Report on the Deliberation Results

December 4, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Suglat Tablets 25 mg and 50 mg
Non-proprietary Name	Ipragliflozin L-Proline (JAN*)
Applicant	Astellas Pharma Inc.
Date of Application	January 11, 2018

Results of Deliberation

In its meeting held on December 3, 2018, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 8, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Suglat Tablets 25 mg and 50 mg
Non-proprietary Name	Ipragliflozin L-Proline
Applicant	Astellas Pharma Inc.
Date of Application	January 11, 2018
Dosage Form/Strength	Each film-coated tablet contains ipragliflozin L-proline equivalent to 25 or 50 mg of ipragliflozin.
Application Classification	Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product administered in combination with insulin therapy has efficacy in the treatment of type 1 diabetes mellitus, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications

Type 2 diabetes mellitus
Type 1 diabetes mellitus

(Underline denotes additions.)

Dosage and Administration

Type 2 diabetes mellitus

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.

Type 1 diabetes mellitus

Suglat is used in combination with insulin. 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.

(Underline denotes additions.)

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

October 1, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Suglat Tablets 25 mg and 50 mg
Non-proprietary Name	Ipragliflozin L-Proline
Applicant	Astellas Pharma Inc.
Date of Application	January 11, 2018
Dosage Form/Strength	Each film-coated tablet contains ipragliflozin L-proline equivalent to 25 or 50 mg of ipragliflozin.

Proposed Indications

Type 2 diabetes mellitus

Type 1 diabetes mellitus

(Underline denotes additions.)

Proposed 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.

(No changes)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

The active ingredient of Suglat, Ipragliflozin L-Proline (hereinafter referred to as ipragliflozin), is a sodium glucose cotransporter 2 (SGLT2) inhibitor. It lowers blood glucose levels by inhibiting glucose reuptake by SGLT2 in the proximal renal tubules, leading to increased glucose excretion in the urine. In Japan, ipragliflozin received marketing approval for the indication of "type 2 diabetes mellitus" in January 2014.

Type 1 diabetes mellitus is caused by destruction of the pancreatic β cells, leading to absolute insulin deficiency. Thus, insulin therapy is the standard of care. However, as insulin therapy requires weight control to avoid weight gain, and the risk of hypoglycemia increases with increasing insulin dose, the insulin dose cannot be increased to an appropriate level in some patients. Since ipragliflozin is an SGLT2 inhibitor that expresses blood glucose-lowering effect independently of insulin, additive blood glucose-lowering effects can be produced without significantly affecting the risk of serious hypoglycemia. Ipragliflozin in combination with insulin therapy is expected to contribute to glycemic control and reduce body weight in patients with type 1 diabetes mellitus.

Claiming that a Japanese phase III study has confirmed the efficacy and safety of ipragliflozin in combination with insulin in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy, the applicant has filed a partial change application for ipragliflozin.

As of September 2018, the development of ipragliflozin for the indication of type 1 diabetes mellitus has not been initiated in any foreign country/region.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

No data relating to quality have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The non-clinical pharmacology data were previously evaluated for the initial approval of ipragliflozin, and no new study data have been submitted.

3.R Outline of the review conducted by PMDA

PMDA confirmed that a single oral dose of ipragliflozin reduced blood glucose levels in streptozotocin (STZ)-induced type 1 diabetic rats in a non-clinical pharmacology study submitted for the initial approval of ipragliflozin.[1)] In addition, ipragliflozin increased urinary glucose excretion and significantly reduced blood glucose levels and HbA1c at doses of ≥0.3 mg/kg, compared with vehicle when ipragliflozin (0.1, 0.3, 1, and 3 mg/kg) or vehicle (0.5% methylcellulose solution) was orally administered to STZ-induced type 1 diabetic male rats (9 weeks of age, 6/group) for 26 days (*J Pharma Pharmacol.* 2014; 66: 975-85). Thus, PMDA concluded that the pharmacologic effects of ipragliflozin on type 1 diabetes mellitus have been demonstrated.

1) A single oral dose of ipragliflozin (0.1, 0.3, and 1 mg/kg) or vehicle (0.5% methylcellulose solution) was administered to male STZ-induced type 1 diabetic rats (10 weeks of age, 6/group). As a result, ipragliflozin significantly decreased the blood glucose AUC compared with vehicle.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The non-clinical pharmacokinetic data were previously evaluated for the initial approval of ipragliflozin, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

No toxicity data have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Ipragliflozin in human biomaterials was quantified using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the lower limits of quantification for unchanged drug in plasma and urine were 1.00 and 2.00 ng/mL, respectively.

6.2 Clinical pharmacology

The applicant submitted the results from a Japanese clinical pharmacology study (Study CL-6001) and a Japanese phase III study (Study CL-6002) in patients with type 1 diabetes mellitus and the results of a population pharmacokinetic analysis, as evaluation data. In this section, the doses of ipragliflozin are expressed as free base.

6.2.1 Japanese clinical pharmacology study (CTD5.3.4.2-1, Study CL-6001 [September 2015 to March 2016])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the pharmacokinetics, pharmacodynamics, and safety of ipragliflozin in Japanese patients with type 1 diabetes mellitus who had inadequate glycemic control with insulin therapy[2)] (target sample size, 40 subjects [10 per group]).

Placebo or ipragliflozin 25, 50, or 100 mg was to be orally administered once daily before breakfast for 14 days. The dose of concomitant insulin during the study period was to be adjusted according to a titration algorithm used by the subject according to their physician's instruction in routine clinical practice. If the subject had a self-monitored blood glucose level of <80 mg/dL, a reduction in insulin dose was to be considered.

All of 43 randomized subjects were included in the safety analysis set. Of whom, 42 subjects with ≥1 pharmacokinetic sample after administration of ipragliflozin were included in the pharmacokinetic analysis set, and 41 subjects with pharmacodynamic assessments on the day of last dosing were included in the primary pharmacodynamic analysis set.

---

2) Key inclusion criteria: Adult patients with type 1 diabetes mellitus who had been treated with insulin therapy for ≥52 weeks at the time of obtaining consent and had HbA1c of ≥7.5% and ≥10.0%, fasting blood C-peptide of ≤0.5 ng/mL, and BMI of ≥20.0 and ≥35.0 kg/m^2 at screening (6-21 days before start of study treatment). The use of hypoglycemic agents other than insulin was prohibited between 12 weeks prior to the start of screening and the end of evaluation phase.

Pharmacokinetic parameters of ipragliflozin on Days 1 and 14 following once daily oral administration are shown in Table 1.

Table 1. Pharmacokinetic parameters of ipragliflozin on Days 1 and 14 following once daily oral administration

Parameter	Ipragliflozin 25 mg (N = 10)		Ipragliflozin 50 mg (N = 12)		Ipragliflozin 100 mg (N = 10)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
C_{max} (ng/mL)	626 ± 128	694 ± 174	1230 ± 289	1400 ± 273	2300 ± 737	2680 ± 346
$AUC_{24\,h}$ (ng·h/mL)	2060 ± 313	2510 ± 495	4650 ± 929	5790 ± 1130	8720 ± 1350	10,600 ± 2050
t_{max} (h)	0.500 [0.467, 1.05]	0.525 [0.500, 1.02]	0.975 [0.433, 3.02]	0.742 [0.467, 2.00]	0.508 [0.450, 1.53]	1.00 [0.500, 1.00]
CL/F (L/h)	—	10.3 ± 2.00	—	8.96 ± 1.88	—	9.80 ± 2.24
$Ae_{24\,h}$ (%)	0.893 ± 0.186	1.09 ± 0.233	1.16 ± 0.367	1.52 ± 0.524	1.02 ± 0.287	1.46 ± 0.369
CL_R (L/h)	0.110 ± 0.0224	0.109 ± 0.0197	0.124 ± 0.0193	0.129 ± 0.0282	0.117 ± 0.0267	0.139 ± 0.0362

Mean ± standard deviation (SD); Median [range] for t_{max}; —, not calculated
C_{max}, maximum plasma concentration; $AUC_{24\,h}$, area under the plasma concentration-time curve up to 24 hours post-dose; t_{max}, time to reach the maximum plasma concentration, CL/F, oral clearance; $A_{e24\,h}$ (%), percentage of drug excreted in urine up to 24 hours post-dose; CL_R, renal clearance

Following once daily oral administration of placebo or ipragliflozin, the changes from baseline to Day 14 in pharmacodynamic parameters (24-hour cumulative urinary glucose excretion, urinary glucose clearance), plasma glucose parameters (plasma glucose $AUC_{24\,h}$, fasting plasma glucose), and the daily insulin dose (daily basal insulin, bolus insulin, and total insulin doses) are shown in Table 2.

Table 2. Changes from baseline to Day 14 in pharmacodynamic parameters, plasma glucose parameters, and daily insulin dose

Parameter	Placebo (N = 10)	Ipragliflozin 25 mg (N = 9)	Ipragliflozin 50 mg (N = 12)	Ipragliflozin 100 mg (N = 10)
24-hour cumulative urinary glucose excretion (g)	−0.118 ± 15.1	63.1 ± 29.6	82.4 ± 44.7	93.9 ± 33.5
Urinary glucose clearance (mL/min)	−0.748 ± 3.74	23.5 ± 7.35	32.6 ± 13.3	41.5 ± 13.6
Plasma glucose $AUC_{24\,h}$ (mg·h/dL)	365 ± 1250	−126 ± 760	−180 ± 1090	−539 ± 545
Fasting plasma glucose (mg/dL)	43.3 ± 73.8	−12.7 ± 86.9	−7.7 ± 26.4	−75.9 ± 59.1
Daily basal insulin dose (IU)	−1.20 ± 3.79	−3.33 ± 4.50	−4.27 ± 4.98	−2.80 ± 3.65
Daily bolus insulin dose (IU)	−0.60 ± 3.86	−2.72 ± 3.70	−3.25 ± 3.14	−6.60 ± 5.42
Daily total insulin dose (IU)	−1.80 ± 6.97	−6.06 ± 6.95	−7.52 ± 7.06	−9.40 ± 7.31

Mean ± SD
Plasma glucose $AUC_{24\,h}$, plasma glucose AUC up to 24 hours post-dose

As to the safety profile, the incidences of adverse events and adverse drug reactions were 100% (11 of 11 subjects) and 90.9% (10 of 11 subjects), respectively, in the placebo group, 100% (10 of 10 subjects) and 100% (10 of 10 subjects), respectively, in the ipragliflozin 25 mg group, 100% (12 of 12 subjects) and 100% (12 of 12 subjects), respectively, in the ipragliflozin 50 mg group, and 90.0% (9 of 10 subjects) and 90.0% (9 of 10 subjects), respectively, in the ipragliflozin 100 mg group. The adverse drug reactions reported were hypoglycemia (8 subjects); hypoglycemia and headache (1 subject); and hypoglycemia, headache, and pyrexia (1 subject) in the placebo group, hypoglycemia (8 subjects); hypoglycemia and β2 microglobulin increased (1 subject); and hypoglycemia and blood ketone body increased (1 subject) in the ipragliflozin 25 mg group, hypoglycemia (9 subjects); hypoglycemia, blood ketone body increased, urine ketone body present, and pollakiuria (1 subject); hypoglycemia and nasopharyngitis (1 subject); and hypoglycemia and papule (1 subject) in the ipragliflozin 50 mg group, and hypoglycemia (7 subjects); hypoglycemia and blood ketone body increased (1 subject); and hypoglycemia, blood ketone body increased, and urine ketone body present (1 subject) in the ipragliflozin 100 mg group. No deaths, serious events, or events leading to treatment discontinuation were reported. There were no clinically meaningful changes in laboratory data, vital signs, or ECG.

6.2.2 Japanese phase III study (CTD5.3.5.1-1, CTD5.3.5.1-1.1, Study CL-6002 [August 2016 to March 2018])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of ipragliflozin in Japanese patients with type 1 diabetes mellitus who had inadequate glycemic control with insulin therapy (target sample size, 150 subjects [50 in the placebo group, 100 in the ipragliflozin group]) [for the details of the study design, and efficacy and safety results, see Section "7.1 Japanese phase III study"].

As to pharmacokinetics, trough plasma ipragliflozin concentrations following administration of ipragliflozin are shown in Table 3.

Table 3. Trough plasma ipragliflozin concentrations following administration of ipragliflozin

Time point	Week 2	Week 4	Week 8	Week 16	Week 24	Week 36	Week 44	Week 52
Ipragliflozin 50 mg	75.2 ± 82.3 (N = 111)	69.2 ± 37.2 (N = 112)	86.5 ± 150 (N = 111)	75.3 ± 63.0 (N = 112)	76.0 ± 53.0 (N = 109)	65.3 ± 44.6 (N = 95)	79.5 ± 146 (N = 94)	66.0 ± 42.8 (N = 94)
Ipragliflozin 100 mg [a)]	—	—	—	—	—	172 ± 243 (N = 67)	132 ± 62.9 (N = 61)	166 ± 232 (N = 65)

Mean ± SD; Unit, ng/mL; —, Not applicable
a) Trough plasma ipragliflozin concentrations in subjects who had their ipragliflozin dose increased from 50 mg to 100 mg

6.2.3 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

Using the plasma ipragliflozin concentration data (554 sampling points) obtained from 114 (54 men, 60 women) of 115 subjects treated with ipragliflozin in a Japanese phase III study in patients with type 1 diabetes mellitus (Study CL-6002), a population pharmacokinetic (PPK) analysis was performed (software used, NONMEM [ver.7.3]).

