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ORIGINAL RESEARCH

Safety and Effectiveness of Ipragliflozin for Type 2 Diabetes in Japan: 12-Month Interim Results of the STELLA-LONG TERM Post-Marketing Surveillance Study

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ABSTRACT

Introduction: The present interim report of the STELLA-LONG TERM study aimed to examine the safety and effectiveness of ipragliflozin in real-word clinical practice in Japan using data up to 12 months. We also evaluated the effect of ipragliflozin on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in patients with normal vs. abnormal liver function.

Methods: This is an ongoing 3-year post-marketing surveillance study. We analyzed data from Japanese type 2 diabetes mellitus (T2DM) patients who were first prescribed ipragliflozin between 17 July 2014 and 16 October 2015 at participating centers in Japan, and whose data were locked by 16 January 2018. The incidence of adverse drug reactions (ADRs) was evaluated for safety. Changes in glycemic control and body weight were evaluated for effectiveness. The effect on liver function was evaluated by changes in the fatty liver index, and changes in AST and ALT were evaluated in patients with normal and abnormal liver function.

Results: The safety analysis set comprised 11,051 patients and the efficacy analysis set comprised 8788 patients. The incidence rates of ADRs and serious ADRs were 14.6% (1616/11,051) and 0.97% (107/11,051), respectively. Significant reductions (all $P < 0.001$ vs. baseline, paired t test) in glycated hemoglobin (− 0.8%), fasting plasma glucose (− 31.9 mg/dL), body weight (− 2.9 kg), and fatty liver index (− 8.7) were observed. In patients with normal liver function at baseline, no clinically significant changes in AST and ALT were observed. In patients with abnormal liver function at baseline, clinically and statistically significant decreases ($P < 0.05$ vs. baseline, two-sample t test) in AST (− 9.0 U/L) and ALT (− 14.7 U/L) levels were observed.

Conclusion: Ipragliflozin was effective and well tolerated in Japanese patients with T2DM over 12 months in the real-world clinical setting. Improvements in liver function parameters (AST and ALT) were observed in T2DM patients with abnormal liver function.

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INTRODUCTION

Ipragliflozin is a sodium–glucose cotransporter 2 (SGLT2) inhibitor that was approved in Japan in January 2014 for the treatment of type 2 diabetes mellitus (T2DM) patients [1]. Although SGLT2 inhibitors are known to provide benefits in relation to the low risk of hypoglycemia and promotion of weight loss [2], there are limited data on the safety and effectiveness of the SGLT2 inhibitor ipragliflozin in the real-world setting in Japan.

Several post-marketing surveillance studies of ipragliflozin have been conducted under the guidance of the Japanese Pharmaceuticals and Medical Devices Agency. The STELLA-LONG TERM study is an ongoing 3-year post-marketing surveillance study of ipragliflozin in Japanese patients with T2DM in real-world clinical practice [3, 4]. Subgroup analyses based on the interim cutoff data have been conducted to evaluate the long-term safety and effectiveness of ipragliflozin in elderly vs. non-elderly patients and stratified by body mass index (BMI) and liver function status (normal vs. abnormal) [5, 6]. Recently published interim reports of the STELLA-LONG TERM study included a pooled analysis of 3-, 12-, and 24-month data [4, 5]. The results of the analyses conducted thus far have shown that ipragliflozin was effective in improving glycemic control without raising new safety concerns in T2DM patients [3, 4], regardless of age [5] or BMI [data on file], and improved liver function in T2DM patients with abnormal liver function [6].

Preclinical study findings have suggested an improvement in liver function with SGLT2 inhibitors [7–16], and a pooled analysis of five randomized controlled trials showed improvements in both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels with the use of ipragliflozin [17]. However, the potential effects of ipragliflozin on liver function-related parameters in T2DM patients, especially in those with abnormal liver function, are poorly understood and warrant further investigation.

The present interim report of the STELLA-LONG TERM study aimed to examine the safety and effectiveness of ipragliflozin in real-world clinical practice in Japan using data from patients up to 12 months of follow-up. We also evaluated the effect of ipragliflozin on AST and ALT levels in patients with normal vs. abnormal liver function.

