometric mean ratios (combination of metformin with ipragliflozin versus metformin alone) and the two-sided 90% CIs for C_{max} and AUC_{10h} were 1.11 [1.03, 1.19] and 1.18 [1.08, 1.28], respectively.

Regarding the pharmacodynamic effects, urinary glucose excretion (mean ± SD) on Day 14 of concomitant treatment was 19.8 ± 22.2 mmol (3564 ± 3996 mg) in the metformin + placebo group and 415.9 ± 174.8 mmol (74,862 ± 31,464 mg) in the metformin + ipragliflozin group.

Regarding safety, 19 adverse events were reported by 8 of 18 subjects in the metformin + placebo group and 15 adverse events were reported by 7 of 18 subjects in the metformin + ipragliflozin group. Among these events, those classified as adverse drug reactions were 9 events reported by 5 of 18 subjects in the metformin + placebo group and 7 events reported by 3 of 18 subjects in the metformin + ipragliflozin group. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

4.(ii).A.(5).2) Drug interaction study with glimepiride (5.3.3.4-2, Study CL-0059 [December 2009 to April 2010])

A randomized, open-label, cross-over study in foreign healthy adult subjects (target sample size, 52; n = 13 per group) was conducted to evaluate pharmacokinetics, pharmacodynamic interactions, and safety after concomitant use of ipragliflozin with glimepiride.

For administration of multiple doses of ipragliflozin plus single doses of glimepiride, the following regimens were used: (1) subjects were to receive a single oral dose of 2 mg of glimepiride under fasted conditions on Day 1, followed by multiple oral doses of 150 mg of ipragliflozin once daily 5 minutes before breakfast from Days 4 to 10, with a concomitant oral dose of 2 mg of glimepiride on Day 8; and (2) subjects were to receive multiple oral doses of 150 mg of ipragliflozin once daily before breakfast on Days 1 to 7, with a concomitant oral dose of 2 mg of glimepiride on Day 5, followed by a single oral dose of 2 mg of glimepiride under fasted conditions on Day 10. For administration of single doses of ipragliflozin plus multiple doses of glimepiride, the following regimens were used: (1) subjects were to receive a single oral dose of 150 mg of ipragliflozin under fasted conditions on Day 1, followed by multiple oral doses of 1 mg of glimepiride once daily before breakfast on Days 4 to 8, with a concomitant oral dose of 150 mg of ipragliflozin on Day 6; and (2) subjects were to receive multiple oral doses of 1 mg of glimepiride once daily before breakfast on Days 1 to 5, with a concomitant oral dose of 150 mg of ipragliflozin on Day 3, followed by a single oral dose of 150 mg of ipragliflozin under fasted conditions on Day 8.

All of the 52 treated subjects were included in the pharmacokinetics, pharmacodynamic effects, and safety analysis sets.

Regarding the pharmacokinetics of glimepiride, the geometric mean ratios (combination of glimepiride with ipragliflozin versus glimepiride alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 1.10 [1.02, 1.19] and 1.05 [1.01, 1.09], respectively. Regarding the pharmacokinetics of ipragliflozin, the geometric mean ratios (combination of ipragliflozin with glimepiride versus ipragliflozin alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.97 [0.89, 1.06] and 0.99 [0.97, 1.02], respectively.

Regarding the pharmacodynamic effects, the geometric mean ratio (combination of ipragliflozin with glimepiride versus ipragliflozin alone) and the two-sided 90% CI for urinary glucose

excretion were 0.92 [0.88, 0.96].

As for adverse events, during the administration of multiple doses of ipragliflozin plus single doses of glimepiride, 42 adverse events were reported by 17 of 26 subjects after treatment with ipragliflozin alone, 36 adverse events were reported by 17 of 26 subjects after treatment with glimepiride alone, and 39 adverse events were reported by 18 of 26 subjects after concomitant treatment. During the administration of single doses of ipragliflozin plus multiple doses of glimepiride, 9 adverse events were reported by 6 of 26 subjects after treatment with ipragliflozin alone, 18 adverse events were reported by 13 of 26 subjects after treatment with glimepiride alone, and 15 adverse events were reported by 11 of 26 subjects after concomitant treatment. Of which, adverse drug reactions occurred in subjects receiving multiple doses of ipragliflozin plus single doses of glimepiride were as follows: 21 events reported by 12 of 26 subjects after treatment with ipragliflozin alone, 17 events were reported by 12 of 26 subjects after treatment with glimepiride alone, and 17 events were reported by 13 of 26 subjects after concomitant treatment. Adverse drug reactions occurred in subjects receiving single doses of ipragliflozin plus multiple doses of glimepiride were as follows: no adverse drug reactions reported by 26 subjects after treatment with ipragliflozin alone, 12 events reported by 8 of 26 subjects after treatment with glimepiride alone, and 3 events reported by 2 of 26 subjects after concomitant treatment. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

4.(ii).A.(5).3) Drug interaction study with pioglitazone (5.3.3.4-3, Study CL-0060 [December 2009])

A randomized, open-label, cross-over study in foreign healthy adult subjects (target sample size, 64; n = 16 per group) was conducted to evaluate pharmacokinetics, pharmacodynamic interactions, and safety after concomitant use of ipragliflozin with pioglitazone hydrochloride (pioglitazone).

For administration of multiple doses of ipragliflozin plus single doses of pioglitazone, the following regimens were used: (1) subjects were to receive a single oral dose of 30 mg of pioglitazone immediately before breakfast on Day 1, followed by multiple oral doses of 150 mg of ipragliflozin once daily immediately before breakfast on Days 5 to 12, with a concomitant oral dose of 30 mg of pioglitazone on Day 9; and (2) subjects were to receive multiple oral doses of 150 mg of ipragliflozin once daily immediately before breakfast on Days 1 to 8, with a concomitant oral dose of 30 mg of pioglitazone on Day 5, followed by a single oral dose of 30 mg of pioglitazone immediately before breakfast on Day 13. For administration of single doses of ipragliflozin plus multiple doses of pioglitazone, the following regimens were used: (1) subjects were to receive a single oral dose of 150 mg of ipragliflozin immediately before breakfast on Day 1, followed by multiple oral doses of 30 mg of pioglitazone once daily immediately before breakfast on Days 5 to 14, with a concomitant oral dose of 150 mg of ipragliflozin on Day 11; and (2) subjects were to receive multiple oral doses of 30 mg of pioglitazone once daily immediately before breakfast on Days 1 to 10, with a concomitant oral dose of 150 mg of ipragliflozin on Day 7, followed by a single oral dose of 150 mg of ipragliflozin immediately before breakfast on Day 17.

All of the 64 treated subjects were included in the pharmacokinetics, pharmacodynamic effects, and safety analysis sets. One subject who received single doses of ipragliflozin plus multiple doses of pioglitazone discontinued the study due to an adverse event (blood creatine phosphokinase increased).

Regarding the pharmacokinetics of pioglitazone, the geometric mean ratios (concomitant treatment with ipragliflozin/treatment with pioglitazone alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.99 [0.88, 1.11] and 1.02 [0.97, 1.07], respectively. Regarding the pharmacokinetics of ipragliflozin, the geometric mean ratios (concomitant treatment with

pioglitazone/treatment with ipragliflozin alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.93 [0.86, 1.01] and 1.00 [0.98, 1.02], respectively.

Regarding the pharmacodynamic effects, the geometric mean ratio (concomitant treatment with pioglitazone/treatment with ipragliflozin alone) and its two-sided 90% CI for urinary glucose excretion were 1.09 [0.97, 1.24].

Regarding safety, during the administration of multiple doses of ipragliflozin plus single doses of pioglitazone, 25 adverse events were reported by 15 of 32 subjects. During the administration of single doses of ipragliflozin plus multiple doses of pioglitazone, 21 adverse events were reported by 14 of 32 subjects. Except for 1 event in 1 subject receiving single doses of ipragliflozin plus multiple doses of pioglitazone, all events were assessed as adverse drug reactions. One subject who received single doses of ipragliflozin plus multiple doses of pioglitazone discontinued the study due to blood creatine phosphokinase increased. No deaths or serious adverse events were reported.

4.(ii).A.(5).4) Drug interaction study with miglitol (5.3.3.4-4, Study CL-0062 [January to March 2010])

A randomized, open-label, six-treatment, three-regimen, three-period cross-over study in Japanese healthy adult male subjects (target sample size, 30) was conducted to evaluate pharmacokinetics and safety after concomitant use of ipragliflozin with miglitol.

For Period 1 to 3, oral doses of 100 mg of ipragliflozin alone, oral doses of 75 mg of miglitol alone, and oral doses of 100 mg of ipragliflozin in combination with 75 mg of miglitol were to be administered under fasted conditions. A washout period of ≥6 days was included between the treatment periods, and use of ipragliflozin and/or miglitol in Periods 2 and 3 were to be determined by the investigator considering the exclusion criteria.

All of the 30 treated subjects were included in the pharmacokinetics and safety analysis sets.

Regarding the pharmacokinetics of miglitol, the geometric mean ratios (concomitant treatment with ipragliflozin/treatment with miglitol alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.76 [0.67, 0.86] and 0.80 [0.72, 0.88], respectively. Regarding the pharmacokinetics of ipragliflozin, the geometric mean ratios (concomitant treatment with miglitol/treatment with ipragliflozin alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 1.03 [0.94, 1.13] and 1.02 [0.99, 1.04], respectively.

Regarding safety, 3 adverse events were reported by 3 of 30 subjects after treatment with ipragliflozin alone, 2 adverse events were reported by 2 of 30 subjects after treatment with miglitol alone, and 2 adverse events were reported by 2 of 30 subjects after concomitant treatment. Of which, events classified as adverse drug reactions were as follows: 1 event reported by 1 of 30 subjects after treatment with ipragliflozin alone, 2 events reported by 2 of 30 subjects after treatment with miglitol alone, and 1 event reported by 1 of 30 subjects after concomitant treatment. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

4.(ii).A.(5).5) Drug interaction study with sitagliptin (5.3.3.4-5, Study CL-0066 [February to March 2010])

A randomized, open-label, cross-over study in foreign healthy adult subjects (target sample size, 64; n = 16 per group) was conducted to evaluate pharmacokinetics, pharmacodynamic interactions, and safety after concomitant use of ipragliflozin with sitagliptin phosphate hydrate (sitagliptin).

For administration of multiple doses of ipragliflozin plus single doses of sitagliptin, the following

regimens were used: (1) subjects were to receive a single oral dose of 100 mg of sitagliptin immediately before breakfast on Day 1, followed by multiple oral doses of 150 mg of ipragliflozin once daily immediately before breakfast on Days 4 to 10, with a concomitant oral dose of 100 mg of sitagliptin on Day 8; and (2) subjects were to receive multiple oral doses of 150 mg of ipragliflozin once daily immediately before breakfast on Days 1 to 7, with a concomitant oral dose of 100 mg of sitagliptin on Day 5, followed by a single oral dose of 100 mg of sitagliptin immediately before breakfast on Day 12. For administration of single doses of ipragliflozin plus multiple doses of sitagliptin, the following regimens were used: (1) subjects were to receive a single oral dose of 150 mg of ipragliflozin immediately before breakfast on Day 1, followed by multiple oral doses of 100 mg of sitagliptin once daily immediately before breakfast on Days 5 to 11, with a concomitant oral dose of 150 mg of ipragliflozin on Day 8; and (2) subjects were to receive multiple oral doses of 100 mg of sitagliptin once daily immediately before breakfast on Days 1 to 7, with a concomitant oral dose of 150 mg of ipragliflozin on Day 4, followed by a single oral dose of 150 mg of ipragliflozin immediately before breakfast on Day 11.

All of the 64 treated subjects were included in the pharmacokinetics, pharmacodynamic effects, and safety analysis sets.

Regarding the pharmacokinetics of sitagliptin, the geometric mean ratios (concomitant treatment with ipragliflozin/treatment with sitagliptin alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.92 [0.83, 1.03] and 1.00 [0.97, 1.03], respectively. Regarding the pharmacokinetics of ipragliflozin, the geometric mean ratio (concomitant treatment with sitagliptin/treatment with ipragliflozin alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.97 [0.90, 1.03] and 0.95 [0.93, 0.97], respectively.

Regarding the pharmacodynamic effects, the geometric mean ratio (concomitant treatment with sitagliptin/treatment with ipragliflozin alone) and its two-sided 90% CI for urinary glucose excretion were 0.77 [0.68, 0.86].

Regarding safety, during the administration of multiple doses of ipragliflozin plus single doses of sitagliptin, 8 adverse events were reported by 5 of 32 subjects after treatment with multiple doses of ipragliflozin, 3 adverse events were reported by 3 of 32 subjects after treatment with a single dose of sitagliptin, and 6 adverse events were reported by 4 of 32 subjects in concomitant treatment. During the administration of single doses of ipragliflozin plus multiple doses of sitagliptin, 3 adverse events were reported by 3 of 32 subjects after treatment with a single dose of ipragliflozin, 6 adverse events were reported by 5 of 32 subjects after treatment with multiple doses of sitagliptin, and 6 adverse events were reported by 5 of 32 subjects after concomitant treatment. Among these, except for 1 event in 1 subject receiving single doses of ipragliflozin plus multiple doses of sitagliptin, all events were assessed as adverse drug reactions. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

4.(ii).A.(5).6) Drug interaction study with mitiglinide (5.3.3.4-6, Study CL-0074 [June to August 2011])

A randomized, open-label, cross-over study in Japanese healthy adult male subjects (target sample size, 60; n = 15 per group) was conducted to evaluate pharmacokinetics and safety after concomitant use of ipragliflozin with mitiglinide calcium hydrate (mitiglinide).

For administration of multiple doses of mitiglinide plus single doses of ipragliflozin, the following regimens were used: (1) subjects were to receive a single oral dose of 100 mg of ipragliflozin 5 minutes before breakfast on Day 1, followed by multiple oral doses of 10 mg of mitiglinide 3 times daily 5 minutes before meals on Days 5 to 8, with a concomitant oral dose of 100 mg of ipragliflozin on Day 6; and (2) subjects were to receive multiple oral doses of 10 mg of mitiglinide 3 times daily 5 minutes before meals on Days 1 to 4, with a concomitant oral dose of 100 mg of

ipragliflozin on Day 2, followed by a single oral dose of 100 mg of ipragliflozin 5 minutes before breakfast on Day 7. For administration of multiple doses of ipragliflozin plus single doses of mitiglinide, the following regimens were used: (1) subjects were to receive a single oral dose of 10 mg of mitiglinide 5 minutes before breakfast on Day 1, followed by multiple oral doses of 100 mg of ipragliflozin once daily 5 minutes before breakfast on Days 3 to 5, with a concomitant oral dose of 10 mg of mitiglinide on Day 5; and (2) subjects were to receive multiple oral doses of 100 mg of ipragliflozin once daily 5 minutes before breakfast on Days 1 to 3, with a concomitant oral dose of 10 mg of mitiglinide on Day 3, followed by a single oral dose of 10 mg of mitiglinide 5 minutes before breakfast on Day 8.

All of the 30 treated subjects were included in the pharmacokinetics and safety analysis sets.

Regarding the pharmacokinetics of mitiglinide, the geometric mean ratios (concomitant treatment with ipragliflozin/treatment with mitiglinide alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.87 [0.77, 0.99] and 1.01 [0.99,1.03], respectively. Regarding the pharmacokinetics of ipragliflozin, the geometric mean ratios (concomitant treatment with mitiglinide/treatment with ipragliflozin alone) and the two-sided 90% CIs for C_{max} and AUC_{inf} were 0.95 [0.90, 1.00] and 1.00 [0.98, 1.03], respectively.

Regarding safety, during the administration of multiple doses of mitiglinide plus single doses of ipragliflozin, 3 adverse events were reported by 2 of 30 subjects after treatment with a single dose of ipragliflozin. During the administration of multiple doses of ipragliflozin plus single doses of mitiglinide, 2 adverse events were reported by 2 of 30 subjects after treatment with a single dose of mitiglinide. Among these, except for 1 event in 1 subject receiving multiple doses of ipragliflozin plus single doses of mitiglinide, all events were assessed as adverse drug reactions. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

4.(ii).A.(5).7) Drug interaction study with furosemide (5.3.3.4-7, Study CL-0054 [July to October 2011])

A randomized, open-label, three-period cross-over study in foreign healthy adult subjects (target sample size, 64; n = ≥8 per sex) was conducted to evaluate pharmacokinetics, pharmacodynamic interactions, and safety after concomitant use of ipragliflozin with furosemide.

For Period 1 to 3, the following regimens were used: multiple doses of 150 mg of ipragliflozin once daily 2 hours before breakfast for 5 days; multiple doses of 40 mg of furosemide once daily 2 hours before breakfast for 5 days; and multiple oral doses of 150 mg of ipragliflozin once daily 2 hours before breakfast for 5 days plus 40 mg of furosemide once daily 2 hours before breakfast for 7 days (5 days of concomitant period). A washout period of ≥7 days was included between the treatment periods.

All of the 24 treated subjects were included in the pharmacokinetics, pharmacodynamic effects, and safety analysis sets.

Regarding the pharmacokinetics of furosemide, the geometric mean ratios (concomitant treatment with ipragliflozin/treatment with furosemide alone) and the two-sided 90% CIs for C_{max} and AUC_{tau} were 1.07 [0.88, 1.30] and 1.06 [0.95, 1.19], respectively. Regarding the pharmacokinetics of ipragliflozin, the geometric mean ratios (concomitant treatment with furosemide/treatment with ipragliflozin alone) and the two-sided 90% CIs for C_{max} and AUC_{tau} were 1.13 [1.05, 1.23] and 1.07 [1.03, 1.10], respectively.

Regarding the pharmacodynamic effects, the geometric mean ratio (concomitant treatment with furosemide/treatment with ipragliflozin alone) and its two-sided 90% CI for urinary glucose excretion on Day 5 were 0.87 [0.81, 0.93]. The geometric mean ratios (concomitant treatment

with ipragliflozin/treatment with furosemide alone) and the two-sided 90% CIs for urinary electrolyte levels of Na, Ca, Cl, K, P, and Mg on Day 5 were 0.99 [0.93, 1.07], 1.00 [0.94, 1.06], 0.98 [0.87, 1.12], 1.04 [0.99, 1.08], 1.04 [0.98, 1.10], and 1.01 [0.95, 1.07], respectively. Similarly, serum electrolyte concentrations were not influenced by concomitant use of ipragliflozin.

Regarding safety, 65 adverse events were reported by 18 of 24 subjects after treatment with ipragliflozin alone, 65 adverse events were reported by 19 of 24 subjects after treatment with furosemide alone, and 134 adverse events were reported by 19 of 24 subjects in concomitant treatment. Of which, events classified as adverse drug reactions were as follows: 54 events reported by 17 of 24 subjects after treatment with ipragliflozin alone, 59 events reported by 17 of 24 subjects after treatment with furosemide alone, and 120 events reported by 19 of 24 subjects (120 events) after concomitant treatment. No deaths, serious adverse events, or discontinuations due to adverse events were reported.

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

Thorough QT/QTc study (5.3.4.1-1, Study CL-0058 [September 2010 to February 2011])

A randomized, double-blind, placebo- and moxifloxacin-controlled, four-period cross-over study in foreign healthy adult subjects (target sample size, 88; n = 22 [10 males and 12 females] per group) was conducted to evaluate the effect on the QT/QTc interval after multiple doses of ipragliflozin.

Multiple oral doses of 100 and 600 mg of ipragliflozin, 400 mg of moxifloxacin (positive control), and placebo were to be administered once daily under fasted conditions for 7 days. A washout period of ≥7 days was included between the treatment periods.

All of the 88 treated subjects were included in the QT and safety analysis sets, of which, 86 subjects with evaluable pharmacokinetic data were included in the pharmacokinetics analysis set.

Regarding the pharmacokinetics, C_{max} (mean ± SD) following a single oral dose of ipragliflozin 100 and 600 mg was 1710 ± 524 and 8627 ± 1883 ng/mL, respectively, and t_{max} was 1.94 ± 0.94 and 1.80 ± 0.90 h, respectively.

Regarding the electrocardiogram (ECG), the difference in least squares means of QTcF[18] between the ipragliflozin and placebo groups on Day 7 peaked at 2 and 10 hours post-dose at doses of 100 and 600 mg of ipragliflozin, respectively, with the values (two-sided 90% CI) of 1.77 [0.15, 3.39] and 2.81 [1.19, 4.44] ms, respectively, resulting in the upper limit of the CI of <10 ms. However, the difference in least squares means of QTcF between the ipragliflozin and placebo groups after dosing of moxifloxacin peaked at 3 hours post-dose with the value (two-sided 90% CI) of 13.35 [11.72, 14.99] ms, and the lower limit of the CI exceeded 5 ms at all time points between 1 to 12 hours post-dose.

Regarding safety, 66 adverse events were reported by 27 of 84 subjects receiving placebo, 59 adverse events were reported by 32 of 85 subjects receiving ipragliflozin 100 mg, 53 adverse events were reported by 26 of 84 subjects receiving ipragliflozin 600 mg, and 63 adverse events were reported by 29 of 83 subjects receiving moxifloxacin. Among these events, those classified as adverse drug reactions were 52 events reported by 22 of 84 subjects receiving placebo, 43 events reported by 25 of 85 subjects receiving ipragliflozin 100 mg, 39 events reported by 22 of 84 subjects receiving ipragliflozin 600 mg, and 45 events reported by 21 of 83 subjects receiving moxifloxacin. Three subjects receiving placebo discontinued the study due to tachycardia (1 subject) and urinary tract infection (2 subjects), and 1 subject receiving ipragliflozin 100 mg and 1 subject receiving ipragliflozin 600 mg discontinued the study due to vaginal infection and drug hypersensitivity, respectively. No deaths or serious adverse events were reported.

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

4.(ii).B.(1) Pharmacokinetics (PK) and pharmacodynamic (PD) effects of ipragliflozin

PMDA asked the applicant to explain the relationship between pharmacokinetics (PK) and pharmacodynamics (PD), taking account of the mechanism of action of ipragliflozin.

The applicant responded as follows:

In healthy adult subjects, the excretion of glucose into urine is rarely found because the glucose in blood is filtered through the renal glomerulus into the primitive urine and subsequently reabsorbed at the proximal renal tubules mainly by SGLT2 into blood. Ipragliflozin inhibits glucose reabsorption mediated by SGLT2 at the proximal renal tubules and acts to promote glucose excretion into urine. Taking account of this mechanism of action, not only SGLT2 inhibition by ipragliflozin but also the filtered load of glucose in the renal glomerulus need to be considered in the discussion of the relationship between PK and PD of ipragliflozin. In order to discuss the effect of exposure to ipragliflozin, the relationship between the single-dose AUC_{inf} and C_{max} and the 72-hour cumulative urinary glucose excretion, a marker of pharmacological activity of ipragliflozin, was examined using the results from the Japanese phase I study (Study CL-0101) and also the relationship between the AUC_{24h} and ΔUGE_{24h} was examined using data from the PK/PD study in patients with renal impairment (Study CL-0073) and the study on circadian variation of blood glucose (Study CL-0070) in addition to those from Study CL-0101. As a result, a pharmacological activity (increase in urinary glucose excretion) that depends on an increase in exposure to ipragliflozin was confirmed, suggesting that exposure to ipragliflozin is an important factor in the discussion of pharmacological activity. In addition, an examination on the relationship between the baseline FPG and the cumulative urinary glucose excretion up to 24 hours post-dose[57] (UGE_{24h}) obtained from Studies CL-0073 and CL-0070 suggested that urinary glucose excretion is strongly affected by blood glucose. Furthermore, in order to evaluate whether or not renal function as measured by creatinine clearance or eGFR affects urinary glucose excretion, the relationship between the eGFR and the change from baseline in urinary glucose excretion was examined using the results from Study CL-0073. The results suggested that urinary glucose excretion is strongly affected by renal function. While the filtered load of glucose decreased substantially with decreasing renal function, urinary glucose excretion[58] did not substantially vary across the groups of subjects with different renal function (50.7% in patients with normal renal function, 53.1% in patients with mild renal impairment, 57.7% in patients with moderate renal impairment). Given the fact that exposure to ipragliflozin in type 2 diabetes mellitus patients with renal impairment was similar to or slightly higher than that in type 2 diabetes mellitus patients with normal renal function, the decrease in urinary glucose excretion observed in type 2 diabetes mellitus patients with renal impairment was thought to be mainly attributable to a decrease in the filtered load of glucose.

Based on the above, the applicant considered that factors affecting the post-dose PK/PD relationship of ipragliflozin included not only exposure to ipragliflozin but also the filtered load of glucose and, particularly in comparison between patients with similar blood glucose levels, receiving the same fixed dose (resulting in exposure within a certain range), renal function as measured by eGFR, creatinine clearance, etc. had substantial effects on urinary glucose excretion observed after administration of ipragliflozin.

PMDA asked the applicant to explain the reason for the higher exposures to ipragliflozin noted in female subjects and in the elderly subjects than in male subjects and in the non-elderly subjects, respectively, following a single dose and multiple doses in the study investigating elderly subjects and gender-related differences (Study CL-0052), as well as the relationship between the exposure and cumulative urinary glucose excretion.

[57] After a single dose in Study CL-0073 and multiple doses in Study CL-0070
[58] Ratio of urinary glucose excretion to the filtered load of glucose

The applicant responded as follows:
Based on consideration of patient characteristics enrolled in the study and study conditions,[59] and on the fact that body surface area was included in the final model as a covariate on CL/F while sex was not included as a significant covariate in the PPK analysis of study patient data, it was presumed that doses adjusted for body weight or body surface area were higher in female subjects than in male subjects, resulting in slightly higher exposure in female subjects. In addition, it was presumed that doses adjusted for body surface area were higher in elderly subjects than in non-elderly subjects, resulting in slightly higher exposure. Body surface area was included in the final model as a covariate on CL/F while age was not included as a significant covariate in the PPK analysis of study patient data. In Study CL-0052, urinary glucose excretion was higher in non-elderly and male groups than in elderly and female groups, respectively, despite higher exposures observed in elderly and female groups than in non-elderly and male groups, respectively. The mean AUC_{24h} values after multiple dosing in each group in this study ranged from 8231 to 14,027 ng·h/mL, which was substantially higher than the EC_{50} value (1590 ng·h/mL) obtained from the model of the blood exposure-urinary glucose excretion relationship and corresponded to exposure at which urinary glucose excretion almost reaches a plateau. Thus, these values are considered to fall outside the range where slight differences in exposure strongly affect the pharmacological effect. Therefore, urinary glucose excretion would presumably depend more on variability in the filtered load of glucose determined by blood glucose level and renal function than on inter-individual variability in exposure. In fact, in the sex and age comparisons in the above study, variability in creatinine clearance[60] was larger than that in AUC_{24h} of glucose and AUC_{24h} of unchanged ipragliflozin[61] and a correlation was observed between creatinine clearance and cumulative urinary glucose excretion. Thus, sex- and age-related variability in creatinine clearance could possibly have an effect on cumulative urinary glucose excretion.

PMDA accepted the response.

4.(ii).B.(2) Use in patients with renal impairment
PMDA asked the applicant to explain the appropriateness of the use of ipragliflozin and the necessity of dose adjustment of ipragliflozin for patients with renal impairment.

The applicant responded as follows:
In the PK/PD study in patients with renal impairment (Study CL-0073), C_{max} and AUC_{inf} of unchanged ipragliflozin following a single oral dose of ipragliflozin 50 mg were approximately 1.12- and 0.94-fold, respectively, in patients with mild renal impairment and were 1.17- and 1.21-fold, respectively, in patients with moderate renal impairment, compared with patients with normal renal function. In addition, in the foreign study in patients with renal impairment (Study CL-0064), C_{max} of unchanged ipragliflozin following a single oral dose of 100 mg of ipragliflozin in patients with mild, moderate, and severe renal impairment was approximately 1.09-, 0.96-, and 1.05-fold that in patients with normal renal function, respectively, indicating no marked differences associated with decreases in renal function, but AUC_{inf} was approximately 1.25-, 1.40-, and 1.47-fold that in patients with normal renal function, respectively, showing an increasing trend associated with decreasing renal function. Safety in patients with mild to

[59] BMI (mean ± SD) (27.2 ± 2.2 kg/m^2 in male subjects, 27.6 ± 2.0 kg/m^2 in female subjects, 28.2 ± 1.8 kg/m^2 in elderly subjects, 26.6 ± 2.2 kg/m^2 in non-elderly subjects), body weight (76.7 ± 7.7 kg in male subjects, 67.9 ± 6.3 kg in female subjects, 71.2 ± 7.7 kg in elderly subjects, 73.3 ± 8.8 kg in non-elderly subjects), height (168.0 ± 7.5 cm in male subjects, 156.7 ± 5.4 cm in female subjects, 158.8 ± 7.2 cm in elderly subjects, 165.8 ± 8.6 cm in non-elderly subjects), body surface area (1.86 ± 0.13 m^2 in male subjects, 1.68 ± 0.10 m^2 in female subjects, 1.73 ± 0.13 m^2 in elderly subjects, 1.81 ± 0.15 m^2 in non-elderly subjects)·

[60] Creatinine clearance (120.3 ± 68.0 mL/min in male subjects, 74.5 ± 24.4 mL/min in female subjects, 70.5 ± 19.8 mL/min in elderly subjects, 124.5 ± 66.3 mL/min in non-elderly subjects)

[61] AUC_{24h} of glucose (135.6 ± 12.2 mmol·h/L in male subjects, 130.4 ± 8.89 mmol·h/L in female subjects, 138.3 ± 10.6 mmol·h/L in elderly subjects, 127.6 ± 8.48 mmol·h/L in non-elderly subjects), AUC_{24h} of unchanged ipragliflozin in plasma (9141 ± 1927 ng·h/mL in male subjects, 12,007 ± 3309 ng·h/mL in female subjects, 12,039 ± 3235 ng·h/mL in elderly subjects, 8846 ± 1573 ng·h/mL in non-elderly subjects)

moderate renal impairment was analyzed using the pooled data from comparative studies.[27] The incidences of adverse events, serious adverse events, and adverse events leading to treatment discontinuation reported in the ipragliflozin 50 mg group were 83.3%, 5.6%, and 9.7%, respectively, for the subgroup of patients[62] with "moderate renal impairment" (categorized according to baseline eGFR), and these incidences were highest in the subgroup of patients with "moderate renal impairment" among the three baseline-eGFR-based subgroups. In the placebo group, however, the incidences of adverse events, serious adverse events, and adverse events leading to treatment discontinuation were 71.0%, 3.2%, and 12.9%, respectively, for the subgroup of patients with "moderate renal impairment." The incidences were similar across the three baseline-eGFR-based subgroups. In addition, in the pooled data from 52-week studies,[32] although the incidence of adverse events related to renal disorder increased with decreasing baseline eGFR (0.3%, 1.2%, and 6.3% for the categories of "normal renal function," "mild renal impairment," and "moderate renal impairment," respectively), the mean eGFR over time showed no irreversible effects on renal function irrespective of severity of renal impairment. Although studies on exposure to ipragliflozin in Japanese patients with severe renal impairment have not been conducted, further increase in exposure in this patient population should be expected given the fact that exposure in Japanese patients with moderate renal impairment was approximately 1.21-fold that in patients with normal renal function. Indeed, exposure to ipragliflozin in foreign patients with severe renal impairment was higher than that in patients with normal renal function. However, the increase in exposure in Japanese patients with severe renal impairment is not likely to significantly affect the safety in light of the following reasons: (1) exposure to ipragliflozin in foreign patients with severe renal impairment was only about 1.47-fold that in patients with normal renal function; (2) tolerability of multiple doses of 600 mg/day of ipragliflozin for 7 or 10 days has been established in healthy adult subjects (foreign phase I study [Study CL-0002], thorough QT/QTc study [Study CL-0058]); (3) no clinically relevant safety concerns have been identified after a dose increase from 50 to 100 mg/day in the studies in patients with type 2 diabetes mellitus; and (4) once daily administration of 300 mg of ipragliflozin for 12 weeks was safe and well tolerated in the foreign phase II studies (foreign phase II dose-finding study [Study CL-0004], foreign phase II metformin combination therapy study [Study CL-0005]).

Based on the above, ipragliflozin may be administered to patients with renal impairment without dose reduction from the pharmacokinetics and safety points of view.

As for the efficacy of ipragliflozin in patients with renal impairment, the change from baseline in 24-hour cumulative urinary glucose excretion after a single dose of ipragliflozin in Japanese patients with type 2 diabetes mellitus with normal renal function, mild renal impairment, and moderate renal impairment was approximately 71, 61, and 38 g, respectively. The change from baseline in 24-hour cumulative urinary glucose excretion was lower in patients with moderate renal impairment than in patients with normal renal function and patients with mild renal impairment (Study CL-0073). Although the results from the pooled data analysis of comparative studies and the study in patients with renal impairment (Study CL-0072) showed that the hypoglycemic activity of ipragliflozin tended to diminish with decreasing renal function, a clinically significant hypoglycemic activity was expected in patients with mild to moderate renal impairment. In addition, the proportion of patients with HbA1c of <7.0% was increased by increasing the dose to 100 mg/day among patients in whom hypoglycemic activity was insufficient at ipragliflozin 50 mg/day, except for patients with moderate renal impairment with baseline eGFR of ≥30 and <60 mL/min/1.73 m^2. On the other hand, because no apparent differences depending on the severity of renal impairment were observed in the proportion of patients in whom HbA1c and fasting plasma glucose decreased after the dose increase, the effects of dose increase of ipragliflozin were expected in all the subgroups.