The characteristics of subjects included in the PPK analysis (median [range]) are as follows: age, 48 [22, 81] years; body weight, 64.2 [47.8, 114.2] kg; height, 163.2 [142.7, 184.6] cm; body surface area, 1.705 [1.37, 2.36] m^2; estimated glomerular filtration rate (eGFR), 94.4 [54.2, 152.7] mL/min/1.73m^2; and glomerular filtration rate (GFR) (eGFR × body surface area/1.73), 92.85 [54.0, 146.3] mL/min.

A 2-compartment model with first-order absorption was developed as the base model. Potential covariates on CL/F including sex, age, body weight, height, body surface area, eGFR, and GFR were tested using the stepwise method. As a result, sex and GFR as covariates on CL/F were incorporated in the final model.

Based on the arithmetic mean GFR (92.63 mL/min) in the 115 subjects enrolled in Study CL-6002, the population mean estimates of CL/F from the final model were 9.36 L/h for men and 8.10 L/h for women. Over the GFR range (54.0-146.3 mL/min) of the 115 subjects, CL/F was suggested to vary from −19.6% to 20.3% change from the population mean.

6.R Outline of the review conducted by PMDA

6.R.1 Rationale for dosing regimen selected for Japanese phase III study

The applicant's explanation about the rationale for the dosing regimen of ipragliflozin selected for a Japanese phase III study in patients with type 1 diabetes mellitus, from the point of view of the pharmacokinetics and pharmacodynamics of ipragliflozin in patients with type 1 or type 2 diabetes mellitus:

As to the pharmacokinetics of ipragliflozin, when ipragliflozin 50 or 100 mg was orally administered once daily before breakfast for 14 days in Study CL-6001 in patients with type 1 diabetes mellitus, following the last dose, the C_{max} values (mean ± SD) were 1400 ± 273 and 2680 ± 346 ng/mL, respectively, and the $AUC_{24\,h}$ values were 5790 ± 1130 and 10,600 ± 2050 ng·h/mL, respectively. On the other hand, when ipragliflozin 50 or 100 mg was orally administered once daily before breakfast for 14 days in Study CL-0070[3)] in patients with type 2 diabetes mellitus submitted for the initial approval of ipragliflozin, following the last dose, the C_{max} values were 1230 ± 255 and 2030 ± 654 ng/mL, respectively, and the $AUC_{24\,h}$ values were 4810 ± 1460 and 9210 ± 3940 ng·h/mL, respectively. There were no major differences in ipragliflozin exposure after multiple oral doses between patients with type 1 and type 2 diabetes mellitus.

As to the pharmacodynamics of ipragliflozin, the effect of ipragliflozin on urinary glucose excretion was evaluated using urinary glucose clearance taking account of blood glucose fluctuations. As a result, following administration of ipragliflozin 50 or 100 mg, the changes in urinary glucose clearance from Day 1 to 2 weeks were 32.6 ± 13.3 and 41.5 ± 13.6 mL/min, respectively, in Study CL-6001 in patients with type 1 diabetes mellitus and 32.9 ± 6.97 and 37.8 ± 6.08 mL/min, respectively, in Study CL-0070 in patients with type 2 diabetes mellitus. There were no major differences in the degree of elevation of urinary glucose clearance between patients with type 1 and type 2 diabetes mellitus.

Based on the above, no major differences were noted in the pharmacokinetics and pharmacodynamics of ipragliflozin between patients with type 1 and type 2 diabetes mellitus after administration of ipragliflozin 50 or 100 mg, and ipragliflozin 50 or 100 mg was expected to produce a similar effect on urinary glucose excretion in patients with type 1 and type 2 diabetes mellitus. Thus, based on the approved dosage and administration for patients with type 2 diabetes mellitus, the following dosing regimen was selected for the Japanese phase III study in patients with type 1 diabetes mellitus to confirm the efficacy and safety of ipragliflozin: The starting dose was 50 mg once daily, and the dose was allowed to be increased up to 100 mg in the case of inadequate efficacy.

3) Study CL-0070: A placebo-controlled, randomized, double-blind study in Japanese patients with type 2 diabetes mellitus (target sample size, 24 subjects) in which placebo or ipragliflozin 50 or 100 mg was orally administered once daily before breakfast for 14 days

PMDA's view:

There are no major problems with the applicant's explanation on selecting a dosing regimen for the Japanese phase III study in patients with type 1 diabetes mellitus (Study CL-6002) after concluding that there are no major differences in the pharmacokinetics and pharmacodynamics of ipragliflozin between patients with type 1 and type 2 diabetes mellitus. The appropriateness of the dosing regimen will continue to be discussed in Section "7.R.5 Dosage and administration."

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results from a Japanese phase III study (Study CL-6002) as evaluation data (Table 4).

Table 4. Listing of efficacy and safety clinical study

Data	Geographical location	Study identity	Phase	Study population	Number of subjects treated	Dosing regimen	Main endpoints
Evaluation	Japan	CL-6002	III	Patients with type 1 diabetes mellitus who had inadequate glycemic control with insulin therapy	175	Placebo or ipragliflozin (50 mg) orally administered once daily in the morning (Double-blind phase, 24 weeks; Open-label phase, 28 weeks)	Efficacy Safety

The clinical study is outlined below. In this section, the doses of ipragliflozin are expressed as free base. HbA1c results are reported in National Glycohemoglobin Standardization Program (NGSP) units.

7.1 Japanese phase III study (CTD5.3.5.1-1, CTD5.3.5.1-1.1, Study CL-6002 [August 2016 to March 2018])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of ipragliflozin in Japanese patients with type 1 diabetes mellitus who had inadequate glycemic control with insulin therapy (target sample size, 150 subjects [50 in the placebo group, 100 in the ipragliflozin group]) [for pharmacokinetics, see Section "6.2.2 Japanese phase III study"].

Key inclusion criteria: adult patients with type 1 diabetes mellitus who had been receiving insulin therapy for ≥12 weeks at 6 weeks prior to the start of double-blind phase (Week −6)[4]; HbA1c of ≥7.5% and ≤11.0% and fasting blood C-peptide of <0.6 ng/mL at Week −6 or Week −2; the difference of HbA1c value between Week −6 and Week −2 was within ± 2.0%; and BMI of ≥20.0 and ≤35.0 kg/m^2 at Week −2. Patients who had received hypoglycemic agents other than insulin and α-glucosidase inhibitors (α-GIs) within the previous 8 weeks at Week −6 and patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2 or serum creatinine >2.0 mg/dL at Week −2) or end-stage renal disease requiring dialysis were excluded.

The study consisted of a run-in phase (6 weeks),[5] a double-blind phase (24 weeks), an open-label phase (28

[4] At 6 weeks prior to the start of double-blind phase (ie, Week −6), patients were considered eligible for the study if they had not switched from an insulin product to another insulin product or switched between continuous subcutaneous insulin infusion and multiple daily injections within the previous 12 weeks. However, patients were allowed to participate in the study if they had switched from an insulin product to another insulin product that has the same ingredients but a different product name or temporarily switched from continuous subcutaneous insulin infusion to multiple daily injections (≤2 weeks).

[5] The run-in phase consisted of a 4-week screening phase and a 2-week single-blind placebo treatment phase.

weeks), and a follow-up phase (4 weeks). A 4-week washout period before the run-in phase was scheduled for subjects who had been receiving concomitant α-GI.

During the double-blind phase, placebo or ipragliflozin 50 mg was to be orally administered once daily before or after breakfast for 24 weeks. During the open-label phase, ipragliflozin 50 mg was to be orally administered once daily before or after breakfast for 28 weeks (hereinafter, subjects who received placebo during the double-blind phase and ipragliflozin during the open-label phase are referred to as "the placebo/ipragliflozin group" and subjects who received ipragliflozin for 52 weeks are referred to as "the continued ipragliflozin group"). If HbA1c at Treatment Week 28 (Week 4 of the open-label phase) was ≥8.0% and there was no safety problem in the judgment of the investigator (sub-investigator), the dose of ipragliflozin was allowed to be increased from 50 mg to 100 mg at Treatment Week 32. However, if there was a safety problem after the dose increase, ipragliflozin was to be continued at a reduced dose of 50 mg, and a further dose increase was prohibited. If a dose reduction of insulin or ipragliflozin was required due to the occurrence of hypoglycemia, a dose reduction of insulin was to be considered first, and then a dose reduction of ipragliflozin also was to be considered as appropriate. At the start of double-blind phase (at Treatment Week 0), the dose of concomitant insulin was recommended to be reduced by 15% from the daily insulin dose at Week −6,[6)] and the insulin dose during the study period was to be adjusted according to a titration algorithm used by the subject according to their physician's instruction in routine clinical practice. Although switching from an insulin product to another insulin product and switching between continuous subcutaneous insulin infusion and multiple daily injections were prohibited between Week −6 and the end of double-blind phase (at Treatment Week 24 or at withdrawal), switching from an insulin product to another insulin product that has the same ingredients but a different product name and temporary switching from continuous subcutaneous insulin infusion to multiple daily injections (≤2 weeks) were permitted.

During the double-blind phase, all of 175 randomized subjects (60 in the placebo group, 115 in the ipragliflozin group) were included in the safety analysis set, and 174 subjects excluding 1 subject with no efficacy data after study drug administration were included in the Full Analysis Set (FAS), which was the primary efficacy analysis set. During the double-blind phase, 9 subjects were discontinued from the study, including 6 subjects in the placebo group (adverse event [3 subjects], protocol deviations [2 subjects], consent withdrawal [1 subject]) and 3 subjects in the ipragliflozin group (consent withdrawal [2 subjects], adverse event [1 subject]). All of 166 subjects who completed the double-blind phase (54 in the placebo group, 112 in the ipragliflozin group) entered the open-label phase. During the entire treatment phase (double-blind phase + open-label phase), 169 subjects who received ≥1 dose of ipragliflozin and had efficacy data after administration of ipragliflozin through the study period (54 in the placebo/ipragliflozin group, 115 in the continued ipragliflozin group) were included in the safety analysis set and in the FAS, and the FAS was the efficacy analysis set. During the open-label phase, 5 subjects were discontinued from the study, including 1 subject in the placebo/ipragliflozin group (hospitalization due to preoperative glycemic control) and 4 subjects in the continued ipragliflozin group

6) Among 174 subjects in the efficacy analysis set, 82 subjects (29 in the placebo group, 53 in the ipragliflozin group) were instructed by the investigator to reduce their daily insulin dose at the start of double-blind phase (at Treatment Week 0), but 92 subjects (30 in the placebo group, 62 in the ipragliflozin group) were not.

(adverse event [3 subjects], consent withdrawal [1 subject]). The dose of ipragliflozin was increased to 100 mg in 24 subjects in the placebo/ipragliflozin group. In the continued ipragliflozin group, treatment with ipragliflozin 50 mg was continued in 68 subjects, and the dose of ipragliflozin was increased to 100 mg in 44 subjects.

The primary efficacy endpoint of the change in HbA1c from baseline (Treatment Week 0) to the end of double-blind phase in the FAS is shown in Table 5, and a statistically significant reduction in HbA1c was observed in the ipragliflozin group compared to the placebo group.

Table 5. Change in HbA1c from baseline to end of double-blind phase (Study CL-6002, FAS)

Treatment group	Baseline	End of double-blind phase	Change from baseline	Treatment difference vs. placebo [a)]	*P*-value [a), b)]
Placebo (N = 59)	8.67 ± 0.79	8.56 ± 0.82	−0.11 ± 0.64	−0.36 [−0.57, −0.14]	0.001
Ipragliflozin (N = 115)	8.68 ± 0.81	8.21 ± 0.97	−0.47 ± 0.74		

Unit, %; Mean ± SD; Treatment difference, adjusted mean [95% confidence interval (CI)]; Last observation carried forward (LOCF)
a) Analysis of covariance (ANCOVA) including treatment group as a fixed effect and baseline HbA1c as a covariate
b) Two-sided significance level of 5%

In a secondary analysis of the primary endpoint, the proportions of subjects with HbA1c at the end of double-blind phase of <8.0% or <7.0% were 23.7% (14 of 59 subjects) and 1.7% (1 of 59 subjects), respectively, in the placebo group, and 47.8% (55 of 115 subjects) and 6.1% (7 of 115 subjects), respectively, in the ipragliflozin group.

The secondary endpoints of the changes in fasting plasma glucose and body weight from baseline (Treatment Week 0) to the end of double-blind phase (mean ± SD) were −1.4 ± 92.7 mg/dL and −0.04 ± 2.02 kg, respectively, in the placebo group, and −45.2 ± 71.7 mg/dL and −2.92 ± 2.34 kg, respectively, in the ipragliflozin group. The change in daily insulin dose from baseline to the end of double-blind phase is shown in Table 6.