METHODS

Study Design and Patients

This is an ongoing 3-year post-marketing surveillance study. Details of the study design, patient selection criteria, and methods are described in the first interim report [3]. This study was performed in compliance with Good Post-marketing Study Practice. Anonymized data were collected from a clinical setting as required by the regulatory authority; therefore, informed consent was waived in compliance with the policies of each study site. All of the medical institutions that agreed to provide data signed a contract with Astellas Pharma Inc.

Data from T2DM patients who were first prescribed ipragliflozin between 17 July 2014 and 16 October 2015 at one of the 2431 participating centers in Japan were recorded in electronic case report forms, collected in an electronic database, and analyzed. Baseline and post-baseline data on the following survey items were collected: demographic characteristics; body weight and blood pressure; duration of diabetes; complications; liver function status; use of concomitant antidiabetic drugs, diuretics, and other drugs; laboratory data [glycated hemoglobin (HbA1c), fasting plasma glucose, estimated glomerular filtration rate (eGFR), fasting serum insulin, AST, and ALT]; and safety data.

Further details on how the survey was conducted have been described previously [3]. The cutoff date for the present 12-month interim report was 16 January 2018.

Treatment

A once-daily dose of ipragliflozin 50 mg was administered before or after breakfast, in accordance with the package insert. In patients with severe hepatic impairment, a lower dose was allowed at the discretion of the attending physician. If the attending physician considered the treatment effectiveness as insufficient, a dose increase to 100 mg was allowed with careful monitoring of the patient's clinical course.

Vital Signs and Laboratory Variables

Changes in vital signs (including systolic and diastolic blood pressure), laboratory parameters, and eGFR were evaluated.

Safety

Adverse drug reactions (ADRs) were evaluated and categorized by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)/J version 20.1. The time to onset of ADRs and continuation/discontinuation of ipragliflozin treatment associated with ADRs were also evaluated.

Effectiveness

Effectiveness outcome measures were changes in glycemic control (HbA1c, fasting plasma glucose, and fasting serum insulin) and body weight.

Liver Function

Liver function assessments included changes in AST, ALT, and fatty liver index. Changes in AST and ALT were evaluated in patients with normal and abnormal liver function. Patients with normal liver function were defined as those with baseline ALT $\leq$ 30 U/L (male) or $\leq$ 20 U/L (female). Patients with abnormal liver function were defined as those with baseline ALT $\geq$ 31 U/L (male) or $\geq$ 21 U/L (female). The fatty liver index was calculated in accordance with an algorithm proposed by Bedogni et al. [18]:

$$\text{Fatty liver index} = \frac{e^{0.953\times\log_e(\text{triglycerides})+0.139\times\text{BMI}+0.718\times\log_e(\text{ggt})+0.053\times\text{waist circumference}-15.745}}{1+e^{0.953\times\log_e(\text{triglycerides})+0.139\times\text{BMI}+0.718\times\log_e(\text{ggt})+0.053\times\text{waist circumference}-15.745}}\times 100.$$

Hepatic steatosis is indicated by a fatty liver index $\geq$ 60 and ruled out by a fatty liver index $<$ 30. The correlation between changes in ALT and other parameters related to glycemic control and blood pressure, among others, was evaluated in patients with abnormal liver function.

Statistical Analysis

The rationale for the study length and sample size calculations have been described previously [3]. No sample size calculation was performed for subgroup comparisons of patients with normal and abnormal liver function. The safety and efficacy analysis sets included all patients observed for up to 12 months. Categorical variables are shown as n (%) and continuous variables are shown as mean $\pm$ standard deviation (SD), unless otherwise specified. Paired t tests were used to evaluate changes in laboratory parameters from baseline to 1, 3, 6, and 12 months. Two-sample t tests were used for comparisons of liver function tests between patients with normal and abnormal liver function. Statistical significance was set at two-sided $P < 0.05$. Adjustments for type I error, based on multiple hypothesis testing, were not performed. In patients with abnormal liver function, Pearson's correlation coefficient and its P value were calculated to evaluate the relationship between changes in ALT and changes

in other parameters. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA) or higher.