[62] Under 3 categories of "normal renal function," "mild renal impairment," and "moderate renal impairment"

Based on the above, the applicant considers that the efficacy of ipragliflozin is expected also in patients with renal impairment. Also, the dose of ipragliflozin may increase to 100 mg/day in patients in whom hypoglycemic activity is insufficient at 50 mg/day. On the other hand, because urinary glucose excretion, a marker of pharmacodynamic effects, tended to decrease with increasing severity of renal impairment and because attenuation of the hypoglycemic activity was also observed, the appropriate precautionary statements should be included in the package insert. In addition, the efficacy of long-term treatment with ipragliflozin has not been evaluated in patients with severe renal impairment. Given the extent of a decrease in urinary glucose excretion observed with increasing severity of renal impairment, the hypoglycemic activity would be substantially attenuated in such a patient population, suggesting that the clinical efficacy is limited and, therefore, appropriate precautionary statements should be included in the package insert.

PMDA considers as follows:
PMDA accepted the response from the pharmacokinetic viewpoint, but issues including the use in patients with renal impairment and the necessity of precautionary statements in the package insert will be reviewed in the clinical section "4.(iii).B.(6).1) Patients with renal impairment."

4.(ii).B.(3) Use in patients with hepatic impairment

PMDA asked the applicant to explain the appropriateness of the use of ipragliflozin and the necessity of dose adjustment of ipragliflozin for patients with hepatic impairment.

The applicant responded as follows:
In the foreign study in patients with hepatic impairment (Study CL-0063), C_{max} and AUC_{inf} of unchanged ipragliflozin following administration of 100 mg of ipragliflozin to patients with moderate hepatic impairment were approximately 1.27- and 1.25-fold those in healthy adult subjects, respectively. Although studies on the effect on pharmacokinetics of ipragliflozin in patients with mild hepatic impairment have not been conducted, exposure in patients with mild hepatic impairment is unlikely to exceed that in patients with moderate hepatic impairment because elimination of ipragliflozin occurs mainly via hepatic metabolism. Studies on the effect on pharmacokinetics of ipragliflozin in patients with severe hepatic impairment have not been conducted either. Although a greater increase in exposure is expected in patients with severe hepatic impairment than in patients with moderate hepatic impairment, the increased exposure in patients with severe hepatic impairment is not considered to substantially affect the safety, in light of the fact that unchanged ipragliflozin exposure in patients with moderate hepatic impairment was increased by approximately 27% and that some contribution of renal metabolism to elimination of ipragliflozin has also been suggested.

As for efficacy in patients with hepatic impairment, although the urinary glucose excretion up to 24 hours post-dose (mean ± SD) in Study CL-0063 was 28,080 ± 10,476 mg in healthy adult subjects and 23,580 ± 10,026 mg in patients with moderate hepatic impairment, no apparent difference exists between healthy adult subjects and patients with moderate hepatic impairment given the large inter-individual variability. Factors affecting urinary glucose excretion after administration of ipragliflozin would include unchanged ipragliflozin exposure, renal function, and blood glucose. Of these, unchanged ipragliflozin exposure tended to be higher in patients with moderate hepatic impairment than in healthy adult subjects, while there was no tendency for renal function in patients with moderate hepatic impairment to be lower than that in healthy adult subjects. In addition, blood glucose did not differ between healthy adult subjects and patients with moderate hepatic impairment. Therefore, factors that decrease urinary glucose excretion in patients with moderate hepatic impairment to less than that in healthy adult subjects cannot be suggested. Indeed, in the pooled data from comparative studies,[27] the mean changes in HbA1c from baseline to the end of the double-blind period in subjects with and without a comorbidity included in "hepatobiliary disorders" were 0.27% and 0.34% in the placebo group, respectively, and -0.82% and -0.66% in the ipragliflozin 50 mg group, respectively, indicating no apparent

effects of hepatic impairment on the change in HbA1c, in light of the difference between ipragliflozin and placebo.

As for safety in patients with hepatic impairment, the incidence of adverse events categorized under "hepatobiliary disorders" in the pooled data from comparative studies[27] was lower in the 50 mg group (1.0%) than in the placebo group (1.9%). In addition, there was no tendency for the incidence of "hepatobiliary disorders" adverse events to increase with increasing treatment duration in the pooled data from 52-week studies.[32] In addition, the mean values of laboratory parameters related to hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) at the end of the treatment period decreased in AST and ALT from baseline and no apparent changes in total bilirubin were observed in the ipragliflozin 50 mg group. There were no cases with abnormal AST or ALT with a level >3-fold the upper limit of normal or with abnormal total bilirubin with a level >2-fold the upper limit of normal in any dose group in the pooled phase II/III studies.[63]

Based on the above, the applicant considered that administration of ipragliflozin to patients with hepatic impairment of mild to moderate without dose reduction poses no problems from a safety viewpoint. However, the increase in exposure to ipragliflozin is expected to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment because ipragliflozin is considered to be mainly metabolized by the liver. However, in light of the fact that an increase in unchanged ipragliflozin exposure (AUC_{inf}) in patients with moderate hepatic impairment was only up to approximately 25% and that some contribution of renal metabolism to elimination of ipragliflozin has also been suggested, the increased exposure in patients with severe hepatic impairment is not likely to significantly affect the safety. However, because there is no clinical experience of ipragliflozin in patients with severe hepatic impairment and its safety has not been established in such a patient population, the appropriate precautionary statements should be included in the package insert.

PMDA accepted the response from the pharmacokinetic viewpoint, but the necessity of precautionary statements in the package insert will be reviewed in the clinical section "4.(iii).B.(6).2) Patients with hepatic impairment."

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, results from Japanese phase I and clinical pharmacology studies (Studies CL-0101, CL-0071, CL-0062, CL-0074, CL-0073, and CL-0070), foreign phase I and clinical pharmacology studies (Studies CL-0001, CL-0002, CL-0055, CL-0057, CL-0058, CL-0052, CL-0063, CL-0064, CL-0054, CL-0059, CL-0060, CL-0066, and CL-0056), Japanese phase II dose-finding study (Study CL-0103), and phase III studies (Studies CL-0105, CL-0121, CL-122, CL-0106, CL-0107, CL-0109, CL-0108, CL-0110, CL-0111, and CL-0072) were submitted. Results of primary studies are shown below. HbA1c are expressed as JDS values.[64]

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

For summaries of studies, Japanese phase I and clinical pharmacology studies (Studies CL-0101, CL-0071, CL-0062, CL-0074, CL-0073, and CL-0070) and foreign phase I and clinical pharmacology studies (Studies CL-0001, CL-0002, CL-0055, CL-0057, CL-0058, CL-0052, CL-

[63] Pooled analysis of the following 11 studies (treatment duration: 12-52 weeks): Japanese phase II dose-finding study (Study CL-0103), Japanese phase III monotherapy study (Study CL-0105), Japanese long-term monotherapy study (Studies CL-0121 and CL-0122), metformin combination therapy study (Study CL-0106), pioglitazone combination therapy study (Study CL-0107), sulfonylurea combination therapy study (Study CL-0109), α-glucosidase inhibitor combination therapy study (Study CL-0108), dipeptidyl peptidase-4 inhibitor combination therapy study (Study CL-0110), nateglinide combination therapy study (Study CL-0111), and study in patients with renal impairment (Study CL-0072).

[64] Values according to Japan Diabetes Society

0063, CL-0064, CL-0054, CL-0059, CL-0060, CL-0066, and CL-0056) as well as clinical safety data, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies."

4.(iii).A.(2) Japanese phase II dose-finding study (5.3.5.1-1, Study CL-0103 [March 2008 to March 2009])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus[65] (target sample size, 310; n = 62 per group) was conducted to evaluate the efficacy and safety of ipragliflozin.

Following the run-in period (consisting of a 4-week screening period and a 2-week single-blind placebo treatment period), ipragliflozin 12.5, 25, 50, or 100 mg or placebo was to be orally administered once daily before breakfast for 12 weeks during the treatment period.

All 361 treated subjects (69 subjects in the placebo group, 74 subjects in the 12.5 mg group, 74 subjects in the 25 mg group, 72 subjects in the 50 mg group, 72 subjects in the 100 mg group) were included in the safety analysis set. Excluding 1 subject in the 12.5 mg group for whom post-dose efficacy data were not available, 360 subjects were included in the full analysis set (FAS) and the FAS was the primary efficacy analysis set. The study was discontinued in 30 subjects, including 10 subjects in the placebo group (worsening of the study disease in 4 subjects, other reasons in 4 subjects, adverse events in 2 subjects), 7 subjects in the 12.5 mg group (worsening of the study disease in 3 subjects, consent withdrawal in 3 subjects, other reasons in 1 subject), 4 subjects in the 25 mg group (consent withdrawal in 2 subjects, adverse events in 1 subject, worsening of the study disease in 1 subject), 5 subjects in the 50 mg group (consent withdrawal in 3 subjects, adverse events in 2 subjects), and 4 subjects in the 100 mg group (adverse events in 3 subjects, inadequate efficacy in 1 subject).

The primary efficacy endpoint, the change in HbA1c from baseline (at the start of the treatment period) to the end of treatment period (at Week 12 or withdrawal) in the FAS, was as shown in Table 16. A statistically significant decrease in HbA1c was observed in all of the ipragliflozin groups compared with the placebo group ($P < 0.001$ for all comparisons, analysis of covariance [ANCOVA] model, two-sided significance level of 5%, with a closed testing procedure for multiplicity adjustment).

[65] Major inclusion criteria: Patients aged ≥20 and <75 years; with fasting blood C-peptide >0.6 ng/mL at screening; with BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥7.0% and ≤10.0% at 2 weeks before the start of the study treatment; and who received treatment with diet/exercise therapy alone, monotherapy with an oral hypoglycemic agent, or treatment with 2 oral hypoglycemic agents at low dose (at ≤50% of the maximum approved dose for each drug). (For patients on oral hypoglycemic therapy, the treatment was suspended after informed consent until the end of the treatment period.)

Table 16. Change in HbA1c from baseline (at the start of the treatment period) to the end of treatment period (at Week 12 or withdrawal) (FAS)

Treatment group	n	Baseline	End of treatment period	Change from baseline to the end of treatment period	Difference relative to placebo [95% CI][a)]	*P*-value[a), c)]
Placebo	n = 69	7.96 ± 0.779	8.44 ± 1.341	0.48 ± 0.975	—	—
12.5 mg	n = 73	7.98 ± 0.887	7.86 ± 1.104	-0.12 ± 0.758	-0.60 [-0837, -0353]	*P* < 0.001
25 mg	n = 74	7.92 ± 0.831	7.46 ± 0.815	-0.47 ± 0.693	-0.95 [-1.192, -0.709]	*P* < 0.001
50 mg	n = 71[b)]	7.93 ± 0.795	7.15 ± 0.759	-0.79 ± 0.567	-1.27 [-1.517, -1.030]	*P* < 0.001
100 mg	n = 72	7.85 ± 0.758	7.05 ± 0.726	-0.79 ± 0.713	-1.29 [-1.534, -1.048]	*P* < 0.001

Unit, %; mean ± SD; -, Not applicable

a) ANCOVA model with baseline HbA1c as a covariate and the treatment group as a fixed effect

b) One subject was excluded due to missing data at the end of the treatment period.

c) Tested at a two-sided significance level of 5%, with a closed testing procedure (pairwise comparisons with the placebo group in the descending order from the 100 mg group) for multiplicity adjustment

The proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period evaluated as one of the secondary analyses of the primary endpoint was 1.4% (1 of 69 subjects) in the placebo group, 1.4% (1 of 73 subjects) in the 12.5 mg group, 6.8% (5 of 74 subjects) in the 25 mg group, 14.1% (10 of 71 subjects) in the 50 mg group, and 19.4% (14 of 72 subjects) in the 100 mg group.

The secondary endpoint, the changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of treatment period, were 9.8 ± 26.17 mg/dL and -0.35 ± 1.488 kg in the placebo group, -17.9 ± 29.60 mg/dL and -1.44 ± 1.311 kg in the 12.5 mg group, -23.0 ± 33.17 mg/dL and -1.72 ± 1.774 kg in the 25 mg group, -31.4 ± 28.67 mg/dL and -1.81 ± 1.508 kg in the 50 mg group, and -45.9 ± 29.68 mg/dL and -2.11 ± 1.733 kg in the 100 mg group, respectively.

Regarding safety, the incidence of adverse events was 68.1% (47 of 69 subjects) in the placebo group, 63.5% (47 of 74 subjects) in the 12.5 mg, 63.5% (47 of 74 subjects) in the 25 mg group, 72.2% (52 of 72 subjects) in the 50 mg group, and 56.9% (41 of 72 subjects) in the 100 mg group. The incidence of adverse drug reactions was 18.8% (13 of 69 subjects) in the placebo group, 16.2% (12 of 74 subjects) in the 12.5 mg group, 25.7% (19 of 74 subjects) in the 25 mg group, 26.4% (19 of 72 subjects) in the 50 mg group, and 25.0% (18 of 72 subjects) in the 100 mg group. Adverse events reported by ≥3 subjects in any group were as shown in Table 17.

Table 17. Adverse events reported by ≥3 subjects in any group (safety analysis set)

Adverse event term	Placebo group (n = 69)	12.5 mg group (n = 74)	25 mg group (n = 74)	50 mg group (n = 72)	100 mg group (n = 72)
Overall	47 (68.1)	47 (63.5)	47 (63.5)	52 (72.2)	41 (56.9)
Constipation	4 (5.8)	1 (1.4)	3 (4.1)	3 (4.2)	1 (1.4)
Diarrhoea	2 (2.9)	3 (4.1)	3 (4.1)	3 (4.2)	2 (2.8)
Thirst	4 (5.8)	3 (4.1)	3 (4.1)	2 (2.8)	3 (4.2)
Cystitis	1 (1.4)	0 (0.0)	0 (0.0)	3 (4.2)	1 (1.4)
Nasopharyngitis	17 (24.6)	9 (12.2)	14 (18.9)	18 (25.0)	11 (15.3)
Contusion	0 (0.0)	1 (1.4)	1 (1.4)	1 (1.4)	3 (4.2)
Beta 2 microglobulin urine increased	1 (1.4)	6 (8.1)	5 (6.8)	3 (4.2)	1 (1.4)
Beta-N-acetyl-D-glucosaminidase increased	0 (0.0)	4 (5.4)	2 (2.7)	0 (0.0)	0 (0.0)
Urine albumin/creatinine ratio increased	2 (2.9)	2 (2.7)	3 (4.1)	2 (2.8)	3 (4.2)
Urine ketone body present	0 (0.0)	0 (0.0)	3 (4.1)	1 (1.4)	3 (4.2)
Bacteria urine identified	2 (2.9)	0 (0.0)	0 (0.0)	3 (4.2)	0 (0.0)
Alpha 1 microglobulin urine increased	1 (1.4)	3 (4.1)	3 (4.1)	0 (0.0)	0 (0.0)
Diabetes mellitus[a)]	6 (8.7)	4 (5.4)	1 (1.4)	0 (0.0)	0 (0.0)
Back pain	4 (5.8)	3 (4.1)	2 (2.7)	1 (1.4)	1 (1.4)
Pollakiuria	2 (2.9)	2 (2.7)	4 (5.4)	6 (8.3)	4 (5.6)
Upper respiratory tract inflammation	2 (2.9)	3 (4.1)	3 (4.1)	1 (1.4)	3 (4.2)

Number of subjects with events (incidence %), MedDRA/J ver.10.1
a) Reported as worsening of diabetes mellitus

No deaths were reported. Serious adverse events were reported by 3 subjects in the placebo group (coronary artery stenosis, sudden hearing loss, and acute myocardial infarction in 1 subject each) and 1 subject in the 12.5 mg group (cataract). However, all these serious adverse events were improved or resolved and a causal relationship with the study drug was ruled out except for acute myocardial infarction. Adverse events leading to study drug discontinuation were reported by 7 subjects in the placebo group (diabetes mellitus in 4 subjects, diabetes mellitus/thirst, sudden hearing loss, and acute myocardial infarction in 1 subject each), 3 subjects in the 12.5 mg group (diabetes mellitus in 2 subjects, diabetes mellitus/thirst/polyuria/pollakiuria in 1 subject), 1 subject in the 25 mg group (diabetes mellitus/urine ketone body present), 2 subjects in the 50 mg group (eczema and ventricular extrasystoles in 1 subject each), and 3 subjects in the 100 mg group (rash/lip swelling, hypoaesthesia, and pollakiuria in 1 subject each). Among these, the events reported by 2 subjects in the placebo group (acute myocardial infarction and diabetes mellitus in 1 subject each), 1 subject in the 25 mg group (diabetes mellitus/urine ketone body present), 2 subjects in the 50 mg group (eczema and ventricular extrasystoles in 1 subject each), and 2 subjects in the 100 mg group (rash/lip swelling and pollakiuria in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events[66] were reported by 2 of 69 subjects in the placebo group, 1 of 74 subjects in the 25 mg group, 1 of 72 subjects in the 50 mg group, and 1 of 72 subjects in the 100 mg group, and the event reported by 1 subject in the 100 mg group was assessed as an adverse drug reaction.

Urinary tract infection-related adverse events[66] were reported by 1 of 69 subjects in the placebo group, 3 of 72 subjects in the 50 mg group, and 1 of 72 subjects in the 100 mg group, and all these events were cystitis. Of these, the events reported by 1 subject in the placebo group and 2 subjects in the 50 mg group were assessed as adverse drug reactions.

Genital infection-related adverse events[67] were reported by 2 of 74 subjects in the 12.5 mg group

[66] Adverse events considered related to the study drug by the investigator
[67] MedDRA preferred terms (for Study CL-0103 only): pruritus genital, vaginal candidiasis, and vaginitis bacterial.

(vaginal candidiasis and pruritus genital in 1 subject each), 2 of 72 subjects in the 50 mg group (vaginal candidiasis/vaginitis bacterial and pruritus genital in 1 subject each), and 1 of 72 subjects in the 100 mg group (pruritus genital), and the events reported by 1 subject in the 50 mg group (vaginal candidiasis/vaginitis bacterial) and 1 subject in the 100 mg group (pruritus genital) were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria[68] were reported by 2 of 69 subjects in the placebo group (pollakiuria), 2 of 74 subjects in the 12.5 mg group (pollakiuria and pollakiuria/polyuria in 1 subject each), 5 of 74 subjects in the 25 mg group (pollakiuria in 4 subjects, polyuria in 1 subject), 6 of 72 subjects in the 50 mg group (pollakiuria), and 6 of 72 subjects in the 100 mg group (pollakiuria in 4 subjects, nocturia and polyuria in 1 subject each), and the events reported by 2 subjects in the placebo group (pollakiuria), 2 subjects in the 25 mg group (pollakiuria), 3 subjects in the 50 mg group (pollakiuria), and 4 subjects in the 100 mg group (pollakiuria in 3 subjects, polyuria in 1 subject) were assessed as adverse drug reactions.

Adverse events observed in 12-lead ECG were reported by 1 subject in the placebo group (acute myocardial infarction) and 2 subjects in the 50 mg group (atrial fibrillation and ventricular extrasystoles in 1 subject each), and all these events were assessed as adverse drug reactions.

Regarding vital signs, there was a tendency for systolic blood pressure to decrease, but no substantial variations in diastolic blood pressure and pulse rate were observed.

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

4.(iii).A.(3).1) Japanese phase III monotherapy study (5.3.5.1-2, Study CL-0105 [January to November 2010])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus[69] (target sample size, 120; n = 60 per group) was conducted to evaluate the efficacy and safety of ipragliflozin.

Following the run-in period (consisting of a 4-week screening period and a 2-week single-blind placebo treatment period), ipragliflozin 50 mg or placebo was to be orally administered once daily before breakfast for 16 weeks.

A total of 129 treated subjects (67 subjects in the placebo group, 62 subjects in the 50 mg group) were included in the safety analysis set and FAS, and the FAS was the primary efficacy analysis set. The study was discontinued in 14 subjects (including 1 subject who discontinued the study prior to receiving study drug for treatment period), including 10 subjects in the placebo group (worsening of the primary disease in 6 subjects, adverse events, inadequate efficacy, consent withdrawal, and lost to follow-up in 1 subject each) and 4 subjects in the 50 mg group (adverse events in 2 subjects, worsening of the primary disease and other reasons in 1 subject each).

The primary efficacy endpoint of the change in HbA1c from baseline (at the start of the treatment period) to the end of treatment period (at Week 16 or withdrawal) in the FAS was as shown in Table 18, showing superiority of the 50 mg group over the placebo group ($P < 0.001$, ANCOVA model, two-sided significance level of 5%).

[68] MedDRA preferred terms: Nocturia, pollakiuria, polyuria, and urine output increased.

[69] Major inclusion criteria: Patients aged ≥20 years; with BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥7.0% and ≤10.0% at 2 weeks before the start of the study treatment; and who received diet/exercise therapy alone or monotherapy or treatment with 2 preparations with low-dose oral hypoglycemic agent(s) (at ≤50% of the maximum approved dose for each drug). (For patients on oral hypoglycemic therapy, the treatment was suspended after informed consent until the end of the treatment period.)

Table 18. Change in HbA1c from baseline (start of the treatment period) to the end of the treatment period (at Week 16 or withdrawal) (FAS)

Treatment group	n	Baseline	End of treatment period	Change from baseline to the end of treatment period	Between-group difference [95% CI][a)]	*P*-value[a), b)]
Placebo	67	7.85 ± 0.678	8.38 ± 1.231	0.52 ± 0.980	-1.23 ［-1.515, -0.938］	*P* < 0.001
50 mg	62	8.00 ± 0.849	7.24 ± 0.839	-0.76 ± 0.694		

Unit, %; mean ± SD

a) ANCOVA model with baseline HbA1c as a covariate and the treatment group and use of oral hypoglycemic agent within 8 weeks before the start of the screening period as fixed effects

b) Two-sided significance level of 5%

The proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period evaluated as one of the secondary analyses of the primary endpoint was 1.5% (1 of 67 subjects) in the placebo group and 12.9% (8 of 62 subjects) in the 50 mg group.

The secondary endpoint, the changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of the treatment period, were 6.3 ± 30.05 mg/dL and -1.03 ± 1.961 kg in the placebo group and -40.2 ± 33.34 mg/dL and -2.31 ± 1.743 kg in the 50 mg group, respectively.

Regarding safety, the incidence of adverse events was 59.7% (40 of 67 subjects) in the placebo group and 53.2% (33 of 62 subjects) in the 50 mg group, and the incidence of adverse drug reactions was 9.0% (6 of 67 subjects) in the placebo group and 16.1% (10 of 62 subjects) in the 50 mg group. Adverse events reported by ≥3 subjects in any group were as shown in Table 19. No adverse drug reactions were reported by ≥3 subjects in any group.

Table 19. Adverse events reported by ≥3 subjects in any group (safety analysis set)

Adverse event	Placebo group (n = 67)	50 mg group (n = 62)
Overall	40 (59.7)	33 (53.2)
Constipation	1 (1.5)	3 (4.8)
Nasopharyngitis	9 (13.4)	7 (11.3)
Tinea pedis	2 (3.0)	3 (4.8)
Diabetes mellitus[a)]	6 (9.0)	0 (0.0)
Back pain	4 (6.0)	1 (1.6)
Headache	4 (6.0)	0 (0.0)
Eczema	1 (1.5)	3 (4.8)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

a) Reported as worsening of diabetes mellitus

No deaths were reported. A serious adverse event was reported by 1 subject in the placebo group (subdural haematoma), but a causal relationship with the study drug was ruled out. Adverse events leading to study drug discontinuation were reported by 6 subjects in the placebo group (diabetes mellitus in 4 subjects, diabetes mellitus/diabetic neuropathy and subdural haematoma in 1 subject each) and 2 subjects in the 50 mg group (eczema and rash in 1 subject each), and the events reported by 2 subjects in the 50 mg group were assessed as adverse drug reactions.

A hypoglycemia-related adverse event was reported by 1 of 62 subjects in the 50 mg group, but a causal relationship with study drug was ruled out.

A urinary tract infection-related adverse event was reported by 1 of 67 subjects in the placebo group (cystitis) and was assessed as an adverse drug reaction.

Genital infection-related adverse events[70] were reported by 2 of 62 subjects in the 50 mg group (pruritus genital and balanoposthitis infective in 1 subject each), and the event of pruritus genital was assessed as an adverse drug reaction.

Adverse events related to pollakiuria and polyuria were reported by 2 of 67 subjects in the placebo group (pollakiuria) and 2 of 62 subjects in the 50 mg group (pollakiuria and polyuria in 1 subject each), and the events reported by 2 subjects in the 50 mg group were assessed as adverse drug reactions.

No clinically significant abnormalities were reported regarding 12-lead ECG[71].

Regarding vital signs, there was a tendency for systolic blood pressure to decrease, but no substantial variations in diastolic blood pressure and pulse rate were observed.

4.(iii).A.(3).2) Japanese long-term monotherapy study (5.3.5.2-4, Study CL-0121 [January 2010 to July 2011])

A randomized, open-label, long-term treatment study in Japanese patients with type 2 diabetes mellitus[72] (target sample size, 150) was conducted to evaluate the efficacy and safety of ipragliflozin.

Following the run-in period (6 weeks), ipragliflozin 50 mg was to be orally administered once daily before or after breakfast for 52 weeks. In addition, the dose was to be increased from 50 to 100 mg at Week 20 on the basis of HbA1c at the start of the treatment period and Week 16.[73]

A total of 182 treated subjects (94 subjects receiving treatment before breakfast, 88 subjects receiving treatment after breakfast) were included in the safety analysis set. Of the subjects, 181 subjects were included in the FAS, excluding 1 subject (after-breakfast group) for whom post-dose efficacy data were not available, and the FAS was the primary efficacy analysis set. The study was discontinued in 41 subjects, including 17 subjects in the before-breakfast group (adverse events in 4 subjects, inadequate efficacy in 3 subjects, worsening of the primary disease in 2 subjects, consent withdrawal in 2 subjects, lost to follow-up in 1 subject, other reasons in 5 subjects) and 24 subjects in the after-breakfast group (adverse events in 9 subjects, inadequate efficacy in 5 subjects, worsening of the primary disease in 3 subjects, consent withdrawal in 3 subjects, other reasons in 4 subjects). The number of subjects for whom the dose was increased to 100 mg (50/100 mg) was 35 subjects in the before-breakfast group and 35 subjects in the after-breakfast group.

Regarding efficacy, the changes in HbA1c (mean ± SD) from baseline (at the start of the treatment period) to Week 20 (LOCF) and to the end of the treatment period in the FAS were -0.58% ± 0.686% (n = 94) and -0.56% ± 0.827% (n = 94) in the before-breakfast group, respectively, and -0.49% ± 0.650% (n = 87) and -0.46% ± 0.773% (n = 87) in the after-breakfast group, respectively. When analyzed by patients with or without dose increase, the changes in HbA1c (mean ± SD) from baseline to Week 20 (LOCF) and to the end of the treatment period were -0.66% ± 0.603% (n = 111) and -0.58% ± 0.663% (n = 111) in the 50/50 mg group, respectively, and -0.33% ± 0.723% (n = 70) and -0.40% ± 0.977% (n = 70) in the 50/100 mg group, respectively. The change

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[70] Adverse events considered related to the study drug by the investigator for phase III studies from Study CL-0105.

[71] Rated on a 3-level scale consisting of "normal," "clinically non-significant abnormality," and "clinically significant abnormality."

[72] Major inclusion criteria: Patients aged ≥20 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥6.5% and ≤9.5% at 2 weeks before the start of the study treatment; and who received diet/exercise therapy alone or monotherapy or treatment with 2 preparations with low-dose oral hypoglycemic agent(s) (at ≤50% of the maximum approved dose for each drug). (For patients on oral hypoglycemic therapy, the treatment was suspended after informed consent until the end of the treatment period.)

[73] Dose increase criteria: Patients with HbA1c of ≥7.0% at the start of the treatment period and ≥7.0% at Week 16, or with HbA1c of <7.0% at the start of the treatment period and ≥6.5% at Week 16, who had no safety concerns in the opinion of the investigator.

in HbA1c over time was as shown in Figure 1.

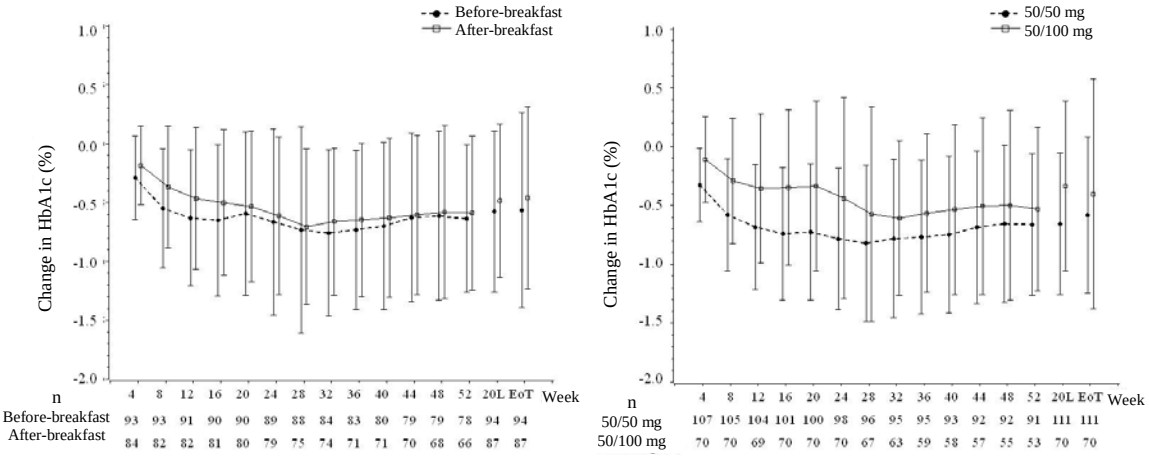

Figure 1. Change in HbA1c (%) over time (FAS) (left, by regimen; right, by dose) (mean ± SD)
20L: Week 20 (LOCF); EoT: End of treatment period

The proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period was 20.2% (19 of 94 subjects) in the before-breakfast group and 27.6% (24 of 87 subjects) in the after-breakfast group, and 36.7% (36 of 98 subjects) in the 50/50 mg group and 7.1% (5 of 70 subjects) in the 50/100 mg group. The changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of the treatment period were -32.9 ± 29.61 mg/dL and -3.51 ± 2.476 kg in the before-breakfast group, -32.4 ± 34.07 mg/dL and -3.31 ± 2.094 kg in the after-breakfast group, -26.7 ± 29.23 mg/dL and -3.19 ± 1.999 kg in the 50/50 mg group, and -42.0 ± 33.42 mg/dL and -3.77 ± 2.679 kg in the 50/100 mg group, respectively.

Regarding safety, the overall incidence of adverse events was 90.1% (164 of 182 subjects) and the incidence of adverse drug reactions was 49.5% (90 of 182 subjects). Adverse events reported by ≥3 subjects in any group (by regimen or by dose) were as shown in Table 20. Adverse drug reactions reported by ≥3 subjects in any group (by regimen or by dose) were constipation (4.3% [4 of 94 subjects] in the before-breakfast group, 5.7% [5 of 88 subjects] in the after-breakfast group, 4.9% [9 of 182 subjects] overall, 3.1% [3 of 98 subjects] in the 50/50 mg group, 7.1% [5 of 70 subjects] in the 50/100 mg group), thirst (10.6% [10 of 94 subjects] in the before-breakfast group, 8.0% [7 of 88 subjects] in the after-breakfast group, 9.3% [17 of 182 subjects] overall, 11.2% [11 of 98 subjects] in the 50/50 mg group, 7.1% [5 of 70 subjects] in the 50/100 mg group), cystitis (2.1% [2 of 94 subjects] in the before-breakfast group, 4.5% [4 of 88 subjects] in the after-breakfast group, 3.3% [6 of 182 subjects] overall, 1.0% [1 of 98 subjects] in the 50/50 mg group, 7.1% [5 of 70 subjects] in the 50/100 mg group), weight decreased (4.3% [4 of 94 subjects] in the before-breakfast group, 11.4% [10 of 88 subjects] in the after-breakfast group, 7.7% [14 of 182 subjects] overall, 8.2% [8 of 98 subjects] in the 50/50 mg group, 4.3% [3 of 70 subjects] in the 50/100 mg group), increased appetite (0.0% [0 of 94 subjects] in the before-breakfast group, 3.4% [3 of 88 subjects] in the after-breakfast group, 1.6% [3 of 182 subjects] overall, 2.0% [2 of 98 subjects] in the 50/50 mg group, 0.0% [0 of 70 subjects] in the 50/100 mg group), pollakiuria (22.3% [21 of 94 subjects] in the before-breakfast group, 22.7% [20 of 88 subjects] in the after-breakfast group, 22.5% [41 of 182 subjects] overall, 21.4% [21 of 98 subjects] in the 50/50 mg group, 20.0% [14 of 70 subjects] in the 50/100 mg group), and polyuria (3.2% [3 of 94 subjects] in the before-breakfast group, 4.5% [4 of 88 subjects] in the after-breakfast group, 3.8% [7 of 182 subjects] overall, 5.1% [5 of 98 subjects] in the 50/50 mg group, 2.9% [2 of 70 subjects] in the 50/100 mg group).