Table 6. Change in daily insulin dose from baseline to end of double-blind phase (Study CL-6002, FAS)

Dose of concomitant insulin [a)]	Treatment group	Baseline	End of double-blind phase	Change from baseline	Treatment difference vs. placebo [b)]
Basal insulin	Placebo (N = 59)	18.9 ± 9.9	19.3 ± 10.1	0.4 ± 2.5	−3.8 [−4.7, −2.8]
	Ipragliflozin (N = 115)	19.2 ± 9.8	15.8 ± 9.4	−3.4 ± 3.5	
Bolus insulin	Placebo (N = 59)	31.5 ± 17.5	31.8 ± 17.4	0.3 ± 3.8	−3.7 [−5.1, −2.2]
	Ipragliflozin (N = 115)	30.1 ± 15.6	26.8 ± 14.0	−3.3 ± 5.5	
Total insulin	Placebo (N = 59)	50.5 ± 25.0	51.1 ± 25.0	0.6 ± 4.5	−7.4 [−9.1, −5.6]
	Ipragliflozin (N = 115)	49.2 ± 22.6	42.6 ± 21.1	−6.6 ± 6.2	

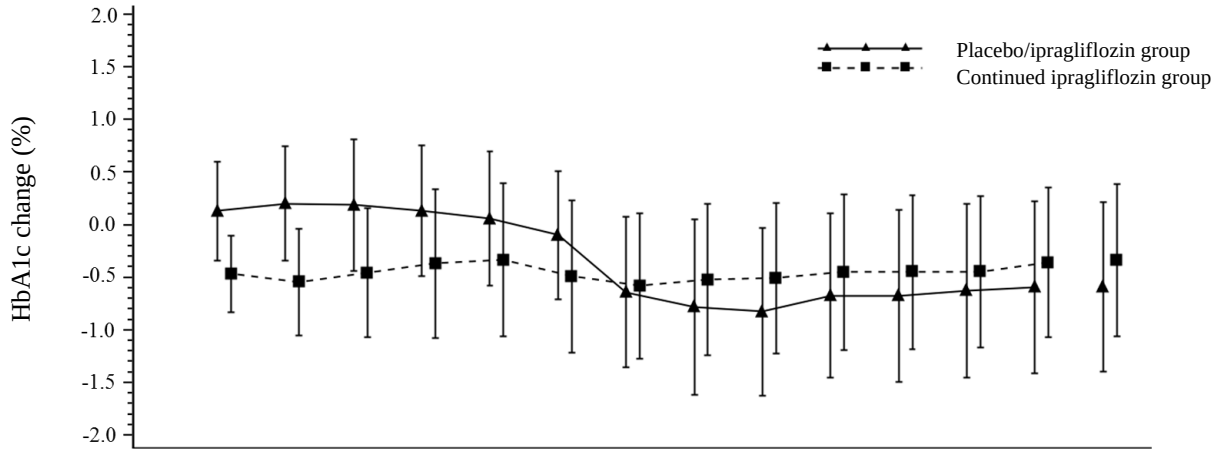
Mean ± SD; Treatment difference, adjusted mean [95% CI]; LOCF
a) Daily dose (IU)
b) ANCOVA including treatment group as a fixed effect and baseline daily insulin dose as a covariate

The changes in HbA1c, fasting plasma glucose, body weight, and the daily insulin dose from before the initiation of treatment with ipragliflozin to the end of the entire treatment phase (double-blind phase + open-label phase) (at Treatment Week 52 or at withdrawal) are shown in Table 7. HbA1c change over time is shown in Figure 1.

Table 7. Changes in HbA1c, fasting plasma glucose, body weight, and daily insulin dose from before initiation of treatment with ipragliflozin [a] to the end of entire treatment phase (double-blind phase + open-label phase) (Study CL-6002, FAS)

Endpoint		Treatment group	Before initiation of treatment with ipragliflozin	End of entire treatment phase	Change
HbA1c (%)		Placebo/Ipragliflozin (N = 54)	8.52 ± 0.78 [c]	8.04 ± 0.61	−0.49 ± 0.64 [c]
		Continued ipragliflozin (N = 115)	8.68 ± 0.81	8.35 ± 0.94	−0.33 ± 0.72
Fasting plasma glucose (mg/dL)		Placebo/Ipragliflozin (N = 54)	187.1 ± 88.1 [c]	145.0 ± 43.7	−42.2 ± 95.7 [c]
		Continued ipragliflozin (N = 115)	191.8 ± 69.0	160.9 ± 58.3 [d]	−30.3 ± 71.9 [d]
Body weight (kg)		Placebo/Ipragliflozin (N = 54)	64.08 ± 9.11 [c]	61.92 ± 9.62	−2.04 ± 2.13 [c]
		Continued ipragliflozin (N = 115)	66.18 ± 11.49	63.04 ± 11.95	−3.13 ± 3.21
Dose of concomitant insulin [b]	Basal insulin	Placebo/Ipragliflozin (N = 54)	19.92 ± 10.19 [c]	17.62 ± 10.34	−2.12 ± 3.33 [c]
		Continued ipragliflozin (N = 115)	19.15 ± 9.80	15.39 ± 9.53	−3.76 ± 3.85
	Bolus insulin	Placebo/Ipragliflozin (N = 54)	30.81 ± 16.58 [c]	28.01 ± 14.92	−2.68 ± 4.85 [c]
		Continued ipragliflozin (N = 115)	30.09±15.62	27.58±16.94	−2.51±7.08
	Total insulin	Placebo/Ipragliflozin (N = 54)	50.73 ± 24.56 [c]	45.63 ± 23.00	−4.80 ± 4.88 [c]
		Continued ipragliflozin (N = 115)	49.24 ± 22.58	42.97 ± 24.26	−6.27 ± 8.16

Mean ± SD; Including subjects with dose increase; LOCF
a) Treatment Week 24 for the placebo/ipragliflozin group, b) Daily dose (IU), c) N = 53, d) N = 114



Week	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52	End of study
No. of subjects															
Placebo/ipragliflozin group	54	54	54	54	54	54	53	54	54	54	53	53	53	53	54
Continued ipragliflozin group	115	114	114	114	113	113	113	112	111	112	112	111	109	109	115

Figure 1. HbA1c change over time from baseline to the end of entire treatment phase (double-blind phase + open-label phase) (including subjects with dose increase)
(Study CL-6002, FAS, Mean ± SD)

As to the safety profile, adverse events or adverse drug reactions reported by ≥2% of subjects in either treatment group during the double-blind phase (24 weeks of treatment) and during the entire treatment phase (52 weeks of treatment) are shown in Table 8 and Table 9, respectively.

Table 8. Adverse events or adverse drug reactions reported by ≥2% of subjects in either treatment group
(Study CL-6002 [Double-blind phase, 24 weeks of treatment], Safety analysis set)

Event term	Placebo (N = 60)		Ipragliflozin (N = 115)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	98.3 (59)	86.7 (52)	99.1 (114)	98.3 (113)
Hypoglycemia	93.3 (56)	85.0 (51)	98.3 (113)	97.4 (112)
Nasopharyngitis	28.3 (17)	0 (0)	28.7 (33)	0 (0)
Blood ketone body increased	1.7 (1)	1.7 (1)	9.6 (11)	8.7 (10)
Headache	1.7 (1)	0 (0)	6.1 (7)	3.5 (4)
Hyperglycaemia	6.7 (4)	0 (0)	4.3 (5)	0 (0)
Thirst	3.3 (2)	3.3 (2)	4.3 (5)	4.3 (5)
Weight decreased	0 (0)	0 (0)	4.3 (5)	4.3 (5)
Pollakiuria	3.3 (2)	3.3 (2)	3.5 (4)	3.5 (4)
Ketosis	1.7 (1)	1.7 (1)	3.5 (4)	3.5 (4)
Pruritus genital	0 (0)	0 (0)	3.5 (4)	3.5 (4)
Nausea	1.7 (1)	0 (0)	2.6 (3)	1.7 (2)
Arthralgia	1.7 (1)	0 (0)	2.6 (3)	0.9 (1)
Constipation	0 (0)	0 (0)	2.6 (3)	2.6 (3)
Muscle spasms	0 (0)	0 (0)	2.6 (3)	0.9 (1)
Eczema	0 (0)	0 (0)	2.6 (3)	0 (0)
Bacteriuria	3.3 (2)	3.3 (2)	1.7 (2)	1.7 (2)
Oropharyngeal pain	3.3 (2)	0 (0)	1.7 (2)	0 (0)
Diarrhoea	6.7 (4)	1.7 (1)	0.9 (1)	0 (0)
Back pain	6.7 (4)	0 (0)	0 (0)	0 (0)
Cystitis	5.0 (3)	3.3 (2)	0 (0)	0 (0)
Abdominal pain	3.3 (2)	1.7 (1)	0 (0)	0 (0)
Hypertension	3.3 (2)	0 (0)	0 (0)	0 (0)

Incidence % (n), MedDRA/J ver.19.0

Table 9. Adverse events or adverse drug reactions reported by ≥2% of subjects in either treatment group
(Study CL-6002 (Entire treatment phase, 52 weeks of treatment), Safety analysis set)

Event term	Placebo/Ipragliflozin [a] (N = 54)		Continued ipragliflozin (N = 115)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	100 (54)	94.4 (51)	100 (115)	100 (115)
Hypoglycemia	96.3 (52)	92.6 (50)	100 (115)	100 (115)
Nasopharyngitis	29.6 (16)	1.9 (1)	42.6 (49)	0 (0)
Blood ketone body increased	7.4 (4)	7.4 (4)	12.2 (14)	11.3 (13)
Headache	7.4 (4)	0 (0)	7.0 (8)	3.5 (4)
Hyperglycaemia	5.6 (3)	0 (0)	8.7 (10)	0 (0)
Thirst	1.9 (1)	1.9 (1)	5.2 (6)	5.2 (6)
Weight decreased	5.6 (3)	3.7 (2)	8.7 (10)	8.7 (10)
Pollakiuria	3.7 (2)	3.7 (2)	4.3 (5)	4.3 (5)
Ketosis	3.7 (2)	3.7 (2)	3.5 (4)	3.5 (4)
Pruritus genital	1.9 (1)	1.9 (1)	4.3 (5)	4.3 (5)
Nausea	0 (0)	0 (0)	2.6 (3)	1.7 (2)
Arthralgia	0 (0)	0 (0)	2.6 (3)	0 (0)
Constipation	0 (0)	0 (0)	5.2 (6)	5.2 (6)
Muscle spasms	3.7 (2)	1.9 (1)	3.5 (4)	0.9 (1)
Eczema	1.9 (1)	0 (0)	5.2 (6)	1.7 (2)
Bacteriuria	0 (0)	0 (0)	3.5 (4)	3.5 (4)
Oropharyngeal pain	0 (0)	0 (0)	3.5 (4)	0.9 (1)
Cystitis	13.0 (7)	13.0 (7)	2.6 (3)	1.7 (2)
Abdominal pain upper	0 (0)	0 (0)	3.5 (4)	0.9 (1)
Hypoaesthesia	1.9 (1)	0 (0)	3.5 (4)	2.6 (3)
Malaise	0 (0)	0 (0)	2.6 (3)	0.9 (1)
Musculoskeletal pain	1.9 (1)	0 (0)	2.6 (3)	0 (0)
Myalgia	0 (0)	0 (0)	2.6 (3)	0 (0)
Upper respiratory tract inflammation	1.9 (1)	0 (0)	4.3 (5)	0.9 (1)
Periodontitis	0 (0)	0 (0)	2.6 (3)	0.9 (1)
Pharyngitis	3.7 (2)	0 (0)	2.6 (3)	0 (0)
Pyrexia	0 (0)	0 (0)	2.6 (3)	1.7 (2)
Gastroenteritis	3.7 (2)	0 (0)	6.1 (7)	0 (0)
Influenza	1.9 (1)	0 (0)	6.1 (7)	0.9 (1)
Blood creatine phosphokinase increased	0 (0)	0 (0)	2.6 (3)	0.9 (1)
Dental caries	1.9 (1)	0 (0)	4.3 (5)	2.6 (3)
Ketonuria	3.7 (2)	3.7 (2)	0.9 (1)	0.9 (1)
Diarrhoea	3.7 (2)	1.9 (1)	1.7 (2)	0.9 (1)
Dysmenorrhoea	3.7 (2)	0 (0)	0.9 (1)	0 (0)
Tonsillitis	3.7 (2)	0 (0)	0 (0)	0 (0)

Incidence % (n), MedDRA/J ver.19.0
a) Events occurring after initiation of treatment with ipragliflozin

No deaths were reported. During the double-blind phase (24 weeks of treatment), serious events occurred in 2 subjects in the placebo group (hypoglycemia; and abdominal abscess), of which 1 event (hypoglycemia) was classified as an adverse drug reaction. During the open-label phase, serious events occurred in 2 subjects in the placebo/ipragliflozin group (vertigo positional; and colon cancer and failure to anastomose) and 2 subjects in the continued ipragliflozin group (deafness neurosensory; and facial paralysis), but a causal relationship to study drug was denied for all those events. During the double-blind phase (24 weeks of treatment), events leading to treatment discontinuation occurred in 3 subjects in the placebo group (urethritis; food craving; and hypoglycemia) and 1 subject in the ipragliflozin group (drug eruption), all of which were classified as adverse drug reactions. During the open-label phase, events leading to treatment discontinuation occurred in 2 subjects in the continued ipragliflozin group (vaginal infection; and blood ketone body increased), both of which were classified as adverse drug reactions.

During the double-blind phase (24 weeks of treatment), the incidences of hypoglycemia-related events[7)] were 93.3% (56 of 60 subjects) in the placebo group and 98.3% (113 of 115 subjects) in the ipragliflozin group, and the incidences of adverse drug reactions were 85.0% (51 of 60 subjects) in the placebo group and 97.4% (112 of 115 subjects) in the ipragliflozin group. Only hypoglycemia reported by 1 subject in the placebo group was classified as major hypoglycemia.[8)] During the open-label phase, the incidences of hypoglycemia-related events were 96.3% (52 of 54 subjects) in the placebo/ipragliflozin group and 100% (115 of 115 subjects) in the continued ipragliflozin group, and the incidences of adverse drug reactions were 92.6% (50 of 54 subjects) in the placebo/ipragliflozin group and 100% (115 of 115 subjects) in the continued ipragliflozin group. Events classified as major hypoglycemia occurred in 1 subject in the placebo/ipragliflozin group and 1 subject in the continued ipragliflozin group (both hypoglycemia), and the event reported by 1 subject in the continued ipragliflozin group was classified as an adverse drug reaction.