RESULTS

Patient Disposition

The disposition of patients is shown in Fig. 1. Of 2431 institutions that agreed to participate in this study, 1941 participated and initially registered 11,424 patients. Survey forms were collected for 9991 patients at 12 months. Out of 11,289 patients included in the locked database, the safety analysis set comprised 11,051 patients at 3 months and 9970 patients at 12 months. Among the 11,051 patients, 2263 patients were excluded from the efficacy analysis set, which subsequently comprised 8788 patients. Patients were excluded mainly because of noncompliance with the study drug (e.g., starting dose other than 50 mg once daily for patients without severe hepatic impairment); unclear effectiveness assessment; or no effectiveness data available for HbA1c, serum fasting insulin or fasting plasma glucose at baseline or post-baseline.

Patient Characteristics

The baseline demographic and clinical characteristics of patients are shown in Table 1. Of the 11,051 patients in the safety analysis set, 6712 (60.7%) were male. In the safety analysis set, the mean ± SD age was 56.9 ± 12.2 years, BMI was 29.1 ± 5.3 kg/m^2, and duration of diabetes was 8.0 ± 6.5 years. Treatments used at baseline and during the survey period are shown in Table 2. Most patients (81.5%) were receiving treatment with concomitant antidiabetic drugs, among which the most common types were dipeptidyl peptidase-4 (DPP-4) inhibitors (56.3%),