Table 20. Adverse events reported by ≥3 subjects in any group (by regimen or by dose) (safety analysis set)

Adverse event	By regimen		Total (n = 182)	By dose[a)]	
	Before breakfast (n = 94)	After breakfast (n = 88)		50/50 mg (n = 98)	50/100 mg (n = 70)
Overall	83 (88.3)	81 (92.0)	164 (90.1)	88 (89.8)	64 (91.4)
Nasopharyngitis	33 (35.1)	33 (37.5)	66 (36.3)	31 (31.6)	32 (45.7)
Pollakiuria	21 (22.3)	20 (22.7)	41 (22.5)	21 (21.4)	14 (20.0)
Weight decreased	4 (4.3)	10 (11.4)	14 (7.7)	8 (8.2)	3 (4.3)
Thirst	10 (10.6)	9 (10.2)	19 (10.4)	11 (11.2)	7 (10.0)
Back pain	8 (8.5)	7 (8.0)	15 (8.2)	10 (10.2)	5 (7.1)
Dental caries	7 (7.4)	5 (5.7)	12 (6.6)	6 (6.1)	6 (8.6)
Constipation	6 (6.4)	5 (5.7)	11 (6.0)	4 (4.1)	6 (8.6)
Cystitis	4 (4.3)	6 (6.8)	10 (5.5)	4 (4.1)	6 (8.6)
Upper respiratory tract inflammation	6 (6.4)	4 (4.5)	10 (5.5)	6 (6.1)	4 (5.7)
Contusion	6 (6.4)	2 (2.3)	8 (4.4)	4 (4.1)	4 (5.7)
Headache	5 (5.3)	5 (5.7)	10 (5.5)	6 (6.1)	4 (5.7)
Influenza	4 (4.3)	4 (4.5)	8 (4.4)	4 (4.1)	4 (5.7)
Polyuria	3 (3.2)	5 (5.7)	8 (4.4)	5 (5.1)	3 (4.3)
Abdominal discomfort	2 (2.1)	5 (5.7)	7 (3.8)	3 (3.1)	4 (5.7)
Gastroenteritis	2 (2.1)	4 (4.5)	6 (3.3)	2 (2.0)	4 (5.7)
Arthralgia	5 (5.3)	2 (2.3)	7 (3.8)	4 (4.1)	2 (2.9)
Heat rash	5 (5.3)	1 (1.1)	6 (3.3)	4 (4.1)	2 (2.9)
Seasonal allergy	2 (2.1)	4 (4.5)	6 (3.3)	4 (4.1)	2 (2.9)
Muscle spasms	0 (0.0)	4 (4.5)	4 (2.2)	3 (3.1)	1 (1.4)
Pharyngitis	4 (4.3)	3 (3.4)	7 (3.8)	4 (4.1)	3 (4.3)
Diarrhoea	4 (4.3)	3 (3.4)	7 (3.8)	3 (3.1)	3 (4.3)
Dyspepsia	3 (3.2)	0 (0.0)	3 (1.6)	1 (1.0)	2 (2.9)
Bronchitis	4 (4.3)	2 (2.3)	6 (3.3)	3 (3.1)	3 (4.3)
Abdominal pain upper	4 (4.3)	2 (2.3)	6 (3.3)	3 (3.1)	2 (2.9)
Gastritis	2 (2.1)	3 (3.4)	5 (2.7)	4 (4.1)	0 (0.0)
Arthropod sting	1 (1.1)	3 (3.4)	4 (2.2)	3 (3.1)	1 (1.4)
Tenosynovitis	1 (1.1)	3 (3.4)	4 (2.2)	3 (3.1)	1 (1.4)
Dizziness	1 (1.1)	3 (3.4)	4 (2.2)	2 (2.0)	1 (1.4)
Oedema peripheral	0 (0.0)	3 (3.4)	3 (1.6)	3 (3.1)	0 (0.0)
Increased appetite	0 (0.0)	3 (3.4)	3 (1.6)	2 (2.0)	0 (0.0)
Spinal compression fracture	1 (1.1)	2 (2.3)	3 (1.6)	3 (3.1)	0 (0.0)
Insomnia	3 (3.2)	2 (2.3)	5 (2.7)	3 (3.1)	2 (2.9)
Blood creatine phosphokinase increased	3 (3.2)	0 (0.0)	3 (1.6)	2 (2.0)	1 (1.4)
Diabetes mellitus	2 (2.1)	4 (4.5)	6 (3.3)	1 (1.0)	4 (5.7)
Gingivitis	2 (2.1)	1 (1.1)	3 (1.6)	3 (3.1)	0 (0.0)
Rash	3 (3.2)	0 (0.0)	3 (1.6)	2 (2.0)	1 (1.4)
Urticaria	2 (2.1)	1 (1.1)	3 (1.6)	3 (3.1)	0 (0.0)
Vulvovaginal candidiasis	2 (2.1)	1 (1.1)	3 (1.6)	3 (3.1)	0 (0.0)
Myalgia	2 (2.1)	1 (1.1)	3 (1.6)	3 (3.1)	0 (0.0)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

a) A summary of the subjects for whom a decision was made at Week 20 about whether to increase the dose

No deaths were reported. Serious adverse events were reported by 8 subjects (spinal compression fracture in 2 subjects, supraventricular tachycardia, iridocyclitis/corneal degeneration/cataract operation, colon cancer/hepatic cancer metastatic/hepatic neoplasm malignant, dyschezia, inguinal hernia, and pulmonary tuberculosis in 1 subject each), but a causal relationship with study drug was ruled out for all these events. Adverse events leading to study drug discontinuation were reported by 18 subjects (diabetes mellitus in 5 subjects, drug eruption in 2 subjects, pollakiuria in 2 subjects, weight decreased/malaise, urine albumin/creatinine ratio increased/protein urine present/blood urine present/red blood cells urine positive, spinal

compression fracture, pollakiuria/increased appetite/cold sweat/dizziness, weight decreased, hydronephrosis/calculus ureteric, colon cancer/hepatic cancer metastatic/hepatic neoplasm malignant, dizziness/hypertension, and diabetes mellitus/hepatic function abnormal in 1 subject each), and the events reported by 11 subjects (drug eruption in 2 subjects, pollakiuria in 2 subjects, weight decreased/malaise, urine albumin/creatinine ratio increased/protein urine present/blood urine present/red blood cells urine positive, pollakiuria/increased appetite/cold sweat/dizziness, weight decreased, hydronephrosis/calculus ureteric, dizziness/hypertension, and hepatic function abnormal in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were reported by 3 of 182 subjects, and the events reported by 2 subjects were assessed as adverse drug reactions.

Urinary tract infection-related adverse events were reported by 11 of 182 subjects (cystitis in 10 subjects, urinary tract infection in 1 subject), and the events reported by 7 subjects (cystitis in 6 subjects, urinary tract infection in 1 subject) were assessed as adverse drug reactions.

Genital infection-related adverse events were reported by 4 of 182 subjects (vulvovaginal candidiasis in 3 subjects, genital herpes/genital candidiasis in 1 subject), and all but 1 event in 1 subject (vulvovaginal candidiasis) were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria were reported by 45 of 182 subjects (pollakiuria in 36 subjects, polyuria/pollakiuria in 5 subjects, polyuria in 3 subjects, nocturia in 1 subject), and all but 1 event in 1 subject (polyuria) were assessed as adverse drug reactions.

No clinically significant abnormalities were reported regarding 12-lead ECG.

No clinically meaningful changes were observed in vital signs.

4.(iii).A.(3).3) Japanese long-term monotherapy study (5.3.5.2-5, Study CL-0122 [May 2012 to April 2013])

An open-label, uncontrolled study in Japanese patients with type 2 diabetes mellitus[74] (target sample size, 145) was conducted to evaluate the safety and efficacy of ipragliflozin.

Following the run-in period (6 weeks), ipragliflozin 50 mg was to be orally administered once daily before breakfast for 24 weeks.

All of the 174 treated subjects were included in the safety analysis set. Of the subjects, 173 subjects were included in the FAS, excluding 1 subject for whom post-dose efficacy data were not available, and the FAS was the primary efficacy analysis set. The study was discontinued in 13 subjects (inadequate efficacy in 5 subjects, adverse events in 4 subjects, worsening of the primary disease in 2 subjects, consent withdrawal in 1 subject, lost to follow-up in 1 subject).

Regarding efficacy, the change in HbA1c (mean ± SD) from baseline (at the start of the treatment period) to the end of the treatment period was -0.32% ± 0.671% (n = 173), and the change in HbA1c over time was as shown in Figure 2.

[74] Major inclusion criteria: Patients aged ≥20 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥6.5% and ≤9.5% at 2 weeks before the start of the study treatment; and who received diet/exercise therapy alone or monotherapy or treatment with 2 preparations with low-dose oral hypoglycemic agent(s) (at ≤50% of the maximum approved dose for each drug). (For patients on oral hypoglycemic therapy, the treatment was suspended after informed consent until the end of the treatment period.)

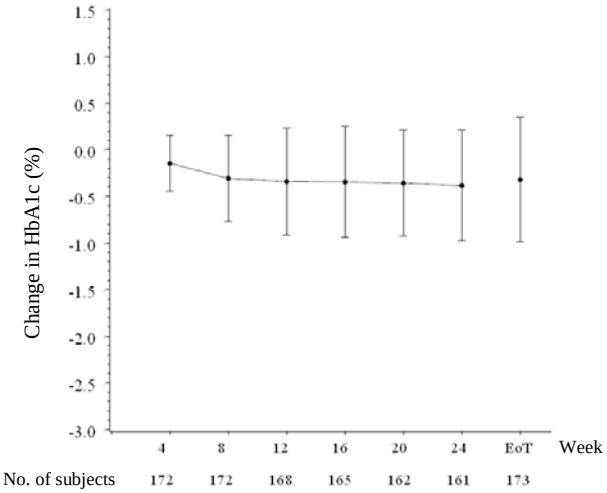

Figure 2. Change in HbA1c (%) over time (FAS) (mean ± SD)
EoT: End of treatment period

The proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period was 26.6% (46 of 173 subjects). The changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of the treatment period were -17.5 ± 24.07 mg/dL (n = 172) and -2.38 ± 1.943 kg (n = 173), respectively.

Regarding safety, the incidence of adverse events was 70.7% (123 of 174 subjects) and the incidence of adverse drug reactions was 31.6% (55 of 174 subjects). Adverse events reported by ≥3 subjects were as shown in Table 21. Adverse drug reactions reported by ≥3 subjects were beta 2 microglobulin urine increased (4.0%, 7 of 174 subjects), pollakiuria (6.9%, 12 of 174 subjects), polyuria (2.9%, 5 of 174 subjects), thirst (3.4%, 6 of 174 subjects), constipation (2.3%, 4 of 174 subjects), and vulvovaginal candidiasis (2.3%, 4 of 174 subjects).

Table 21. Adverse events reported by ≥3 subjects (safety analysis set)

Adverse event	Total (n = 174)
Overall	123 (70.7)
Nasopharyngitis	54 (31.0)
Pollakiuria	12 (6.9)
Beta 2 microglobulin urine increased	11 (6.3)
Constipation	7 (4.0)
Thirst	7 (4.0)
Gastroenteritis	7 (4.0)
Headache	6 (3.4)
Polyuria	5 (2.9)
Eczema	5 (2.9)
Diarrhoea	4 (2.3)
Vulvovaginal candidiasis	4 (2.3)
Dizziness	4 (2.3)
Abdominal pain	3 (1.7)
Dental caries	3 (1.7)
Gingivitis	3 (1.7)
Influenza	3 (1.7)
Ligament sprain	3 (1.7)
Diabetes mellitus	3 (1.7)
Oropharyngeal pain	3 (1.7)

Number of subjects with events (incidence %), MedDRA/J ver.15.0

No deaths were reported. Serious adverse events were reported by 4 subjects (cerebral infarction, anaemia, coronary artery stenosis, and cervical myelopathy in 1 subject each), and the event reported by 1 subject (cerebral infarction) was assessed as an adverse drug reaction. Adverse events leading to study drug discontinuation were reported by 6 subjects (diabetes mellitus in 2 subjects, cerebral infarction, vomiting/nausea/headache, urticaria, and coronary artery stenosis in 1 subject each), and the events reported by 3 subjects (cerebral infarction, vomiting/nausea/headache, and urticaria in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were reported by 3 subjects, and all these events were assessed as adverse drug reactions.

Urinary tract infection-related adverse events were reported by 4 of 174 subjects (cystitis in 2 subjects, urinary tract infection in 1 subject, asymptomatic bacteriuria in 1 subject), and all these events were assessed as adverse drug reactions.

Genital infection-related adverse events were reported by 6 of 174 subjects (vulvovaginal candidiasis in 4 subjects, vulvitis and atrophic vulvovaginitis in 1 subject each), and all these events were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria were reported by 17 of 174 subjects (pollakiuria in 12 subjects, polyuria in 5 subjects), and all these events were assessed as adverse drug reactions.

Regarding 12-lead ECG, clinically significant abnormalities were reported by 3 of 174 subjects (atrial fibrillation, ventricular extrasystoles, and tricuspid valve incompetence in 1 subject each), and the event reported by 1 subject (ventricular extrasystoles) was assessed as an adverse drug reaction.

No clinically meaningful changes were observed in vital signs.

4.(iii).A.(3).4) Metformin combination therapy study (5.3.5.1-3, Study CL-0106 [May 2010 to November 2011])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus who responded inadequately to metformin[75] (target sample size, 150; n = 100 for the ipragliflozin group, n = 50 for the placebo group) was conducted to evaluate the efficacy and safety of concomitant use of ipragliflozin with metformin.

Following the run-in period (consisting of a 4-week screening period and a 2-week single-blind placebo treatment period), placebo or ipragliflozin 50 mg was to be orally administered once daily before breakfast for 24 weeks for Treatment Period I (double-blind period). For Treatment Period II, ipragliflozin 50 mg was to be orally administered once daily before breakfast for 28 weeks to subjects whose HbA1c was <8.0% and lower than their baseline HbA1c value at Week 20 of Treatment Period I (double-blind period). The dose was to be increased from 50 to 100 mg according to the dose increase criteria.[76] The regimen of metformin was to be maintained from 6 weeks before screening.

[75] Major inclusion criteria: Patients aged ≥20 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥7.0% and ≤9.5% at 2 weeks before the start of the study treatment; who have received monotherapy with fixed-dose metformin for ≥6 weeks up to screening. (For patients on another oral hypoglycemic therapy, study treatment was started at least 6 weeks after discontinuation of such therapy.)

[76] Dose increase criteria: Patients with HbA1c of ≥7.0% and <8.0% at Week 20 of Treatment Period I and with their Week 20 HbA1c lower than that at the start of treatment, who had no safety concerns in the opinion of the investigator.

For Treatment Period I (double-blind period), a total of the 168 treated subjects (56 subjects in the placebo group, 112 subjects in the ipragliflozin group) were included in the safety analysis set and FAS. Of 152 subjects who completed Treatment Period I (double-blind period) (42 subjects in the placebo group, 110 subjects in the ipragliflozin group), 106 subjects (10 subjects in the placebo group, 96 subjects in the ipragliflozin group) entered Treatment Period II. For Treatment Period II, 122 subjects who received at least one dose of ipragliflozin during the study period and from whom post-dose efficacy data were obtained (10 subjects in the placebo/ipragliflozin group, 112 subjects in the ipragliflozin extension group) were included in the safety analysis set and FAS. The FAS was the primary efficacy analysis set for both Treatment Periods I (double-blind period) and II. The study was discontinued in 16 subjects during Treatment Period I (double-blind period), including 14 subjects in the placebo group (worsening of diabetes mellitus in 7 subjects, consent withdrawal in 4 subjects, adverse events in 1 subject, inadequate efficacy in 2 subjects) and 2 subjects in the ipragliflozin group (worsening of diabetes mellitus and adverse events in 1 subject each). In Treatment Period II, 6 subjects (adverse events in 2 subjects, inadequate efficacy in 2 subjects, and other reasons in 2 subjects) discontinued the study. The number of subjects for whom the dose was increased to 100 mg was 9 subjects in the placebo group and 43 subjects in the ipragliflozin group during Treatment Period I (double-blind period).

The primary efficacy endpoint of the change in HbA1c from baseline to the end of Treatment Period I (double-blind period) in the FAS was as shown in Table 22, showing superiority of the ipragliflozin group over the placebo group ($P < 0.001$, ANCOVA model, two-sided significance level of 5%).

Table 22. Change in HbA1c from baseline to the end of Treatment Period I (double-blind period) (at Week 24 or withdrawal) (FAS)

Treatment group	n	Baseline	End of Treatment Period I (double-blind period)	Change from baseline to the end of Treatment Period I (double-blind period)	Between-group difference [95% CI][a)]	*P* value[a), b)]
Placebo	56	7.98 ± 0.738	8.36 ± 0.902	0.38 ± 0.703	-1.29 [-1.497, -1.092]	$P < 0.001$
Ipragliflozin	112	7.85 ± 0.714	6.98 ± 0.707	-0.87 ± 0.655		

Unit, %; mean ± SD

a) ANCOVA model with baseline HbA1c as a covariate and the treatment group as a fixed effect

b) Two-sided significance level of 5%

The proportion of subjects who achieved HbA1c <6.5% at the end of Treatment Period I (double-blind period) evaluated as one of the secondary analyses of the primary endpoint was 0.0% (0 of 56 subjects) in the placebo group and 19.6% (22 of 112 subjects) in the ipragliflozin group.

The secondary endpoint, the changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of Treatment Period I (double-blind period), were 10.7 ± 27.46 mg/dL and -0.63 ± 1.679 kg in the placebo group and -22.2 ± 26.72 mg/dL and -2.33 ± 1.798 kg in the ipragliflozin group, respectively.

The change in HbA1c (mean ± SD) from baseline to the end of the treatment period was -0.90% ± 0.262% in the placebo/ipragliflozin group (n = 10) and -0.95% ± 0.671% in the ipragliflozin extension group (n = 112), and the change in HbA1c over time was as shown in Figure 3.

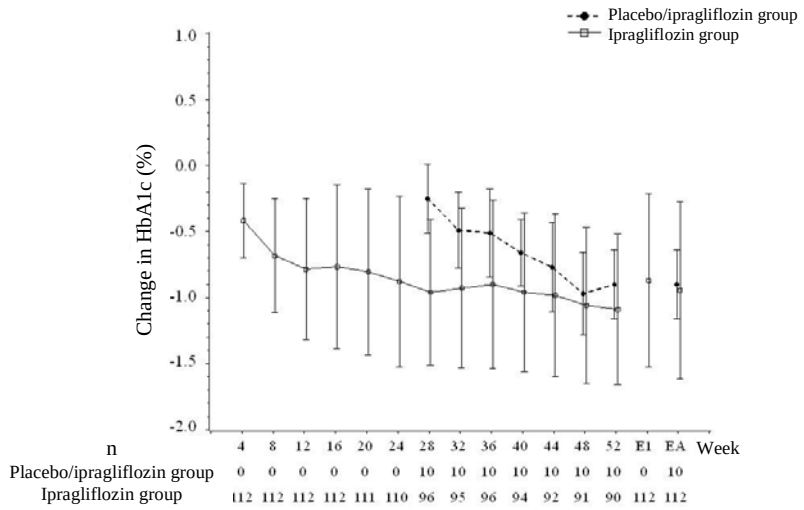

Figure 3. Change in HbA1c (%) over time (FAS) (mean ± SD)
E1, End of Treatment Period I (double-blind period); EA, End of treatment period

Regarding safety during Treatment Period I (double-blind period), the incidence of adverse events was 80.4% (45 of 56 subjects) in the placebo group and 71.4% (80 of 112 subjects) in the ipragliflozin group, and the incidence of adverse drug reactions was 21.4% (12 of 56 subjects) in the placebo group and 29.5% (33 of 112 subjects) in the ipragliflozin group. Adverse events reported by ≥3 subjects in any group were as shown in Table 23. Adverse drug reactions reported by ≥3 subjects in any group was pollakiuria (1.8% [1 of 56 subjects] in the placebo group, 5.4% [6 of 112 subjects] in the ipragliflozin group).

Table 23. Adverse events reported by ≥3 subjects in any group (safety analysis set) (24 weeks)

Adverse event	Placebo group (n = 56)	Ipragliflozin group (n = 112)
Overall	45 (80.4)	80 (71.4)
Constipation	1 (1.8)	5 (4.5)
Dyspepsia	0 (0.0)	4 (3.6)
Nausea	0 (0.0)	3 (2.7)
Periodontal disease	2 (3.6)	3 (2.7)
Vomiting	0 (0.0)	3 (2.7)
Bronchitis	0 (0.0)	5 (4.5)
Nasopharyngitis	20 (35.7)	29 (25.9)
Blood creatine phosphokinase increased	3 (5.4)	1 (0.9)
Diabetes mellitus	8 (14.3)	1 (0.9)
Back pain	2 (3.6)	6 (5.4)
Dizziness	1 (1.8)	3 (2.7)
Headache	1 (1.8)	4 (3.6)
Pollakiuria	1 (1.8)	6 (5.4)
Upper respiratory tract inflammation	3 (5.4)	4 (3.6)
Eczema	1 (1.8)	3 (2.7)
Hypertension	3 (5.4)	1 (0.9)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

No deaths were reported. Serious adverse events were reported by 2 subjects in the placebo group (cataract and anal abscess in 1 subject each) and 2 subjects in the ipragliflozin group (diabetes mellitus and carpal tunnel syndrome in 1 subject each), but a causal relationship with the study drug was ruled out. Adverse events leading to study drug discontinuation were reported by 8

subjects in the placebo group (diabetes mellitus in 7 subjects, anal abscess in 1 subject) and 2 subjects in the ipragliflozin group (pruritus genital and diabetes mellitus in 1 subject each), and the events reported by 1 subject in the placebo group (diabetes mellitus) and 1 subject in the ipragliflozin group (pruritus genital) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were not reported.

Urinary tract infection-related adverse events were reported by 2 of 56 subjects in the placebo group (cystitis in both subjects) and 2 of 112 subjects in the ipragliflozin group (cystitis in both subjects), and the events reported by 1 subject each in the placebo and the ipragliflozin groups were assessed as adverse drug reactions.

Genital infection-related adverse events were not reported by subjects in the placebo group, but reported by 5 of 112 subjects in the ipragliflozin group (vulvovaginal candidiasis in 2 subjects, pruritus genital, erosive balanitis, and genital infection fungal in 1 subject each), and all these events were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria were reported by 1 of 56 subjects in the placebo group (pollakiuria) and 6 of 112 subjects in the ipragliflozin group (pollakiuria in 4 subjects, pollakiuria/polyuria and pollakiuria/urine output increased in 1 subject each), and all these events were assessed as adverse drug reactions.

No clinically significant abnormalities were reported regarding 12-lead ECG.

No clinically meaningful changes were observed in vital signs.

Regarding safety of 52-week treatment, the incidence of adverse events was 90.0% (9 of 10 subjects) in the placebo/ipragliflozin group and 86.6% (97 of 112 subjects) in the ipragliflozin extension group, and the incidence of adverse drug reactions was 60.0% (6 of 10 subjects) in the placebo/ipragliflozin group and 42.9% (48 of 112 subjects) in the ipragliflozin extension group. Adverse events reported by ≥3 subjects in any group were as shown in Table 24. Adverse drug reactions reported by ≥3 subjects in any group were constipation (10.0% [1 of 10 subjects] in the placebo/ipragliflozin group, 3.6% [4 of 112 subjects] in the ipragliflozin extension group), hepatic function abnormal (0.0% [0 of 10 subjects] in the placebo/ipragliflozin group, 2.7% [3 of 112 subjects] in the ipragliflozin extension group), vulvovaginal candidiasis (10.0% [1 of 10 subjects] in the placebo/ipragliflozin group, 2.7% [3 of 112 subjects] in the ipragliflozin extension group), weight decreased (0.0% [0 of 10 subjects] in the placebo/ipragliflozin group, 5.4% [6 of 112 subjects] in the ipragliflozin extension group), pollakiuria (10.0% [1 of 10 subjects] in the placebo/ipragliflozin group, 6.3% [7 of 112 subjects] in the ipragliflozin extension group), pruritus genital (10.0% [1 of 10 subjects] in the placebo/ipragliflozin group, 2.7% [3 of 112 subjects] in the ipragliflozin extension group), and upper respiratory tract inflammation (0.0% [0 of 10 subjects] in the placebo/ipragliflozin group, 2.7% [3 of 112 subjects] in the ipragliflozin extension group).

Table 24. Adverse events reported by ≥3 subjects in any group (safety analysis set) (52 weeks)

Adverse event	Placebo/ipragliflozin group[a)] (n = 10)	Ipragliflozin extension group (n = 112)
Overall	9 (90.0)	97 (86.6)
Diabetic retinopathy	0 (0.0)	4 (3.6)
Abdominal discomfort	0 (0.0)	3 (2.7)
Abdominal pain upper	0 (0.0)	3 (2.7)
Cheilitis	0 (0.0)	3 (2.7)
Constipation	2 (20.0)	8 (7.1)
Dental caries	0 (0.0)	4 (3.6)
Diarrhoea	0 (0.0)	3 (2.7)
Dyspepsia	0 (0.0)	5 (4.5)
Gastritis	0 (0.0)	3 (2.7)
Nausea	0 (0.0)	4 (3.6)
Periodontal disease	1 (10.0)	4 (3.6)
Vomiting	0 (0.0)	4 (3.6)
Thirst	0 (0.0)	3 (2.7)
Hepatic function abnormal	0 (0.0)	3 (2.7)
Seasonal allergy	0 (0.0)	4 (3.6)
Bronchitis	0 (0.0)	6 (5.4)
Cystitis	1 (10.0)	3 (2.7)
Gastroenteritis	0 (0.0)	3 (2.7)
Nasopharyngitis	2 (20.0)	39 (34.8)
Onychomycosis	0 (0.0)	3 (2.7)
Pharyngitis	0 (0.0)	5 (4.5)
Vulvovaginal candidiasis	1 (10.0)	3 (2.7)
Contusion	0 (0.0)	3 (2.7)
Weight decreased	0 (0.0)	6 (5.4)
Back pain	1 (10.0)	8 (7.1)
Dizziness	0 (0.0)	4 (3.6)
Headache	0 (0.0)	8 (7.1)
Insomnia	0 (0.0)	4 (3.6)
Pollakiuria	1 (10.0)	7 (6.3)
Pruritus genital	1 (10.0)	3 (2.7)
Upper respiratory tract inflammation	0 (0.0)	6 (5.4)
Eczema	0 (0.0)	4 (3.6)

Number of subjects with events (incidence %), MedDRA/J ver.12.1
a) Adverse events that occurred after the start of ipragliflozin treatment.

No deaths were reported during Treatment Period II. Serious adverse events were reported by 1 subject in the placebo/ipragliflozin group (cataract) and 3 subjects in the ipragliflozin extension group (subdural haematoma/hepatic neoplasm malignant, rheumatoid arthritis, and gastroenteritis in 1 subject each), but a causal relationship with the study drug was ruled out for all these events. Adverse events leading to study drug discontinuation were reported by 2 subjects in the ipragliflozin extension group (subdural haematoma and weight decreased in 1 subject each), and the event reported by 1 subject (weight decreased) was assessed as an adverse drug reaction.

Hypoglycemia-related adverse events were not reported.

Urinary tract infection-related adverse events were reported by 2 subjects in the ipragliflozin extension group (urinary tract infection and cystitis in 1 subject each), but a causal relationship with the study drug was ruled out for all these events.

Genital infection-related adverse events were reported by 2 subjects in the placebo/ipragliflozin group (vulvovaginal candidiasis and balanitis candida in 1 subject each) and 3 subjects in the ipragliflozin extension group (pruritus genital in 2 subjects, vulvovaginal candidiasis in 1 subject), and all these events were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria were reported by 1 subject in the placebo/ipragliflozin group (pollakiuria) and 2 subjects in the ipragliflozin extension group (pollakiuria and polyuria in 1 subject each), and all these events were assessed as adverse drug reactions.

Regarding 12-lead ECG, a clinically significant abnormality was reported by 1 subject (electrocardiogram T wave inversion).

No clinically meaningful changes were observed in vital signs.

4.(iii).A.(3).5) Pioglitazone combination therapy study (5.3.5.1-4, Study CL-0107 [September 2010 to April 2012])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus who responded inadequately to pioglitazone[77] (target sample size, 150; n = 100 for the ipragliflozin group, n = 50 for the placebo group) was conducted to evaluate the efficacy and safety of concomitant use of ipragliflozin with pioglitazone.

Following the run-in period (consisting of a 4-week screening period and a 2-week single-blind placebo treatment period), ipragliflozin 50 mg or placebo was to be orally administered once daily before breakfast for 24 weeks for Treatment Period I (double-blind period). For Treatment Period II, ipragliflozin 50 mg was to be orally administered once daily before breakfast for 28 weeks for subjects whose HbA1c was <8.0% and lower than their baseline HbA1c value at Week 20 of Treatment Period I (double-blind period). The dose was to be increased from 50 to 100 mg according to the dose increase criteria.[76] The regimen of pioglitazone was to be maintained from 4 weeks before screening.

For Treatment Period I (double-blind period), a total of 151 treated subjects[78] (54 subjects in the placebo group, 97 subjects in the ipragliflozin group) were included in the safety analysis set and FAS. Of 133 subjects who completed Treatment Period I (double-blind period) (44 subjects in the placebo group, 89 subjects in the ipragliflozin group), 84 subjects (15 subjects in the placebo group, 69 subjects in the ipragliflozin group, respectively) entered Treatment Period II. For Treatment Period II, 112 subjects who received at least one dose of ipragliflozin during the study period and from whom post-dose efficacy data were obtained (15 subjects in the placebo/ipragliflozin group, 97 subjects in the ipragliflozin extension group) were included in the safety analysis set and FAS. The FAS was the primary efficacy analysis set for both Treatment Period I (double-blind period) and II. The study was discontinued in 19 subjects during Treatment Period I (double-blind period), including 10 subjects in the placebo group (worsening of diabetes mellitus in 6 subjects, adverse events in 1 subject, consent withdrawal in 1 subject, inadequate efficacy in 2 subjects) and 9 subjects in the ipragliflozin group (worsening of diabetes mellitus in 1 subject, adverse events in 3 subjects, consent withdrawal in 3 subjects, lost to follow-up in 1 subject, protocol deviations in 1 subject). In Treatment Period II, 3 subjects (adverse events in 1 subject, consent withdrawal in 2 subjects) discontinued the study. The number of subjects for whom the dose was increased to 100 mg was 10 subjects in the placebo group and 33 subjects in the ipragliflozin group during Treatment Period I (double-blind period).

The primary efficacy endpoint of the change in HbA1c from baseline to the end of Treatment

[77] Major inclusion criteria: Patients aged ≥20 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥7.0% and ≤9.5% at 2 weeks before the start of the study treatment; who have received monotherapy with fixed-dose pioglitazone for ≥4 weeks up to screening. (For patients on another oral hypoglycemic therapy, the run-in period was initiated at least 4 weeks after discontinuation of such therapy.)

[78] Of 152 subjects for whom the study drug was prescribed, 1 subject was excluded because the treatment status with the study drug was unknown.

Period I (double-blind period) in the FAS was as shown in Table 25, showing superiority of the ipragliflozin group over the placebo group ($P < 0.001$, ANCOVA model, two-sided significance level of 5%).

Table 25. Change in HbA1c from baseline to the end of Treatment Period I (double-blind period) (at Week 24 or withdrawal) (FAS)

Treatment group	n	Baseline	End of Treatment Period I (double-blind period)	Change from baseline to the end of Treatment Period I (double-blind period)	Between-group difference [95% CI][a)]	*P*-value[a), b)]
Placebo	54	7.99 ± 0.638	8.20 ± 1.051	0.21 ± 0.799	-0.87 [-1.100, -0.646]	$P < 0.001$
Ipragliflozin	97	7.84 ± 0.666	7.21 ± 0.750	-0.64 ± 0.602		

Unit, %; mean ± SD
a) ANCOVA model with baseline HbA1c as a covariate and the treatment group as a fixed effect
b) Two-sided significance level of 5%

The proportion of subjects who achieved HbA1c <6.5% at the end of Treatment Period I (double-blind period) evaluated in one of the secondary analyses of the primary endpoint was 0.0% (0 of 54 subjects) in the placebo group and 8.2% (8 of 97 subjects) in the ipragliflozin group.

The changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of Treatment Period I (double-blind period), the secondary endpoint, were 6.1 ± 30.99 mg/dL and 0.51 ± 2.186 kg in the placebo group and -36.4 ± 33.35 mg/dL and -2.29 ± 2.050 kg in the ipragliflozin group, respectively.

The change in HbA1c (mean ± SD) from baseline to the end of the treatment period was -0.45% ± 0.334% in the placebo/ipragliflozin group (n = 15) and -0.74% ± 0.688% in the ipragliflozin extension group (n = 97), and the change in HbA1c over time was as shown in Figure 4.

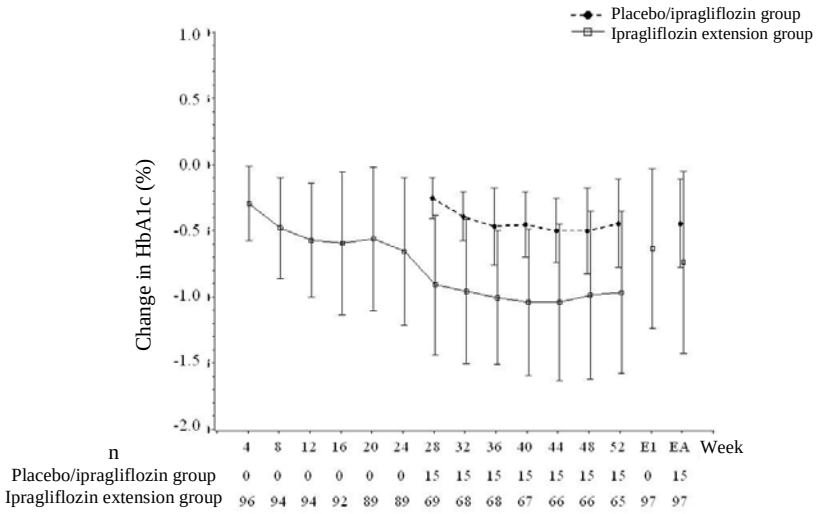

Figure 4. Change in HbA1c (%) over time (FAS) (mean ± SD)
E1, End of Treatment Period I (double-blind period); EA, End of treatment period

Regarding safety during Treatment Period I (double-blind period), the incidence of adverse events was 68.5% (37 of 54 subjects) in the placebo group and 72.2% (70 of 97 subjects) in the ipragliflozin group, and the incidence of adverse drug reactions was 9.3% (5 of 54 subjects) in the placebo group and 25.8% (25 of 97 subjects) in the ipragliflozin group. Adverse events

reported by ≥3 subjects in any group were as shown in Table 26. Adverse drug reactions reported by ≥3 subjects in any group were thirst (0.0% [0 of 54 subjects] in the placebo group, 5.2% [5 of 97 subjects] in the ipragliflozin group), pollakiuria (0.0% [0 of 54 subjects] in the placebo group, 11.3% [11 of 97 subjects] in the ipragliflozin group), and polyuria (0.0% [0 of 54 subjects] in the placebo group, 3.1% [3 of 97 subjects] in the ipragliflozin group).