There were no clinically relevant changes in vital signs or 12-lead ECG throughout the entire treatment phase (52 weeks of treatment).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

In a Japanese phase III study (Study CL-6002), the treatment difference (ipragliflozin minus placebo) in change in HbA1c from baseline to the end of double-blind phase was −0.36% [95% CI: −0.57%, −0.14%], demonstrating superior efficacy of ipragliflozin over placebo in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy (Table 5). The treatment difference in change in the daily insulin dose from baseline to the end of double-blind phase (adjusted mean [95% CI]) was −3.8 [−4.7, −2.8] IU for basal insulin, −3.7 [−5.1, −2.2] IU for bolus insulin, and −7.4 [−9.1, −5.6] IU for total insulin, and there was a trend towards decreasing basal, bolus, and total insulin doses in the ipragliflozin group compared to the placebo group (Table 6). As for the long-term efficacy of ipragliflozin, the change in HbA1c from baseline to the end of study in the continued ipragliflozin group was −0.33% ± 0.72% (mean ± SD), demonstrating a reduction in HbA1c from baseline over 52 weeks (Table 7, Figure 1).

In view of the above results etc., PMDA concluded that the efficacy of ipragliflozin added to insulin therapy in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy was demonstrated.

---

7) Identified by the investigator based on the definitions (1) to (4). (1) Documented symptomatic hypoglycemia, typical symptoms of hypoglycemia with a measured plasma glucose of ≤70 mg/dL, (2) Asymptomatic hypoglycemia, no typical symptoms of hypoglycemia but measured plasma glucose is ≤70 mg/dL, (3) Probable symptomatic hypoglycemia, symptoms of hypoglycemia not accompanied by a plasma glucose measurement but are presumed to be caused by a plasma glucose concentration ≤70 mg/dL, and (4) Relative hypoglycemia, typical symptoms of hypoglycemia in a person with diabetes mellitus but with a measured plasma glucose concentration >70 mg/dL.

8) Hypoglycemia requiring assistance from another person

7.R.2 Safety

The applicant's explanation:

The occurrence of adverse events in a Japanese phase III study (Study CL-6002) is shown in Table 10. During the double-blind phase (24 weeks of treatment), the incidence of adverse events was similar between the ipragliflozin and placebo groups while the incidence of adverse drug reactions tended to be higher in the ipragliflozin group than in the placebo group. However, no serious events occurred in the ipragliflozin group, there was no trend towards more frequent events leading to treatment discontinuation in the ipragliflozin group than in the placebo group, and most of the reported events were mild in severity. The safety profile of ipragliflozin during the entire treatment phase including the open-label phase (52 weeks of treatment) showed no trend towards a substantial increase in serious events or events leading to treatment discontinuation with prolonged treatment, and most of the events occurring in the placebo/ipragliflozin and continued ipragliflozin groups were mild in severity. Moderate adverse events reported by ≥2 subjects were hypoglycemia (5 subjects), influenza (2 subjects), and blood ketone body increased (2 subjects) in the continued ipragliflozin group. Except for influenza (1 subject) and blood ketone body increased (1 subject), these events were classified as adverse drug reactions. A severe event occurring in the placebo/ipragliflozin group was failure to anastomose (1 subject), which was classified as a serious event, but its causal relationship to study drug was denied.

Table 10. Occurrence of adverse events in Study CL-6002
(Double-blind phase, 24 weeks of treatment; Entire treatment phase, 52 weeks of treatment; Safety analysis set)

Event term		24 weeks of treatment		52 weeks of treatment	
		Placebo (N = 60)	Ipragliflozin (N = 115)	Placebo/Ipragliflozin [a)] (N = 54)	Continued ipragliflozin (N = 115)
Any adverse event		98.3 (59)	99.1 (114)	100 (54)	100 (115)
Any adverse drug reaction		86.7 (52)	98.3 (113)	94.4 (51)	100 (115)
Serious events		3.3 (2)	0 (0)	3.7 (2)	1.7 (2)
Serious adverse drug reactions		1.7 (1)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation		5.0 (3)	0.9 (1)	0 (0)	2.6 (3)
Adverse drug reactions leading to treatment discontinuation		5.0 (3)	0.9 (1)	0 (0)	2.6 (3)
Severity	Mild	86.7 (52)	88.7 (102)	92.6 (50)	78.3 (90)
	Moderate	10.0 (6)	10.4 (12)	5.6 (3)	21.7 (25)
	Severe	1.7 (1)	0 (0)	1.9 (1)	0 (0)

Incidence % (n)
a) Events occurring after initiation of treatment with ipragliflozin

In Study CL-6002, the occurrence of events of special interest based on the risk management plan (draft) for ipragliflozin, etc. is shown in Table 11. During the double-blind phase (24 weeks of treatment), the incidences of hypoglycemia-related events, events related to increased ketone bodies, genital infection-related events, pollakiuria- or polyuria-related events, events related to decreased body weight, and skin and subcutaneous tissue disorders tended to be higher in the ipragliflozin group than in the placebo group. Analyses were performed for these events as shown below.

Table 11. Occurrence of events of special interest (Study CL-6002, Safety analysis set)

Event term	24 weeks of treatment		52 weeks of treatment	
	Placebo (N = 60)	Ipragliflozin (N = 115)	Placebo/Ipragliflozin [l] (N = 54)	Continued ipragliflozin (N = 115)
Hypoglycemia-related events [a]	93.3 (56)	98.3 (113)	96.3 (52)	100 (115)
Events related to increased ketone bodies [b]	3.3 (2)	13.0 (15)	13.0 (7)	17.4 (20)
Urinary tract infection-related events [c]	10.0 (6)	3.5 (4)	13.0 (7)	7.8 (9)
Genital infection-related events [d]	0 (0)	5.2 (6)	3.7 (2)	7.8 (9)
Pollakiuria- or polyuria-related events [e]	3.3 (2)	6.1 (7)	5.6 (3)	7.0 (8)
Events related to decreased fluid volume [f]	5.0 (3)	6.1 (7)	3.7 (2)	7.0 (8)
Events related to decreased body weight [g]	0 (0)	4.3 (5)	5.6 (3)	8.7 (10)
Renal disorders [h]	1.7 (1)	1.7 (2)	0 (0)	1.7 (2)
Fractures [i]	0 (0)	0 (0)	1.9 (1)	1.7 (2)
Malignant tumors [i]	0 (0)	0 (0)	1.9 (1)	0 (0)
Cardiovascular diseases [j]	0 (0)	0.9 (1)	0 (0)	3.5 (4)
Skin and subcutaneous tissue disorders [k]	3.3 (2)	7.8 (9)	11.1 (6)	12.2 (14)

Incidence % (n)

a) Events collected based on footnote 7 to this Review Report, b) Events identified by Preferred terms (PTs) blood ketone body increased, ketonuria, ketosis, and urine ketone body present that were selected by the applicant, c) Events identified by PTs asymptomatic bacteriuria, bacteriuria, cystitis, and urethritis that were selected by the applicant, d) Events identified by PTs genital candidiasis, pruritus genital, vaginal infection, vulvovaginal candidiasis, and vulvovaginal pruritus that were selected by the applicant, e) Events identified by PTs pollakiuria, polyuria, and urine output increased that were selected by the applicant, f) Events identified by PTs blood pressure decreased, dehydration, hypotension, syncope, and thirst that were selected by the applicant, g) Events identified by PT weight decreased, h) Events in High Level Group Terms (HLGTs) renal disorders (excl nephropathies) and nephropathies, i) Collected by the applicant from among the reported events based on PTs falling under each category. j) Events identified by Standardised MedDRA queries (SMQs) central nervous system haemorrhages and cerebrovascular conditions (broad), and myocardial infarction (broad), k) Events in System Organ Class (SOC) skin and subcutaneous tissue disorders, l) Events occurring after initiation of treatment with ipragliflozin

During the double-blind phase (24 weeks of treatment), the incidence of hypoglycemia-related events tended to be slightly higher in the ipragliflozin group than in the placebo group, while in the ipragliflozin group, no serious events or events leading to treatment discontinuation occurred, most of the events were mild in severity, and no severe events were reported. A similar trend was observed for the occurrence of hypoglycemia-related events following administration of ipragliflozin also during the entire treatment phase including the open-label phase (52 weeks of treatment), and no serious events or events leading to treatment discontinuation were reported [for the details of the occurrence of hypoglycemia-related events, see Section "7.R.2.1 Hypoglycemia"]. During the double-blind phase (24 weeks of treatment), events related to increased ketone bodies occurred in 2 subjects in the placebo group (blood ketone body increased; and ketosis, 1 subject each) and 15 subjects in the ipragliflozin group (blood ketone body increased [11 subjects]; and ketosis [4 subjects]), and except for 1 case of blood ketone body increased in the ipragliflozin group, all those events were classified as adverse drug reactions. In the continued ipragliflozin group during the open-label phase, blood ketone body increased (4 subjects), ketonuria and ketonuria (1 subject), urine ketone body present (1 subject), and ketosis (1 subject) were reported, and all those events except for 1 event of ketonuria were classified as adverse drug reactions. Through the entire treatment phase (52 weeks of treatment), an event leading to treatment discontinuation occurred in 1 subject in the continued ipragliflozin group during the open-label phase (blood ketone body increased), which was mild in severity and resolved without treatment. No serious events related to increased ketone bodies were reported [for the details of safety including clinical chemistry data relating to ketone bodies, see Section "7.R.2.2 Blood ketone body increased"]. During the double-blind phase (24 weeks of treatment), genital infection-related events occurred in 6 subjects in the ipragliflozin group (pruritus genital [4 subjects]; genital candidiasis [1 subject]; and vulvovaginal pruritus [1 subject]). In the continued ipragliflozin group during the open-label phase, vaginal infection; pruritus genital; and vulvovaginal candidiasis (1 subject each) occurred. All those events except for 1 case of vulvovaginal candidiasis in the continued ipragliflozin group were classified as adverse drug reactions. Through the entire treatment phase (52

weeks of treatment), an event leading to treatment discontinuation occurred in 1 subject in the continued ipragliflozin group (vaginal infection) during the open-label phase, and this event was mild in severity, treated with medications, and then resolved. No serious genital infection-related events were reported, and all of the events were mild in severity. Pollakiuria- or polyuria-related events occurred in 2 subjects in the placebo group (pollakiuria [2 subjects]) and 7 subjects in the ipragliflozin group (pollakiuria [4 subjects]; urine output increased [2 subjects]; and polyuria [1 subject]) during the double-blind phase (24 weeks of treatment), and pollakiuria occurred in 1 subject in the continued ipragliflozin group during the open-label phase. Although all those events were classified as adverse drug reactions, no serious events or events leading to treatment discontinuation were reported in either treatment group through the entire treatment phase (52 weeks of treatment), and all of the reported events were mild in severity. Events related to decreased body weight occurred in 5 subjects in the ipragliflozin group (weight decreased [5 subjects]) during the double-blind phase (24 weeks of treatment) and weight decreased occurred in 5 subjects in the continued ipragliflozin group during the open-label phase, all of which were classified as adverse drug reactions. Through the entire treatment phase (52 weeks of treatment), no serious events or events leading to treatment discontinuation were reported in either treatment group, and all of the reported events were mild in severity except for 1 moderate event in the continued ipragliflozin group during the open-label phase. Skin and subcutaneous tissue disorders occurred in 2 subjects in the placebo group (ingrowing nail; and rash, 1 subject each) and 9 subjects in the ipragliflozin group (eczema [3 subjects]; dermatitis; drug eruption; leukoderma; urticaria; miliaria; and skin fissures, 1 subject each) during the double-blind phase (24 weeks of treatment), among which rash in the placebo group and dermatitis, drug eruption, and urticaria in the ipragliflozin group were classified as adverse drug reactions. In the continued ipragliflozin group during the open-label phase, skin and subcutaneous tissue disorders occurred in 6 subjects (dermatitis contact and eczema; dry skin and rash; eczema; eczema and urticaria; dermatitis atopic; and pruritus, 1 subject each), of which dermatitis contact and eczema; eczema and urticaria; and pruritus (1 subject each) were classified as adverse drug reactions. Through the entire treatment phase (52 weeks of treatment), an event leading to treatment discontinuation occurred in 1 subject in the ipragliflozin group (drug eruption) during the double-blind phase (24 weeks of treatment), which was moderate in severity, treated with medications, and then resolved. No serious skin and subcutaneous tissue disorders were reported.

The occurrence of events of special interest by time from onset of therapy in the continued ipragliflozin group in Study CL-6002 is shown in Table 12. There was a trend towards a high incidence through Treatment Week 12 for most of these events, and no substantial increases in the incidences of events of special interest occurred with prolonged treatment period.