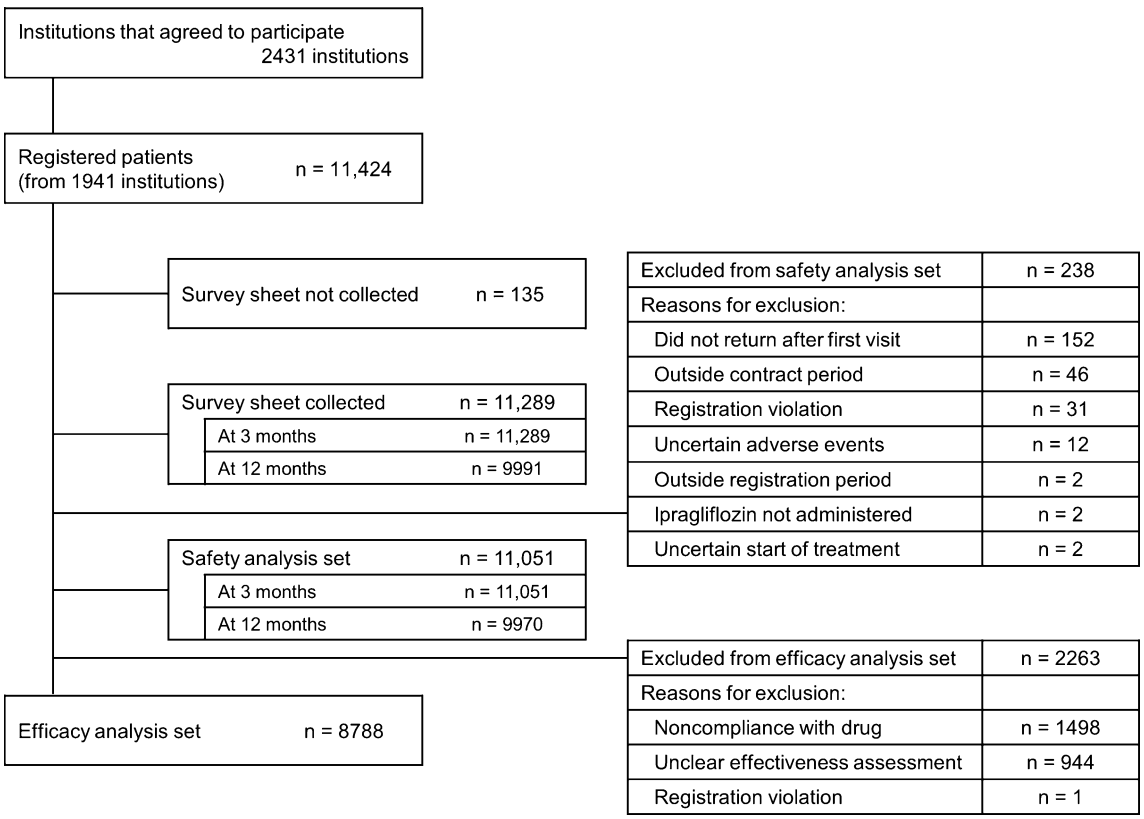


Fig. 1 Patient disposition

Table 1 Patient characteristics at baseline

	Number of patients (%) or mean ± SD	
	Safety analysis set	**Efficacy analysis set**
Total	11,051 (100.0)	8788 (100.0)
Sex		
Male	6712 (60.7)	5384 (61.3)
Female	4339 (39.3)	3404 (38.7)
Age, years		
n	11,051	8788
	56.9 ± 12.2	56.4 ± 12.0
Body weight, kg		
n	8170	6901
	78.1 ± 17.3	78.5 ± 17.2
BMI, kg/m^2		
n	7489	6336
	29.1 ± 5.3	29.2 ± 5.3
Inpatient/outpatient		
Inpatient	183 (1.7)	153 (1.7)
Outpatient	10,868 (98.3)	8635 (98.3)
Duration of diabetes, years		
n	7247	5942
	8.0 ± 6.5	8.0 ± 6.4
Duration of diabetes, category		
< 5 years	2593 (23.5)	2116 (24.1)
≥ 5 years to < 10 years	2171 (19.6)	1775 (20.2)
≥ 10 years to < 15 years	1425 (12.9)	1179 (13.4)
≥ 15 years	1058 (9.6)	872 (9.9)
Unknown	3804 (34.4)	2846 (32.4)
Complications		
No	1637 (14.8)	1293 (14.7)
Yes	9321 (84.3)	7443 (84.7)
Unknown	93 (0.8)	52 (0.6)
Type of complication (some patients had more than one complication)		
Diabetic neuropathy	956 (8.7)	787 (9.0)
Diabetic nephropathy	1819 (16.5)	1516 (17.3)

Table 1 continued

	Number of patients (%) or mean ± SD	
	Safety analysis set	**Efficacy analysis set**
Diabetic retinopathy	884 (8.0)	741 (8.4)
Cardiovascular and cerebrovascular disease	1027 (9.3)	748 (8.5)
Myocardial infarction	146 (1.3)	118 (1.3)
Angina pectoris	467 (4.2)	323 (3.7)
Heart failure	230 (2.1)	161 (1.8)
Arteriosclerosis obliterans	139 (1.3)	99 (1.1)
Cerebrovascular disease	261 (2.4)	201 (2.3)
Hypertension	6183 (55.9)	4921 (56.0)
Dyslipidemia (hyperlipidemia)	7055 (63.8)	5657 (64.4)
Osteoporosis	184 (1.7)	142 (1.6)
Hyperuricemia	1042 (9.4)	812 (9.2)
Urinary tract infection	21 (0.2)	18 (0.2)
Genital infection	8 (0.1)	6 (0.1)
Malignant tumor	79 (0.7)	62 (0.7)
Other	4050 (36.6)	3264 (37.1)
Hepatic function status*		
Normal	8320 (75.3)	6525 (74.2)
Mild impairment	2110 (19.1)	1761 (20.0)
Moderate impairment	299 (2.7)	252 (2.9)
Severe impairment	10 (0.1)	9 (0.1)
Unknown	312 (2.8)	241 (2.7)
Renal function status*		
Normal	9215 (83.4)	7338 (83.7)
Mild impairment	1396 (12.6)	1110 (12.6)
Moderate impairment	125 (1.1)	98 (1.1)
Severe impairment	10 (0.1)	7 (0.1)
Unknown	305 (2.8)	235 (2.7)
eGFR, mL/min/1.73 m^2		
n	6757	5682
	82.1 ± 21.7	82.4 ± 21.5

Table 1 continued

	Number of patients (%) or mean ± SD	
	Safety analysis set	**Efficacy analysis set**
eGFR, category, mL/min/1.73 m^2		
≥ 90	2162 (19.6)	1841 (20.9)
≥ 60 to < 90	3685 (33.3)	3117 (35.5)
≥ 45 to < 60	722 (6.5)	582 (6.6)
≥ 30 to < 45	155 (1.4)	120 (1.4)
< 30	33 (0.3)	22 (0.3)
Unknown	4294 (38.9)	3106 (35.3)

*Judged by the attending physician using the classification criteria for seriousness of adverse drug reactions of pharmaceuticals [33]
BMI body mass index, *eGFR* estimated glomerular filtration rate, *SD* standard deviation

metformin (42.3%), and sulfonylureas (28.2%). Only 7.6% of patients were receiving concomitant diuretics.