Table 26. Adverse events reported by ≥3 subjects in any group (safety analysis set) (24 weeks)

Adverse event	Placebo group (n = 54)	Ipragliflozin group (n = 97)
Overall	37 (68.5)	70 (72.2)
Dental caries	3 (5.6)	3 (3.1)
Diarrhoea	4 (7.4)	1 (1.0)
Gastritis	0 (0.0)	3 (3.1)
Thirst	0 (0.0)	5 (5.2)
Nasopharyngitis	10 (18.5)	25 (25.8)
Contusion	3 (5.6)	2 (2.1)
Diabetes mellitus	8 (14.8)	1 (1.0)
Back pain	0 (0.0)	3 (3.1)
Pollakiuria	0 (0.0)	12 (12.4)
Polyuria	0 (0.0)	3 (3.1)
Eczema	0 (0.0)	4 (4.1)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

One death was reported.[79] Serious adverse events were reported by 2 subjects in the placebo group (actinic keratosis/Bowen's disease and cataract operation in 1 subject each) and 1 subject in the ipragliflozin group (clavicle fracture), but a causal relationship with the study drug was ruled out. Adverse events leading to study drug discontinuation were reported by 6 subjects in the placebo group (diabetes mellitus in 5 subjects, actinic keratosis/Bowen's disease in 1 subject) and 2 subjects in the ipragliflozin group (pruritus generalised/urinary tract infection and diabetes mellitus in 1 subject each), and the events reported by 1 subject in the ipragliflozin group (pruritus generalised/urinary tract infection) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were not reported by subjects in the placebo group, but were reported by 1 of 97 subjects in the ipragliflozin group and the event was assessed as an adverse drug reaction.

Urinary tract infection-related adverse events were reported by 1 of 54 subjects in the placebo group (cystitis) and 3 of 97 subjects in the ipragliflozin group (cystitis in 2 subjects, urinary tract infection in 1 subject), and all but 1 event in 1 subject in the ipragliflozin group (cystitis) were assessed as adverse drug reactions.

Genital infection-related adverse events were not reported by subjects in the placebo group, but were reported by 2 of 97 subjects in the ipragliflozin group (pruritus genital and vulvovaginal candidiasis in 1 subject each) and these events were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria were not reported by subjects in the placebo group, but were reported by 13 of 97 subjects in the ipragliflozin group (pollakiuria in 10 subjects, pollakiuria/polyuria in 2 subjects, polyuria in 1 subject), and all but 1 event in 1 subject (pollakiuria) were assessed as adverse drug reactions.

No clinically significant abnormalities were reported regarding 12-lead ECG.

[79] The patient suffered tsunami damage and was excluded from the safety analysis set because treatment status with the study drug was unknown.

No clinically meaningful changes were observed in vital signs.

Regarding safety of 52-week treatment, the incidence of adverse events was 73.3% (11 of 15 subjects) in the placebo/ipragliflozin group and 81.4% (79 of 97 subjects) in the ipragliflozin extension group, and the incidence of adverse drug reactions was 6.7% (1 of 15 subjects) in the placebo/ipragliflozin group and 30.9% (30 of 97 subjects) in the ipragliflozin extension group. Adverse events reported by ≥3 subjects in any group were as shown in Table 27. Adverse drug reactions reported by ≥3 subjects in any group were thirst (0.0% [0 of 15 subjects] in the placebo/ipragliflozin group, 5.2% [5 of 97 subjects] in the ipragliflozin extension group), pollakiuria (6.7% [1 of 15 subjects] in the placebo/ipragliflozin group, 11.3% [11 of 97 subjects] in the ipragliflozin extension group), and polyuria (0.0% [0 of 15 subjects] in the placebo/ipragliflozin group, 3.1% [3 of 97 subjects] in the ipragliflozin extension group).

Table 27. Adverse events reported by ≥3 subjects in any group (safety analysis set) (52 weeks)

Adverse event	Placebo/ipragliflozin group[a)] (n = 15)	Ipragliflozin extension group (n = 97)
Overall	11 (73.3)	79 (81.4)
Diabetic retinopathy	0 (0.0)	3 (3.1)
Dental caries	1 (6.7)	4 (4.1)
Diarrhoea	1 (6.7)	3 (3.1)
Gastritis	0 (0.0)	4 (4.1)
Oedema peripheral	0 (0.0)	3 (3.1)
Thirst	0 (0.0)	5 (5.2)
Cystitis	0 (0.0)	3 (3.1)
Influenza	0 (0.0)	3 (3.1)
Nasopharyngitis	4 (26.7)	34 (35.1)
Contusion	2 (13.3)	4 (4.1)
Arthralgia	0 (0.0)	6 (6.2)
Back pain	0 (0.0)	5 (5.2)
Pollakiuria	1 (6.7)	12 (12.4)
Polyuria	0 (0.0)	3 (3.1)
Pruritus genital	0 (0.0)	3 (3.1)
Rhinitis allergic	0 (0.0)	4 (4.1)
Eczema	0 (0.0)	6 (6.2)

Number of subjects with events (incidence %), MedDRA/J ver.12.1
a) Adverse events that occurred after the start of ipragliflozin treatment

No deaths were reported during Treatment Period II. Serious adverse events were reported by 1 subject in the placebo/ipragliflozin group (contusion/rotator cuff syndrome) and 2 subjects in the ipragliflozin extension group (multiple fractures and pyelonephritis in 1 subject each), and the event reported by 1 subject in the ipragliflozin extension group (pyelonephritis) was assessed as an adverse drug reaction. Adverse events leading to study drug discontinuation were reported by 1 subject in the ipragliflozin extension group (pyelonephritis) and the event was assessed as an adverse drug reaction.

Hypoglycemia-related adverse events were not reported.

Urinary tract infection-related adverse events were reported by 1 subject in the ipragliflozin extension group (bacteriuria/cystitis/pyelonephritis), and these events were assessed as adverse drug reactions.

Genital infection-related adverse events were reported by 1 subject in the placebo/ipragliflozin group (vulvovaginal candidiasis) and 2 subjects in the ipragliflozin extension group (pruritus genital, and vulvovaginal candidiasis in 1 subject each), and the events reported by 2 subjects in the ipragliflozin extension group were assessed as adverse drug reactions.

An adverse event related to pollakiuria and polyuria was reported by 1 subject in the placebo/ipragliflozin group (pollakiuria) and the event was assessed as an adverse drug reaction.

Regarding 12-lead ECG, a clinically significant abnormality was reported by 1 subject (sinus tachycardia).

No clinically meaningful changes were observed in vital signs.

4.(iii).A.(3).6) Sulfonylurea combination therapy study (5.3.5.1-5, Study CL-0109 [September 2010 to April 2012])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus who responded inadequately to a sulfonylurea (SU)[80] (target sample size, 225; n = 150 for the ipragliflozin group, n = 75 for the placebo group) was conducted to evaluate the efficacy and safety of concomitant use of ipragliflozin with SU.

Following the run-in period (consisting of a 4-week screening period and a 2-week single-blind placebo treatment period), ipragliflozin 50 mg or placebo was to be orally administered once daily before breakfast for 24 weeks for Treatment Period I (double-blind period). For Treatment Period II, ipragliflozin 50 mg was to be orally administered once daily before breakfast for 28 weeks for subjects whose HbA1c was <8.0% and lower than their baseline HbA1c value at Week 20 of Treatment Period I (double-blind period). The dose was to be increased from 50 to 100 mg according to the dose increase criteria.[76] The regimen of SU was to be maintained from 4 weeks before screening.

For Treatment Period I (double-blind period), a total of 242 treated subjects[81] (76 subjects in the placebo group, 166 subjects in the ipragliflozin group) were included in the safety analysis set. Of the subjects, 240 subjects (75 subjects in the placebo group, 165 subjects in the ipragliflozin group) were included in the FAS, excluding 2 subjects for whom post-dose efficacy data were not available. Of 212 subjects who completed Treatment Period I (double-blind period) (57 subjects in the placebo group, 155 subjects in the ipragliflozin group), 141 subjects (13 subjects in the placebo group, 128 subjects in the ipragliflozin group) entered Treatment Period II. For Treatment Period II, 179 subjects who received at least one dose of ipragliflozin during the study period (13 subjects in the placebo/ipragliflozin group, 166 subjects in the ipragliflozin extension group) were included in the safety analysis set. Excluding 1 subject for whom post-dose efficacy data were not available, 178 subjects (13 subjects in the placebo/ipragliflozin group, 165 subjects in the ipragliflozin extension group) were included in the FAS. The FAS was the primary efficacy analysis set for both Treatment Period I (double-blind period) and II. The study was discontinued in 31 subjects during Treatment Period I (double-blind period), including 20 subjects in the placebo group (adverse events in 4 subjects, worsening of diabetes mellitus in 8 subjects, inadequate efficacy in 5 subjects, consent withdrawal in 2 subjects, other reasons in 1 subject) and 11 subjects in the ipragliflozin group (adverse events in 6 subjects, worsening of diabetes mellitus in 1 subject, consent withdrawal in 2 subjects, other reasons in 1 subject, lost to follow-up in 1 subject). In Treatment Period II, 10 subjects (adverse events in 7 subjects, inadequate efficacy in 1 subject, consent withdrawal in 1 subject, other reasons in 1 subject) discontinued the study. The number of subjects for whom the dose was increased to 100 mg was 7 subjects in the placebo group and 71 subjects in the ipragliflozin group during Treatment Period I (double-blind

[80] Major inclusion criteria: Patients aged ≥20 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2, fasting plasma glucose ≥126 mg/dL, and HbA1c of ≥7.0% and ≤9.5% at 2 weeks before the start of the study treatment; who have received monotherapy with fixed-dose SU (any 1 drug among glibenclamide, gliclazide, or glimepiride) for ≥4 weeks up to screening. (For patients on another oral hypoglycemic therapy, the run-in period was initiated at least 4 weeks after discontinuation of such therapy.)

[81] Of 243 subjects for whom the study drug was prescribed, 1 subject was excluded because the treatment status with the study drug was unknown.

period).

The primary efficacy endpoint of the change in HbA1c from baseline to the end of Treatment Period I (double-blind period) in the FAS was as shown in Table 28, showing superiority of the ipragliflozin group over the placebo group ($P < 0.001$, ANCOVA model, two-sided significance level of 5%).

Table 28. Change in HbA1c from baseline to the end of Treatment Period I (double-blind period) (at Week 24 or withdrawal) (FAS)

Treatment group	n	Baseline	End of Treatment Period I (double-blind period)	Change from baseline to the end of Treatment Period I (double-blind period)	Between-group difference [95% CI][a)]	*P*-value[a), b)]
Placebo	75	7.94 ± 0.727	8.26 ± 1.106	0.32 ± 0.954	-1.14 [-1.340, -0.932]	$P < 0.001$
Ipragliflozin	165	7.98 ± 0.641	7.14 ± 0.671	-0.83 ± 0.715		

Unit, %; mean ± SD
a) ANCOVA model with baseline HbA1c as a covariate and the treatment group as a fixed effect
b) Two-sided significance level of 5%

The proportion of subjects who achieved HbA1c <6.5% at the end of Treatment Period I (double-blind period) evaluated as one of the secondary analyses of the primary endpoint was 5.3% (4 of 75 subjects) in the placebo group and 13.3% (22 of 165 subjects) in the ipragliflozin group.

The secondary endpoint, the changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of Treatment Period I (double-blind period), were -1.0 ± 40.20 mg/dL and -0.88 ± 1.785 kg in the placebo group and -41.4 ± 30.80 mg/dL and -2.33 ± 2.154 kg in the ipragliflozin group, respectively.

The change in HbA1c (mean ± SD) from baseline to the end of the treatment period was -0.61% ± 0.482% in the placebo/ipragliflozin group (n = 13) and -0.84% ± 0.712% in the ipragliflozin extension group (n = 165), and the change in HbA1c over time was as shown in Figure 5.

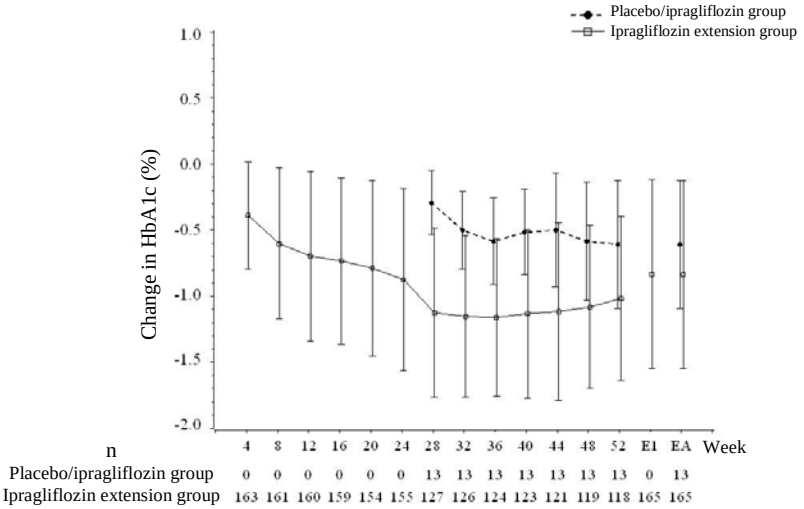

Figure 5. Change in HbA1c (%) over time (FAS) (mean ± SD)
E1, End of Treatment Period I (double-blind period); EA, End of treatment period

Regarding safety during Treatment Period I (double-blind period), the incidence of adverse events

was 61.8% (47 of 76 subjects) in the placebo group and 75.9% (126 of 166 subjects) in the ipragliflozin group, and the incidence of adverse drug reactions was 23.7% (18 of 76 subjects) in the placebo group and 23.5% (39 of 166 subjects) in the ipragliflozin group. Adverse events reported by ≥3 subjects in any group were as shown in Table 29. Adverse drug reactions reported by ≥3 subjects in any group were constipation (1.3% [1 of 76 subjects] in the placebo group, 2.4% [4 of 166 subjects] in the ipragliflozin group), thirst (1.3% [1 of 76 subjects] in the placebo group, 6.0% [10 of 166 subjects] in the ipragliflozin group), cystitis (3.9% [3 of 76 subjects] in the placebo group, 0.6% [1 of 166 subjects] in the ipragliflozin group), beta 2 microglobulin increased (0.0% [0 of 76 subjects] in the placebo group, 1.8% [3 of 166 subjects] in the ipragliflozin group), diabetes mellitus (3.9% [3 of 76 subjects] in the placebo group, 0.0% [0 of 166 subjects] in the ipragliflozin group), pollakiuria (1.3% [1 of 76 subjects] in the placebo group, 8.4% [14 of 166 subjects] in the ipragliflozin group), and polyuria (1.3% [1 of 76 subjects] in the placebo group, 3.0% [5 of 166 subjects] in the ipragliflozin group).

Table 29. Adverse events reported by ≥3 subjects in any group (safety analysis set) (24 weeks)

Adverse event	Placebo group (n = 76)	Ipragliflozin group (n = 166)
Overall	47 (61.8)	126 (75.9)
Diabetic retinopathy	1 (1.3)	3 (1.8)
Abdominal pain upper	3 (3.9)	5 (3.0)
Constipation	1 (1.3)	9 (5.4)
Dental caries	0 (0.0)	5 (3.0)
Diarrhoea	2 (2.6)	7 (4.2)
Gastritis	2 (2.6)	3 (1.8)
Stomatitis	0 (0.0)	7 (4.2)
Malaise	3 (3.9)	1 (0.6)
Thirst	1 (1.3)	12 (7.2)
Bronchitis	1 (1.3)	3 (1.8)
Cystitis	3 (3.9)	1 (0.6)
Gastroenteritis	1 (1.3)	4 (2.4)
Influenza	0 (0.0)	4 (2.4)
Nasopharyngitis	18 (23.7)	45 (27.1)
Pharyngitis	1 (1.3)	3 (1.8)
Beta 2 microglobulin urine increased	0 (0.0)	3 (1.8)
Diabetes mellitus	15 (19.7)	1 (0.6)
Back pain	0 (0.0)	3 (1.8)
Intervertebral disc protrusion	0 (0.0)	3 (1.8)
Musculoskeletal stiffness	3 (3.9)	0 (0.0)
Cervicobrachial syndrome	0 (0.0)	3 (1.8)
Pollakiuria	1 (1.3)	14 (8.4)
Polyuria	1 (1.3)	5 (3.0)
Upper respiratory tract inflammation	2 (2.6)	3 (1.8)
Eczema	1 (1.3)	3 (1.8)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

One death was reported.[82] Serious adverse events were reported by 3 subjects in the placebo group (gastric polyps, thalamic infarction, and diabetes mellitus in 1 subject each) and 6 subjects in the ipragliflozin group (spinal column stenosis, retinopathy proliferative, intervertebral disc protrusion, Parkinson's disease, osteomyelitis/subcutaneous abscess/hyperkeratosis, and idiopathic thrombocytopenic purpura[83] in 1 subject each), but a causal relationship with the study drug was ruled out for all these events except the event of thalamic infarction. Adverse events leading to study drug discontinuation were reported by 11 subjects in the placebo group (diabetes mellitus in 8 subjects, gastric polyps, thalamic infarction, and abdominal discomfort/pruritus

[82] The patient was affected by a natural disaster and was excluded from the safety analysis set because treatment status with the study drug was unknown.

[83] The event was assessed as a serious adverse event during Treatment Period II.

genital in 1 subject each) and 12 subjects in the ipragliflozin group (spinal column stenosis, hyperkeratosis, thirst/chest discomfort/polyuria/pollakiuria, amnesia, retinopathy proliferative, diabetes mellitus, Meniere's disease, hypoglycaemia, alcoholic liver disease,[84] idiopathic thrombocytopenic purpura,[84] iron deficiency anaemia,[84] and Parkinson's disease in 1 subject each), and the events reported by 3 subjects in the placebo group (pruritus genital, diabetes mellitus, and thalamic infarction in 1 subject each) and 3 subjects in the ipragliflozin group (thirst/chest discomfort/polyuria/pollakiuria, Meniere's disease, and iron deficiency anaemia in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were reported by 1 of 76 subjects in the placebo group and 2 of 166 subjects in the ipragliflozin group, and all but the event in 1 subject in the ipragliflozin group were assessed as adverse drug reactions.

Urinary tract infection-related adverse events were reported by 3 of 76 subjects in the placebo group (cystitis in all these subjects) and 2 of 166 subjects in the ipragliflozin group (cystitis and prostatitis in 1 subject each), and all these events were assessed as adverse drug reactions.

Genital infection-related adverse events were reported by 3 of 76 subjects in the placebo group (pruritus genital, cervicitis, and balanoposthitis in 1 subject each) and 1 of 166 subjects in the ipragliflozin group (vaginitis bacterial), and the events reported by 2 subjects in the placebo group (pruritus genital and balanoposthitis in 1 subject each) were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria were reported by 2 of 76 subjects in the placebo group (pollakiuria and polyuria in 1 subject each) and 16 of 166 subjects in the ipragliflozin group (pollakiuria in 10 subjects, pollakiuria/polyuria in 4 subjects, nocturia and polyuria in 1 subject each), and all but 1 event in 1 subject in the ipragliflozin group (nocturia) were assessed as adverse drug reactions.

Regarding 12-lead ECG, a clinically significant abnormality was reported by 1 of 166 subjects in the ipragliflozin group (electrocardiogram T wave biphasic).

No clinically meaningful changes were observed in vital signs.

Regarding the safety of 52-week treatment, the incidence of adverse events was 76.9% (10 of 13 subjects) in the placebo/ipragliflozin group and 86.7% (144 of 166 subjects) in the ipragliflozin extension group, and the incidence of adverse drug reactions was 23.1% (3 of 13 subjects) in the placebo/ipragliflozin group and 31.3% (52 of 166 subjects) in the ipragliflozin extension group. Adverse events reported by ≥3 subjects in any group were as shown in Table 30. Adverse drug reactions reported by ≥3 subjects in any group were constipation (7.7% [1 of 13 subjects] in the placebo/ipragliflozin group, 3.6% [6 of 166 subjects] in the ipragliflozin extension group), thirst (0.0% [0 of 13 subjects] in the placebo/ipragliflozin group, 6.0% [10 of 166 subjects] in the ipragliflozin extension group), cystitis (0.0% [0 of 13 subjects] in the placebo/ipragliflozin group, 2.4% [4 of 166 subjects] in the ipragliflozin extension group), beta 2 microglobulin urine increased (0.0% [0 of 13 subjects] in the placebo/ipragliflozin group, 2.4% [4 of 166 subjects] in the ipragliflozin extension group), weight decreased (0.0% [0 of 13 subjects] in the placebo/ipragliflozin group, 2.4% [4 of 166 subjects] in the ipragliflozin extension group), pollakiuria (0.0% [0 of 13 subjects] in the placebo/ipragliflozin group, 9.0% [15 of 166 subjects] in the ipragliflozin extension group), and polyuria (0.0% [0 of 13 subjects] in the placebo/ipragliflozin group, 3.0% [5 of 166 subjects] in the ipragliflozin extension group).

[84] The event occurred during Treatment Period I and the study was discontinued during Treatment Period II.

Table 30. Adverse events reported by ≥3 subjects in any group (safety analysis set) (52 weeks)

Adverse event	Placebo/ipragliflozin group (n = 13)[a)]	Ipragliflozin extension group (n = 166)
Overall	10 (76.9)	144 (86.7)
Conjunctivitis	0 (0.0)	3 (1.8)
Diabetic retinopathy	0 (0.0)	6 (3.6)
Abdominal discomfort	0 (0.0)	3 (1.8)
Abdominal pain upper	0 (0.0)	7 (4.2)
Constipation	2 (15.4)	14 (8.4)
Dental caries	0 (0.0)	7 (4.2)
Diarrhoea	0 (0.0)	8 (4.8)
Gastritis	0 (0.0)	5 (3.0)
Gingivitis	0 (0.0)	3 (1.8)
Periodontitis	0 (0.0)	4 (2.4)
Stomatitis	0 (0.0)	8 (4.8)
Toothache	0 (0.0)	3 (1.8)
Thirst	0 (0.0)	12 (7.2)
Hepatic steatosis	0 (0.0)	3 (1.8)
Bronchitis	0 (0.0)	5 (3.0)
Cystitis	0 (0.0)	4 (2.4)
Gastroenteritis	1 (7.7)	8 (4.8)
Herpes zoster	0 (0.0)	4 (2.4)
Hordeolum	0 (0.0)	5 (3.0)
Influenza	0 (0.0)	5 (3.0)
Nasopharyngitis	4 (30.8)	64 (38.6)
Pharyngitis	0 (0.0)	5 (3.0)
Contusion	0 (0.0)	3 (1.8)
Tooth fracture	0 (0.0)	3 (1.8)
Beta 2 microglobulin urine increased	1 (7.7)	5 (3.0)
Blood creatine phosphokinase increased	0 (0.0)	3 (1.8)
Weight decreased	0 (0.0)	4 (2.4)
Hypoglycaemia	0 (0.0)	3 (1.8)
Arthralgia	0 (0.0)	3 (1.8)
Back pain	1 (7.7)	6 (3.6)
Myalgia	0 (0.0)	5 (3.0)
Trigger finger	0 (0.0)	3 (1.8)
Cervicobrachial syndrome	0 (0.0)	4 (2.4)
Dizziness	0 (0.0)	4 (2.4)
Hypoaesthesia	1 (7.7)	3 (1.8)
Insomnia	0 (0.0)	3 (1.8)
Pollakiuria	0 (0.0)	15 (9.0)
Polyuria	0 (0.0)	5 (3.0)
Upper respiratory tract inflammation	1 (7.7)	7 (4.2)
Oropharyngeal pain	0 (0.0)	5 (3.0)
Eczema	0 (0.0)	8 (4.8)

Number of subjects with events (incidence %), MedDRA/J ver.12.1
a) Adverse events that occurred after the start of ipragliflozin treatment

No deaths were reported during Treatment Period II. Serious adverse events were reported by 6 subject in the ipragliflozin extension group (angina pectoris, prostate cancer, lacunar infarction, colonic polyp, enterocolitis/Mallory-Weiss syndrome, and meniscus lesion/ligament rupture in 1 subject each), but a causal relationship with the study drug was ruled out for all these events. Adverse events leading to study drug discontinuation were reported by 4 subjects in the ipragliflozin extension group (angina pectoris, enterocolitis/Mallory-Weiss syndrome, lacunar infarction, and benign prostatic hyperplasia in 1 subject each), but a causal relationship with the study drug was ruled out for all these events.

Hypoglycemia-related adverse events were reported by 5 subjects in the ipragliflozin extension

group, and all but the event in 1 subject were assessed as adverse drug reactions.

Urinary tract infection-related adverse events were reported by 1 subject in the placebo/ipragliflozin group (urethritis) and 3 subjects in the ipragliflozin extension group (cystitis in all these subjects), and all these events were assessed as adverse drug reactions.

Genital infection-related adverse events were reported by 2 subjects in the ipragliflozin extension group (vulvovaginal candidiasis and balanoposthitis in 1 subject each), and the event reported by 1 subject (vulvovaginal candidiasis) was assessed as an adverse drug reaction.

An adverse event related to pollakiuria and polyuria was reported by 1 subject in the ipragliflozin extension group (pollakiuria) and the event was assessed as an adverse drug reaction.

Regarding 12-lead ECG, a clinically significant abnormality was reported by 2 subjects in the ipragliflozin extension group (angina pectoris and tachycardia in 1 subject each).

No clinically meaningful changes were observed in vital signs.

4.(iii).A.(3).7) α-glucosidase inhibitor combination therapy study (5.3.5.2-1, Study CL-0108 [October 2010 to May 2012])

An open-label, uncontrolled, long-term treatment study in Japanese patients with type 2 diabetes mellitus who responded inadequately to an α-glucosidase inhibitor (α-GI)[85] (target sample size, 100 subjects in the ipragliflozin group) was conducted to evaluate the efficacy and safety of concomitant use of ipragliflozin with α-GI.

Ipragliflozin 50 mg was to be orally administered once daily before breakfast for 52 weeks. In addition, the dose was to be increased from 50 to 100 mg at Week 20 on the basis of HbA1c at the start of the treatment period and Week 16.[73] The regimen of α-GI was to be maintained from 4 weeks before the start of the run-in period.

A total of 113 treated subjects were included in the safety analysis set and FAS. The FAS was the primary efficacy analysis set. The study was discontinued in 26 subjects (inclusion/exclusion criteria violations in 2 subjects, adverse events in 10 subjects, inadequate efficacy in 1 subject, consent withdrawal in 2 subjects, lost to follow-up in 1 subject, other reasons in 10 subjects). The number of subjects for whom the dose was increased to 100 mg was 42 subjects.

Regarding efficacy, the change in HbA1c (mean ± SD) from baseline (at the start of the treatment period) to Week 20 (LOCF) in the FAS was -0.72% ± 0.614% (n = 109). The change in HbA1c over time was as shown in Figure 6.

[85] Major inclusion criteria: Patients aged ≥20 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥6.5% and ≤9.5% at 2 weeks before the start of the study treatment; who have received monotherapy with fixed-dose α-GI for ≥4 weeks prior to screening. (For patients on another oral hypoglycemic therapy, the run-in period was initiated at least 4 weeks after discontinuation of such therapy.)

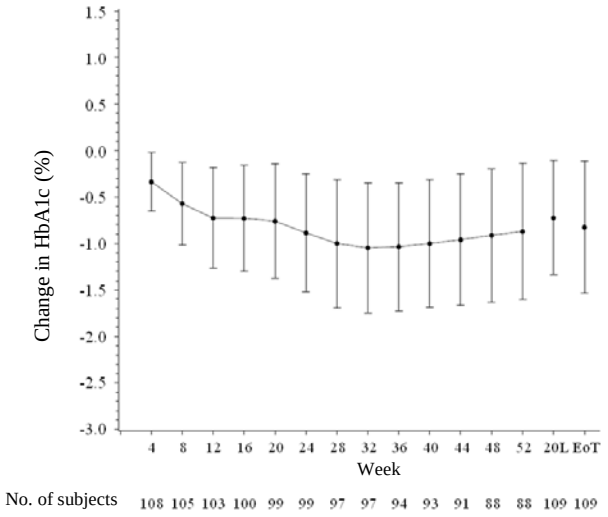

Figure 6. Change in HbA1c (%) over time (FAS) (mean ± SD)
20L, Week 20 (LOCF); EoT, End of treatment period

The proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period was 42.2% (46 of 109 subjects). The changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of the treatment period were -35.7 ± 29.95 mg/dL (n = 109) and -2.78 ± 2.321 kg (n = 113), respectively.

Regarding safety, the overall incidence of adverse events was 77.0% (87 of 113 subjects) and that of adverse drug reactions was 33.6% (38 of 113 subjects). Adverse events reported by ≥3 subjects overall were as shown in Table 31. Adverse drug reactions reported by ≥3 subjects overall were constipation (2.7%, 3 of 113 subjects), thirst (6.2%, 7 of 113 subjects), beta 2 microglobulin urine increased (3.5%, 4 of 113 subjects), weight decreased (4.4%, 5 of 113 subjects), and pollakiuria (8.8%, 10 of 113 subjects).

Table 31. Adverse events reported by ≥3 subjects overall (safety analysis set)

Adverse event	Adverse event (n = 113)
Overall	87 (77.0)
Constipation	6 (5.3)
Dental caries	4 (3.5)
Diarrhoea	4 (3.5)
Reflux oesophagitis	3 (2.7)
Stomatitis	5 (4.4)
Thirst	8 (7.1)
Bronchitis	3 (2.7)
Gastroenteritis	4 (3.5)
Nasopharyngitis	46 (40.7)
Beta 2 microglobulin urine increased	4 (3.5)
Weight decreased	5 (4.4)
Arthralgia	5 (4.4)
Back pain	7 (6.2)
Pollakiuria	10 (8.8)
Upper respiratory tract inflammation	5 (4.4)
Eczema	5 (4.4)

Number of subjects with event (incidence %) MedDRA/J ver. 12.1

No deaths were reported. Serious adverse events were reported by 12 subjects (acute myocardial

infarction, inguinal hernia, pyelonephritis/calculus ureteric, pain, prostatic specific antigen increased, gastric cancer stage 0, anisakiasis, intervertebral disc protrusion, herpes zoster, prostate cancer, bile duct cancer, and nephrolithiasis in 1 subject each), and the events reported by 4 subjects (acute myocardial infarction, pain, pyelonephritis/calculus ureteric, and nephrolithiasis in 1 subject each) were assessed as adverse drug reactions. Adverse events leading to study drug discontinuation were reported by 10 subjects (rash, drug eruption, acute myocardial infarction, weight decreased, pyelonephritis/calculus ureteric/hydronephrosis, pain, gastric cancer stage 0, intervertebral disc protrusion, prostate cancer, and bile duct cancer in 1 subject each), and the events reported by 6 subjects (rash, drug eruption, acute myocardial infarction, weight decreased, pyelonephritis/calculus ureteric/hydronephrosis, and pain in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were not reported.

Urinary tract infection-related adverse events were reported by 2 of 113 subjects (pyelonephritis and cystitis in 1 subject each), and both events were assessed as adverse drug reactions.

Genital infection-related adverse events were reported by 3 of 113 subjects (pruritus genital in 2 subjects, vulvovaginal candidiasis in 1 subject), and all these events were assessed as adverse drug reactions.

Adverse events related to pollakiuria and polyuria were reported by 10 of 113 subjects (pollakiuria in 9 subjects, pollakiuria/polyuria in 1 subject), and all these events were assessed as adverse drug reactions.

Regarding 12-lead ECG, a clinically significant abnormality was reported by 1 of 113 subjects (ST elevation) and the abnormality was assessed as a serious adverse event.

No clinically meaningful changes were observed in vital signs.

4.(iii).A.(3).8) Dipeptidyl peptidase-4 inhibitor combination therapy study (5.3.5.2-2, Study CL-0110 [October 2010 to June 2012])

An open-label, uncontrolled, long-term treatment study in Japanese patients with type 2 diabetes mellitus who responded inadequately to a dipeptidyl peptidase-4 (DPP-4) inhibitor[86] (target sample size, 100 subjects in the ipragliflozin group) was conducted to evaluate the efficacy and safety of concomitant use of ipragliflozin with a DPP-4 inhibitor.

Ipragliflozin 50 mg was to be orally administered once daily before breakfast for 52 weeks. In addition, the dose was to be increased from 50 to 100 mg at Week 20 on the basis of HbA1c levels at the start of the treatment period and Week 16.[73] The regimen of the DPP-4 inhibitor was to be maintained from 4 weeks before the start of the run-in period.

A total of 106 treated subjects were included in the safety analysis set and FAS. The FAS was the primary efficacy analysis set. The study was discontinued in 13 subjects (adverse events in 6 subjects, consent withdrawal in 6 subjects, other reasons in 1 subject). The number of subjects for whom the dose was increased to 100 mg was 35 subjects.