Table 12. Occurrence of events of special interest [a)] by time from onset of therapy in the continued ipragliflozin group (Study CL-6002, Safety analysis set)

Event term	Weeks 0-12 (N = 115)	Weeks 12-24 (N = 114)	Weeks 24-36 (N = 113)	Weeks 36-48 (N = 112)	Week 48 onwards (N = 110)
Any adverse event	97.4 (112)	97.4 (111)	92.9 (105)	84.8 (95)	90.0 (99)
Hypoglycemia-related events	97.4 (112)	93.9 (107)	87.6 (99)	79.5 (89)	84.5 (93)
Events related to increased ketone bodies	11.3 (13)	2.6 (3)	1.8 (2)	3.6 (4)	1.8 (2)
Urinary tract infection-related events	1.7 (2)	1.8 (2)	0 (0)	3.6 (4)	1.8 (2)
Genital infection-related events	3.5 (4)	1.8 (2)	1.8 (2)	0 (0)	0.9 (1)
Pollakiuria- or polyuria-related events	6.1 (7)	0 (0)	0.9 (1)	0 (0)	0 (0)
Events related to decreased fluid volume	6.1 (7)	0 (0)	0.9 (1)	0 (0)	0 (0)
Events related to decreased body weight	3.5 (4)	0.9 (1)	2.7 (3)	1.8 (2)	0.9 (1)
Renal disorders	1.7 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Fractures	0 (0)	0 (0)	0.9 (1)	0.9 (1)	0 (0)
Malignant tumors	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular diseases	0 (0)	0.9 (1)	0.9 (1)	0.9 (1)	0.9 (1)
Skin and subcutaneous tissue disorders	1.7 (2)	6.1 (7)	5.3 (6)	0.9 (1)	0 (0)

Incidence % (n)
a) See footnotes a)-k) to Table 11.

In order to assess the safety of ipragliflozin in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy, adverse events in Study CL-6002 (Tables 10 and 11) were compared with adverse events from pooled data from studies in patients with type 2 diabetes mellitus (the data had been submitted for the initial approval of ipragliflozin)[9)] (Table 13), although this comparison is not rigorous because of the differences in subject characteristics (e.g., the use of insulin therapy), study design, and the method of collecting events of special interest. The incidence of overall adverse events tended to be higher in Study CL-6002 than in the pooled data from studies in patients with type 2 diabetes mellitus, but Study CL-6002 showed a high incidence of adverse events also in the placebo group as in the ipragliflozin group. There was no trend towards a higher incidence of serious events or events leading to treatment discontinuation in Study CL-6002. As to events of special interest, the incidences of hypoglycemia-related events and events related to increased ketone bodies tended to be particularly high in Study CL-6002. The cause of the high incidence of hypoglycemia-related events in Study CL-6002 was considered to be the occurrence of hypoglycemia associated with insulin therapy because all subjects in Study CL-6002 received insulin therapy, and no subjects received insulin therapy in the pooled studies in patients with type 2 diabetes mellitus. Actually, the incidence of hypoglycemia-related events was high also in the placebo group in Study CL-6002. The high incidence of overall adverse events in Study CL-6002 was due to frequently reported hypoglycemia-related events. As to events related to increased ketone bodies, the incidence of urine ketone body present was similar between the placebo and ipragliflozin groups based on the pooled data from the double-blind studies in patients with type 2 diabetes mellitus, whereas the incidence of events related to increased ketone bodies tended to be higher in the ipragliflozin group in Study CL-6002. In a long-term treatment study in patients with type 2 diabetes mellitus (Study CL-0122), clinical chemistry data relating to ketone bodies, i.e. the mean levels of serum total

9) Pooled data from double-blind studies were obtained from pooled analysis of 6 studies: a Japanese phase II dose-finding study (Study CL-0103), a Japanese phase III monotherapy study (Study CL-0105), a metformin combination therapy study (Study CL-0106), a pioglitazone combination therapy study (Study CL-0107), a sulfonylurea combination therapy study (Study CL-0109), and a study in patients with renal impairment (Study CL-0072). Pooled data from 52-week treatment studies were obtained from pooled analysis of subjects treated with ipragliflozin for 52 weeks in 8 studies: a Japanese long-term monotherapy study (Study CL-0121), a metformin combination therapy study (Study CL-0106), a pioglitazone combination therapy study (Study CL-0107), a sulfonylurea combination therapy study (Study CL-0109), an α-GI combination therapy study (Study CL-0108), a dipeptidyl peptidase-4 (DPP-4) inhibitor combination therapy study (Study CL-0110), a nateglinide combination therapy study (Study CL-0111), and a study in patients with renal impairment (Study CL-0072). In both pooled analyses, adverse events were translated into the terms on MedDRA/J ver.15.0 and collected, and cardiovascular diseases were collected by referring to SMQ (MedDRA/J ver.15.0) and selecting the relevant MedDRA PTs.

ketone bodies, acetoacetic acid, and 3-hydroxybutyric acid were 98.66, 31.11, and 67.64 μmol/L, respectively, at baseline and 159.52, 45.82, and 113.71 μmol/L, respectively, after the last dose, and the maximum level of serum total ketone bodies during the treatment period was 1040.0 μmol/L. In Study CL-6002, these clinical chemistry levels tended to be high after administration of ipragliflozin [see Section "7.R.2.2 Blood ketone body increased"]. However, in Study CL-6002, no serious events related to increased ketone bodies or diabetic ketoacidosis occurred following administration of ipragliflozin.

Table 13. Occurrence of adverse events and events of special interest
(Pooled data from studies in patients with type 2 diabetes mellitus [a), b)]; Safety analysis set)

Event term		24 weeks of treatment [a)]		52 weeks of treatment [b)]
		Placebo (N = 368)	Ipragliflozin (N = 628)	Ipragliflozin [c)] (N = 1017)
Any adverse event		67.9 (250)	72.9 (458)	86.1 (876)
Any adverse drug reaction		16.8 (62)	25.3 (159)	38.0 (386)
Serious events		3.5 (13)	2.5 (16)	7.2 (73)
Serious adverse drug reactions		0.8 (3)	0.2 (1)	1.2 (12)
Events leading to treatment discontinuation		11.4 (42)	4.6 (29)	8.6 (87)
Adverse drug reactions leading to treatment discontinuation		2.2 (8)	1.9 (12)	3.9 (40)
Severity	Mild	62.0 (228)	67.8 (426)	74.8 (761)
	Moderate	5.2 (19)	4.9 (31)	9.7 (99)
	Severe	0.8 (3)	0.2 (1)	1.6 (16)
Hypoglycemia-related events [d)]		0.8 (3)	1.0 (6)	2.4 (24)
Events related to increased ketone bodies [e)]		0.3 (1)	0.2 (1)	0.4 (4)
Urinary tract infection-related events [f)]		2.7 (10)	1.8 (11)	3.2 (33)
Genital infection-related events [g)]		0.8 (3)	2.1 (13)	2.5 (25)
Pollakiuria- or polyuria-related events [h)]		2.4 (9)	8.4 (53)	13.5 (137)
Events related to decreased fluid volume [i)]		1.6 (6)	4.6 (29)	7.6 (77)
Events related to decreased body weight [j)]		0.5 (2)	1.1 (7)	3.8 (39)
Renal disorders [j)]		0 (0)	0.3 (2)	1.3 (13)
Fractures [k)]		0.8 (3)	0.5 (3)	1.6 (16)
Malignant tumors [l)]		0.3 (1)	0.5 (3)	1.5 (15)
Cardiovascular diseases [j)]		2.7 (10)	1.1 (7)	2.3 (23)
Skin and subcutaneous tissue disorders [j)]		6.3 (23)	9.1 (57)	13.9 (141)

Incidence % (n), a) Pooled data from double-blind studies listed in footnote 9 to this Review Report. b) Pooled data from 52-week treatment studies listed in footnote 9 to this Review Report. c) Also including dose increases to 100 mg/day from Treatment Week 20 onward in b) Studies CL-0121, CL-0108, CL-0110, and CL-0111 and dose increases to 100 mg/day from Treatment Week 24 onward (the open-label phase) in b) Studies CL-0106, CL-0107, CL-0109, and CL-0072. d) Hypoglycemia-related events were collected in the judgment of the investigator. e) Events identified by PT urine ketone body present that was selected by the applicant were collected. f) Urinary tract infection-related events were collected in the judgment of the investigator. g) Genital infection-related events were collected in the judgment of the investigator. Events identified by PTs pruritus genital, vaginal candidiasis, and vaginitis bacterial that were selected by the applicant in Study CL-0103 only. h) Events identified by PTs nocturia, pollakiuria, polyuria, and urine output increased that were selected by the applicant. i) Events identified by PTs blood pressure decreased, blood urea increased, dehydration, hypotension, orthostatic hypotension, presyncope, syncope, thirst, and urine output decreased that were selected by the applicant. j) Events related to decreased body weight, renal disorders, cardiovascular diseases, and skin and subcutaneous tissue disorders were collected based on footnotes g), h), j), and k) to Table 11, respectively. k) Events identified by PTs clavicle fracture, facial bones fracture, femoral neck fracture, fibula fracture, foot fracture, hand fracture, humerus fracture, multiple fractures, rib fracture, spinal compression fracture, and tibia fracture that were selected by the applicant. l) Events identified by PTs bile duct cancer, Bowen's disease, colon cancer, gastric cancer, gastric cancer stage 0, hepatic neoplasm malignant, oesophageal carcinoma, uterine cancer, small intestine carcinoma, metastatic hepatic cancer, large intestine carcinoma, prostate cancer, non-small cell lung cancer, and thyroid cancer that were selected by the applicant.

Based on the above, no new events of potentially clinical relevance occurred in Study CL-6002. When the data from Study CL-6002 were compared with the pooled data from studies in patients with type 2 diabetes mellitus, the incidences of hypoglycemia-related events and events related to increased ketone bodies were particularly high in Study CL-6002, but no serious events occurred following administration of ipragliflozin, and no risk requiring a new precaution was detected. Thus, appropriate safety management is possible by providing similar precautions as those for the previously approved indication of type 2 diabetes mellitus.

PMDA's view:

Given the safety data from Japanese clinical studies, the safety of ipragliflozin in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy is acceptable, provided that appropriate precautionary statements about the events to be described later are included in the package insert. Based on the occurrence of adverse events in Study CL-6002 and the results of comparison with the pooled data from studies in patients with type 2 diabetes mellitus, further analyses were performed for hypoglycemia-related events and events related to increased ketone bodies, which were reported at a particularly high incidence following administration of ipragliflozin.

7.R.2.1 Hypoglycemia

The applicant's explanation:

The occurrence of hypoglycemia-related events in a Japanese phase III study (Study CL-6002) is shown in Table 14. During the double-blind phase (24 weeks of treatment), the rates of documented symptomatic hypoglycemia, asymptomatic hypoglycemia, and probable symptomatic hypoglycemia were higher in the ipragliflozin group than in the placebo group. Major hypoglycemia[8)] occurred in 1 subject in the placebo group during the double-blind phase (24 weeks of treatment). During the entire treatment phase including the open-label phase (52 weeks of treatment), major hypoglycemia occurred in 1 subject in the placebo/ipragliflozin group after the initiation of treatment with ipragliflozin and 1 subject in the continued ipragliflozin group. As the event reported by 1 subject in the placebo/ipragliflozin group occurred 7 days after the last dose of ipragliflozin, its causal relationship to study drug was denied.

Table 14. Occurrence of hypoglycemia-related events in Study CL-6002
(Double-blind phase, 24 weeks of treatment; Entire treatment phase, 52 weeks of treatment; Safety analysis set)

Event term		24 weeks of treatment		52 weeks of treatment	
		Placebo (N = 60)	Ipragliflozin (N = 115)	Placebo/Ipragliflozin [a)] (N = 54)	Continued ipragliflozin (N = 115)
Adverse events		93.3 (56)	98.3 (113)	96.3 (52)	100 (115)
		1399 [52.2]	3412 [64.3]	1897 [56.0]	6303 [51.5]
Adverse drug reactions		85.0 (51)	97.4 (112)	92.6 (50)	100 (115)
		1170 [43.7]	3335 [62.8]	1614 [47.7]	5770 [47.2]
Serious events		1.7 (1)	0 (0)	0 (0)	0 (0)
		1 [0]	0 [0]	0 [0]	0 [0]
Events leading to treatment discontinuation		1.7 (1)	0 (0)	0 (0)	0 (0)
		1 [0]	0 [0]	0 [0]	0 [0]
Adverse events by category	Documented symptomatic hypoglycemia [b)]	80.0 (48)	89.6 (103)	88.9 (48)	92.2 (106)
		742 [27.7]	1648 [31.0]	1060 [31.3]	3065 [25.1]
	Documented symptomatic hypoglycemia [b)] and plasma glucose ≤50 mg/dL	61.7 (37)	65.2 (75)	68.5 (37)	70.4 (81)
		205 [7.7]	470 [8.9]	237 [7.0]	811 [6.6]
	Asymptomatic hypoglycemia [b)]	85.0 (51)	84.3 (97)	83.3 (45)	89.6 (103)
		599 [22.4]	1676 [31.6]	751 [22.2]	3093 [25.3]
	Asymptomatic hypoglycemia [b)] and plasma glucose ≤50 mg/dL	30.0 (18)	43.5 (50)	25.9 (14)	47.8 (55)
		59 [2.2]	218 [4.1]	57 [1.7]	396 [3.2]
	Probable symptomatic hypoglycemia [b)]	3.3 (2)	9.6 (11)	9.3 (5)	9.6 (11)
		4 [0.1]	49 [0.9]	21 [0.6]	59 [0.5]
	Relative hypoglycemia [b)]	13.3 (8)	14.8 (17)	11.1 (6)	20.9 (24)
		54 [2.0]	39 [0.7]	65 [1.9]	86 [0.7]

Upper row, Incidence % (n); Lower row, No. of events [Rate per patient-years]
a) Events occurring after initiation of treatment with ipragliflozin
b) Documented symptomatic hypoglycemia, typical symptoms of hypoglycemia with a measured plasma glucose of ≤70 mg/dL; Asymptomatic hypoglycemia, no typical symptoms of hypoglycemia but measured plasma glucose is ≤70 mg/dL; Probable symptomatic hypoglycemia, symptoms of hypoglycemia not accompanied by a plasma glucose measurement but are presumed to be caused by a plasma glucose concentration ≤70 mg/dL; and Relative hypoglycemia, typical symptoms of hypoglycemia in a person with diabetes mellitus but with a measured plasma glucose concentration >70 mg/dL.