Vital Signs

The changes from baseline in vital signs are shown in Table 3. Statistically significant decreases (all $P < 0.05$) were observed in systolic blood pressure (− 4.3 ± 14.6 mmHg), diastolic blood pressure (− 2.6 ± 10.0 mmHg), and heart rate (− 0.9 ± 9.4 beats/min) from baseline to 12 months.

Laboratory Variables

The changes from baseline in laboratory parameters are shown in Table 3. Significant decreases (both $P < 0.05$) were observed in AST (− 4.6 ± 16.3 U/L) and ALT (− 7.9 ± 21.1 U/L) levels from baseline to 12 months. Mean changes in total cholesterol (− 2.5 ± 30.7 mg/dL), low-density lipoprotein cholesterol (− 4.0 ± 26.7 mg/dL), and triglyceride levels (− 16.3 ± 143.2 mg/dL) showed significant decreases (all $P < 0.05$), and mean changes in high-density lipoprotein cholesterol (2.9 ± 9.2 mg/dL) showed a significant increase from baseline to 12 months. Mean changes in serum uric acid concentration (− 0.29 ± 0.95 mg/dL) also showed a significant decrease ($P < 0.05$) from baseline to 12 months. Mean changes in hematocrit (1.9 ± 2.8%) and blood urea nitrogen (1.2 ± 3.7 mg/dL) showed a significant increase ($P < 0.05$) from baseline to 12 months. Changes in eGFR from baseline are shown in Fig. 2a. The eGFR decreased significantly (− 2.3 ± 11.2 mL/min/1.73 m^2) at 12 months from a baseline value of 82.1 ± 21.7 mL/min/1.73 m^2 ($P < 0.001$).

Safety

Safety was assessed in 11,051 patients in the safety analysis set. ADRs are listed in Table 4 by SOC, together with the rates of these ADRs in clinical trials prior to ipragliflozin approval [19–24]. Overall, 2239 ADRs in 1616 patients were reported with an incidence rate of 14.6%. The most common class of ADRs was renal and urinary disorders, which occurred in 644 patients (5.8%), followed by investigations in 205 patients (1.9%), infections and infestations in 201 patients (1.8%), metabolism and nutrition disorders in 161 patients (1.5%), and skin and subcutaneous tissue disorders in 147 patients (1.3%). All other classes of ADRs occurred in less than 1% of patients. In the present survey, no new unreported safety concerns were observed.

Table 2 Treatments used at baseline and during the survey period

	Number of patients (%) or mean ± SD	
	Safety analysis set	**Efficacy analysis set**
Total		
–	11,051 (100.0)	8788 (100.0)
Initial dose of ipragliflozin, mg		
25	1421 (12.9)	0
50	9612 (87.0)	8788 (100.0)
75	0	0
100	14 (0.1)	0
Other	4 (0.0)	0
Daily dose of ipragliflozin, mg		
n	11,051	8788
	47.5 ± 8.5	50.3 ± 2.8
Concomitant treatment		
Concomitant antidiabetic drugs		
No	1964 (17.8)	1489 (16.9)
Yes	9006 (81.5)	7248 (82.5)
Unknown	81 (0.7)	51 (0.6)
Number of concomitant antidiabetic drugs		
n	11,051	8788
	1.6 ± 1.2	1.6 ± 1.2
Max	6	6
Min	0	0
0	2189 (19.8)	1680 (19.1)
1	3129 (28.3)	2441 (27.8)
2	3195 (28.9)	2613 (29.7)
3	1837 (16.6)	1487 (16.9)
≥ 4	619 (5.6)	515 (5.9)
Unknown	82 (0.7)	52 (0.6)
Type of concomitant antidiabetic drugs (some patients had more than one concomitant drug)		
DPP-4 inhibitor	6222 (56.3)	5028 (57.2)
Metformin	4670 (42.3)	3891 (44.3)
Sulfonylurea	3117 (28.2)	2474 (28.2)
Insulin injection	1213 (11.0)	1003 (11.4)