Regarding efficacy, the change in HbA1c (mean ± SD) from baseline (at the start of the treatment period) to Week 20 (LOCF) in the FAS was -0.75% ± 0.596% (n = 105). The change in HbA1c

[86] Major inclusion criteria: Patients aged ≥20 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥6.5% and ≤9.5% at 2 weeks before the start of the study treatment; who have received monotherapy with a fixed-dose DPP-4 inhibitor for ≥4 weeks up to screening. (For patients on another oral hypoglycemic therapy, the run-in period was initiated at least 4 weeks after discontinuation of such therapy.)

over time was as shown in Figure 7.

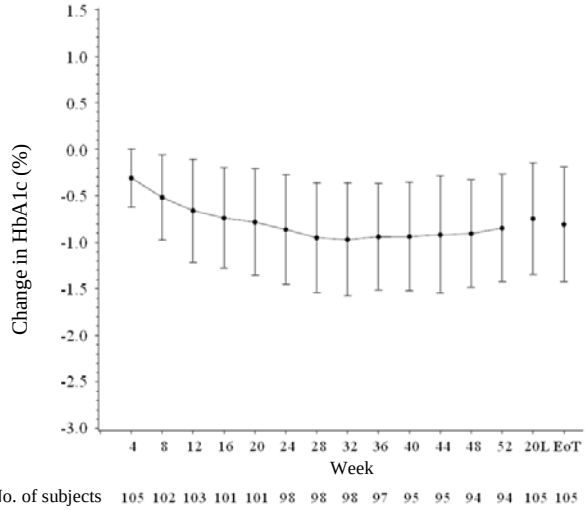

Figure 7. Change in HbA1c (%) over time (FAS) (mean ± SD)
20L, Week 20 (LOCF); EoT, End of treatment period

The proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period was 43.8% (46 of 105 subjects). The changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of the treatment period were -34.1 ± 27.55 mg/dL (n = 106) and -2.70 ± 2.427 kg (n = 106), respectively.

Regarding safety, the overall incidence of adverse events was 83.0% (88 of 106 subjects) and that of adverse drug reactions was 43.4% (46 of 106 subjects). Adverse events reported by ≥3 subjects overall were as shown in Table 32. Adverse drug reactions reported by ≥3 subjects overall were constipation (3.8%, 4 of 106 subjects), thirst (4.7%, 5 of 106 subjects), nasopharyngitis (2.8%, 3 of 106 subjects), headache (2.8%, 3 of 106 subjects), and pollakiuria (15.1%, 16 of 106 subjects).

Table 32. Adverse events reported by ≥3 subjects overall (safety analysis set)

Adverse event	Adverse event (n = 106)
Overall	88 (83.0)
Asthenopia	3 (2.8)
Conjunctivitis	3 (2.8)
Constipation	7 (6.6)
Dental caries	3 (2.8)
Diarrhoea	3 (2.8)
Periodontitis	4 (3.8)
Toothache	3 (2.8)
Oedema peripheral	3 (2.8)
Thirst	5 (4.7)
Hepatic steatosis	3 (2.8)
Nasopharyngitis	52 (49.1)
Tinea pedis	3 (2.8)
Joint sprain	4 (3.8)
Alanine aminotransferase increased	3 (2.8)
Aspartate aminotransferase increased	3 (2.8)
Weight decreased	3 (2.8)
Arthralgia	4 (3.8)
Back pain	10 (9.4)
Myalgia	3 (2.8)
Periarthritis	6 (5.7)
Musculoskeletal stiffness	3 (2.8)
Headache	5 (4.7)
Hypoaesthesia	4 (3.8)
Insomnia	4 (3.8)
Pollakiuria	17 (16.0)
Rhinitis allergic	3 (2.8)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

No deaths were reported. Serious adverse events were reported by 5 subjects (renal disorder, chest discomfort, ileus, tendon rupture, and rib fracture/tibia fracture/fibula fracture/traumatic liver injury/deep vein thrombosis in 1 subject each), and the event reported by 1 subject (renal disorder) was assessed as an adverse drug reaction.

Adverse events leading to study drug discontinuation were reported by 6 subjects (myalgia, benign neoplasm of choroid, weight decreased, dysuria, renal disorder, and multiple injuries/rib fracture/tibia fracture/fibula fracture/traumatic liver injury in 1 subject each), and the events reported by 3 subjects (weight decreased, dysuria, and renal disorder in 1 subject each) were assessed as adverse drug reactions.

A hypoglycemia-related adverse event was reported by 1 of 106 subjects and the event was assessed as an adverse drug reaction.

A urinary tract infection-related adverse event was reported by 1 of 106 subjects (urethritis) and the event was assessed as an adverse drug reaction.

Genital infection-related adverse events were not reported.

Adverse events related to pollakiuria and polyuria were reported by 19 of 106 subjects (pollakiuria in 16 subjects, pollakiuria/polyuria, nocturia, and polyuria in 1 subject each), and all but 1 event in 1 subject (pollakiuria) were assessed as adverse drug reactions.

Regarding 12-lead ECG, a clinically significant abnormality was reported by 1 of 106 subjects (atrial fibrillation) and the abnormality was assessed as an adverse event.

No clinically meaningful changes were observed in vital signs.

4.(iii).A.(3).9) Nateglinide combination therapy study (5.3.5.2-3, Study CL-0111 [January 2011 to October 2012])

An open-label, uncontrolled, long-term treatment study in Japanese patients with type 2 diabetes mellitus who responded inadequately to nateglinide[87] (target sample size, 100 subjects in the ipragliflozin group) was conducted to evaluate the efficacy and safety of concomitant use of ipragliflozin with nateglinide.

Ipragliflozin 50 mg was to be orally administered once daily before breakfast for 52 weeks. In addition, the dose was to be increased from 50 to 100 mg at Week 20 on the basis of HbA1c at the start of the treatment period and Week 16.[73] The regimen of nateglinide was to be maintained from 4 weeks before the start of the run-in period.

A total of 122 treated subjects were included in the safety analysis set. Excluding 2 subjects for whom post-dose efficacy data were not available, 120 subjects were included in the FAS. The FAS was the primary efficacy analysis set. The study was discontinued in 18 subjects (adverse events in 8 subjects, inadequate efficacy in 2 subjects, worsening of diabetes mellitus in 1 subject, consent withdrawal in 2 subjects, protocol deviations in 2 subjects, other reasons in 3 subjects). The number of subjects for whom the dose was increased to 100 mg was 47 subjects.

Regarding efficacy, the change in HbA1c (mean ± SD) from baseline (at the start of the treatment period) to Week 20 (LOCF) in the FAS was -0.78% ± 0.662% (n = 118). The change in HbA1c over time was as shown in Figure 8.

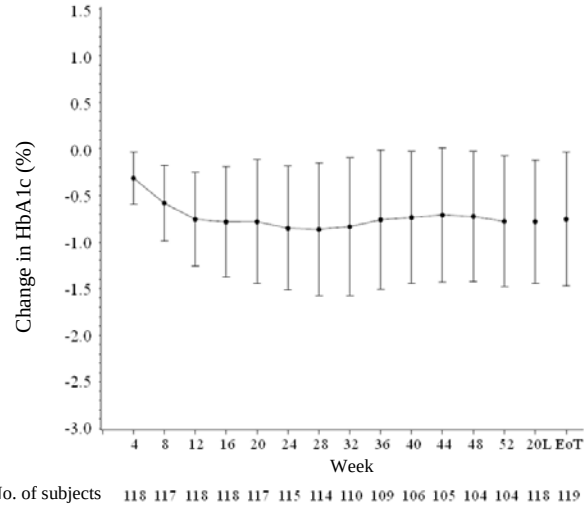

Figure 8. Change in HbA1c (%) over time (FAS) (mean ± SD)
20L, Week 20 (LOCF); EoT, End of treatment period

The proportion of subjects who achieved HbA1c <6.5% at the end of the treatment period was 30.5% (36 of 118 subjects). The changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of the treatment period were -31.1 ± 33.27 mg/dL (n = 120) and -2.41 ±

[87] Major inclusion criteria: Patients aged ≥20; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥6.5% and ≤9.5% at 2 weeks before the start of the study treatment; who have received monotherapy with fixed-dose nateglinide for ≥4 weeks up to screening. (For patients on another oral hypoglycemic therapy, the run-in period was initiated at least 4 weeks after discontinuation of such therapy.)

2.538 kg (n = 120), respectively. Regarding safety, the overall incidence of adverse events was 86.9% (106 of 122 subjects) and that of adverse drug reactions was 28.7% (35 of 122 subjects). Adverse events reported by ≥3 subjects overall were as shown in Table 33. Adverse drug reactions reported by ≥3 subjects overall were thirst (5.7%, 7 of 122 subjects), pollakiuria (5.7%, 7 of 122 subjects), polyuria (2.5%, 3 of 122 subjects), and pruritus genital (2.5%, 3 of 122 subjects).

Table 33. Adverse events reported by ≥3 subjects overall (safety analysis set)

Adverse event	Adverse event (n = 122)
Overall	106 (86.9)
Cataract	4 (3.3)
Constipation	5 (4.1)
Dental caries	4 (3.3)
Diarrhoea	5 (4.1)
Gastritis	3 (2.5)
Reflux oesophagitis	3 (2.5)
Stomatitis	3 (2.5)
Toothache	4 (3.3)
Thirst	8 (6.6)
Bronchitis	9 (7.4)
Gastroenteritis	3 (2.5)
Nasopharyngitis	42 (34.4)
Pharyngitis	3 (2.5)
Contusion	8 (6.6)
Beta 2 microglobulin urine increased	4 (3.3)
Blood triglycerides increased	3 (2.5)
Dyslipidaemia	4 (3.3)
Back pain	8 (6.6)
Myalgia	4 (3.3)
Pain in extremity	4 (3.3)
Musculoskeletal stiffness	3 (2.5)
Dizziness	4 (3.3)
Pollakiuria	9 (7.4)
Polyuria	3 (2.5)
Pruritus genital	3 (2.5)
Rhinitis allergic	3 (2.5)
Eczema	5 (4.1)
Rash	3 (2.5)
Urticaria	4 (3.3)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

No deaths were reported. Serious adverse events were reported by 9 subjects (angina pectoris in 2 subjects [3 events], non-small cell lung cancer, humerus fracture, femoral neck fracture, prostate cancer, gastric cancer, lacunar infarction, and oesophageal carcinoma in 1 subject each), and the event reported by 1 subject (prostate cancer) was assessed as an adverse drug reaction. Adverse events leading to study drug discontinuation were reported by 9 subjects (urticaria in 2 subjects, pruritus genital, non-small cell lung cancer, humerus fracture, femoral neck fracture, prostate cancer, diabetes mellitus, and pollakiuria in 1 subject each), and the events reported by 5 subjects (urticaria in 2 subjects, pollakiuria, pruritus genital, and prostate cancer in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were reported by 5 of 122 subjects, and the events reported by 3 subjects were assessed as adverse drug reactions.

Urinary tract infection-related adverse events were reported by 3 of 122 subjects (cystitis in 2 subjects, cystitis noninfective in 1 subject), and the events reported by 2 subjects (cystitis and cystitis noninfective in 1 subject each) were assessed as adverse drug reactions.

Genital infection-related adverse events were reported by 2 of 122 subjects (tinea cruris and vulvovaginal candidiasis in 1 subject each), and the event reported by 1 subject (vulvovaginal candidiasis) was assessed as an adverse drug reaction.

Adverse events related to pollakiuria and polyuria were reported by 12 of 122 subjects (pollakiuria in 8 subjects, polyuria in 2 subjects, nocturia and pollakiuria/polyuria in 1 subject each), and the events reported by 10 subjects (pollakiuria in 6 subjects, polyuria in 2 subjects, nocturia and pollakiuria/polyuria in 1 subject each) were assessed as adverse drug reactions.

Regarding 12-lead ECG, clinically significant abnormalities were reported by 1 of 122 subjects (right axis deviation/left posterior hemiblock) but the abnormalities were not assessed as adverse events because these had been noted before the start of the study treatment.

Regarding vital signs, although slight decreases in mean systolic and diastolic blood pressures were observed, no apparent changes in the mean pulse rate were observed.

4.(iii).A.(3).10) Study in patients with renal impairment (5.3.5.1-6, Study CL-0072 [January 2011 to November 2012])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese patients with type 2 diabetes mellitus with mild to moderate renal impairment[88] (target sample size, 150; 100 subjects in the ipragliflozin group, 50 subjects in placebo group) was conducted to evaluate the efficacy and safety of ipragliflozin as well as the effect of renal function on them. Subjects were stratified according to severity of renal impairment (mild, moderate).

Following the run-in period (consisting of a 4-week screening period and a 2-week single-blind placebo treatment period), ipragliflozin 50 mg or placebo was to be orally administered once daily before breakfast for 24 weeks for Treatment Period I (double-blind period). For Treatment Period II, ipragliflozin 50 mg was to be orally administered once daily before breakfast for 28 weeks. The dose was to be increased from 50 to 100 mg according to the dose increase criteria.[89] The regimen of oral hypoglycemic agent (α-GI, SU, pioglitazone) was to be maintained from 12 weeks before screening.

For Treatment Period I (double-blind period), a total of 165 treated subjects (46 subjects in the placebo group, 119 subjects in the ipragliflozin group) were included in the safety analysis set. Of the subjects, 164 subjects (46 subjects in the placebo group, 118 subjects in the ipragliflozin group) were included in the FAS, excluding 1 subject for whom post-dose efficacy data were not available. Of 149 subjects who completed Treatment Period I (double-blind period) (42 subjects in the placebo group, 107 subjects in the ipragliflozin group), 143 subjects (41 subjects in the placebo group, 102 subjects in the ipragliflozin group) entered Treatment Period II. For Treatment Period II, 160 subjects who received at least one dose of ipragliflozin during the study period (41 subjects in the placebo/ipragliflozin group, 119 subjects in the ipragliflozin extension group) were included in the safety analysis set. Excluding 1 subject for whom post-dose efficacy data were not available, 159 subjects (41 subjects in the placebo/ipragliflozin group, 118 subjects in the ipragliflozin extension group) were included in the FAS. The FAS was the primary efficacy analysis set for both Treatment Period I (double-blind period) and II. The study was discontinued in 16 subjects during Treatment Period I (double-blind period), including 4 subjects in the placebo group (adverse events in 3 subjects, worsening of the study disease in 1 subject) and 12 subjects

[88] Major inclusion criteria: Patients aged ≥20 and <75 years; with a BMI of ≥20.0 and ≤45.0 kg/m^2 and HbA1c of ≥6.5% and ≤8.5% at 2 weeks before the start of the study treatment; who have received treatment with diet/exercise therapy alone or monotherapy with a fixed-dose oral hypoglycemic agent (α-GI, SU, pioglitazone) for ≥12 weeks up to screening.

[89] Dose increase criteria: Patients with HbA1c of ≥7.0% at the start of the treatment period and ≥7.0% at Week 20, or with HbA1c of <7.0% at the start of the treatment period and ≥6.5% at Week 20, who had no safety concerns in the opinion of the investigator.

in the ipragliflozin group (inclusion criteria deviations/exclusion criteria violations in 1 subject, adverse events in 9 subjects, inadequate efficacy in 1 subject, other reasons in 1 subject). In Treatment Period II, the study was discontinued in 13 subjects (adverse events in 9 subjects, worsening of the study disease in 1 subject, consent withdrawal in 3 subjects). The number of subjects for whom the dose was increased to 100 mg was 26 subjects in the placebo group and 34 subjects in the ipragliflozin group during Treatment Period I (double-blind period).

Regarding efficacy, the change in HbA1c from baseline to the end of Treatment Period I (double-blind period) in the FAS was as shown in Table 34.

Table 34. Change in HbA1c from baseline to the end of Treatment Period I (double-blind period) (at Week 24 or withdrawal) (FAS)

	Treatment group	n	Baseline	End of Treatment Period I (double-blind period)	Change from baseline to the end of Treatment Period I (double-blind period)	Between-group difference [95% CI]
Total	Placebo	46	7.12 ± 0.536	6.95 ± 0.671	-0.17 ± 0.516	-0.25 [-0.414, -0.082][a)]
	Ipragliflozin	118	7.12 ± 0.550	6.70 ± 0.659	-0.42 ± 0.510	
Mild renal impairment	Placebo	23	7.17 ± 0.523	6.92 ± 0.618	-0.26 ± 0.522	-0.35 [-0.545, -0.153][b)]
	Ipragliflozin	60	7.05 ± 0.485	6.49 ± 0.462	-0.56 ± 0.397	
Moderate renal impairment	Placebo	23	7.07 ± 0.554	6.97 ± 0.732	-0.09 ± 0.507	-0.17 [-0.448, 0.099][b)]
	Ipragliflozin	58	7.19 ± 0.605	6.91 ± 0.762	-0.28 ± 0.575	

Unit, %; mean ± SD
Mild renal impairment, 60≤ eGFR <90 mL/min/1.73 m^2; moderate renal impairment, 30≤ eGFR <60 mL/min/1.73 m^2
a) ANCOVA model with baseline HbA1c as a covariate and the treatment group and severity of renal impairment as fixed effects
b) ANCOVA model with of baseline HbA1c as a covariate and the treatment group as a fixed effect

The proportion of subjects who achieved HbA1c <6.5% at the end of Treatment Period I (double-blind period) was 23.9% (11 of 46 subjects) in the placebo group and 41.5% (49 of 118 subjects) in the ipragliflozin group. When summarized by renal function categories, the proportions were 21.7% (5 of 23 subjects) in the placebo group and 56.7% (34 of 60 subjects) in the ipragliflozin group among subjects with mild renal impairment, and 26.1% (6 of 23 subjects) in the placebo group and 25.9% (15 of 58 subjects) in the ipragliflozin group among subjects with moderate renal impairment, respectively.

The changes in fasting plasma glucose and body weight (mean ± SD) from baseline to the end of Treatment Period I (double-blind period) were -4.2 ± 20.17 mg/dL and -0.06 ± 1.470 kg in the placebo group and -12.4 ± 22.66 mg/dL and -1.87 ± 1.584 kg in the ipragliflozin group, respectively. When summarized by renal function categories, the changes were -3.2 ± 21.06 mg/dL and -0.19 ± 1.746 kg in the placebo group and -16.2 ± 20.24 mg/dL and -1.88 ± 1.730 kg in the ipragliflozin group among subjects with mild renal impairment, and -5.2 ± 19.66 mg/dL and 0.07 ± 1.157 kg in the placebo group and -8.6 ± 24.51 mg/dL and -1.85 ± 1.431 kg in the ipragliflozin group among subjects with moderate renal impairment, respectively.

The change in HbA1c (mean ± SD) from baseline to the end of the treatment period was -0.33% ± 0.500% in the placebo/ipragliflozin group (n = 41) and -0.44% ± 0.592% in the ipragliflozin extension group (n = 118). When summarized by renal function categories, the changes were -0.40% ± 0.580% in the placebo/ipragliflozin group (n = 22) and -0.54% ± 0.478% in the ipragliflozin extension group (n = 60) among subjects with mild renal impairment, and -0.25% ± 0.388% in the placebo/ipragliflozin group (n = 19) and -0.33% ± 0.678% in the ipragliflozin extension group (n = 58) among subjects with moderate renal impairment, respectively. The change in HbA1c over time was as shown in Figure 9 and Figure 10.

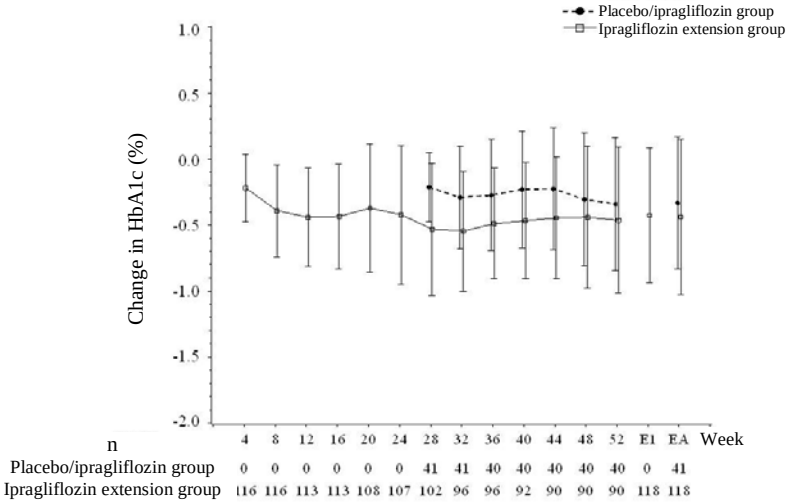

Figure 9. Change in HbA1c (%) over time (FAS) (mean ± SD)
E1, End of Treatment Period I (double-blind period); EA, End of treatment period

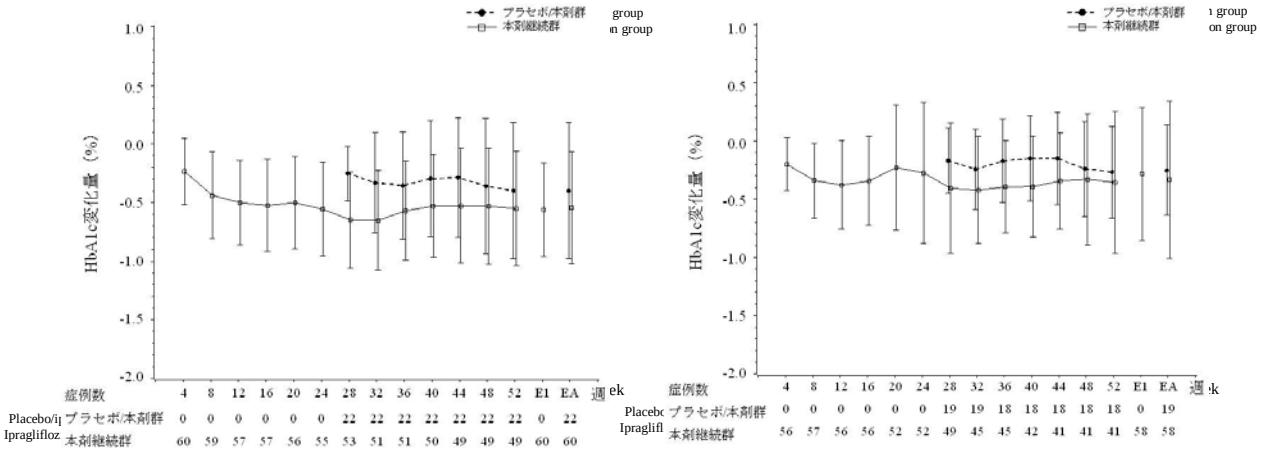

Figure 10. Change in HbA1c (%) over time (FAS) (left, mild renal impairment; right, moderate renal impairment) (mean ± SD)
E1: End of Treatment Period I (double-blind period), EA: End of treatment period

Regarding safety during Treatment Period I (double-blind period), the incidence of adverse events was 73.9% (34 of 46 subjects) in the placebo group and 81.5% (97 of 119 subjects) in the ipragliflozin group, and the incidence of adverse drug reactions was 17.4% (8 of 46 subjects) in the placebo group and 27.7% (33 of 119 subjects) in the ipragliflozin group. Adverse events reported by ≥3 subjects in any group (either in the ipragliflozin or placebo group overall) were as shown in Table 35. Adverse drug reactions reported by ≥3 subjects in any group (either in the ipragliflozin or placebo group overall) were constipation (0 % [0 of 46 subjects] in the placebo group, 5.0% [6 of 119 subjects] in the ipragliflozin group), thirst (2.2% [1 of 46 subjects] in the placebo group, 2.5% [3 of 119 subjects] in the ipragliflozin group), beta 2 microglobulin urine increased (0% [0 of 46 subjects] in the placebo group, 2.5% [3 of 119 subjects] in the ipragliflozin group), weight decreased (0% [0 of 46 subjects] in the placebo group, 3.4% [4 of 119 subjects] in the ipragliflozin group), and pollakiuria (4.3% [2 of 46 subjects] in the placebo group, 8.4% [10 of 119 subjects] in the ipragliflozin group).

Table 35. Adverse events reported by ≥3 subjects in any group (either in the ipragliflozin or placebo group overall) (safety analysis set) (24 weeks)

Adverse event	Total		Mild renal impairment		Moderate renal impairment	
	Placebo (n = 46)	Ipragliflozin (n = 119)	Placebo (n = 23)	Ipragliflozin (n = 61)	Placebo (n = 23)	Ipragliflozin (n = 58)
Overall	34 (73.9)	97 (81.5)	18 (78.3)	49 (80.3)	16 (69.6)	48 (82.8)
Anaemia	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.2)
Abdominal pain upper	0 (0.0)	3 (2.5)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.4)
Constipation	2 (4.3)	9 (7.6)	1 (4.3)	5 (8.2)	1 (4.3)	4 (6.9)
Dental caries	1 (2.2)	3 (2.5)	1 (4.3)	0 (0.0)	0 (0.0)	3 (5.2)
Diarrhoea	0 (0.0)	4 (3.4)	0 (0.0)	3 (4.9)	0 (0.0)	1 (1.7)
Gastritis	1 (2.2)	3 (2.5)	0 (0.0)	1 (1.6)	1 (4.3)	2 (3.4)
Thirst	1 (2.2)	3 (2.5)	1 (4.3)	2 (3.3)	0 (0.0)	1 (1.7)
Gastroenteritis	1 (2.2)	3 (2.5)	0 (0.0)	2 (3.3)	1 (4.3)	1 (1.7)
Nasopharyngitis	16 (34.8)	25 (21.0)	5 (21.7)	13 (21.3)	11 (47.8)	12 (20.7)
Beta 2 microglobulin urine increased	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Weight decreased	1 (2.2)	4 (3.4)	1 (4.3)	2 (3.3)	0 (0.0)	2 (3.4)
Diabetes mellitus	1 (2.2)	4 (3.4)	0 (0.0)	0 (0.0)	1 (4.3)	4 (6.9)
Back pain	4 (8.7)	5 (4.2)	2 (8.7)	3 (4.9)	2 (8.7)	2 (3.4)
Pain in extremity	1 (2.2)	4 (3.4)	0 (0.0)	2 (3.3)	1 (4.3)	2 (3.4)
Dizziness	0 (0.0)	5 (4.2)	0 (0.0)	1 (1.6)	0 (0.0)	4 (6.9)
Headache	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Hypoaesthesia	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Insomnia	3 (6.5)	1 (0.8)	1 (4.3)	0 (0.0)	2 (8.7)	1 (1.7)
Pollakiuria	2 (4.3)	10 (8.4)	2 (8.7)	5 (8.2)	0 (0.0)	5 (8.6)
Dermatitis contact	1 (2.2)	5 (4.2)	1 (4.3)	2 (3.3)	0 (0.0)	3 (5.2)

Number of subjects with events (incidence %), MedDRA/J ver.12.1

No deaths were reported. Serious adverse events were reported by 2 subjects in the placebo group (atrioventricular block complete and appendicitis perforated/peritonitis/postoperative wound infection/abdominal abscess in 1 subject each) and 9 subjects in the ipragliflozin group (hepatic neoplasm malignant, spinal ligament ossification, small intestine carcinoma, thyroid cancer, osteoarthritis/postoperative thrombosis, cerebral infarction, atrial flutter/upper gastrointestinal haemorrhage, haemolytic anaemia/diabetes mellitus,[83] and colonic polyp in 1 subject each), but a causal relationship with the study drug was ruled out except for the events in 1 subject in the placebo group (atrioventricular block complete) and in 2 subjects in the ipragliflozin group (haemolytic anaemia, upper gastrointestinal haemorrhage). Adverse events leading to study drug discontinuation were reported by 4 subjects in the placebo group (atrioventricular block complete, abdominal abscess, malaise, and diabetes mellitus in 1 subject each) and 14 subjects in the ipragliflozin group (pruritus in 2 subjects, gastroenteritis, spinal ligament ossification, blood creatinine increased, small intestine carcinoma, thyroid cancer, osteoarthritis, cerebral infarction, tachycardia, diabetic retinopathy, diabetes mellitus,[84] upper gastrointestinal haemorrhage, and haemolytic anaemia[84] in 1 subject each), the events reported by 2 subjects in the placebo group (atrioventricular block complete and malaise in 1 subject each) and 5 subjects in the ipragliflozin group (pruritus in 2 subjects, gastroenteritis, upper gastrointestinal haemorrhage, and haemolytic anaemia in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were reported by 1 of 119 subjects in the ipragliflozin group and the event was assessed as an adverse drug reaction.

Urinary tract infection-related adverse events were reported by 2 of 46 subjects in the placebo group (asymptomatic bacteriuria and cystitis in 1 subject each) and 1 of 119 subjects in the ipragliflozin group (cystitis), and the events reported by 2 subjects in the placebo group were assessed as adverse drug reactions.

Genital infection-related adverse events were not reported by subjects in the placebo group, but were reported by 1 of 119 subjects in the ipragliflozin group (vulvovaginal candidiasis) and the event was assessed as an adverse drug reaction.

Adverse events related to pollakiuria and polyuria were reported by 2 of 46 subjects in the placebo group (pollakiuria in both subjects) and 10 of 119 subjects in the ipragliflozin group (pollakiuria in 9 subjects, pollakiuria/polyuria in 1 subject) and these events were assessed as adverse drug reactions.

Regarding 12-lead ECG, clinically significant abnormalities were reported by 1 of 46 subjects in the placebo group (ventricular extrasystoles) and 2 of 119 subjects in the ipragliflozin group (negative T wave/limb lead low voltage and atrial fibrillation in 1 subject each).

No clinically meaningful changes were observed in vital signs.

Regarding safety of 52-week treatment, the incidence of adverse events was 68.3% (28 of 41 subjects) in the placebo/ipragliflozin group and 93.3% (111 of 119 subjects) in the ipragliflozin extension group, and the incidence of adverse drug reactions was 19.5% (8 of 41 subjects) in the placebo/ipragliflozin group and 39.5% (47 of 119 subjects) in the ipragliflozin extension group. Adverse events reported by ≥3 subjects in any group (either in the placebo/ipragliflozin group or the ipragliflozin extension group overall) were as shown in Table 36. Adverse drug reactions reported by ≥3 subjects in any group (either in the placebo/ipragliflozin group or the ipragliflozin extension group overall) were anaemia (0.0% [0 of 41 subjects] in the placebo/ipragliflozin group, 2.5% [3 of 119 subjects] in the ipragliflozin extension group), constipation (2.4% [1 of 41 subjects] in the placebo/ipragliflozin group, 7.6% [9 of 119 subjects] in the ipragliflozin extension group), thirst (4.9% [2 of 41 subjects] in the placebo/ipragliflozin group, 3.4% [4 of 119 subjects] in the ipragliflozin extension group), beta 2 microglobulin urine increased (0.0% [0 of 41 subjects] in the placebo/ipragliflozin group, 3.4% [4 of 119 subjects] in the ipragliflozin extension group), weight decreased (0.0% [0 of 41 subjects] in the placebo/ipragliflozin group, 4.2% [5 of 119 subjects] in the ipragliflozin extension group), dizziness (0.0% [0 of 41 subjects] in the placebo/ipragliflozin group, 3.4% [4 of 119 subjects] in the ipragliflozin extension group), tremor (0.0% [0 of 41 subjects] in the placebo/ipragliflozin group, 2.5% [3 of 119 subjects] in the ipragliflozin extension group), and pollakiuria (7.3% [3 of 41 subjects] in the placebo/ipragliflozin group, 9.2% [11 of 119 subjects] in the ipragliflozin extension group).