Based on the above, as hypoglycemia occurs frequently with insulin therapy targeting near-normal glycemic control in patients with type 1 diabetes mellitus, caution is required. Meanwhile, ipragliflozin lowers blood glucose, but does not tend to increase the risk of serious hypoglycemia in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy. Thus, there should be no clinically relevant concerns.

7.R.2.2 Blood ketone body increased

The applicant's explanation:

The changes from baseline in laboratory values of ketone bodies (serum total ketone bodies, acetoacetic acid, and 3-hydroxybutyric acid) in a Japanese phase III study (Study CL-6002) are shown in Table 15. During the double-blind phase (24 weeks of treatment), the changes from baseline in serum total ketone bodies, acetoacetic acid, and 3-hydroxybutyric acid tended to increase in the ipragliflozin group compared to the placebo group. The proportions of subjects with a shift to high levels of serum total ketone bodies, acetoacetic acid, and 3-hydroxybutyric acid (a shift from below the upper limit of normal to above the upper limit of normal) were 31.0% (9 of 29 subjects), 15.6% (7 of 45 subjects), and 27.6% (8 of 29 subjects), respectively, in the placebo group, and 57.9% (33 of 57 subjects), 44.2% (38 of 86 subjects), and 59.3% (32 of 54 subjects), respectively, in the ipragliflozin group, showing higher proportions in the ipragliflozin group. These proportions tended to further increase in the continued ipragliflozin group treated with ipragliflozin for 52 weeks compared to the ipragliflozin group treated with ipragliflozin for 24 weeks (64.9% [37 of 57 subjects], 54.7% [47 of 86 subjects], and 66.7% [36 of 54 subjects], respectively, in the continued ipragliflozin group). The mean increases from baseline in these 3 laboratory values in the continued ipragliflozin group remained within a certain range through the entire treatment phase (52 weeks of treatment) (approximately 1.80- to 2.53-, 1.77- to 2.35-, and 1.82- to 2.60-fold the mean levels at baseline, respectively), but these values tended to return towards baseline levels during the follow-up phase (approximately 1.23-, 1.21-, and 1.24-fold the mean levels at baseline, respectively). In the continued ipragliflozin group, a laboratory finding of diabetic ketoacidosis, i.e. serum total ketone bodies ≥3000 μmol/L, were observed in 1 or 2 subjects per time point between Treatment Weeks 4 and 20, 1 subject at Treatment Week 44, and 1 subject at Treatment Week 48, whereas no subjects had serum total ketone bodies ≥5000 μmol/L (a withdrawal criterion for individual subjects) or developed diabetic ketoacidosis.

Table 15. Changes in laboratory values of ketone bodies in Study CL-6002
(Double-blind phase, 24 weeks of treatment; Entire treatment phase, 52 weeks of treatment; Safety analysis set)

		24 weeks of treatment		52 weeks of treatment	
		Placebo (N = 60)	Ipragliflozin (N = 115)	Placebo/Ipragliflozin [a] (N = 54)	Continued ipragliflozin (N = 115)
Total ketone bodies	Baseline	186.48 ± 185.34	200.78 ± 212.32	158.45 ± 139.02 [c]	200.78 ± 212.32
	End of treatment phase	166.50 ± 147.72 [b]	383.24 ± 346.20	405.00 ± 481.83	447.89 ± 433.50
	Change from baseline to end of treatment phase	−21.96 ± 163.32 [b]	182.47 ± 336.70	251.38 ± 467.00 [c]	247.11 ± 416.59
Acetoacetic acid	Baseline	56.89 ± 50.72	56.26 ± 52.14	49.78 ± 36.15 [c]	56.26 ± 52.14
	End of treatment phase	52.91 ± 39.90 [b]	101.08 ± 81.27	114.22 ± 134.34	113.27 ± 100.81
	Change from baseline to end of treatment phase	−4.36 ± 46.75 [b]	44.81 ± 80.40	65.68 ± 131.08 [c]	57.01 ± 99.34
3-hydroxybutyric acid	Baseline	129.59 ± 136.19	144.57 ± 162.54	108.64 ± 104.32 [c]	144.57 ± 162.54
	End of treatment phase	113.54 ± 109.35 [b]	282.17 ± 268.21	290.70 ± 349.34	334.52 ± 345.30
	Change from baseline to end of treatment phase	−17.64 ± 118.66 [b]	137.60 ± 259.57	185.64 ± 338.07 [c]	189.95 ± 329.10

Unit, μmol/L; Mean ± SD
Reference range: total ketone bodies, 26.0-122 μmol/L; acetoacetic acid, 13.0-69.0 μmol/L; 3-hydroxybutyric acid, ≤76.0 μmol/L
a) Baseline refers to Treatment Week 24 before the initiation of treatment with ipragliflozin, b) N = 59, c) N = 53

Based on the above, when patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy are treated with ipragliflozin, ketone bodies may be elevated within a clinically acceptable range, even with good glycemic control, due to increased fatty acid metabolism associated with a reduction in the insulin dose or increased urinary glucose excretion caused by ipragliflozin. However, ketoacidosis was not reported in Japanese clinical studies. As elevation of ketone bodies may lead to ketoacidosis, an appropriate precautionary statement is necessary. On the other hand, no new precautionary statement about ketoacidosis is necessary because ketoacidosis has already been listed in the precautions section etc. of the current package insert for Suglat.

PMDA's view on hypoglycemia and blood ketone body increased associated with ipragliflozin in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy:
According to Japanese clinical study data, the use of ipragliflozin resulted in an increase in the rate of hypoglycemia-related events, an increase in the incidence of events related to increased ketone bodies, a trend towards increasing blood ketone bodies, etc. However, no serious hypoglycemia or hypoglycemia leading to treatment discontinuation following administration of ipragliflozin was reported, and the occurrence of major hypoglycemia was also very limited. Likewise, also as to blood ketone body increased, no serious events such as ketoacidosis were observed. In view of the above situation and the observed benefits presented in Section "7.R.1 Efficacy," the use of ipragliflozin is acceptable in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy, whereas further precautionary statements about hypoglycemia and ketoacidosis (e.g. the insulin dose needs to be adjusted appropriately when ipragliflozin is used in combination with insulin therapy) are needed. The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3 Clinical positioning of ipragliflozin

The applicant's explanation:
Type 1 diabetes mellitus accounts for approximately 6% of all cases of diabetes (*Journal of the Japan Diabetes Society*. 2015; 58: 426-36) and is caused by destruction of the pancreatic β cells, leading to absolute insulin deficiency. Insulin therapy is the standard of care for patients with type 1 diabetes mellitus. However, as insulin

therapy requires weight control to avoid weight gain, and the risk of hypoglycemia increases with increasing insulin dose, the insulin dose cannot be increased to an appropriate level in some patients. Oral hypoglycemic agents that can be used in patients with type 1 diabetes mellitus are limited, when compared with patients with type 2 diabetes mellitus. Although the clinical use of α-GI indicated for improvement in post-prandial hyperglycemia in patients with diabetes mellitus is possible, α-GI improves HbA1c to a lesser degree compared to other hypoglycemic agents, medication adherence is a problem as α-GI needs to be administered immediately before each meal, and α-GI causes adverse reactions of gastrointestinal symptoms such as diarrhoea. Since the blood glucose-lowering effect of ipragliflozin, an SGLT2 inhibitor, is insulin-independent, additive blood glucose-lowering effects can be produced without significantly affecting the risk of serious hypoglycemia when ipragliflozin is added to insulin therapy in patients with type 1 diabetes mellitus. Thus, ipragliflozin in combination with insulin therapy is expected to contribute to glycemic control. Furthermore, ipragliflozin is expected to reduce body weight and is associated with a low risk of gastrointestinal symptoms (diarrhoea, etc.), which are observed with α-GI, and once-daily oral ipragliflozin should be more convenient and help improve adherence. Based on the above, ipragliflozin can become a new treatment to be used in combination with insulin therapy for patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy.

PMDA's view:

The applicant's explanation (ipragliflozin in combination with insulin therapy in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy is expected to contribute to glycemic control) is understood, and the clinical study has confirmed its efficacy and safety [see Section "7.R.1 Efficacy" and Section "7.R.2 Safety"]. Thus, ipragliflozin can become a new treatment option to be added to insulin therapy for patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy.

7.R.4 Indications

PMDA's view:

Since the efficacy of ipragliflozin in combination with insulin therapy in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy has been demonstrated [see Section "7.R.1 Efficacy"] and its safety is considered acceptable [see Section "7.R.2 Safety"], the indication of ipragliflozin can be expanded to cover type 1 diabetes mellitus. However, taking also account of the patient population included in clinical studies of ipragliflozin and the clinical positioning of ipragliflozin [see Section "7.R.3 Clinical positioning of ipragliflozin"], it should be noted that the intended population is patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy and that ipragliflozin is used in combination with insulin therapy, and the relevant statements need to be included in the indications or precautions for indications section of the package insert. The above points will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation:

The pharmacokinetic and pharmacodynamic data from a clinical pharmacology study in patients with type 1 diabetes mellitus (Study CL-6001) were compared with those from a clinical pharmacology study in patients with type 2 diabetes mellitus (Study CL-0070 [3)]) submitted for the initial approval of ipragliflozin. As a result, there were no major differences between patients with type 1 and type 2 diabetes mellitus with respect to the pharmacokinetics/pharmacodynamics of ipragliflozin after administration of ipragliflozin 50 or 100 mg. Thus, based on the approved dosage and administration for patients with type 2 diabetes mellitus, the following dosing regimen was selected for a Japanese phase III study (Study CL-6002): The starting dose was 50 mg once daily, and the dose was allowed to be increased up to 100 mg in the case of inadequate efficacy [see Section "6.R.1 Rationale for the dosing regimen selected for Japanese phase III study"].

In Study CL-6002, when ipragliflozin 50 mg was administered once daily for 24 weeks, the treatment difference in change in HbA1c from baseline to the end of double-blind phase [95% CI] (ipragliflozin minus placebo) was −0.36 [−0.57, −0.14]%, demonstrating the superiority of ipragliflozin over placebo (Table 5), and there were no major safety problems. As a result of assessing the efficacy of an increased dose of ipragliflozin in subjects receiving once daily ipragliflozin 50 mg who had HbA1c ≥8.0% at Treatment Week 28 and had their dose increased to 100 mg at Treatment Week 32, the changes in HbA1c, fasting plasma glucose, and body weight from before the dose increase (Treatment Week 32) to Treatment Week 52 were 0.02%, −6.6 mg/dL, and −0.23 kg, respectively. While the change in HbA1c remained almost unchanged after the dose increase, the proportion of subjects with a ≥0.3% point reduction in HbA1c from before the dose increase (Treatment Week 32) to 12 weeks (Treatment Week 44) or 20 weeks (Treatment Week 52) after the dose increase was 37.2% (16 of 43 subjects) and 28.6% (12 of 42 subjects), respectively, and the proportion of subjects with a ≥0.5% point reduction in HbA1c was 11.6% (5 of 43 subjects) and 19.0% (8 of 42 subjects), respectively. Given these findings, increasing the dose to 100 mg/day in the case of inadequate efficacy at 50 mg/day was considered useful. As a result of assessing the safety of an increased dose of ipragliflozin, the occurrence of adverse events before the dose increase (ipragliflozin 50 mg) and after the dose increase (ipragliflozin 100 mg) in the placebo/ipragliflozin and continued ipragliflozin groups is shown in Table 16. None of the events occurred apparently more frequently after the dose increase, and there were no major safety problems.

Table 16. Occurrence of adverse events before and after dose increase of ipragliflozin (Study CL-6002, Safety analysis set)

Event term	Placebo/Ipragliflozin [a] (N = 24)		Continued ipragliflozin (N = 44)	
	Before dose increase (3.8 patient-years)	After dose increase (11.2 patient-years)	Before dose increase (27.3 patient-years)	After dose increase (20.2 patient-years)
Any adverse event	95.8 (23)	100 (24)	100 (44)	97.7 (43)
	228 [60.6]	575 [51.3]	1474 [54.0]	800 [39.7]
Any adverse drug reaction	83.3 (20)	91.7 (22)	100 (44)	90.9 (40)
	202 [53.7]	406 [36.3]	1370 [50.2]	596 [29.6]
Serious events	0 (0)	4.2 (1)	0 (0)	2.3 (1)
	0 [0]	2 [0.2]	0 [0]	1 [0.0]
Events leading to treatment discontinuation	0 (0)	0 (0)	2.3 (1)	2.3 (1)
	0 [0]	0 [0]	1 [0.0]	1 [0.0]
Hypoglycemia-related events [b]	83.3 (20)	95.8 (23)	100 (44)	90.9 (40)
	204 [54.2]	520 [46.4]	1333 [48.8]	691 [34.3]
Events related to increased ketone bodies [b]	0 (0)	8.3 (2)	18.2 (8)	4.5 (2)
	0 [0]	2 [0.2]	8 [0.3]	2 [0.1]

Upper row, Incidence % (n); Lower row, No. of events [Rate per patient-years]
a) Events occurring after initiation of treatment with ipragliflozin
b) See footnotes a) and b) to Table 11.