Table 2 continued

	Number of patients (%) or mean ± SD	
	Safety analysis set	**Efficacy analysis set**
α-Glucosidase inhibitor	1150 (10.4)	918 (10.4)
Thiazolidinedione	949 (8.6)	774 (8.8)
GLP-1 receptor agonist	380 (3.4)	333 (3.8)
Fast-acting insulin secretagogue	340 (3.1)	279 (3.2)
Others	840 (7.6)	657 (7.5)
Concomitant diuretics		
No	10,108 (91.5)	8065 (91.8)
Yes	839 (7.6)	643 (7.3)
Unknown	104 (0.9)	80 (0.9)
Type of concomitant diuretics (some patients had more than one concomitant drug)		
Thiazide diuretic	215 (1.9)	168 (1.9)
Loop diuretic	204 (1.8)	151 (1.7)
Potassium-sparing diuretic	172 (1.6)	133 (1.5)
Vasopressin antagonist	6 (0.1)	5 (0.1)
Osmotic diuretic	1 (0.0)	0
Carbonate dehydratase inhibitor	0	0
Others	365 (3.3)	287 (3.3)
Other concomitant drugs		
No	3051 (27.6)	2436 (27.7)
Yes	7876 (71.3)	6275 (71.4)
Unknown	124 (1.1)	77 (0.9)
Type of other concomitant drugs (some patients had more than one concomitant drug)		
Antihypertensive drug	4934 (44.6)	3923 (44.6)
ARB	2519 (22.8)	2019 (23.0)
CCB	2306 (20.9)	1790 (20.4)
ARB + CCB	1373 (12.4)	1107 (12.6)
Statin	4151 (37.6)	3280 (37.3)
Antiplatelet drug	974 (8.8)	737 (8.4)
Antipeptic ulcer drug	989 (8.9)	790 (9.0)
Antihyperuricemic drug	726 (6.6)	564 (6.4)

Table 2 continued

	Number of patients (%) or mean ± SD	
	Safety analysis set	**Efficacy analysis set**
Others	3801 (34.4)	3002 (34.2)

ARB angiotensin receptor blocker, *CCB* calcium channel blocker, *DPP-4* dipeptidyl peptidase-4, *GLP-1* glucagon-like peptide-1, *SD* standard deviation

Serious ADRs reported during the survey period are shown in Table 5. Overall, serious ADRs were observed in 107 patients (0.97%). These included nervous system disorders (21 cases in total: cerebral infarction, 11; lacunar infarction, 3; cerebral hemorrhage, 2; depressed level of consciousness, dizziness, somnolence, transient ischemic attack, and putamen hemorrhage, 1 each); neoplasms benign, malignant, and unspecified (20 cases in total: pancreatic carcinoma, 6; colon cancer, 5; breast cancer female, 2; metastases to lymph nodes, pancreatic carcinoma metastatic, squamous cell carcinoma of skin, lung neoplasm malignant, prostate cancer, lung neoplasm, thyroid cancer, and intraductal proliferative breast lesion, 1 each); cardiac disorders (19 cases in total: acute myocardial infarction and myocardial infarction, 5 each; angina unstable, 3; angina pectoris and cardiac failure congestive, 2 each; atrial fibrillation, cardiovascular disorder, and coronary artery disease, 1 each); infections and infestations (9 cases in total: urinary tract infection, 3; pyelonephritis acute, 2; *Escherichia* sepsis, liver abscess, peritonsillar abscess, pneumonia, and genital herpes simplex, 1 each); hepatobiliary disorders (7 cases in total: cholecystitis and hepatic cirrhosis, 2 each; cholecystitis acute, cholelithiasis, jaundice cholestatic, and liver disorder, 1 each); metabolism and nutrition disorders (6 cases in total: dehydration and hypoglycemia, 2 each; hyperglycemia and hyperphagia, 1 each); renal and urinary disorders (6 cases in total: renal disorder, 2; hematuria, neurogenic bladder, renal vessel disorder, and ureterolithiasis, 1 each); skin and subcutaneous tissue disorders (4 cases in total: drug eruption, eczema, skin ulcer, and urticaria, 1 each); injury, poisoning, and procedural complications (4 cases in total: fall, femoral neck fracture, foot fracture, ligament sprain; road traffic accident; subarachnoid hemorrhage; contusion and brain contusion, 1 each); eye disorders (3 cases in total: retinal hemorrhage, 2; diabetic retinopathy, 1); vascular disorders (3 cases in total: hypertension, 2; varicose vein, 1); gastrointestinal disorders (3 cases in total: duodenal ulcer, gastric ulcer hemorrhage, gastroesophageal reflux disease, and pancreatitis acute, 1 each); psychiatric disorders (2 cases of depression); endocrine disorders (1 case of hypothyroidism); ear and labyrinth disorders (1 case of sudden hearing loss); reproductive system and breast disorders (1 case of prostatitis); general disorders and administration site conditions (1 case of thirst); and investigations (1 case of gamma-glutamyl transferase increased).