Table 36. Adverse events reported by ≥3 subjects in any group (either in the placebo/ipragliflozin group or ipragliflozin extension group overall) (safety analysis set) (52 weeks)

Adverse event	Total		Mild renal impairment		Moderate renal impairment	
	Placebo/ ipragliflozin group (n = 41)[a)]	Ipragliflozin extension group (n = 119)	Placebo/ ipragliflozin group (n = 22)[a)]	Ipragliflozin extension group (n = 61)	Placebo/ ipragliflozin group (n = 19)[a)]	Ipragliflozin extension group (n = 58)
Overall	28 (68.3)	111 (93.3)	16 (72.7)	57 (93.4)	12 (63.2)	54 (93.1)
Anaemia	0 (0.0)	5 (4.2)	0 (0.0)	1 (1.6)	0 (0.0)	4 (6.9)
Conjunctivitis	0 (0.0)	3 (2.5)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.4)
Abdominal pain upper	0 (0.0)	4 (3.4)	0 (0.0)	1 (1.6)	0 (0.0)	3 (5.2)
Constipation	1 (2.4)	14 (11.8)	0 (0.0)	7 (11.5)	1 (5.3)	7 (12.1)
Dental caries	0 (0.0)	6 (5.0)	0 (0.0)	1 (1.6)	0 (0.0)	5 (8.6)
Diarrhoea	0 (0.0)	5 (4.2)	0 (0.0)	3 (4.9)	0 (0.0)	2 (3.4)
Dyspepsia	0 (0.0)	3 (2.5)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.4)
Gastritis	1 (2.4)	6 (5.0)	1 (4.5)	2 (3.3)	0 (0.0)	4 (6.9)
Haemorrhoids	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Periodontal disease	0 (0.0)	4 (3.4)	0 (0.0)	2 (3.3)	0 (0.0)	2 (3.4)
Periodontitis	0 (0.0)	4 (3.4)	0 (0.0)	2 (3.3)	0 (0.0)	2 (3.4)
Reflux oesophagitis	0 (0.0)	5 (4.2)	0 (0.0)	1 (1.6)	0 (0.0)	4 (6.9)
Vomiting	1 (2.4)	3 (2.5)	1 (4.5)	2 (3.3)	0 (0.0)	1 (1.7)
Hepatic steatosis	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Thirst	2 (4.9)	6 (5.0)	2 (9.1)	4 (6.6)	0 (0.0)	2 (3.4)
Bronchitis	0 (0.0)	5 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.6)
Gastroenteritis	0 (0.0)	5 (4.2)	0 (0.0)	2 (3.3)	0 (0.0)	3 (5.2)
Influenza	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Nasopharyngitis	16 (39.0)	42 (35.3)	9 (40.9)	24 (39.3)	7 (36.8)	18 (31.0)
Helicobacter infection	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Scratch	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.2)
Contusion	0 (0.0)	5 (4.2)	0 (0.0)	1 (1.6)	0 (0.0)	4 (6.9)
Beta 2 microglobulin urine increased	0 (0.0)	4 (3.4)	0 (0.0)	2 (3.3)	0 (0.0)	2 (3.4)
Weight decreased	0 (0.0)	6 (5.0)	0 (0.0)	2 (3.3)	0 (0.0)	4 (6.9)
Diabetes mellitus	0 (0.0)	5 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.6)
Hyperuricaemia	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.2)
Arthritis	0 (0.0)	3 (2.5)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.4)
Back pain	1 (2.4)	6 (5.0)	0 (0.0)	4 (6.6)	1 (5.3)	2 (3.4)
Pain in extremity	0 (0.0)	4 (3.4)	0 (0.0)	2 (3.3)	0 (0.0)	2 (3.4)
Spinal osteoarthritis	0 (0.0)	3 (2.5)	0 (0.0)	1 (1.6)	0 (0.0)	2 (3.4)
Intervertebral disc protrusion	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Musculoskeletal stiffness	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.2)
Dizziness	1 (2.4)	7 (5.9)	0 (0.0)	2 (3.3)	1 (5.3)	5 (8.6)
Headache	2 (4.9)	4 (3.4)	1 (4.5)	3 (4.9)	1 (5.3)	1 (1.7)
Hypoaesthesia	1 (2.4)	4 (3.4)	1 (4.5)	2 (3.3)	0 (0.0)	2 (3.4)
Tremor	0 (0.0)	4 (3.4)	0 (0.0)	3 (4.9)	0 (0.0)	1 (1.7)
Pollakiuria	3 (7.3)	12 (10.1)	3 (13.6)	6 (9.8)	0 (0.0)	6 (10.3)
Renal impairment	1 (2.4)	3 (2.5)	0 (0.0)	0 (0.0)	1 (5.3)	3 (5.2)
Dermatitis contact	0 (0.0)	6 (5.0)	0 (0.0)	3 (4.9)	0 (0.0)	3 (5.2)
Dry skin	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)
Eczema	1 (2.4)	3 (2.5)	1 (4.5)	1 (1.6)	0 (0.0)	2 (3.4)
Pruritus	0 (0.0)	4 (3.4)	0 (0.0)	2 (3.3)	0 (0.0)	2 (3.4)
Rash	0 (0.0)	4 (3.4)	0 (0.0)	1 (1.6)	0 (0.0)	3 (5.2)
Orthostatic hypotension	0 (0.0)	3 (2.5)	0 (0.0)	2 (3.3)	0 (0.0)	1 (1.7)

Number of subjects with events (incidence %), MedDRA/J ver.12.1
a) Adverse events that occurred after the start of ipragliflozin treatment

One death was reported in the placebo/ipragliflozin group (death[90]) during Treatment Period II and assessed as an adverse drug reaction.[91] Serious adverse events were reported by 2 subjects in the placebo/ipragliflozin group (death and rotator cuff syndrome in 1 subject each) and 11

[90] Described as due to acute heart failure in the post-mortem report
[91] The death was considered by the investigator to be "possibly related" to the study drug, but the applicant has determined the causal relationship between the death and study drug "can be excluded" because the death is highly attributable to patient predispositions such as complications.

subjects in the ipragliflozin extension group (appendicitis perforated, uterine cancer, cerebral infarction, benign prostatic hyperplasia, angina unstable, large intestine carcinoma, cystitis haemorrhagic/inflammation, pneumonia pneumococcal, heat illness, Still's disease adult onset, and cataract in 1 subject each), but a causal relationship with the study drug was ruled out except for the events in 1 subject in the placebo/ipragliflozin group (death) and 3 subjects in the ipragliflozin extension group (uterine cancer, angina unstable, and large intestine carcinoma in 1 subject each). Adverse events leading to study drug discontinuation were reported by 1 subject in the placebo/ipragliflozin group (death) and 7 subjects in the ipragliflozin extension group (oedema/renal impairment, uterine cancer, cerebral infarction, angina unstable, pneumonia pneumococcal, vulvitis, and Still's disease adult onset in 1 subject each), and the events reported by 1 subject in the placebo/ipragliflozin group (death) and 3 subjects in the ipragliflozin extension group (uterine cancer, angina unstable, and vulvitis in 1 subject each) were assessed as adverse drug reactions.

Hypoglycemia-related adverse events were reported by 6 subjects in the ipragliflozin extension group, and all but the event in 1 subject were assessed as adverse drug reactions.

Urinary tract infection-related adverse events were reported by 2 subjects in the ipragliflozin extension group (cystitis and prostatitis in 1 subject each), and the event reported by 1 subject (prostatitis) was assessed as an adverse drug reaction.

Genital infection-related adverse events were reported by 1 subject in the ipragliflozin extension group (vulvitis) and the event was assessed as an adverse drug reaction.

Adverse events related to pollakiuria and polyuria were reported by 3 subjects in the placebo/ipragliflozin group (pollakiuria in all these subjects) and 3 subjects in the ipragliflozin extension group (pollakiuria in 2 subjects, nocturia in 1 subject), and all but the event in 1 subject in the ipragliflozin extension group (pollakiuria) were assessed as adverse drug reactions.

Regarding 12-lead ECG, clinically significant abnormalities were reported by 1 subject in the ipragliflozin extension group (complete left bundle branch block/ventricular extrasystoles/atrial fibrillation) and these events were assessed as adverse drug reactions.

No clinically meaningful changes were observed in vital signs.

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

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

The applicant explained as follows:

Ipragliflozin is a selective SGLT2 inhibitor, which serves as an oral hypoglycemic agent with a novel mechanism of action that involves a decrease in blood glucose resulting from the excretion of glucose into urine mediated by inhibition of glucose reabsorption via SGLT2 located on the proximal renal tubules. The risk of hypoglycemia posed by ipragliflozin is considered to be low because the decrease in blood glucose is not dependent on the action of insulin. In addition, the once-daily dosage regimen of ipragliflozin is expected to provide good medication compliance. Furthermore, ipragliflozin is expected to reduce body weight because of release of glucose out of the body, while SU and thiazolidinedion drugs have been known to increase body weight: SU drug-induced insulin secretion results in anabolic effects of increased insulin, and thiazolidinedion drugs promote adipocyte differentiation through stimulation of peroxisome proliferator-activated receptor γ. Based on the above characteristics, ipragliflozin is expected to be a new treatment option for type 2 diabetes mellitus.

PMDA considers that ipragliflozin can be a new treatment option for type 2 diabetes mellitus based on the efficacy and safety of ipragliflozin monotherapy and combination therapies

demonstrated in clinical studies [see "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety"].

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

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

PMDA considers as follows:

In the Japanese phase III monotherapy study (Study CL-0105), the primary endpoint was the change in HbA1c from baseline (at the start of the treatment period) to the end of the treatment period (at Week 16 or withdrawal). The difference in the change in HbA1c between the ipragliflozin 50 mg and placebo groups [95% CI] was -1.23 [-1.515, -0.938], demonstrating superiority of ipragliflozin 50 mg group over the placebo group (Table 18). The proportion of subjects who achieved HbA1c of <6.5% at the end of the treatment period (1.5% in the placebo group, 12.9% in the ipragliflozin 50 mg group) and the change in fasting plasma glucose (6.3 ± 30.05 mg/dL in the placebo group, -40.2 ± 33.34 mg/dL in the ipragliflozin 50 mg group) were also higher in the ipragliflozin 50 mg group than in the placebo group. In addition, the effect of baseline HbA1c on the efficacy was investigated. The difference in the change in HbA1c from baseline (at the start of the treatment period) to the end of the treatment period (at Week 16 or withdrawal) between the ipragliflozin 50 mg and placebo groups [95% CI] was -1.04 [-1.346, -0.736] in the subgroups of subjects with baseline HbA1c of <8.0% and -1.45 [-2.052, -0.850] in the subgroups of subjects with baseline HbA1c of of ≥8.0%, showing efficacy in both subgroups. Furthermore, although an inconsistent inclusion criterion on HbA1c (6.5%-9.5%) used in the Japanese long-term monotherapy studies (Studies CL-0121 and CL-0122) with that used in the Study CL-0105 (7.0%-10.0%) may have influenced the change in HbA1c, the long-term studies suggested the persistence of effectiveness until Week 24 (Study CL-0122) and Week 52 (Study CL-0121). Based on the above findings, the efficacy of ipragliflozin monotherapy has been demonstrated.

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

The applicant explained as follows:

In the ipragliflozin/metformin combination therapy study (Study CL-0106), ipragliflozin/pioglitazone combination therapy study (Study CL-0107), and ipragliflozin/SU combination therapy study (Study CL-0109), each of which included a 24-week double-blind (placebo controlled) period, the primary endpoint was the change in HbA1c from baseline (at the start of the treatment period) to the end of Treatment Period I (double-blind period). The differences in the changes in HbA1c between the ipragliflozin and placebo groups (95% CI) in Studies CL-0106, CL-0107, and CL-0109 were -1.29 [-1.497, -1.092], -0.87 [-1.100, -0.646], and -1.14 [-1.340, -0.932], respectively, demonstrating superiority of the ipragliflozin group over the placebo group (Table 22, Table 25, Table 28). In addition, the differences in the changes in HbA1c according to baseline HbA1c levels from baseline (at the start of the treatment period) to the end of Treatment Period I (at Week 24 or withdrawal) between the ipragliflozin 50 mg and placebo groups (95% CI) in Studies CL-0106, CL-0107, and CL-0109 were -1.21 [-1.450, -0.974], -0.74 [-0.948, -0.528], and -0.91 [-1.157, -0.655], respectively, in the subgroups of subjects with baseline HbA1c of <8.0%, and -1.41 [-1.755, -1.067], -1.06 [-1.537, -0.584], and -1.41 [-1.733, -1.086], respectively, in the subgroups of subjects with baseline HbA1c of ≥8.0%, showing efficacy in both subgroups. Furthermore, the change in efficacy endpoints from baseline to the end of the treatment period (52-week) by type of combination therapy was as shown in Table 37, demonstrating the persistence of effectiveness.

Table 37. Change in efficacy endpoints from baseline to the end of the treatment period (52-week) by type of combination therapy (FAS)

Endpoint	Ipragliflozin + metformin[a)] (Study CL-0106)	Ipragliflozin + pioglitazone[a)] (Study CL-0107)	Ipragliflozin + SU[a)] (Study CL-0109)	Ipragliflozin + α-GI (Study CL-0108)	Ipragliflozin + DPP-4 inhibitor (Study CL-0110)	Ipragliflozin + nateglinide (Study CL-0111)
Change in HbA1c (%)	-0.95 ± 0.671 (n = 112)	-0.74 ± 0.688 (n = 97)	-0.84 ± 0.712 (n = 165)	-0.82 ± 0.712 (n = 109)	-0.81 ± 0.617 (n = 105)	-0.75 ± 0.720 (n = 118)
Change in fasting plasma glucose (mg/dL)	-30.0 ± 26.82 (n = 112)	-35.4 ± 33.47 (n = 97)	-37.7 ± 30.35 (n = 165)	-35.7 ± 29.95 (n = 109)	-34.1 ± 27.55 (n = 106)	-31.1 ± 33.27 (n = 120)
Proportion of subjects who achieved HbA1c <6.5% (%) (No. of subjects who achieved HbA1c <6.5% /evaluated subjects)	19.6 (22/112)	15.5 (15/97)	14.5 (24/165)	42.2 (46/109)	43.8 (46/105)	30.5 (36/118)

Mean ± SD
a) Ipragliflozin extension group

PMDA considers that the efficacy of these combination therapies has been demonstrated by the results of the 6 clinical studies despite the variation in the change in HbA1c among these combination therapies.

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

As a result of reviewing the incidence of adverse events and adverse drug reactions in each of the pooled analyses (Table 38) and by type of therapy (Table 39), PMDA considers that no major safety concerns associated with ipragliflozin have been observed.

Table 38. Incidence of adverse events and adverse drug reactions in each of the pooled analyses[a)] (safety analysis set)

	Pooled data from comparative studies		Pooled data from 52-week studies	Pooled data from phase II/III studies
	Placebo group (n = 368)	Ipragliflozin 50 mg group (n = 628)	Ipragliflozin 50 mg group[b)] (n = 1017)	All ipragliflozin groups[c)] (n = 1624)
Adverse events	250 (67.9) [3961.9]	458 (72.9) [3840.6]	876 (86.1) [3414.0]	1277 (78.6) [3480.8]
Adverse drug reactions	62 (16.8) [560.3]	159 (25.3) [935.3]	386 (38.0) [734.0]	537 (33.1) [771.2]
Serious adverse events	13 (3.5) [113.4]	16 (2.5) [73.6]	73 (7.2) [94.9]	82 (5.0) [84.4]
Adverse events leading to study drug discontinuation	42 (11.4) [306.8]	29 (4.6) [121.5]	87 (8.6) [114.3]	105 (6.5) [112.3]

Number of subjects with events (incidence %) [Incidence rate (events per1000 patient-years)]
a) For specific studies included in each of the pooled analyses, see footnotes 27, 32, and 63.
b) Including subjects for whom the dose was increased to 100 mg/day
c) Subjects who received 12.5 to 100 mg of ipragliflozin

Table 39. Incidence of adverse events and adverse drug reactions by type of therapy[a)] (safety analysis set) (52 weeks)

	Ipragliflozin alone (Study CL-0121) (n = 182)	Ipragliflozin + metformin (Study CL-0106) (n = 112)	Ipragliflozin + pioglitazone (Study CL-0107) (n = 97)	Ipragliflozin + SU (Study CL-0109) (n = 166)	Ipragliflozin + α-GI (Study CL-0108) (n = 113)	Ipragliflozin + DPP-4 inhibitor (Study CL-0110) (n = 106)	Ipragliflozin + nateglinide (Study CL-0111) (n = 122)
Adverse events	164 (90.1)	97 (86.6)	79 (81.4)	144 (86.7)	87 (77.0)	88 (83.0)	106 (86.9)
Adverse drug reactions	90 (49.5)	48 (42.9)	30 (30.9)	52 (31.3)	38 (33.6)	46 (43.4)	35 (28.7)
Serious adverse events	8 (4.4)	5 (4.5)	3 (3.1)	12 (7.2)	12 (10.6)	5 (4.7)	9 (7.4)
Adverse events leading to study drug discontinuation	18 (9.9)	4 (3.6)	3 (3.1)	16 (9.6)	10 (8.8)	6 (5.7)	9 (7.4)

Number of subjects with events (incidence %)
a) Including subjects for whom the dose was increased to 100 mg/day.

PMDA's view on the impact of dose or type of concomitant oral hypoglycemic agents on safety is as follows:
During Treatment Period I (24-week double-blind period) of the ipragliflozin/metformin combination therapy study (Study CL-0106), the incidence of adverse events was 71.4% (35 of 49 subjects), in the concomitant use with metformin 500 mg/day, 71.0% (44 of 62 subjects) in the concomitant use with metformin 750 mg/day, and 100% (1 of 1 subject) in the concomitant use with metformin >750 mg/day, showing no dose-dependent differences. The same tendency was seen until Week 52. During Treatment Period I (double-blind period) of the ipragliflozin/pioglitazone combination therapy study (Study CL-0107), the incidence of adverse events was 70.2% (33 of 47 subjects) in the concomitant use with pioglitazone <30 mg/day and 74.0% (37 of 50 subjects) in the concomitant use with pioglitazone ≥30 mg/day, showing no dose-dependent differences. The incidence of adverse events through Week 52 in the ipragliflozin 50 + 50 mg and 50 + 100 mg groups was 100% (14 of 14 subjects) and 87.5% (14 of 16 subjects), respectively, in the concomitant use with pioglitazone <30 mg/day, and 81.8% (18 of 22 subjects) and 82.4% (14 of 17 subjects), respectively, in the concomitant use with pioglitazone ≥30 mg/day, showing no tendency toward an increase in the incidence of adverse events with increasing dose of pioglitazone. During Treatment Period I (double-blind period) of the ipragliflozin/SU combination therapy study (Study CL-0109), the incidence of adverse events by type of SU was 53.8% (7 of 13 subjects) in the concomitant use with glibenclamide, 73.7% (14 of 19 subjects) in the concomitant use with gliclazide, and 78.4% (105 of 134 subjects) in the concomitant use with glimepiride. The incidence of adverse events through Week 52 in the ipragliflozin 50 + 50 mg and 50 + 100 mg groups was 0.0% (0 of 1 subject) and 63.6% (7 of 11 subjects), respectively, in the concomitant use with glibenclamide, 81.8% (9 of 11 subjects) and 100% (4 of 4 subjects), respectively, in the concomitant use with gliclazide, and 91.1% (41 of 45 subjects) and 89.3% (50 of 56 subjects), respectively, in the concomitant use with glimepiride. As for open-label 52-week studies, the incidence of adverse events by type of α-GI in the ipragliflozin/α-GI combination therapy study (Study CL-0108) was 66.7% (10 of 15 subjects) in the concomitant use with acarbose, 90.0% (36 of 40 subjects) in the concomitant use with voglibose, and 70.7% (41 of 58 subjects) in the concomitant use with miglitol. The incidence of adverse events by type of DPP-4 inhibitor in the ipragliflozin/DPP-4 inhibitor combination therapy study (Study CL-0110) was 85.2% (75 of 88 subjects) in the concomitant use with sitagliptin phosphate hydrate, 72.7% (8 of 11 subjects) in the concomitant use with alogliptin benzoate, and 71.4% (5 of 7 subjects) in the concomitant use with vildagliptin. Among SU, α-GI, and DPP-4 inhibitor, variation in the incidence of adverse events was observed depending on the types of drugs, but evaluation capacity is limited due to the bias in the number of subjects.

Based on the above, the safety of ipragliflozin is acceptable in view of the incidences of adverse events and adverse drug reactions reported by the subjects receiving ipragliflozin alone or with concomitant drugs, given that appropriate cautions are provided. Also, no specific problems have been observed regarding the effects of dose level or type of concomitant oral hypoglycemic agents on the safety, but it is necessary to continue to collect the safety information via post-marketing surveillance in light of the limited experience of combination use of ipragliflozin with high-dose metformin of >750 mg/day and some of the concomitant oral hypoglycemic agents with limited investigation on the effect on safety. PMDA conducted a further review with regard to the following events of special interest for safety evaluation.

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

The applicant explained as follows:
The incidence and incidence rate of hypoglycemia-related adverse events in the pooled data from comparative studies[27] were similar between the placebo and the ipragliflozin 50 mg groups, which were found to be 0.8% (3 of 368 subjects) and 26.7 events per 1000 patient-years in the placebo

group, respectively, and 1.0% (6 of 628 subjects) and 25.8 events per 1000 patient-years in the ipragliflozin 50 mg group, respectively. These were found to be 2.4% (24 of 1017 subjects) and 33.7 events per 1000 patient-years in the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled data from 52-week studies,[32] and 1.9% (31 of 1624 subjects) and 32.8 events per 1000 patient-years in all ipragliflozin dose groups in the pooled phase II/III studies[63] (subjects who received 12.5-100 mg of ipragliflozin), respectively. All but 3 moderate events were mild in severity, with no severe events reported. The hypoglycemia-related adverse event leading to treatment discontinuation was reported by only 1 subject (while receiving 50 mg; mild) in the ipragliflozin/SU combination therapy study (Study CL-0109). The incidence of hypoglycemia-related adverse events by study was as shown in Table 40, showing no trend toward increased risk of hypoglycemia as compared with placebo even in combination with SU that is considered to have an increased risk of hypoglycemia. No characteristic trend in the time of onset of hypoglycemia-related adverse events was noted in the pooled data from 52-week studies (Table 41).

Table 40. Incidence of hypoglycemia-related adverse events by study (safety analysis set)

Study (No.)	16- or 24-week[a)]		52-week
	Placebo group	Ipragliflozin 50 mg group	Ipragliflozin 50 mg group[b)]
Monotherapy			
Japanese phase III monotherapy study (Study CL-0105)	0/67 (0.0)	1/62 (1.6)	—
Japanese long-term monotherapy study (Study CL-0121)	—	—	3/182 (1.6)
Japanese long-term monotherapy study (Study CL-0122)	—	3/174 (1.7)	—
Combination therapy			
Ipragliflozin + metformin (Study CL-0106)	0/56 (0.0)	0/112 (0.0)	0/112 (0.0)
Ipragliflozin + pioglitazone (Study CL-0107)	0/54 (0.0)	1/97 (1.0)	1/97 (1.0)
Ipragliflozin + SU (Study CL-0109)	1/76 (1.3)	2/166 (1.2)	7/166 (4.2)
Ipragliflozin + α-GI (Study CL-0108)	—	—	0/113 (0.0)
Ipragliflozin + DPP-4 inhibitor (Study CL-0110)	—	—	1/106 (0.9)
Ipragliflozin + nateglinide (Study CL-0111)	—	—	5/122 (4.1)

Number of subjects with events/evaluated subjects (incidence %)

a) Only Study CL-0105 was conducted as 16-week study.

b) Including subjects for whom the dose was increased to 100 mg/day

Table 41. Incidence of hypoglycemia-related adverse events by time of onset (safety analysis set) (pooled data from 52-week studies[a)])

Adverse event	Time of onset (Day)[b)]					Total (n = 1017)
	1-84 (n = 1017)	85-168 (n = 990)	169-252 (n = 951)	253-336 (n = 847)	≥337 (n = 811)	
Hypoglycemia-related adverse events	10 (1.0)	3 (0.3)	9 (0.9)	3 (0.4)	2 (0.2)	24 (2.4)
Vision blurred	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Feeling abnormal	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)
Hunger	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.3)
Malaise	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Hypoglycaemia	3 (0.3)	2 (0.2)	3 (0.3)	1 (0.1)	1 (0.1)	10 (1.0)
Hypoglycaemia unawareness	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dizziness	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.3)
Tremor	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.3)
Cold sweat	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.3)

Number of subjects with events (incidence %), MedDRA/J ver.15.0

a) The ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day)

b) Day 1 was defined as the first day the study drug was prescribed.

Based on the above, the ipragliflozin monotherapy and combination therapies are unlikely to cause major hypoglycemia.

PMDA accepted the applicant's explanation, but considers that the applicant should provide information on the observed trend toward increased incidence of hypoglycemia-related adverse events in the subjects receiving ipragliflozin in combination with SU or nateglinide compared with ipragliflozin alone. In addition, it is necessary to continue to collect information on hypoglycemia via post-marketing surveillance because hypoglycemia has been considered to affect the patient's prognosis.

4.(iii).B.(3).2) Adverse events related to urinary tract and genital infections

The applicant explained as follows:

In the pooled data from comparative studies, the incidence of urinary tract infection-related adverse events was 2.7% (10 of 368 subjects) in the placebo group and 1.8% (11 of 628 subjects) in the ipragliflozin 50 mg group; the incidence was lower in the ipragliflozin group than in the placebo group. The incidence among female subjects, which was found to be 7.6% (9 of 118 subjects) in the placebo group and 4.1% (8 of 197 subjects) in the ipragliflozin 50 mg group, was higher than that among male subjects, which was found to be 0.4% (1 of 250 subjects) in the placebo group and 0.7% (3 of 431 subjects) in the ipragliflozin 50 mg group, but there was no trend toward higher incidence in the ipragliflozin group compared with the placebo group. In the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled data from 52-week studies and in all ipragliflozin dose groups (subjects who received 12.5-100 mg of ipragliflozin) in the pooled data from phase II/III studies, the total incidence of urinary tract infection-related adverse events among men and women was 3.2% (33 of 1017 subjects) and 2.6% (43 of 1624 subjects), respectively, although the treatment duration was different from that of the pooled data from comparative studies. Severe pyelonephritis was reported by 2 subjects, but resolved after treatment discontinuation. Other events were mild in severity.

In the pooled data from comparative studies, the incidence of genital infection-related adverse events was 0.8% (3 of 368 subjects) in the placebo group and 2.1% (13 of 628 subjects) in the ipragliflozin 50 mg group; the incidence was higher in the ipragliflozin group than in the placebo group. The incidence among female subjects, which was found to be 1.7% (2 of 118 subjects) in the placebo group and 5.1% (10 of 197 subjects) in the ipragliflozin 50 mg group, was higher than that among male subjects, which was found to be 0.4% (1 of 250 subjects) in the placebo group and 0.7% (3 of 431 subjects) in the ipragliflozin 50 mg group. In the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled data from 52-week studies and in all ipragliflozin groups (subjects who received 12.5-100 mg of ipragliflozin) in the pooled data from phase II/III studies, the total incidence of genital infection-related adverse events among males and females was 2.5% (25 of 1017 subjects) and 2.5% (41 of 1624 subjects), respectively, although the treatment duration was different from that of the pooled data from comparative studies. All events were mild in severity.

Thus, neither apparent difference in the incidence of urinary tract infection-related adverse events between the placebo and the ipragliflozin groups nor an increasing trend in the incidence with increasing treatment duration was noted. On the other hand, the incidence of genital infections was higher in the ipragliflozin group than in the placebo group, especially among females, but all events were mild in severity. Therefore, ipragliflozin is unlikely to cause clinically significant genital infections.

PMDA asked the applicant to explain the potential for aggravation of urinary tract or genital infection.

The applicant responded as follows:

Urinary tract infection was reported by 43 subjects in the ipragliflozin group in the Japanese phase II/III studies. Of the events, those reported by 41 subjects were non-serious and those reported by

40 subjects did not aggravate despite continued treatment (treatment was discontinued for the remaining 1 subject). However, serious pyelonephritis was reported by 2 subjects, including 1 subject in whom a lower urinary tract infection developed into an upper urinary tract infection.[92] Contribution of ipragliflozin to the events occurring in these 2 subjects is unknown, but it is advisable to check whether or not the patient has urinary tract infection during treatment with ipragliflozin for the purpose of preventing progress in severity of urinary tract infection and if so, to avoid treatment with ipragliflozin until completion of treatment of upper urinary tract infection given the potential for proliferation of the causative organisms resulting from the mechanism of action of ipragliflozin. Therefore, relevant cautions will be provided. As for genital infection, for the importance of actions against progress in severity would be low because no subjects have experienced progress in severity in the clinical study and because development to a systemic infection is not expected even though ipragliflozin increases the occurnace of genital infection.

PMDA considers that cautions need to be provided regarding both urinary tract and genital infections because appropriate actions should be taken not only against urinary tract infections but also against genital infections. In addition, it is necessary to continue to collect information on urinary tract and genital infections via post-marketing surveillance.

4.(iii).B.(3).3) Adverse events related to pollakiuria and polyuria (including dysuria, anuria, oliguria, urinary retention)

The applicant explained as follows:

In the pooled data from comparative studies, the incidence of adverse events related to pollakiuria and polyuria was 2.4% (9 of 368 subjects) in the placebo group and 8.4% (53 of 628 subjects) in the ipragliflozin 50 mg group; the incidence was higher in the ipragliflozin group than in the placebo group. In the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled 52-week studies and in all ipragliflozin dose groups (subjects who received 12.5-100 mg of ipragliflozin) in the pooled phase II/III studies, the incidence was 13.5% (137 of 1017 subjects) and 11.1% (180 of 1624 subjects), respectively. Most events were mild in severity, with no severe events reported. The pooled data from comparative studies were used to evaluate the safety in patients with or without any concurrent lower urinary tract diseases, including benign prostatic hyperplasia, neurogenic bladder, hypertonic bladder, and bladder neck sclerosis, because an increase in urine volume induced by those diseases may affect the safety. As a result, the incidence of adverse events related to pollakiuria and polyuria was found to be 9.1% (1 of 11 subjects) in the placebo group and 25.0% (6 of 24 subjects) in the ipragliflozin 50 mg group among subjects with the complications, and 2.2% (8 of 357 subjects) in the placebo group and 7.8% (47 of 604 subjects) in the ipragliflozin 50 mg group among subjects without the complications; the incidences were high in the ipragliflozin groups irrespective of the presence of the complications.

As described above, although adverse events related to pollakiuria and polyuria were frequently reported by subjects receiving ipragliflozin, most events were mild in severity. Therefore, ipragliflozin is unlikely to cause clinically significant adverse events related to pollakiuria and polyuria.

PMDA asked the applicant to explain whether ipragliflozin may be used in patients with dysuria, urinary retention, anuria, and oliguria.

The applicant responded as follows:

[92] The subject experienced bacteriuria on Day 218 and cystitis on Day 271, but continued to receive ipragliflozin while being monitored for both events. Subsequently, medication was administered against pyelonephritis that occurred on Day 278, and treatment with ipragliflozin was discontinued. The pyelonephritis was reversed on Day 299.

Specific cautions do not need to be provided regarding dysuria for the following reasons: no marked increase in urine volume induced by treatment with ipragliflozin has been reported and no specific cautions are provided in the package inserts of diuretic drugs; for infections such as cystitis resulting from dysuria, no increase in the incidence of adverse events related to ipragliflozin has been noted. As for untreated urinary retention, however, ipragliflozin may worsen the condition and the efficacy of ipragliflozin is significantly diminished in patients with anuria or oliguria. Cautions will be provided to consider treatment with other drugs in patients with urinary retention, anuria, or oliguria.

PMDA considers as follows:
The risks associated with pollakiuria and polyuria are acceptable, given that appropriate cautions are provided. However, there was a tendency for adverse events related to pollakiuria and polyuria to occur at the earlier stage of treatment (up to Day 14). In addition, myocardial infarction was reported on Day 6 by 1 subject (50 mg group) in the study on circadian variation of blood glucose (Study CL-0070). The investigator considered that the event may have been potentially related to the change in body fluid volume associated with an increase in urine volume. Thus, it should be cautioned that the patient's condition must be closely monitored before and after the start of the treatment in order to check the occurrence of pollakiuria and polyuria. The applicant's proposed actions to provide cautions against urinary retention, anuria, and oliguria are appropriate. In addition, it is necessary to continue to collect information on adverse events related to pollakiuria and polyuria via post-marketing surveillance.

4.(iii).B.(3).4) Impact on body weight (body fluid volume) and electrolytes
The applicant explained as follows:
In the Japanese phase II dose-finding study (Study CL-0103, 12-week), the change in body weight (mean ± SD) from baseline to the end of the treatment period was -0.35 ± 1.488 kg in the placebo group, -1.44 ± 1.311 kg in the ipragliflozin 12.5 mg group, -1.72 ± 1.774 kg in the ipragliflozin 25 mg group, -1.81 ± 1.508 kg in the ipragliflozin 50 mg group, and -2.11 ± 1.733 kg in the ipragliflozin 100 mg group. Similarly, in Japanese phase III monotherapy study (Study CL-0105, 16-week), a decrease in body weight was greater in the ipragliflozin 50 mg group than in the placebo group, as the change in body weight was found to be -2.31 ± 1.743 kg in the ipragliflozin 50 mg group and -1.03 ± 1.961 kg in the placebo group. Also in the ipragliflozin/metformin combination therapy study (Study CL-0106), ipragliflozin/pioglitazone combination therapy study (Study CL-0107), and ipragliflozin/SU combination therapy study (Study CL-0109), the decrease in body weight was greater in the ipragliflozin 50 mg group than in the placebo group at the end of Treatment Period I (24-week double-blind period).

Ipragliflozin releases the excess blood glucose out of the body by inhibiting glucose reabsorption at the proximal renal tubules. The promotion of urinary glucose excretion by ipragliflozin may result in an increase in urine osmolarity and an increase in urine volume through osmotic diuresis, thereby leading to a decrease in body fluid volume. In Studies CL-0103 and CL-0105, although there was a tendency for some parameters (haematocrit, blood urea nitrogen [BUN], red blood cell count, hemoglobin) to increase during treatment with ipragliflozin, these values tended to return to baseline after the end of study treatment. These parameters are expected to increase with decreasing body fluid volume. The systolic blood pressure tended to decrease during treatment with ipragliflozin, but tended to return to baseline after the end of study treatment. The changes in parameter values over time as shown above suggested a decrease in body fluid volume. However, the fact that about half of the body weight loss during treatment with ipragliflozin returned during the follow-up period suggested that factors other than a decrease in body fluid volume may be involved in the weight loss. In addition, the results of an exploratory measurement of blood ketone body fractions in the study on circadian variation of blood glucose (Study CL-0070) showed an apparent post-dose increase in the values of each fraction in the ipragliflozin groups, suggesting the possibility of enhancement of fatty acid metabolism. Therefore, an

increase in fat utilization due to enhancement of fatty acid metabolism was inferred to have partly contributed to the weight loss [see "4.(iii).B.(3).5) Adverse events related to urine ketone body"].

Furthermore, an increasing trend in hematocrit, BUN, serum Mg, serum P, urinary Ca, urinary Mg, and urinary P started at Week 2 and the trend continued during the rest of the treatement period in the pooled data from comparative studies. However, these changes were minor and tended to resolve during the follow-up period after the end of treatment with ipragliflozin. Adverse events related to decrease in body fluid volume[93] more frequently occurred in the ipragliflozin group than in the placebo group; the incidences of the events were found to be 1.6% (6 of 368 subjects) in the placebo group and 4.6% (29 of 628 subjects) in the ipragliflozin 50 mg group. In the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled data from 52-week studies and in all ipragliflozin dose groups (subjects who received 12.5-100 mg of ipragliflozin) in the pooled data from phase II/III studies, the incidences of adverse events related to decrease in body fluid volume were 7.6% (77 of 1017 subjects) and 6.3% (103 of 1624 subjects), respectively, although the treatment duration was different from that of the pooled data from comparative studies. All but 1 moderate event were mild in severity, with no severe events reported. The frequency by time of onset was highest between Day 1 and Day 84 (Table 42).