In Study CL-6002, only 1 subject in the continued ipragliflozin group required a dose reduction to 50 mg/day after a dose increase to 100 mg/day, and the reason for the dose reduction in this subject was as follows: The dose was reduced to 50 mg/day at the discretion of the investigator because local laboratory testing for urine ketone bodies after the dose increase to 100 mg/day (at Treatment Week 36) produced a result (2+) (before the dose increase, (+)). There was no particular trend in the characteristics of this subject, and there were no major safety problems after the dose increase as shown in Table 16. However, as with the previously approved dosage and administration, the need for a dose increase should be determined cautiously with careful monitoring of the patient's clinical course.

PMDA's view:

There is no major problem with the proposed dosage and administration for patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy based on the results from clinical studies that evaluated the pharmacokinetics, efficacy, and safety of ipragliflozin (as with dosage and administration for patients with type 2 diabetes mellitus, ipragliflozin 50 mg should be 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.). However, taking also account of the patient population included in clinical studies of ipragliflozin and the clinical positioning of ipragliflozin [see Section "7.R.3 Clinical positioning of ipragliflozin"], it should be noted that ipragliflozin is not an alternative to insulin therapy for patients with type 1 diabetes mellitus and that ipragliflozin is used in combination with insulin therapy, and the relevant statements need be included in the dosage and administration or precautions for dosage and administration section of the package insert. The above points will be discussed at the Expert Discussion.

7.R.6 Special populations

7.R.6.1 Patients with renal impairment

The applicant's explanation:

The occurrence of adverse events by degree of renal impairment (baseline eGFR [mL/min/1.73 m^2]: normal, ≥90; mild impairment, ≥60 and <90; moderate impairment, ≥30 and <60) in a Japanese phase III study (Study CL-6002) is shown in Table 17 and Table 18. Although rigorous comparison is difficult due to the limited

number of patients with moderate renal impairment in Study CL-6002, comparisons in the placebo and ipragliflozin groups during the double-blind phase (24 weeks of treatment) showed no trend towards substantial differences in the incidence of adverse events according to the degree of renal impairment, and comparisons in the continued ipragliflozin group during the entire treatment phase (52 weeks of treatment) also showed no apparent effects of renal impairment.

Table 17. Occurrence of adverse events [a)] by degree of renal impairment
(Study CL-6002 [Double-blind phase, 24 weeks of treatment]; Safety analysis set)

Event term	Normal		Mild impairment		Moderate impairment	
	Placebo (N = 31)	Ipragliflozin (N = 64)	Placebo (N = 28)	Ipragliflozin (N = 48)	Placebo (N = 1)	Ipragliflozin (N = 3)
Any adverse event	96.8 (30)	98.4 (63)	100 (28)	100 (48)	100 (1)	100 (3)
Any adverse drug reaction	87.1 (27)	96.9 (62)	85.7 (24)	100 (48)	100 (1)	100 (3)
Serious events	0 (0)	0 (0)	7.1 (2)	0 (0)	0 (0)	0 (0)
Serious adverse drug reactions	0 (0)	0 (0)	3.6 (1)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation	3.2 (1)	1.6 (1)	7.1 (2)	0 (0)	0 (0)	0 (0)
Adverse drug reactions leading to treatment discontinuation	3.2 (1)	1.6 (1)	7.1 (2)	0 (0)	0 (0)	0 (0)
Hypoglycemia-related events	90.3 (28)	96.9 (62)	96.4 (27)	100 (48)	100 (1)	100 (3)
Events related to increased ketone bodies	6.5 (2)	15.6 (10)	0 (0)	10.4 (5)	0 (0)	0 (0)
Urinary tract infection-related events	9.7 (3)	6.3 (4)	7.1 (2)	0 (0)	100 (1)	0 (0)
Genital infection-related events	0 (0)	4.7 (3)	0 (0)	6.3 (3)	0 (0)	0 (0)
Pollakiuria- or polyuria-related events	3.2 (1)	6.3 (4)	3.6 (1)	6.3 (3)	0 (0)	0 (0)
Events related to decreased fluid volume	3.2 (1)	6.3 (4)	7.1 (2)	6.3 (3)	0 (0)	0 (0)
Events related to decreased body weight	0 (0)	4.7 (3)	0 (0)	4.2 (2)	0 (0)	0 (0)
Renal disorders	0 (0)	1.6 (1)	3.6 (1)	2.1 (1)	0 (0)	0 (0)
Fractures	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Malignant tumors	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular diseases	0 (0)	0 (0)	0 (0)	2.1 (1)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	3.2 (1)	10.9 (7)	3.6 (1)	4.2 (2)	0 (0)	0 (0)

Incidence % (n)
a) See footnotes a)-k) to Table 11 for definition of events of special interest.

Table 18. Occurrence of adverse events [a] by degree of renal impairment
(Study CL-6002 [Entire treatment phase, 52 weeks of treatment]; Safety analysis set)

Event term	Normal		Mild impairment		Moderate impairment	
	Placebo/Ipragliflozin [b] (N = 21)	Continued ipragliflozin (N = 64)	Placebo/Ipragliflozin [b] (N = 31)	Continued ipragliflozin (N = 48)	Placebo/Ipragliflozin [b] (N = 1)	Continued ipragliflozin (N = 3)
Any adverse event	100 (21)	100 (64)	100 (31)	100 (48)	100 (1)	100 (3)
Any adverse drug reaction	90.5 (19)	100 (64)	96.8 (30)	100 (48)	100 (1)	100 (3)
Serious events	0 (0)	0 (0)	6.5 (2)	4.2 (2)	0 (0)	0 (0)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation	0 (0)	3.1 (2)	0 (0)	2.1 (1)	0 (0)	0 (0)
Adverse drug reactions leading to treatment discontinuation	0 (0)	3.1 (2)	0 (0)	2.1 (1)	0 (0)	0 (0)
Hypoglycemia-related events	95.2 (20)	100 (64)	96.8 (30)	100 (48)	100 (1)	100 (3)
Events related to increased ketone bodies	14.3 (3)	20.3 (13)	12.9 (4)	14.6 (7)	0 (0)	0 (0)
Urinary tract infection-related events	4.8 (1)	10.9 (7)	16.1 (5)	4.2 (2)	100 (1)	0 (0)
Genital infection-related events	4.8 (1)	6.3 (4)	3.2 (1)	10.4 (5)	0 (0)	0 (0)
Pollakiuria- or polyuria-related events	0 (0)	6.3 (4)	9.7 (3)	8.3 (4)	0 (0)	0 (0)
Events related to decreased fluid volume	0 (0)	7.8 (5)	6.5 (2)	6.3 (3)	0 (0)	0 (0)
Events related to decreased body weight	9.5 (2)	7.8 (5)	3.2 (1)	10.4 (5)	0 (0)	0 (0)
Renal disorders	0 (0)	1.6 (1)	0 (0)	2.1 (1)	0 (0)	0 (0)
Fractures	4.8 (1)	1.6 (1)	0 (0)	2.1 (1)	0 (0)	0 (0)
Malignant tumors	0 (0)	0 (0)	3.2 (1)	0 (0)	0 (0)	0 (0)
Cardiovascular diseases	0 (0)	3.1 (2)	0 (0)	4.2 (2)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	0 (0)	15.6 (10)	16.1 (5)	8.3 (4)	100 (1)	0 (0)

Incidence % (n)
a) See footnotes a)-k) to Table 11 for definition of events of special interest.
b) Events occurring after initiation of treatment with ipragliflozin

Based on the above, although the number of patients with moderate renal impairment was limited in Study CL-6002, there was no major problem with the safety of ipragliflozin in patients with renal impairment.

PMDA's view:

Although Study CL-6002 showed no trend towards a particularly increased safety risk in the subgroups by degree of renal impairment, taking also account of the limited number of patients with moderate renal impairment assessed and the mechanism of action of ipragliflozin, a similar precautionary statement regarding use in patients with renal impairment as that for the previously approved indication, is necessary.

7.R.6.2 Patients with hepatic impairment

The applicant's explanation:

The occurrence of adverse events in patients with or without hepatic impairment (concomitant conditions in SOC "Hepatobiliary disorders") in a Japanese phase III study (Study CL-6002) is shown in Table 19 and Table 20. Although the subgroup of patients with hepatic impairment was smaller than the subgroup of patients without hepatic impairment in Study CL-6002, no trend towards substantial differences in the incidence of adverse events according to the presence or absence of hepatic impairment was found in comparisons in the placebo and ipragliflozin groups during the double-blind phase (24 weeks of treatment) or comparisons in the continued ipragliflozin group during the entire treatment phase (52 weeks of treatment).

Table 19. Occurrence of adverse events [a)] in patients with or without hepatic impairment
(Study CL-6002 [Double-blind phase, 24 weeks of treatment]; Safety analysis set)

Event term	Without hepatic impairment		With hepatic impairment	
	Placebo (N = 52)	Ipragliflozin (N = 97)	Placebo (N = 8)	Ipragliflozin (N = 18)
Any adverse event	98.1 (51)	99.0 (96)	100 (8)	100 (18)
Any adverse drug reaction	86.5 (45)	97.9 (95)	87.5 (7)	100 (18)
Serious events	3.8 (2)	0 (0)	0 (0)	0 (0)
Serious adverse drug reactions	1.9 (1)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation	5.8 (3)	1.0 (1)	0 (0)	0 (0)
Adverse drug reactions leading to treatment discontinuation	5.8 (3)	1.0 (1)	0 (0)	0 (0)
Hypoglycemia-related events	92.3 (48)	97.9 (95)	100 (8)	100 (18)
Events related to increased ketone bodies	3.8 (2)	12.4 (12)	0 (0)	16.7 (3)
Urinary tract infection-related events	9.6 (5)	3.1 (3)	12.5 (1)	5.6 (1)
Genital infection-related events	0 (0)	5.2 (5)	0 (0)	5.6 (1)
Pollakiuria- or polyuria-related events	3.8 (2)	6.2 (6)	0 (0)	5.6 (1)
Events related to decreased fluid volume	3.8 (2)	6.2 (6)	12.5 (1)	5.6 (1)
Events related to decreased body weight	0 (0)	5.2 (5)	0 (0)	0 (0)
Renal disorders	1.9 (1)	2.1 (2)	0 (0)	0 (0)
Fractures	0 (0)	0 (0)	0 (0)	0 (0)
Malignant tumors	0 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular diseases	0 (0)	0 (0)	0 (0)	5.6 (1)
Skin and subcutaneous tissue disorders	1.9 (1)	8.2 (8)	12.5 (1)	5.6 (1)

Incidence % (n)
a) See footnotes a)-k) to Table 11 for definition of events of special interest.

Table 20. Occurrence of adverse events [a)] in patients with or without hepatic impairment
(Study CL-6002 [Entire treatment phase, 52 weeks of treatment]; Safety analysis set)

Event term	Without hepatic impairment		With hepatic impairment	
	Placebo/Ipragliflozin [b)] (N = 47)	Continued ipragliflozin (N = 97)	Placebo/Ipragliflozin [b)] (N = 7)	Continued ipragliflozin (N = 18)
Any adverse event	100 (47)	100 (97)	100 (7)	100 (18)
Any adverse drug reaction	95.7 (45)	100 (97)	85.7 (6)	100 (18)
Serious events	2.1 (1)	1.0 (1)	14.3 (1)	5.6 (1)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation	0 (0)	3.1 (3)	0 (0)	0 (0)
Adverse drug reactions leading to treatment discontinuation	0 (0)	3.1 (3)	0 (0)	0 (0)
Hypoglycemia-related events	95.7 (45)	100 (97)	100 (7)	100 (18)
Events related to increased ketone bodies	12.8 (6)	16.5 (16)	14.3 (1)	22.2 (4)
Urinary tract infection-related events	12.8 (6)	8.2 (8)	14.3 (1)	5.6 (1)
Genital infection-related events	4.3 (2)	8.2 (8)	0 (0)	5.6 (1)
Pollakiuria- or polyuria-related events	6.4 (3)	7.2 (7)	0 (0)	5.6 (1)
Events related to decreased fluid volume	4.3 (2)	7.2 (7)	0 (0)	5.6 (1)
Events related to decreased body weight	6.4 (3)	9.3 (9)	0 (0)	5.6 (1)
Renal disorders	0 (0)	2.1 (2)	0 (0)	0 (0)
Fractures	0 (0)	2.1 (2)	14.3 (1)	0 (0)
Malignant tumors	2.1 (1)	0 (0)	0 (0)	0 (0)
Cardiovascular diseases	0 (0)	3.1 (3)	0 (0)	5.6 (1)
Skin and subcutaneous tissue disorders	12.8 (6)	13.4 (13)	0 (0)	5.6 (1)

Incidence % (n)
a) See footnotes a)-k) to Table 11 for definition of events of special interest.
b) Events occurring after initiation of treatment with ipragliflozin

Based on the above, there was no major problem with the safety of ipragliflozin in patients with hepatic impairment in Study CL-6002.

PMDA's view:

Although Study CL-6002 showed no trend towards a particularly increased safety risk in patients with hepatic impairment, taking also account of the limited number of patients with hepatic impairment assessed and the pharmacokinetic profile of ipragliflozin, a similar precautionary statement regarding use in patients with hepatic impairment as that for the previously approved indication, is necessary.