Table 42. Incidence of adverse events related to decrease in body fluid volume by time of onset (safety analysis set) (pooled 52-week studies[a])

Adverse event	Time of onset (Day)[b]					Total (n = 1017)
	1-84 (n = 1017)	85-168 (n = 990)	169-252 (n = 951)	253-336 (n = 847)	≥337 (n = 811)	
Adverse events related to decrease in body fluid volume	58 (5.7)	7 (0.7)	11 (1.2)	5 (0.6)	2 (0.2)	77 (7.6)
Thirst	54 (5.3)	4 (0.4)	9 (0.9)	1 (0.1)	0 (0.0)	66 (6.5)
Blood pressure decreased	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)
Blood urea increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine output decreased	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)
Dehydration	3 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	4 (0.4)
Presyncope	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)
Syncope	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)
Orthostatic hypotension	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)	5 (0.5)

Number of subjects with events (incidence %), MedDRA/J ver.15.0

a) The ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day)

b) Day 1 was defined as the first day the study drug was prescribed.

A subgroup analysis of parameters potentially affected by the decreased body fluid volume was conducted according to baseline HbA1c (<8.0% or ≥8.0%). The results showed no apparent effects of baseline HbA1c on decrease in body fluid volume.

PMDA asked the applicant to explain whether the age or the use of a concomitant diuretic drug has an impact on the incidence of adverse events related to decrease in body fluid volume.

The applicant responded as follows:

The impacts on body fluid volume[94] and on electrolytes[95] were evaluated according to age (≥65 or <65) and the use of a concomitant diuretic drug (loop diuretics, thiazide diuretics, thiazide-like diuretics, or potassium-sparing diuretics) using the pooled data from comparative studies. As for the impact on body fluid volume, the subgroup analysis of pooled data from comparative studies showed increases in haematocrit and BUN and decreases in systolic and diastolic blood pressures

[93] Thirst, blood pressure decreased, blood urea increased, urine output decreased, dehydration, presyncope, syncope, hypotension, and orthostatic hypotension (blood urea increased and hypotension were not reported in the 52-week studies)

[94] Adverse events related to hematocrit, BUN, variation in systolic/diastolic blood pressures, and decrease in body fluid volume

[95] Change in serum electrolytes (Na, K, Cl, Ca, Mg, P) and urine electrolytes (Na, K, Cl, Ca, Mg, P) over time

in the ipragliflozin 50 mg group compared with the placebo group in any subgroups, but no apparent effects of age or the use of a concomitant diuretic drug were noted. In addition, the incidence of adverse events related to decrease in body fluid volume was not affected by age or the use of a concomitant diuretic drug. Similar results were obtained for the impact on electrolytes. Based on the above, the applicant considers that there is a little need to provide cautions about the impact of ipragliflozin on body fluid volume and electrolytes. However, since there was a tendency for mild fluid loss due to osmotic diuretic action of ipragliflozin to occur, precautionary statements will be included in the package insert in order to prevent dehydration, diabetic ketoacidosis, and hyperglycemic hyperosmolar coma in patients with potential risk of fluid loss. Similar precautionary statements will be included in the "Use in the Elderly" section.

PMDA considers as follows:
The applicant's explanation is acceptable, but there is concern that ipragliflozin may aggravate dehydration by increasing urine volume in patients with inadequate glycemic control who met exclusion criteria for clinical studies and that dehydration risk may be increased depending on the age, concomitant drugs (including diuretics), and the external environment such as seasons. Therefore, appropriate cautions including those proposed by the applicant should be provided and it is necessary to continue to collect information on effects on body weight (body fluid volume) and electrolytes via post-marketing surveillance. The above issues will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(3).5) Adverse events related to urine ketone body

The applicant explained as follows:
In the pooled data from comparative studies, the proportion of patients who converted to urine ketone body-positive (≥ ±) after administration of ipragliflozin peaked at 2 weeks post-dose in all dose groups, but no apparent dose-dependent increase in the incidence was observed. Similar changes over time were observed also in the pooled data from 52-week studies, with the values returning to near baseline levels during the follow-up period after the end of treatment with ipragliflozin. Since patients who are positive for urine ketone body are generally considered to have inadequately-controlled diabetes mellitus, the relationships of the levels of ketone bodies with fasting plasma glucose, free fatty acids, and body weight were investigated in 10 subjects who had been tested 4+ for urine ketone body after administration of ipragliflozin in the pooled data from phase II/III studies. As a result, fasting plasma glucose values when subjects were tested 4+ for urine ketone body were <130 mg/dL[96] except for 1 time point in 1 subject. Free fatty acid levels were above baseline in 8 subjects, and body weight values at the corresponding time point were lower than the preceding values by ≥1.5 kg in 7 subjects.

The change in total serum ketone body levels over time noted in the study on circadian variation of blood glucose (Study CL-0070) was as shown in Table 43; the levels increased in the ipragliflozin group but were lower than "≥3000 μmol/L," which is a laboratory finding of ketoacidosis.

[96] As the target value for prevention of complications, the Japan Diabetes Society defines blood glucose level that corresponds to HbA1c <7% as <130 mg/dL ("Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013" edited by Japan Diabetes Society).

Table 43. Change in total serum ketone body levels over time observed in the study on circadian variation of blood glucose (Study CL-0070) (safety analysis set)

Time point	Placebo group (n = 10)	Ipragliflozin 50 mg group (n = 10)	Ipragliflozin 100 mg group (n = 10)
Day 1	110.92 ± 140.696	78.16 ± 52.898	98.81 ± 75.087
Day 15	125.26 ± 170.368	268.77 ± 174.564[a)]	365.11 ± 264.306[a)]
Last evaluation	125.26 ± 170.368	268.77 ± 174.564[a)]	347.60 ± 255.269
Follow-up	80.79 ± 68.425[a)]	51.16 ± 26.533	44.71 ± 16.537

Unit, μmol/L; mean ± SD

a) n = 9 (excluding 1 subject for whom treatment was discontinued)

The above results suggested that the positive urine ketone body test result found after administration of ipragliflozin was not associated with inadequate glycemic control, and that enhancement of fatty acid metabolism as a compensation for the partial energy release out of the body due to the urinary glucose excretion promoting activity of ipragliflozin can lead to an increase in urine ketone bodies. However, the degree of the increase was not considered to be clinically significant. The package insert will includes the following precautionary statements that a positive urine ketone body test result may be found and that an increase in ketone bodies associated with treatment with ipragliflozin should be comprehensively determined in patients based on the status of the patient's diabetes mellitus separately from an increase in ketone bodies resulting from an inadequate insulin action, and that appropriate measures should be taken in patients with poorly controlled diabetes mellitus.

PMDA accepted the applicant's explanation, but there is a concern that ipragliflozin may decrease body fluid volume and induce acute diabetic complications associated with an increase in ketone bodies in patients with type 2 diabetes mellitus with decreased insulin secretion. It is necessary to continue to collect information on adverse events related to urine ketone body via post-marketing surveillance.

4.(iii).B.(3).6) Impact on bone metabolism

The applicant explained as follows:

In the phase III studies excluding the Japanese long-term monotherapy study (Study CL-0122), the impact on bone metabolism was evaluated using 6 major markers of bone metabolism (serum bone alkaline phosphatase, serum type I collagen cross-linked C-telopeptide, tartrate-resistant acid phosphatase, urinary type I collagen cross-linked N-telopeptide, 25-hydroxyvitamin D, intact parathyroid hormone). As a result, no apparent effects on bone metabolism were observed, although variations in some blood and urine markers in postmenopausal women were observed in the pooled data from comparative studies. Similar variations were observed in the pooled data from 52-week studies. The results obtained from men and premenopausal women were also similar to those from postmenopausal women.

The incidence of fractures as adverse events in the pooled data from comparative studies was similar between the ipragliflozin and placebo groups; the incidences were 0.8% (3 of 368 subjects) in the placebo group and 0.5% (3 of 628 subjects) in the ipragliflozin 50 mg group. The incidences of fractures in the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled data from 52-week studies and in all ipragliflozin dose groups (subjects who received 12.5-100 mg of ipragliflozin) in the pooled data from phase II/III studies were 1.6% (16 of 1017 subjects) and 1.4% (23 of 1624 subjects), respectively, although the treatment duration was different from that of the pooled data from comparative studies. Thus, no apparent effects on bone metabolism were observed.

PMDA accepted the applicant's explanation, but since the number of subjects and treatment duration in the clinical studies were limited, it is necessary to continue to collect information on the impact on bone metabolism via post-marketing surveillance.

4.(iii).B.(3).7) Cardiovascular risks

The applicant explained as follows:

The review results using definition of cardiovascular events based on term extraction using Standardized MedDRA Queries (SMQ) "Central nervous system haemorrhages and cerebrovascular conditions" and "Myocardial infarction" (broad search) showed that the incidence of cardiovascular events in the pooled data from comparative studies was lower in the ipragliflozin 50 mg group; the incidences were 2.7% (10 of 368 subjects) in the placebo group and 1.1% (7 of 628 subjects) in the ipragliflozin 50 mg group. The hazard ratio of the ipragliflozin 50 mg group to the placebo group [95% CI] for a cardiovascular event was 0.41 [0.150, 1.101]. The incidence rate was 66.7 per 1000 patient-years in the placebo group and 29.5 per 1000 patient-years in the ipragliflozin 50 mg group.

The incidence of cardiovascular events in the pooled data from 52-week studies was 2.3% (23 of 1017 subjects). The incidence of cardiovascular events was 0.3% at the start of treatment and shifted to 0.4%, 0.8%, and 0.7% in this order with a 12-week interval. The incidence rate was 26.5 per 1000 patient-years. In all ipragliflozin dose groups (subjects who received 12.5-100 mg of ipragliflozin) in the pooled data from phase II/III studies, the incidence of cardiovascular events was 1.5% (25 of 1624 subjects) and the incidence rate was 22.9 per 1000 person-years. Among these, 5 subjects (0.3%) resulted in treatment discontinuation. All but 6 moderate and 2 severe events were mild in severity. Thus, there was no apparent increasing trend in the incidence of cardiovascular events.

Table 44. Incidence of cardiovascular events (safety analysis set)

	Pooled data from comparative studies		Pooled data from 52-week studies	Pooled data from phase II/III studies
	Placebo group (n = 368)	Ipragliflozin 50 mg group (n = 628)	Ipragliflozin 50 mg group[a)] (n = 1017)	All ipragliflozin groups[b)] (n = 1624)
Adverse events	10 (2.7)	7 (1.1)	23 (2.3)	25 (1.5)
Adverse drug reactions	3 (0.8)	0	3 (0.3)	4 (0.2)
Estimated hazard ratio [95% CI] for a cardiovascular event as compared with the placebo group	—	0.41 [0.150, 1.101]	—	—
No. of adverse events	10	8	26	28
No. of adverse drug reactions	3	0	3	4
Adverse events leading to study drug discontinuation	2 (0.5)	1 (0.2)	4 (0.4)	5 (0.3)
Adverse drug reactions leading to study drug discontinuation	2 (0.5)	0 (0.0)	1 (0.1)	2 (0.1)
Adverse events by severity				
Mild	8 (2.2)	6 (1.0)	16 (1.6)	17 (1.0)
Moderate	0 (0.0)	1 (0.2)	5 (0.5)	6 (0.4)
Severe	2 (0.5)	0 (0.0)	2 (0.2)	2 (0.1)

Number of subjects with events (incidence %)

a) Including subjects for whom the dose was increased to 100 mg/day

b) Subjects who received 12.5 to 100 mg of ipragliflozin

In addition, the impact on putative risk predictors for cardiovascular diseases including hypoglycemia, body weight gain, blood pressure, lipid metabolism parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride), and ECG findings was evaluated. As a result,

the incidence of hypoglycemia-related adverse events in the pooled data from comparative studies was similar between the ipragliflozin 50 mg and placebo groups [see "4.(iii).B.(3).1) Hypoglycemia"], and no severe hypoglycemia was reported. Body weight loss from baseline ranged from 1.44 to 2.33 kg in the ipragliflozin groups in each of the comparative studies; it was greater than that in the placebo group. The mean change in blood pressures from baseline to the end of the treatment period in the pooled data from comparative studies was -0.7 mmHg in the placebo group and -4.1 mmHg in the ipragliflozin 50 mg group for systolic blood pressures, and -0.4 mmHg in the placebo group and -2.6 mmHg in the ipragliflozin 50 mg group for diastolic blood pressures, showing a greater decreasing trend in the ipragliflozin 50 mg group. As for lipid metabolism parameters, total and LDL cholesterols were unchanged while an increasing treand in HDL cholesterol and a decreasing trend in triglycerides were noted in the ipragliflozin 50 mg group in the pooled data from comparative studies, but neither of these changes was great enough to increase the risk. As for ECG findings, there was no apparent increasing trend in abnormal findings after administration of ipragliflozin and, in addition, no effects of ipragliflozin on the QTc interval were observed in the thorough QT/QTc study in healthy adult subjects (Study CL-0058). Also in the pooled data from 52-week studies, no changes were observed that were great enough to increase the risk of cardiovascular diseases.

Thus, no changes were observed that were great enough to increase the risk of cardiovascular diseases after administration of ipragliflozin.

PMDA accepted the applicant's explanation. However, it is suggested that ipragliflozin may decrease body fluid volume [see "4.(iii).B.(3).4) Impact on body weight (body fluid volume) and electrolytes"] and the number of subjects and treatment duration in the clinical studies were limited. Thus, it is necessary to continue to collect information on cardiovascular risks via post-marketing surveillance.

4.(iii).B.(3).8) Malignant tumours

The applicant explained as follows:

The incidence of malignant tumours in the pooled data from comparative studies was similar among all groups; it was found to be 0.3% (1 of 368 subjects) in the placebo group, 0.5% (3 of 628 subjects) in the ipragliflozin 50 mg group, and 0.4% (3 of 848 subjects) in all ipragliflozin dose groups. The hazard ratio [95% CI] of the ipragliflozin 50 mg group to the placebo group for a malignant tumour was 1.60 [0.165, 15.414], and that of all ipragliflozin dose groups to the placebo group was 1.27 [0.132, 12.236]. The incidence of adverse events classified into the System Organ Class "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" was lower in the ipragliflozin 50 mg group (0.6%, 4 of 628 subjects) and all ipragliflozin dose groups (0.5%, 4 of 848 subjects) than in the placebo group (1.1%, 4 of 368 subjects). The incidence of malignant tumours in the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled data from 52-week studies was 1.5% (15 of 1017 subjects), and there was no apparent increasing trend in the incidence with increasing treatment duration. The hazard ratio [95% CI] of the ipragliflozin 50 mg group to the placebo group for a malignant tumour was 2.11 [0.261, 17.140]. The incidence in all ipragliflozin groups (subjects who received 12.5-100 mg of ipragliflozin) in the pooled data from phase II/III studies was 0.9% (15 of 1624 subjects) (Table 45), and the hazard ratio [95% CI] of the ipragliflozin 50 mg group to the placebo group for a malignant tumour was 1.45 [0.180, 11.702]. In the pooled data from phase II/III studies, malignant tumours were observed in 10 organs including the liver (3 subjects), prostate (3 subjects), stomach (2 subjects), and large intestine (2 subjects), but no characteristic trend in the time of onset of malignant tumours was observed for each organ. In addition, no abnormalities exceeding the screening criteria (>3-fold the upper limit of normal) were observed in urinary metanephrine and normetanephrine values measured in some of the clinical studies.

Table 45. Incidence of malignant tumours (safety analysis set)

	Pooled data from comparative studies			Pooled data from 52-week studies	Pooled data from phase II/III studies
	Placebo group (n = 368)	Ipragliflozin 50 mg group (n = 628)	All ipragliflozin groups[b)] (n = 848)	Ipragliflozin 50 mg group[c)] (n = 1017)	All ipragliflozin groups[b)] (n = 1624)
Adverse events[a)]	1 (0.3) 1 [6.7]	3 (0.5) 3 [11.1]	3 (0.4) 3 [9.1]	15 (1.5) 17 [15.3]	15 (0.9) 17 [12.3]
Adverse drug reactions[a)]	0 (0.0) 0 [0.0]	0 (0.0) 0 [0.0]	0 (0.0) 0 [0.0]	3 (0.3) 3 [3.1]	3 (0.2) 3 [2.5]
Adverse events leading to study drug discontinuation	1 (0.3)	2 (0.3)	2 (0.2)	9 (0.9)	9 (0.6)
Adverse drug reactions leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (0.1)

Number of cases (incidence %)

a) Upper column: Number of cases (incidence %), lower column: Number of events [/1000 patient-years]

b) Subjects who received 12.5 to 100 mg of ipragliflozin

c) Including subjects for whom the dose was increased to 100 mg/day.

Furthermore, an analysis of epidemiological data[97] showed no apparent increase in the incidence of malignant tumours due to ipragliflozin (ratio of the observed to the expected number of cases [95% CI]; 0.602 [0.0152, 3.3558] for the placebo group, 1.087 [0.6083, 1.7927] in all ipragliflozin dose groups). Based on the above, the relationship between ipragliflozin and development of malignant tumours is unlikely to exist.

PMDA accepted the applicant's explanation, but the number of subjects and treatment duration in the clinical studies were limited. Thus, it is necessary to continue to collect information on malignant tumours via post-marketing surveillance.

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

PMDA considers as follows:

"The Guideline for Clinical Evaluation of Oral Hypoglycemic Agents" (PFSB/ELD Notification No. 0709-1 dated July 9, 2010) (the OAD guideline) states that when a study drug is confirmed to be useful in, e.g., clinical studies of two-drug concomitant therapies with the study drug and the approved oral hypoglycemic agents (concomitant therapies expected to be administered to patients in clinical practice) conducted based on the OAD guideline, the appropriate description of the indication is "type 2 diabetes mellitus." The appropriate description of the indication for ipragliflozin is "type 2 diabetes mellitus" because, for this application, the efficacy of monotherapy and combination therapies has been demonstrated in clinical studies conducted in accordance with the OAD guideline [see "4.(iii).B.(2) Efficacy"], and because their safety is considered acceptable [see "4.(iii).B.(3) Safety"].

4.(iii).B.(5) Dosage and administration

4.(iii).B.(5).1) Dosage regimen

The applicant explained as follows:

[97] Based on the incidence of malignant tumours in Japanese population by sex and age (Matsuda T et al., *Jpn J Clin Oncol.* 2012;42:139-47), the expected number of patients with malignant tumours among the Japanese population with the same sex and age composition as that of participants in the phase II/III studies was calculated by treatment group. Based on the reported hazard ratio (1.21-1.3) for the incidence of malignant tumours in Japanese patients with diabetes compared with Japanese population without diabetes (Inoue M et al., *Arch Intern Med.* 2006;166:1871-7), the expected number of patients with malignant tumours in the Japanese phase II/III studies was assumed to be 1.2-fold the calculated expected number of those patients. The ratio of the observed number of patients with malignant tumours to the calculated expected number of patients with malignant tumours in the Japanese phase II/III studies was calculated by treatment group.

The results of a phase I study (Study CL-0101) showed that the half-life of plasma concentrations of unchanged ipragliflozin after multiple oral doses of ipragliflozin after breakfast is approximately 11 to 15 hours, and confirmed the urinary glucose excretion promoting activity up to 24 hours post-dose. In addition, the study on circadian variation of blood glucose (Study CL-0070) showed that the blood glucose lowering effects persists for 24 hours by once-daily administration for 14 days. Furthermore, the efficacy of ipragliflozin administered once daily before breakfast was demonstrated in the Japanese phase II dose-finding study (Study CL-0103) and in the subsequent Japanese phase III monotherapy study (Study CL-0105). The evaluation of the efficacy of ipragliflozin administered before versus after breakfast in the Japanese long-term monotherapy study (Study CL-0121) showed that change in HbA1c from pre-dose to post-dose did not differ between the timing of dose (Week 20 [LOCF]; -0.58% ± 0.686% [n = 94] for administration before breakfast, -0.49% ± 0.650% [n = 87] for administration after breakfast). Based on the above, once daily oral administration is considered to be appropriate as the regimen of ipragliflozin.

PMDA considers that there is no problem with once-daily oral administration of ipragliflozin, but in light of the following facts, the necessity of specifying the timing of dose will be finalized, taking account of comments to be raised in the Expert Discussion: (i) whether efficacy following administration after a midday or evening meal achieves the same degree of efficacy following administration before or after a morning meal remains unclear from the mechanism of action and pharmacokinetics of ipragliflozin; (ii) attention should be paid in terms of safety, etc. because the effects of ipragliflozin administered after the evening meal peak during sleep hours.

4.(iii).B.(5).2) Dose

The applicant explained as follows:

In the Japanese phase II dose-finding study (Study CL-0103), the between-group differences (adjusted mean) relative to placebo in the change in HbA1c from baseline to the end of the treatment period were -0.60% in the 12.5 mg group, -0.95% in the 25 mg group, -1.27% in the 50 mg group, and -1.29% in the 100 mg group; the results were similar between the 50 and 100 mg groups (Table 16). In addition, no major safety problems were observed in any of ipragliflozin dose groups. In the Japanese phase III monotherapy study (Study CL-0105), the difference (adjusted mean) between the ipragliflozin 50 mg and placebo groups in the change in HbA1c from baseline to the end of the treatment period was -1.23%, showing superiority of the ipragliflozin 50 mg group over the placebo group (Table 18), and no major safety problems were observed in the ipragliflozin 50 mg group. Based on the above, 50 mg/day is considered to be appropriate as the recommended dose of ipragliflozin.

As for the efficacy of ipragliflozin at the increased dose, a dose increase to 100 mg/day in subjects who had not responded adequately to the 50 mg/day dose was considered useful, given that the proportion of patients who achieved HbA1c <7.0% or <6.5% at the end of the treatment period was higher in the 100 mg group than in the 50 mg group in Study CL-0103 (the proportion of patients who achieved HbA1c <7.0% in the 100mg group and the 50 mg group was 54.2% and 46.5%, respectively, and the proportion of patients who achieved HbA1c <6.5% was 19.4% and 14.1%, respectively). The change in HbA1c over time and the change in HbA1c from baseline and that from the time of dose increase decision (Week 20) in subjects with or without dose increase in the Japanese long-term monotherapy study (Study CL-0121) were as shown in Table 46. In addition, the proportion of subjects in whom HbA1c decreased by ≥0.3% and ≥0.5% at 12 weeks after the dose increase from the levels before the dose increase was 42.9% (27 of 63 subjects) and 20.6% (13 of 63 subjects), respectively; thus, a dose increase to 100 mg/day in subjects who had not responded adequately to the 50 mg/day was considered useful. The usefulness of the dose increase to 100 mg/day was demonstrated also in other studies of the combination therapies.

Table 46. Change in HbA1c over time, and the change in HbA1c from baseline and that from the time of dose increase decision (Week 20) in subjects with or without dose increase (FAS)

	50/50 mg group				50/100 mg group			
	n	HbA1c	Change from baseline	Change from Week 20 (LOCF)	n	HbA1c	Change from baseline	Change from Week 20 (LOCF)
Baseline	98	7.31 ± 0.692	—	—	70	7.82 ± 0.847	—	—
Week 20 of treatment period	98	6.58 ± 0.421	-0.73 ± 0.577	—	70	7.49 ± 0.639	-0.33 ± 0.723	—
Week 52 of treatment period	91	6.62 ± 0.472	-0.66 ± 0.601	0.06 ± 0.312	53	7.21 ± 0.471	-0.53 ± 0.695	-0.12 ± 0.452
Week 20 (LOCF)	98	6.58 ± 0.421	-0.73 ± 0.577	—	70	7.49 ± 0.639	-0.33 ± 0.723	—
End of treatment period	98	6.67 ± 0.581	-0.64 ± 0.657	0.08 ± 0.386	70	7.42 ± 0.829	-0.40 ± 0.977	-0.07 ± 0.547

Mean ± SD (%); -, Not applicable

As for the safety of ipragliflozin at the increased dose, the 50/100 mg group included 375 subjects and the median treatment duration after the dose increase was 204.0 days in the pooled data from 52-week studies. The incidences (by time of onset, i.e., before and after the dose increase decision) of adverse events, serious adverse events, adverse events leading to study drug discontinuation, adverse events by organ system or syndrome, and adverse events of special interest including hypoglycemia-related adverse events were similar between the 50/50 mg and 50/100 mg groups (Table 47).

Table 47. Incidence rates of adverse events before and after the dose increase (safety analysis set)

	50/50 mg group (n = 503)		50/100 mg group (n = 375)	
	Before dose increase	After dose increase	Before dose increase	After dose increase
Any event	3631.7 (333)	2892.4 (380)	3895.0 (278)	3181.7 (265)
Serious adverse events	38.1 (7)	86.2 (26)	44.3 (6)	95.2 (16)
Adverse events leading to study drug discontinuation	9.5 (2)	55.4 (16)	44.3 (7)	77.9 (13)
Constipation	71.5 (14)	36.9 (12)	107.7 (17)	82.2 (17)
Thirst	147.7 (30)	15.4 (5)	133.0 (20)	21.6 (5)
Beta 2 microglobulin urine increased	28.6 (6)	27.7 (9)	38.0 (5)	17.3 (4)
Pollakiuria	266.9 (56)	6.2 (2)	291.3 (45)	34.6 (8)
Eczema	33.4 (7)	36.9 (12)	44.3 (7)	21.6 (5)
Adverse events by organ system or syndrome				
Hypoglycemia-related adverse events	33.4 (6)	21.5 (6)	19.0 (3)	51.9 (6)
Urinary tract infection-related adverse events	14.3 (3)	58.5 (14)	31.7 (5)	26.0 (6)
Genital infection-related adverse events	38.1 (7)	15.4 (5)	44.3 (7)	43.3 (7)
Adverse events related to pollakiuria or polyuria	338.4 (64)	12.3 (4)	329.3 (45)	47.6 (11)
Adverse events related to decrease in body fluid volume	157.3 (32)	46.2 (13)	145.7 (20)	26.0 (5)
Cardiovascular events	14.3 (2)	18.5 (6)	19.0 (3)	43.3 (9)
Adverse events related to renal disorder	4.8 (1)	18.5 (6)	0.0 (0)	13.0 (3)
Fracture	9.5 (2)	33.8 (9)	0.0 (0)	26.0 (4)
Malignant tumours	0.0 (0)	18.5 (6)	6.3 (1)	13.0 (3)

Number of events per 1000 patient-years (number of subjects with event), MedDRA/J ver.15.0

The applicant considers that it is necessary to make a careful decision on the necessity of dose increase focusing on safety because 8 subjects needed dose reduction to 50 mg/day after the dose increase to 100 mg/day with no specific correlation with subjects' baseline characteristics.

PMDA considers as follows:
There is no problem with the usual dose of 50 mg/day of ipragliflozin. There are no major problems in permitting a dose increase to 100 mg/day in patients with inadequate response to the 50 mg/day dose since the change in HbA1c was improved by ≥0.3% at 12 weeks after the dose increase from the levels before the dose increase in a substantial number of subjects, but this issue will be finalized, taking account of comments to be raised in the Expert Discussion. The appropriateness of dose in patients with hepatic impairment will be reviewed in "4.(iii).B.(6).2) Patients with hepatic impairment."

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

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

The applicant explained the relationship between renal impairment and efficacy as follows:
In the Japanese PK/PD study in patients with renal impairment (Study CL-0073), urinary glucose excretion after a single oral dose of 50 mg of ipragliflozin was evaluated in patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2), patients with mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2), and patients with moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2). As a result, the mean changes in urinary glucose excretion from baseline to 24 hours post-dose were reported to be approximately 71 g in patients with normal renal function, 61 g in patients with mild renal impairment, and 38 g in patients with moderate renal impairment, showing the value was the smallest in patients with moderate renal impairment. In the study in patients with renal impairment (Study CL-0072), the changes in HbA1c (mean ± SD) from baseline to the end of Treatment Period I (24-week double-blind period) were -0.26% ± 0.522% in the placebo group and -0.56% ± 0.397% in the ipragliflozin 50 mg group for patients with mild renal impairment and -0.09% ± 0.507% in the placebo group and -0.28% ± 0.575% in the ipragliflozin 50 mg group for patients with moderate renal impairment. In addition, an evaluation by severity of renal impairment in the pooled comparative studies[27] showed that the between-group difference (adjusted mean) relative to placebo in the change in HbA1c from baseline to the end of Treatment Period I (double-blind period) was -0.98% in the groups of subjects with mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2) and -0.37% in the groups of subjects with moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2), demonstrating a greater decrease in the ipragliflozin group.

PMDA asked the applicant to explain the effect of difference in severity of renal impairment on efficacy categorizing baseline eGFR (mL/min/1.73 m^2) into the following 4 groups: ≥90, ≥60 and <90, ≥45 and <60, and ≥30 and <45.

The applicant responded as follows:
The evaluation results of primary efficacy endpoints by severity of renal impairment were as shown in Table 48. In the groups of subjects with baseline eGFR of ≥90, ≥60 and <90, and ≥45 and <60, the proportion of patients who achieved HbA1c <7.0% or <6.5% at the end of Treatment Period I (double-blind period) increased in the ipragliflozin group, and the increments were greater than those in the placebo group. For the group of subjects with baseline eGFR of ≥30 and <45, although the evaluation was limited due to the small number of subjects in the placebo group (3 subjects), ipragliflozin is expected to be effective in some patients.

Table 48. Evaluation results of primary efficacy endpoints by severity of renal impairment (pooled comparative studies) (FAS)

	eGFR (mL/min/1.73 m^2)								
	≥90		≥60 and <90		≥45 and <60		≥30 and <45[a)]		<30[a)]
	Placebo group (n = 146)	Ipragliflozin 50 mg group (n = 206)	Placebo group (n = 190)	Ipragliflozin 50 mg group (n = 347)	Placebo group (n = 28)	Ipragliflozin 50 mg group (n = 56)	Placebo group (n = 3)	Ipragliflozin 50 mg group (n = 16)	Ipragliflozin 50 mg group (n = 1)
HbA1c (%)									
Baseline	8.06 ± 0.752	8.01 ± 0.740	7.75 ± 0.691	7.72 ± 0.726	7.37 ± 0.681	7.33 ± 0.644	6.97 ± 0.723	7.23 ± 0.756	7.80
End of Treatment Period I (double-blind period)	8.44 ± 1.089	7.11 ± 0.789	8.06 ± 1.207	7.02 ± 0.666	7.50 ± 1.137	7.00 ± 0.931	6.60 ± 0.520	6.99 ± 0.815	7.50
Change in HbA1c from baseline to the end of Treatment Period I (double-blind period)	0.38 ± 0.817	-0.89 ± 0.693	0.31 ± 0.939	-0.70 ± 0.571	0.13 ± 0.827	-0.33 ± 0.730	-0.37 ± 0.208	-0.24 ± 0.633	-0.30
Adjusted mean difference relative to the placebo group [95% CI][b)]	-1.29 [-1.445, -1.131]		-0.98 [-1.108, -0.855]		-0.44 [-0.799, -0.088]		0.20 [-0.582, 0.981]		
Fasting plasma glucose (mg/dL)									
Baseline	181.8 ± 35.11	176.0 ± 35.17	169.5 ± 34.04	166.1 ± 34.00	149.2 ± 27.16	154.9 ± 33.64	128.3 ± 47.92	139.6 ± 21.06	172.0
End of Treatment Period I (double-blind period)	188.5 ± 38.02	137.5 ± 25.22	172.2 ± 41.99	137.3 ± 22.96	156.1 ± 43.32	134.7 ± 29.00	115.0 ± 35.68	141.7 ± 28.17	125.0
Change in fasting plasma glucose from baseline to the end of Treatment Period I (double-blind period)	7.4 ± 32.49	-38.5 ± 31.15	2.8 ± 29.98	-28.8 ± 29.93	7.0 ± 27.72	-20.2 ± 27.18	-13.3 ± 12.90	2.1 ± 32.86	-47.0
Subjects with HbA1c <7.0%									
No. of subjects at baseline (%)	2 (1.4)	8 (3.9)	17 (8.9)	41 (11.8)	8 (28.6)	19 (33.9)	2 (66.7)	6 (37.5)	0 (0.0)
No. of subjects at the end of Treatment Period I (double-blind period) (%)	5 (3.4)	94 (45.6)	32 (16.8)	172 (49.6)	10 (35.7)	36 (65.5)	2 (66.7)	10 (62.5)	0 (0.0)
Subjects with HbA1c <6.5%									
No. of subjects at baseline (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	0 (0.0)	1 (1.8)	0 (0.0)	2 (12.5)	0 (0.0)
No. of subjects at the end of Treatment Period I (double-blind period) (%)	1 (0.7)	32 (15.5)	10 (5.3)	70 (20.2)	4 (14.3)	13 (23.6)	2 (66.7)	4 (25.0)	0 (0.0)

Mean ± SD

a) One subject in the ipragliflozin 50 mg group, who was allocated to the group of subjects with moderate renal impairment in Study CL-0072, which used eGFR at the start of the placebo run-in period to allocate subjects into groups of mild or moderate renal impairment, was classified as eGFR of <30 in this pooled analysis, which used eGFR at the start of ipragliflozin for severity classification. No subject in the placebo group was classified as such.

b) ANCOVA model with baseline HbA1c as a covariate and treatment and study as fixed effects

Since the decrease in urinary glucose excretion noted in patients with type 2 diabetes mellitus with renal impairment was inferred to be mainly due to a decrease in GFR, ipragliflozin was expected to exert glucose lowering effects in patients with high baseline HbA1c, who are estimated to have high eGFR, even with moderate renal impairment. On the other hand, in patients with renal impairment including those with severe impairment, although a dose reduction of ipragliflozin is not necessary from the standpoint of safety and pharmacokinetics, there is a tendency for urinary glucose excretion to decrease with decreasing severity of renal impairment, and diminishment of hypoglycemic activity has also been observed. Therefore, a precautionary statement that administration to patients with severe renal impairment is not recommend will be included in the package insert.

In addition, the applicant explained safety in patients with renal impairment as follows:
In the Japanese phase II dose-finding study (Study CL-0103), the mean changes in eGFR from baseline to the end of the treatment period were 3.02 mL/min/1.73 m^2 in the placebo group, 2.80 mL/min/1.73 m^2 in the 12.5 mg group, 1.66 mL/min/1.73 m^2 in the 25 mg group, 0.37 mL/min/1.73 m^2 in the 50 mg group, and -1.66 mL/min/1.73 m^2 in the 100 mg group, indicating a slight decreasing trend in the high-dose groups. In the Japanese phase III monotherapy study (Study CL-0105), the changes were 2.11 mL/min/1.73 m^2 in the placebo group and -1.22 mL/min/1.73 m^2 in the 50 mg groups, indicating a slight decrease in the 50 mg group. However, the impact of ipragliflozin on GFR was considered to be limited because the observed decreases were small, were not amplified with increasing treatment duration, and tended to resolve during the follow-up period. On the other hand, the exposure (AUC_{inf}) in patients with moderate renal impairment in Study CL-0073 was approximately 1.21-fold that in patients with normal renal function. Although no studies on exposure to ipragliflozin in Japanese patients with severe renal impairment have been conducted, exposure to ipragliflozin in foreign patients with severe renal impairment was higher (about 1.47-fold) than that in patients with normal renal function. The increased exposure in Japanese patients with renal impairment is not considered to significantly affect the safety in light of the following facts: (i) tolerability of multiple doses of ipragliflozin at 600 mg/day for 7 or 10 days has been established in healthy adult subjects (foreign phase I study [Study CL-0002], thorough QT/QTc study [Study CL-0058]); (ii) no clinically relevant safety concerns have been identified after a dose increase from 50 to 100 mg/day in the studies.

As for the impact of ipragliflozin on renal function, although the mean eGFR at Week 2 slightly decreased from baseline in the ipragliflozin 50 mg group across the subgroups of subjects with baseline eGFR of ≥90, ≥60 and <90, and ≥30 and <60 in the pooled data from comparative studies, the change was transient, and no apparent difference in the change in eGFR from baseline to the end of Treatment Period I (double-blind period) was found between the placebo and the ipragliflozin 50 mg groups, irrespective of the severity of renal impairment. In addition, since no apparent impact of ipragliflozin on the change in eGFR from baseline to the end of the treatment period was noted irrespective of the severity of renal impairment in the pooled 52-week studies, the change in mean eGFR over time does not suggest an irreversible effect of ipragliflozin on renal function even in patients with moderate renal impairment.

As for adverse events, the incidence of adverse events at the end of Treatment Period I (double-blind period) in the pooled data from comparative studies was highest in subjects with baseline eGFR of ≥45 and <60 in the ipragliflozin 50 mg group; it was found to be 85.7% (Table 49). The incidences of serious adverse events and adverse events leading to study drug discontinuation in the ipragliflozin 50 mg group were mostly no higher than those in the placebo group although there was an increasing trend in the incidences with decreasing baseline eGFR. However, no apparent effects of baseline eGFR on the incidences of adverse events, serious adverse events, and adverse events leading to study drug discontinuation were noted in the placebo group. Among the commonly reported adverse events in the ipragliflozin 50 mg group, the incidence of "beta 2 microglobulin urine increased" tended to increase with decreasing baseline eGFR. As for laboratory parameters related to impairment of renal function, the renal tubules, or the glomerulus, the mean changes in urinary beta 2 microglobulin and urinary alpha 1 microglobulin from baseline to the end of the treatment period were greater in the group of subjects with baseline eGFR of ≥30 and <45.

The incidence of adverse events in the ipragliflozin 50 mg group (including subjects for whom the dose was increased to 100 mg/day) in the pooled data from 52-week studies (Table 50) was higher among subjects with baseline eGFR of ≥45 and <60 (95.2%) and ≥30 and <45 (94.1%) than among subjects with baseline eGFR of ≥90 (86.3%) and ≥60 and <90 (84.8%). The

incidences of serious adverse events and adverse events leading to study drug discontinuation increased with decreasing baseline eGFR. The incidence of adverse events related to renal disorder increased with decreasing baseline eGFR (0.3%, 1.2%, 3.2%, and 17.6% in patients with baseline eGFR of ≥90, ≥60 and <90, ≥45 and <60, and ≥30 and <45, respectively). Adverse events related to renal disorder in patients with eGFR of ≥30 and <45 were hydronephrosis (1 subject) and renal impairment (2 subjects), but a causal relationship of the events to the study drug was ruled out. As for laboratory parameters related to impairment of renal function, the renal tubules, or the glomerulus, the mean changes in urinary beta 2 microglobulin and urinary alpha 1 microglobulin from baseline to the end of the treatment period were greater among patients with baseline eGFR of ≥30 and <45. The evaluation results showed that the incidence of adverse events by baseline eGFR did not differ between patients receiving monotherapy and those receiving combination therapy.

Table 49. Incidence of adverse events by baseline eGFR (safety analysis set) (pooled data from comparative studies)

	eGFR (mL/min/1.73 m^2)								
	≥90		≥60 and <90		≥45 and <60		≥30 and <45		<30[a)]
	Placebo group (n = 146)	Ipragliflozin 50 mg group (n = 207)	Placebo group (n = 191)	Ipragliflozin 50 mg group (n = 348)	Placebo group (n = 28)	Ipragliflozin 50 mg group (n = 56)	Placebo group (n = 3)	Ipragliflozin 50 mg group (n = 16)	Ipragliflozin 50 mg group (n = 1)
Adverse events	96 (65.8)	148 (71.5)	132 (69.1)	249 (71.6)	19 (67.9)	48 (85.7)	3 (100)	12 (75.0)	1 (100)
Serious adverse events	4 (2.7)	4 (1.9)	8 (4.2)	8 (2.3)	1 (3.6)	2 (3.6)	0 (0.0)	2 (12.5)	0 (0.0)
Adverse events leading to study drug discontinuation	18 (12.3)	8 (3.9)	20 (10.5)	14 (4.0)	3 (10.7)	5 (8.9)	1 (33.3)	2 (12.5)	0 (0.0)

Number of subjects with event (incidence %)

a) No subject in the placebo group was classified as such.

Table 50. Incidence of adverse events by baseline eGFR (safety analysis set) (pooled data from 52-week studies)

	eGFR (mL/min/1.73 m^2)				
	≥90	≥60 and <90	≥45 and <60	≥30 and <45	<30
	Ipragliflozin 50 mg group[a)] (n = 350)	Ipragliflozin 50 mg group[a)] (n = 586)	Ipragliflozin 50 mg group[a)] (n = 63)	Ipragliflozin 50 mg group[a)] (n = 17)	Ipragliflozin 50 mg group[a)] (n = 1)
Adverse events	302 (86.3)	497 (84.8)	60 (95.2)	16 (94.1)	1 (100)
Serious adverse events	20 (5.7)	41 (7.0)	7 (11.1)	5 (29.4)	0 (0.0)
Adverse events leading to study drug discontinuation	26 (7.4)	48 (8.2)	7 (11.1)	6 (35.3)	0 (0.0)

Number of subjects with event (incidence %)

a) Including subjects for whom the dose was increased to 100 mg/day.

PMDA considers as follows:

As for efficacy, given the facts that urinary glucose excretion after administration of ipragliflozin decreased depending on the severity of renal impairment and that despite a limit to interpretation of the study result, there was no difference in the changes in HbA1c and fasting plasma glucose between the placebo and the ipragliflozin groups in the subgroup of patients with eGFR of ≥30 and <45 in Study CL-0072, adequate efficacy of ipragliflozin cannot be expected in type 2 diabetes mellitus patients with moderate or severe renal impairment. In addition, a precautionary statement proposed by the applicant that administration to patients with severe renal impairment is not recommend will be included in the package insert. Information on loss of efficacy due to a decrease in renal function in patients with moderate or severe renal impairment should be

provided given the efficacy was not supported by the data on HbA1c and fasting plasma glucose in the subgroup of patients with eGFR of <45.

As for safety, the applicant explained that there were no tendencies for subjects with renal impairment to experience adverse events more frequently, to suffer a further reduction in renal function, or to suffer an increase in apparent risk of variation in laboratory parameters related to renal impairment. PMDA accepted the applicant's explanation. However, taking into account that the loss of efficacy was observed in patients with moderate or severe renal impairment, the use of ipragliflozin should be carefully considered. Since the number of subjects in the clinical studies was limited, it is necessary to continue to collect information on the impact of ipragliflozin on renal function as well as safety and efficacy in patients with renal impairment via post-marketing surveillance. The above issues will be finalized, taking account of comments from the Expert Discussion.

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

The applicant explained as follows:

The Japanese phase II and phase III studies excluded patients with AST or ALT of >2-fold (>3-fold in Studies CL-0103, CL-0105, and CL-0121) the upper limit of normal; therefore, the safety in these patient populations has not been evaluated.

The incidences of adverse events, serious adverse events, and adverse events leading to study drug discontinuation found in the pooled data from comparative studies, pooled data from 52-week studies, and pooled data from phase II/III studies were evaluated according to the presence of concurrent hepatic impairment (Table 51).

The incidence of adverse events in the pooled data from comparative studies was slightly higher in the ipragliflozin 50 mg group (73.7%) than in the placebo group (66.4%) among the subgroup of patients without concurrent hepatic impairment, but was similar between both groups among the subgroup of patients with concurrent hepatic impairment. The incidences of serious adverse events and adverse events leading to study drug discontinuation tended to be lower in the ipragliflozin 50 mg group than in the placebo group, with no apparent effects depending on the presence of concurrent hepatic impairment. In the pooled data from 52-week studies, 3 of 8 subjects for whom the dose was reduced from 100 to 50 mg/day had concurrent "hepatobiliary disorders" in the SOC (hepatic steatosis in 2 subjects, gallbladder polyp in 1 subject).

Table 51. Incidences of adverse events in subjects with and without concurrent hepatic impairment (safety analysis set)

	Without concurrent hepatic impairment				With concurrent hepatic impairment			
	Pooled data from comparative studies		Pooled data from 52-week studies	Pooled data from phase II/III studies	Pooled data from comparative studies		Pooled data from 52-week studies	Pooled data from phase II/III studies
	Placebo group (n = 244)	Ipragliflozin 50 mg group (n = 395)	Ipragliflozin 50 mg group[a)] (n = 632)	All ipragliflozin groups[b)] (n = 1028)	Placebo group (n = 124)	Ipragliflozin 50 mg group (n = 233)	Ipragliflozin 50 mg group[a)] (n = 385)	All ipragliflozin groups[b)] (n = 596)
Adverse events	162 (66.4)	291 (73.7)	541 (85.6)	794 (77.2)	88 (71.0)	167 (71.7)	335 (87.0)	483 (81.0)
Serious adverse events	8 (3.3)	11 (2.8)	52 (8.2)	57 (5.5)	5 (4.0)	5 (2.1)	21 (5.5)	25 (4.2)
Adverse events leading to study drug discontinuation	26 (10.7)	19 (4.8)	54 (8.5)	62 (6.0)	16 (12.9)	10 (4.3)	33 (8.6)	43 (7.2)

Number of subjects with event (incidence %)

a) Including subjects for whom the dose was increased to 100 mg/day

b) Subjects who received 12.5 to 100 mg of ipragliflozin

In the pooled data from 52-week studies, no apparent effects on the incidences of adverse events and adverse events leading to study drug discontinuation were observed regarless of the presence or absence of concurrent hepatic impairment. The incidence of serious adverse events was slightly higher in the subgroup of patients without concurrent hepatic impairment (8.2%) than in the subgroup of patients with concurrent hepatic impairment (5.5%). In evaluations for each concomitant drug used in the 52-week studies, serious adverse events were more frequently reported by patients "with" concurrent hepatobiliary disorders than by patients "without" concurrent hepatobiliary disorders among the group of patients who received concomitant administration of pioglitazone, but no apparent effects on the incidence of adverse events were observed regardless of the presence of concurrent hepatobiliary disorders among patients who received concomitant administration with the other drugs (Table 52).

Table 52. Incidence of adverse events in subjects with and without concurrent "hepatobiliary disorders" (SOC) by concomitant drug (safety analysis set) (pooled data from 52-week studies)

	Concurrent "hepatobiliary disorders"	Monotherapy	Ipragliflozin + metformin	Ipragliflozin + pioglitazone	Ipragliflozin + SU	Ipragliflozin + α-GI	Ipragliflozin + DPP-4 inhibitor	pragliflozin+ nateglinide
Adverse events	No	112/127 (88.2)	54/62 (87.1)	62/75 (82.7)	124/138 (89.9)	67/84 (79.8)	49/62 (79.0)	73/84 (86.9)
	Yes	84/91 (92.3)	43/50 (86.0)	32/37 (86.5)	71/80 (88.8)	33/45 (73.3)	39/44 (88.6)	33/38 (86.8)
Serious adverse events	No	11/127 (8.7)	3/62 (4.8)	0/75 (0.0)	16/138 (11.6)	10/84 (11.9)	5/62 (8.1)	7/84 (8.3)
	Yes	3/91 (3.3)	2/50 (4.0)	5/37 (13.5)	5/80 (6.3)	4/45 (8.9)	0/44 (0.0)	2/38 (5.3)
Adverse events leading to study drug discontinuation	No	14/127 (11.0)	3/62 (4.8)	3/75 (4.0)	17/138 (12.3)	7/84 (8.3)	4/62 (6.5)	6/84 (7.1)
	Yes	10/91 (11.0)	1/50 (2.0)	3/37 (8.1)	8/80 (10.0)	6/45 (13.3)	2/44 (4.5)	3/38 (7.9)

Number of patients who experienced an adverse event or adverse drug reaction/total number of patients in the relevant group (%)

As for safety in patients with moderate hepatic impairment, the least squares mean ratio of C_{max} and AUC_{inf} of unchanged ipragliflozin in foreign patients with moderate hepatic impairment (Child-Pugh B, score 7-9) versus healthy adult subjects after a single oral dose of 100 mg of ipragliflozin under fasted conditions in the foreign study in patients with hepatic impairment (Study CL-0063) was slightly higher in patients with moderate hepatic impairment; the ratios were found to be 1.268 and 1.249, respectively, after adjustment for the fixed effect of treatment and covariates of age and BMI. All adverse events reported by patients with moderate hepatic impairment were transient and mild in severity. Based on the above, dose reduction of ipragliflozin is not necessary in patients with mild or moderate hepatic impairment from a safety standpoint.

As for impact on the gastrointestinal tract and liver, which is a matter of concern from the viewpoint of toxicological findings observed in the non-clinical toxicity studies, the incidence of adverse events classified under the SOC "gastrointestinal disorders" in the pooled data from comparative studies was higher in the ipragliflozin 50 mg group (21.7%) than in the placebo group (14.7%). Adverse events reported by ≥2% of subjects in the ipragliflozin 50 mg group were constipation (4.8%), diarrhoea (2.9%), and dental caries (2.4%). Among these, constipation occurred with a 2-fold incidence of that in the placebo group (2.4%); all events were mild in severity and no subjects discontinued the treatment. In the pooled data from 52-week studies, there was no increasing trend in the incidences of adverse events classified under the "gastrointestinal disorders" and constipation with increasing treatment duration.

On the other hand, the incidence of adverse events classified under the "hepatobiliary disorders" in the pooled data from comparative studies was lower in the ipragliflozin 50 mg group (1.0%) than in the placebo group (1.9%). There was no increasing trend in the incidence of adverse events classified under the "hepatobiliary disorders" in the pooled data from 52-week studies with increasing treatment duration. An evaluation of the means of laboratory parameters related to hepatic function (AST, ALT, total bilirubin) at the end of the treatment period showed decreases in AST and ALT from baseline and no apparent change in total bilirubin in the ipragliflozin 50 mg group. In addition, an increase in intra-patient variability was not observed in the ipragliflozin groups, and there were no subjects with abnormal AST or ALT with a level >3-fold the upper limit of normal and with abnormal total bilirubin with a level >2-fold the upper limit of normal in any dose group in the pooled data from phase II/III studies.

As for efficacy, the mean change in HbA1c from baseline to the end of Treatment Period I (double-blind period) in the pooled data from comparative studies did not vary regardless of the presence or absence of concurrent hepatic impairment; the mean changes in HbA1c in patients with and without concurrent hepatic impairment were 0.27% and 0.34%, respectively, in the placebo group and -0.82% and -0.66%, respectively, in the ipragliflozin 50 mg group. In addition, based on the results of Study CL-0063, the impact of hepatic impairment on urinary glucose excretion was not considered to be substantial.

Based on the above, the applicant considers that there is no major problem with the safety of ipragliflozin at doses of 50 and 100 mg/day in patients with mild to moderate hepatic impairment. For patients with severe hepatic impairment, the package insert will include precautionary statements that careful administration of ipragliflozin is recommended and that a lower starting dose (25 mg/day) is required, in light of the facts that ipragliflozin is mainly metabolized by the liver, that a concern exists about increased exposure, and that clinical experience has been limited.

PMDA considers as follows:
PMDA largely accepted the applicant's explanation. However, since no Japanese clinical studies have been conducted in patients with moderate hepatic impairment, it is necessary to continue to collect information on safety and efficacy in patients with hepatic impairment including safety of dose increase to 100 mg/day via post-marketing surveillance. Further discussion is needed regarding the appropriateness of the dose including the starting dose in patients with severe hepatic impairment (25 mg/day) and the necessity of precautionary statements. The above issues will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(6).3) Elderly

The applicant explained as follows:
No apparent effects of age (<65 or ≥65) were observed on the incidences of adverse events, serious adverse events, and adverse events leading to study drug discontinuation (Table 53). The incidence of adverse events by concomitant drug in the pooled data from 52-week studies was as shown in Table 54, showing no apparent difference in the incidence by age group between monotherapy and each combination therapy. In the pooled data from 52-week studies, 6 of 8 subjects for whom the dose was reduced from 100 to 50 mg were ≥65 years of age.

Table 53. Incidence of adverse events by age (<65 or ≥65) (safety analysis set)

	<65			≥65		
	Pooled data from comparative studies		Pooled data from 52-week studies	Pooled data from comparative studies		Pooled data from 52-week studies
	Placebo (n = 250)	Ipragliflozin 50 mg group (n = 421)	Ipragliflozin 50 mg group[a)] (n = 690)	Placebo group (n = 118)	Ipragliflozin 50 mg group (n = 207)	Ipragliflozin 50 mg group[a)] (n = 327)
Adverse events	169 (67.6)	304 (72.2)	593 (85.9)	81 (68.6)	154 (74.4)	283 (86.5)
Serious adverse events	5 (2.0)	9 (2.1)	35 (5.1)	8 (6.8)	7 (3.4)	38 (11.6)
Adverse events leading to study drug discontinuation	27 (10.8)	15 (3.6)	44 (6.4)	15 (12.7)	14 (6.8)	43 (13.1)

Number of subjects with event (incidence %)

a) Including subjects for whom the dose was increased to 100 mg/day.

Table 54. Incidence of adverse events by concomitant drug and age (<65 or ≥65) (safety analysis set) (pooled data from 52-week studies)

	Age (years)	Monotherapy	Ipragliflozin + metformin	Ipragliflozin +pioglitazone	Ipragliflozin + SU	Ipragliflozin + α-GI	Ipragliflozin + DPP-4 inhibitor	Ipragliflozin + nateglinide
Adverse events	65>	136/149 (91.3)	72/86 (83.7)	67/79 (84.8)	120/134 (89.6)	66/90 (73.3)	66/76 (86.8)	66/76 (86.8)
	65≤	60/69 (87.0)	25/26 (96.2)	27/33 (81.8)	75/84 (89.3)	34/39 (87.2)	22/30 (73.3)	40/46 (87.0)
Adverse drug reactions	65>	70/149 (47.0)	36/86 (41.9)	28/79 (35.4)	42/134 (31.3)	29/90 (32.2)	35/76 (46.1)	21/76 (27.6)
	65≤	36/69 (52.2)	12/26 (46.2)	9/33 (27.3)	30/84 (35.7)	13/39 (33.3)	11/30 (36.7)	14/46 (30.4)
Serious adverse events	65>	5/149 (3.4)	3/86 (3.5)	3/79 (3.8)	7/134 (5.2)	9/90 (10.0)	4/76 (5.3)	4/76 (5.3)
	65≤	9/69 (13.0)	2/26 (7.7)	2/33 (6.1)	14/84 (16.7)	5/39 (12.8)	1/30 (3.3)	5/46 (10.9)
Adverse events leading to study drug discontinuation	65>	11/149 (7.4)	3/86 (3.5)	3/79 (3.8)	10/134 (7.5)	8/90 (8.9)	3/76 (3.9)	6/76 (7.9)
	65≤	13/69 (18.8)	1/26 (3.8)	3/33 (9.1)	15/84 (17.9)	5/39 (12.8)	3/30 (10.0)	3/46 (6.5)

As for adverse events of special interest in the pooled data from comparative studies, the incidence of genital infection-related adverse events in the 50 mg group versus the placebo group was higher in the subgroup of patients aged <65 (2.9% versus 0.8%) than in the subgroup of patients aged ≥65 (0.5% versus 0.8%). The incidence of thirst in the 50 mg group versus the placebo group was higher in the subgroup of patients aged <65 (4.5% versus 1.2%) than in the subgroup of patients aged ≥65 (2.9% versus 2.5%), but the incidence of adverse events related to a decrease in body fluid volume was similar between these age subgroups. However, the incidence of beta 2 microglobulin urine increased in the 50 mg group versus the placebo group was higher in the subgroup of patients aged ≥65 (3.4% versus 0.0%) than in the subgroup of patients aged <65 (1.0% versus 0.8%). Increases in hematocrit and BUN, and a decrease in systolic and diastolic blood pressures, which could potentially be associated with decrease in body fluid volume, were similar between the age subgroups.

As for effects of increased age on pharmacokinetics, there was a tendency for exposure to be higher in elderly patients than in non-elderly patients due to a difference in body surface area, but the degree is not considered to be great. As described above, although the results from clinical studies suggested that there are no problems with safety in the elderly patients, it should be cautioned that ipragliflozin should be administered while monitoring the patient's condition, in light of the fact that ipragliflozin induces osmotic diuresis through the promotion of urinary glucose excretion since elderly patients often have reduced physiological functions and since dehydration due to decreased sensitivity to thirst is likely to occur.

PMDA considers as follows:
Table 53 shows a tendency for the incidences of serious adverse events and adverse events leading to study drug discontinuation to be higher in the subgroup of patients aged ≥65 than in the subgroup of patients aged <65 in the pooled data from 52-week studies. In this regard, since there was no specific trend in the observed events and no substantial differences were observed between the placebo and the ipragliflozin 50 mg groups in the pooled data from comparative studies, there are no major problems with the use of ipragliflozin in the elderly, given that appropriate cautions are provided. However, it is necessary to continue to collect information on safety in the elderly via post-marketing surveillance. The above issues will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(7) Post-marketing investigations
The applicant explained as follows:
A post-marketing surveillance study with a planned sample size of 10,000 and an observation period of 3 years will be conducted to evaluate the safety and efficacy of long-term treatment with ipragliflozin. The priority investigation items will be safety in malnourished patients, adverse events related to decrease in body fluid volume, hypoglycemia, malignant tumours, impact on cardiovascular system, and safety of concomitant use of ipragliflozin with insulin or a GLP-1 receptor agonist.

PMDA considers as follows:
It is also necessary to collect information, including the impact of dose level (especially, concomitant use of ipragliflozin with the dose of >750 mg/day of metformin) and type of concomitant drug on the safety, adverse events related to urinary tract and genital infections, adverse events related to pollakiuria and polyuria, adverse events related to urine ketone body, bone metabolism, and safety and efficacy in patients with renal or hepatic impairment and in the elderly. In addition, appropriate safety measures need to be taken in light of the following facts: (i) ipragliflozin is a drug with a novel mechanism of action which has only recently been approved overseas; (ii) the incidence of adverse events associated with decrease in body fluid volume may be increased in clinical settings depending on the external environment such as seasons, as compared with that in clinical studies; (iii) urinary tract infections, which may aggravate unless detected at an early stage, might be detected at a later stage in clinical practice than in clinical studies. Details of post-marketing surveillance will be finalized, taking account of comments from the Expert Discussion.

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

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

This will be described in Review Report (2).

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.1-1, 5.3.5.1-1, 5.3.5.1-2, 5.3.5.1-3, 5.3.5.1-4, 5.3.5.1-5, 5.3.5.1-6, 5.3.5.2-1, 5.3.5.2-2, 5.3.5.2-3, 5.3.5.2-4). As a result, protocol deviations (e.g., enrollment of subjects who did not fulfill the inclusion criteria and those who met exclusion criteria, noncompliance with withdrawal criteria, missing laboratory parameters) and cases where screening tests had been performed prior to the date of informed consent were found at some trial sites. In addition, some of the above protocol deviations had not been detected by the sponsor's monitors. Although the above findings requiring improvement were noted, since these cases were appropriately handled, PMDA concluded that the clinical studies as a whole

were performed in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of ipragliflozin in patients with type 2 diabetes mellitus has been demonstrated and the safety of ipragliflozin is acceptable in view of its observed benefits. Ipragliflozin is an oral hypoglycemic agent with a novel mechanism of action that provides a new treatment option for type 2 diabetes mellitus. The following issues need to be further investigated: whether or not ipragliflozin can be indicated for the treatment of type 2 diabetes mellitus patients with moderate to severe renal impairment; impact of the dose or type of concomitant oral hypoglycemic agents on the safety; impact on hypoglycemia, urinary tract and genital infections, pollakiuria, polyuria, body weight (body fluid volume), and electrolytes; adverse events related to urine ketone body; bone metabolism, cardiovascular risk, and malignant tumours; safety in patients with renal or hepatic impairment and in the elderly.

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

Review Report (2)

November 6, 2013

I. Product Submitted for Registration

[Brand name]	Suglat Tablets 25 mg and 50 mg
[Non-proprietary name]	Ipragliflozin L-Proline
[Applicant]	Astellas Pharma Inc.
[Date of application]	March 13, 2013

II. Content of the Review

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

(1) Efficacy

1) Efficacy of monotherapy

PMDA considers that the efficacy of monotherapy has been demonstrated based on the results of the Japanese phase III monotherapy study (Study CL-0105) and Japanese long-term monotherapy studies (Studies CL-0121 and CL-0122).

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

2) Efficacy of combination therapies

PMDA considers that the efficacy of each of the combination therapies has been demonstrated based on the results of the metformin combination therapy study (Study CL-0106), pioglitazone combination therapy study (Study CL-0107), SU combination therapy study (Study CL-0109), α-GI combination therapy study (Study CL-0108), DPP-4 inhibitor combination therapy study (Study CL-0110), and nateglinide combination therapy study (Study CL-0111).

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

(2) Safety

PMDA considers as follows:

The safety of ipragliflozin is acceptable in view of the incidences of adverse events and adverse drug reactions associated with monotherapy and each of the combination therapies, given that appropriate cautions are provided. In addition, based on the review of events of special interest for safety evaluation (hypoglycemia, urinary tract infection- and genital infection-related adverse events, adverse events related to pollakiuria and polyuria, impact on body weight [body fluid volume] and electrolytes, etc.), it is necessary to continue to collect information via post-marketing surveillance although currently no major problems have been identified. Furthermore, it is necessary to collect information on the impact of dose level or the type of concomitant oral hypoglycemic agents on the safety via post-marketing surveillance.

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

Based on the above, PMDA instructed the applicant to take actions, and confirmed that

appropriate actions had been taken regarding the precautionary statements in the package insert [for post-marketing investigations, see "(6) Risk management plan (draft)"].

(3) Indication

PMDA considers that the appropriate indication of ipragliflozin is "type 2 diabetes mellitus" because the efficacy of monotherapy and combination therapies have been demonstrated in the results from clinical studies conducted in accordance with the OAD guideline and that the safety is acceptable.

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

(4) Dosage and administration

PMDA considers as follows:

There is no problem with a once daily oral administration of ipragliflozin. However, since the effects of ipragliflozin administered after the evening meal peak during sleep hours and therefore attention should be paid in terms of a safety, it is appropriate to clearly specify the timing of doses of which efficacy and safety have been evaluated in clinical studies (i.e., before or after breakfast) in the dosage and administration section.

There is no problem with the usual dose of 50 mg/day of ipragliflozin, and also there is no major problem in permitting a dose increase to 100 mg/day in patients with inadequate response to the dose of 50 mg/day.

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

Based on the above, PMDA instructed the applicant to revise the dosage and administration as shown below.

The applicant responded that the dosage and administration will be revised as shown below.

[Dosage and administration]

The usual adult dosage is 50 mg of ipragliflozin orally administered once daily <u>before or after breakfast</u>. However, the dose may be increased up to 100 mg once daily with careful monitoring of the patient's clinical course in the case of inadequate efficacy.

(Underline denotes additions)

(5) Special populations

1) Patients with renal impairment

PMDA considers as follows:

Because adequate efficacy cannot be expected in type 2 diabetes mellitus patients with moderate or severe renal impairment, information on loss of efficacy due to a decrease in renal function in this patient population should be provided. Since the number of subjects in the clinical studies was limited, it is necessary to continue to collect information on the impact of ipragliflozin on renal function as well as safety and efficacy in patients with renal impairment via post-marketing surveillance.

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

Based on the above, PMDA instructed the applicant to include precautionary statements in the Precautions for Indications section of the package insert regarding use in patients with moderate or severe renal impairment and confirmed that appropriate actions had been taken [for post-marketing investigations, see "(6) Risk management plan (draft)"].

2) Patients with hepatic impairment

PMDA considers that no Japanese clinical studies have been conducted in patients with moderate hepatic impairment and that it is necessary to continue to collect information on safety and efficacy in patients with hepatic impairment including safety of dose increase to 100 mg/day via post-marketing surveillance. With regard to the issue of whether to include a caution statement to use a starting dose of 25 mg/day in patients with severe hepatic impairment in the precautions for dosage and administration section, it is appropriate to delete the description "25 mg/day" because no supporting data for it exist.

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

Based on the above, PMDA instructed the applicant to modify the Precautions for Dosage and Administration section and confirmed that appropriate actions had been taken [for post-marketing investigations, see "(6) Risk management plan (draft)"].

3) Elderly

PMDA considers that there are no major problems with safety in the elderly, given that appropriate cautions are provided. Nevertheless, it is necessary to continue to collect information on safety in the elderly via post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors [for post-marketing investigations, see "(6) Risk management plan (draft)"].

(6) Risk management plan (draft)

Based on the review in "4.(iii).B.(7) Post-marketing investigations" of the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the following points should be additionally evaluated in the risk management plan.

- Impact of dose level (especially, concomitant use with the doses of >750 mg/day of metformin) and type of concomitant drug on the safety
- Adverse events related to urinary tract and genital infections
- Adverse events related to pollakiuria and polyuria
- Adverse events related to ketone body
- Impact on bone metabolism
- Safety and efficacy in patients with renal or hepatic impairment
- Effects of ipragliflozin on renal function
- A surveillance focusing on adverse events in all the elderly patients treated with ipragliflozin

PMDA instructed the applicant to take actions regarding the above points, and the applicant presented the risk management plan (Table 55, Table 56) and an outline (draft) of specified use-results surveys, as shown below. PMDA confirmed that there were no problems with the contents.

Table 55. Safety and efficacy specifications of the risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypoglycemia • Genital infection • Urinary tract infection • Pollakiuria/polyuria • Adverse events related to decrease in body fluid volume	• Impact of body weight loss on safety • Impact of increase in ketone bodies • Renal disorder • Fracture • Malignant tumour • Cardiovascular disease	• Safety of use in the elderly • Safety of use in patients with renal impairment • Safety of use in patients with hepatic impairment • Safety of combination use of ipragliflozin with an insulin preparation or GLP-1 analog
Efficacy specification		
• Efficacy of long-term treatment		

Table 56. Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Pharmacovigilance activities equivalent to early post-marketing phase vigilance (information collection and evaluation) • Post-marketing clinical studies[a)] • Long-term specified drug use-results surveys • Specified drug use-results surveys (for the elderly)	• Preparation and distribution of materials for proper use of ipragliflozin (Guides for proper use for healthcare professionals/brochures for patients and families) • Provision of information based on early post-marketing phase vigilance • Provision of information same as that of early post-marketing phase vigilance

a) Clinical studies on combination therapy with an insulin preparation and on combination therapy with a GLP-1 analog are planned to be conducted after obtaining approval of ipragliflozin.

Table 57. Outline of the long-term specified drug use-results survey plan (draft)

Objective	To confirm the safety and efficacy of long-term treatment of ipragliflozin for 3 years
Survey method	Central registration method
Patient population	Patients with type 2 diabetes mellitus
Observation period	3 years
Planned sample size	10,000
Primary investigation items	Patient demographic factors, details on administration of ipragliflozin, concomitant drugs, efficacy evaluation (HbA1c, etc.), safety evaluation (impact on cardiovascular system, malignant tumours, and other adverse events, etc.)

Table 58. Outline of the specified drug use-results survey plan (draft) (for the elderly)

Objective	To confirm the safety of ipragliflozin in the elderly
Survey method	Central registration method
Patient population	Patients aged ≥65 years with type 2 diabetes mellitus
Observation period	1 year
Planned sample size	All patients who received ipragliflozin within 3 months after the release date (estimated to be approximately 6000 patients)
Primary investigation items	Patient characteristics, details on administration of ipragliflozin, concomitant drugs, safety evaluation (adverse events related to decrease in body fluid volume, urinary tract infections, and other adverse events, etc.)

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

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

IV. Overall Evaluation

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

[Indication]	Type 2 diabetes mellitus
[Dosage and administration]	The usual adult dosage is 50 mg of ipragliflozin orally administered once daily before or after breakfast. However, the dose may be increased up to 100 mg once daily with careful monitoring of the patient's clinical course in the case of inadequate efficacy.