7.R.6.3 Elderly

The applicant's explanation:

The occurrence of adverse events by age group (<65 years, ≥65 years) in a Japanese phase III study (Study CL-6002) is shown in Table 21 and Table 22. Although the number of subjects aged ≥65 years was limited in Study CL-6002, no trend towards substantial differences in the incidence of adverse events between subjects aged <65 years and those aged ≥65 years was found in comparisons in the placebo and ipragliflozin groups during the double-blind phase (24 weeks of treatment) or comparisons in the continued ipragliflozin group during the entire treatment phase (52 weeks of treatment) by age group.

Table 21. Occurrence of adverse events [a)] by age group (Study CL-6002 [Double-blind phase, 24 weeks of treatment]; Safety analysis set)

Event term	<65 years		≥65 years	
	Placebo (N = 53)	Ipragliflozin (N = 96)	Placebo (N = 7)	Ipragliflozin (N = 19)
Any adverse event	98.1 (52)	99.0 (95)	100 (7)	100 (19)
Any adverse drug reaction	86.8 (46)	97.9 (94)	85.7 (6)	100 (19)
Serious events	3.8 (2)	0 (0)	0 (0)	0 (0)
Serious adverse drug reactions	1.9 (1)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation	5.7 (3)	1.0 (1)	0 (0)	0 (0)
Adverse drug reactions leading to treatment discontinuation	5.7 (3)	1.0 (1)	0 (0)	0 (0)
Hypoglycemia-related events	92.5 (49)	97.9 (94)	100 (7)	100 (19)
Events related to increased ketone bodies	3.8 (2)	14.6 (14)	0 (0)	5.3 (1)
Urinary tract infection-related events	11.3 (6)	4.2 (4)	0 (0)	0 (0)
Genital infection-related events	0 (0)	5.2 (5)	0 (0)	5.3 (1)
Pollakiuria- or polyuria-related events	1.9 (1)	6.3 (6)	14.3 (1)	5.3 (1)
Events related to decreased fluid volume	3.8 (2)	6.3 (6)	14.3 (1)	5.3 (1)
Events related to decreased body weight	0 (0)	4.2 (4)	0 (0)	5.3 (1)
Renal disorders	0 (0)	1.0 (1)	14.3 (1)	5.3 (1)
Fractures	0 (0)	0 (0)	0 (0)	0 (0)
Malignant tumors	0 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular diseases	0 (0)	0 (0)	0 (0)	5.3 (1)
Skin and subcutaneous tissue disorders	3.8 (2)	8.3 (8)	0 (0)	5.3 (1)

Incidence % (n)

a) See footnotes a)-k) to Table 11 for definition of events of special interest.

Table 22. Occurrence of adverse events [a] by age group (Study CL-6002 [Entire treatment phase, 52 weeks of treatment]; Safety analysis set)

Event term	<65 years		≥65 years	
	Placebo/Ipragliflozin [b] (N = 47)	Continued ipragliflozin (N = 96)	Placebo/Ipragliflozin [b] (N = 7)	Continued ipragliflozin (N = 19)
Any adverse event	100 (47)	100 (96)	100 (7)	100 (19)
Any adverse drug reaction	93.6 (44)	100 (96)	100 (7)	100 (19)
Serious events	2.1 (1)	0 (0)	14.3 (1)	10.5 (2)
Serious adverse drug reactions	0 (0)	0 (0)	0 (0)	0 (0)
Events leading to treatment discontinuation	0 (0)	3.1 (3)	0 (0)	0 (0)
Adverse drug reactions leading to treatment discontinuation	0 (0)	3.1 (3)	0 (0)	0 (0)
Hypoglycemia-related events	95.7 (45)	100 (96)	100 (7)	100 (19)
Events related to increased ketone bodies	14.9 (7)	17.7 (17)	0 (0)	15.8 (3)
Urinary tract infection-related events	14.9 (7)	8.3 (8)	0 (0)	5.3 (1)
Genital infection-related events	4.3 (2)	7.3 (7)	0 (0)	10.5 (2)
Pollakiuria- or polyuria-related events	4.3 (2)	6.3 (6)	14.3 (1)	10.5 (2)
Events related to decreased fluid volume	2.1 (1)	7.3 (7)	14.3 (1)	5.3 (1)
Events related to decreased body weight	4.3 (2)	8.3 (8)	14.3 (1)	10.5 (2)
Renal disorders	0 (0)	1.0 (1)	0 (0)	5.3 (1)
Fractures	2.1 (1)	2.1 (2)	0 (0)	0 (0)
Malignant tumors	0 (0)	0 (0)	14.3 (1)	0 (0)
Cardiovascular diseases	0 (0)	3.1 (3)	0 (0)	5.3 (1)
Skin and subcutaneous tissue disorders	10.6 (5)	12.5 (12)	14.3 (1)	10.5 (2)

Incidence % (n)
a) See footnotes a)-k) to Table 11 for definition of events of special interest.
b) Events occurring after initiation of treatment with ipragliflozin

Based on the above, no particular trend was observed for the occurrence of adverse events by age group (<65 years, ≥65 years) in Study CL-6002, and there was no major problem with the safety of ipragliflozin in the elderly.

PMDA's view:

Although there are no particular concerns about safety in the elderly based on the occurrence of adverse events by age group in Study CL-6002, taking also account of the limited number of elderly patients assessed and the mechanism of action of ipragliflozin, a similar precautionary statement regarding use in elderly patients as that for the previously approved indication, is necessary.

7.R.7 Post-marketing investigations

The applicant's explanation:

The incidences of hypoglycemia-related events and events related to increased ketone bodies were higher in the ipragliflozin group than in the placebo group and there was a trend towards increasing blood ketone bodies following administration of ipragliflozin in a Japanese phase III study of ipragliflozin in combination with insulin therapy. Thus, in the safety specification included in the risk management plan (draft) for ipragliflozin, "hypoglycemia" and "ketoacidosis and the impact of increased ketone bodies" are considered to be particular concerns that should be addressed when administering ipragliflozin to patients with type 1 diabetes mellitus. A post-marketing database survey to collect the relevant information from patients with type 1 diabetes mellitus treated with or without ipragliflozin and compare the occurrence of these events is currently under planning. The details of the method of collecting information, etc., are under consideration.

PMDA's view:

There is no particular problem with the applicant's policy of post-marketing survey, which will be discussed also at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD5.3.5.1-1, CTD5.3.5.1-1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that ipragliflozin administered in combination with insulin therapy has efficacy in the treatment of type 1 diabetes mellitus, and that ipragliflozin has acceptable safety in view of its benefits. Ipragliflozin added to insulin therapy offers a new treatment option for patients with type 1 diabetes mellitus.

PMDA has concluded that ipragliflozin may be approved if ipragliflozin is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 7, 2018

Product Submitted for Approval

Brand Name	Suglat Tablets 25 mg and 50 mg
Non-proprietary Name	Ipragliflozin L-Proline
Applicant	Astellas Pharma Inc.
Date of Application	January 11, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

1.1 Efficacy

PMDA's view:

In a Japanese phase III study (Study CL-6002), the treatment difference(ipragliflozin minus placebo) in change in HbA1c from baseline to the end of double-blind phase was −0.36% [95% CI: −0.57%, −0.14%], demonstrating superior efficacy of ipragliflozin over placebo in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy. The treatment difference in change in the daily insulin dose from baseline to the end of double-blind phase (adjusted mean [95% CI]) was −3.8 [−4.7, −2.8] IU for basal insulin, −3.7 [−5.1, −2.2] IU for bolus insulin, and −7.4 [−9.1, −5.6] IU for total insulin, and there was a trend towards decreasing basal, bolus, and total insulin doses in the ipragliflozin group compared to the placebo group. As for the long-term efficacy of ipragliflozin, the change in HbA1c from baseline to the end of study in the continued ipragliflozin group was −0.33% ± 0.72% (mean ± SD), demonstrating a reduction in HbA1c from baseline over 52 weeks.

In view of the above results etc., PMDA concluded that the efficacy of ipragliflozin added to insulin therapy in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy was demonstrated.

The expert advisors supported the above conclusion by PMDA.

1.2 Safety

PMDA's view:

Given the safety data from Japanese clinical studies, the safety of ipragliflozin in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy is acceptable, provided that appropriate precautionary statements about hypoglycemia and ketoacidosis to be described later are included in the package insert. As to hypoglycemia and ketoacidosis, according to Japanese clinical study data, the use of ipragliflozin resulted in an increase in the rate of hypoglycemia-related events, an increase in the incidence of events related to increased ketone bodies, a trend towards increasing blood ketone bodies, etc. Thus, further precautionary statements about hypoglycemia and ketoacidosis (e.g. the insulin dose needs to be adjusted appropriately when ipragliflozin is used in combination with insulin therapy) are needed. It is also necessary to make an effort to collect post-marketing safety information on these events.

The expert advisors supported the above conclusion by PMDA.

Based on the above, PMDA requested that the applicant include the relevant precautionary statements in the package insert and confirmed that the applicant took appropriate action [for the main precautionary statements about hypoglycemia and ketoacidosis, see Section "1.4 Dosage and administration" and for post-marketing investigations, see Section "1.5 Risk management plan (draft)"].

1.3 Indications

PMDA's view:

Since the efficacy of ipragliflozin in combination with insulin therapy in patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy has been demonstrated [see Review Report (1) Section "7.R.1 Efficacy"] and its safety is considered acceptable [see Review Report (1) Section "7.R.2 Safety"], the indication of ipragliflozin can be expanded to cover type 1 diabetes mellitus. However, taking also account of the patient population included in clinical studies of ipragliflozin and the clinical positioning of ipragliflozin, it is necessary to appropriately advise that the intended population is patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy.

The expert advisors supported the above conclusion by PMDA.

PMDA instructed the applicant to add the following statement in the precautions for indications section of the package insert and confirmed that the applicant took appropriate action.

Precautions for Indications

Suglat should be used only in patients who have inadequate glycemic control despite adequate and optimized insulin therapy.

1.4 Dosage and administration

PMDA's view:

There is no major problem with the proposed dosage and administration for patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy based on the results from clinical studies that evaluated the pharmacokinetics, efficacy, and safety of ipragliflozin (as with dosage and administration for patients with type 2 diabetes mellitus, ipragliflozin 50 mg should be 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.). However, taking also account of the patient population included in clinical studies of ipragliflozin and the clinical positioning of ipragliflozin, it should be clearly stated in the dosage and administration section that ipragliflozin is used in combination with insulin therapy, and it is necessary to appropriately advise that ipragliflozin is not an alternative to insulin therapy for patients with type 1 diabetes mellitus.

The expert advisors supported the above conclusion by PMDA.

PMDA instructed the applicant to modify the proposed dosage and administration statement as shown below and add the following statements in the precautions for dosage and administration section, and confirmed that the applicant took appropriate action.

Dosage and Administration

Type 1 diabetes mellitus

Suglat is used in combination with insulin. 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.

Precautions for Dosage and Administration

- Suglat is not an alternative to insulin. If insulin is stopped, acute hyperglycaemia or ketoacidosis may occur. Do not stop insulin during treatment with Suglat.
- When Suglat is used in combination with insulin, a dose reduction of insulin should be considered to reduce the risk of hypoglycemia. Note that excessive dose reduction increases the risk of ketoacidosis. In a clinical study, it was recommended that the daily insulin dose should be reduced by 15%.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for ipragliflozin should include the safety specification presented in Table 23, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 24.

Table 23. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Hypoglycemia · Genital infection · Urinary tract infection · Pollakiuria/polyuria · Events related to decreased fluid volume such as dehydration · Ketoacidosis and impact of increased ketone bodies	· Impact of decreased body weight on safety · Renal disorders · Fractures · Malignant tumors · Cardiovascular diseases · Leg amputation	· Safety of ipragliflozin in the elderly · Safety of ipragliflozin in patients with renal impairment · Safety of ipragliflozin in patients with hepatic impairment
Efficacy specification		
None		

Table 24. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
· Early post-marketing phase vigilance · Post-marketing database survey (hypoglycemia) · Post-marketing database survey (ketoacidosis, impact of increased ketone bodies)	· Disseminate information gathered from early post-marketing phase vigilance · Develop and distribute informative materials for proper use (a guide for proper use to healthcare professionals, patient information leaflet)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition. Since the current application is for a new indication and a new dosage, the re-examination period for the indication and the dosage and administration claimed in the current application is 4 years.

Indications

Type 2 diabetes mellitus

Type 1 diabetes mellitus

(Underline denotes additions.)

Dosage and Administration

Type 2 diabetes mellitus

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.

Type 1 diabetes mellitus

Suglat is used in combination with insulin. 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.

(Underline denotes additions.)

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

Adverse drug reaction	Adverse event for which a causal relationship to study drug cannot be ruled out
AUC	Area under the plasma concentration-time curve
BMI	Body mass index
CL/F	Oral clearance
C_{max}	Maximum plasma concentration
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
GFR	Glomerular filtration rate
HbA1c	Glycosylated haemoglobin Hemoglobin A1c
ipragliflozin	Ipragliflozin L-Proline
LOCF	Last observation carried forward
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
PMDA	Pharmaceuticals and medical devices agency
PPK	Population pharmacokinetics
PT	Preferred terms
SGLT2	Sodium glucose cotransporter 2
SMQ	Standardised MedDRA queries
SOC	System Organ Class
STZ	Streptozotocin
The product	Suglat Tablets 25 mg and 50 mg
α-GI	Alpha-glucosidase inhibitor