ADRs of special interest are shown in Table 6. The incidence of these ranged from 0.02% (fracture) to 5.2% (polyuria/pollakiuria). Although 571 patients (5.2%) reported polyuria/pollakiuria, only one of these events was considered serious. These included 438 pollakiuria ADRs (4.0%) and 293 polyuria ADRs (2.7%). Volume depletion-related events, including dehydration, were reported in 196 patients (1.8%), and nine (0.08%) events were considered serious. ADRs associated with volume depletion included pollakiuria (26 ADRs, 0.24%), polyuria (16 ADRs, 0.14%), thirst (16 ADRs, 0.14%), cerebral infarction (three ADRs, 0.03%), and lacunar infarction (one ADR, 0.01%). Skin complications were reported in 166 patients (1.5%), of which four (0.04%) cases were considered serious. Skin complication-related ADRs included drug eruption (42 ADRs, 0.38%), pruritus (34 ADRs, 0.31%), pruritus genital (25 ADRs, 0.23%), rash (18 ADRs, 0.16%), and eczema (17 ADRs, 0.15%). Genital infection was reported in 135 patients (1.2%), of

Table 3 Changes from baseline in vital signs and laboratory parameters

Parameters	Actual value		Change from baseline			
	Baseline	12 months	1 month	3 months	6 months	12 months
SBP (mmHg)	133.3 ± 15.1 (n = 7161)	129.3 ± 13.5 (n = 5418)	− 3.8 ± 13.3* (n = 5185)	− 3.8 ± 14.0* (n = 6303)	− 3.4 ± 14.6* (n = 5315)	− 4.3 ± 14.6* (n = 4973)
DBP (mmHg)	78.4 ± 11.0 (n = 7159)	75.9 ± 10.2 (n = 5414)	− 1.9 ± 9.4* (n = 5184)	− 2.0 ± 9.7* (n = 6300)	− 1.7 ± 10.1* (n = 5309)	− 2.6 ± 10.0* (n = 4968)
Heart rate (beats/min)[a]	77.9 ± 12.3 (n = 5191)	76.5 ± 11.6 (n = 4040)	− 0.6 ± 8.7* (n = 3481)	− 0.8 ± 9.1* (n = 4270)	− 0.9 ± 9.4* (n = 3593)	− 0.9 ± 9.4* (n = 3325)
AST (GOT) (U/L)	30.2 ± 19.4 (n = 5823)	25.5 ± 14.3 (n = 4381)	− 1.9 ± 12.1* (n = 3253)	− 3.4 ± 14.0* (n = 4652)	− 4.5 ± 15.1* (n = 3998)	− 4.6 ± 16.3* (n = 3799)
ALT (GPT) (U/L)	38.2 ± 29.1 (n = 5892)	30.3 ± 22.8 (n = 4439)	− 3.2 ± 14.7* (n = 3280)	− 5.8 ± 18.7* (n = 4735)	− 7.4 ± 20.2* (n = 4053)	− 7.9 ± 21.1* (n = 3868)
γ-GTP (U/L)	58.7 ± 70.8 (n = 5433)	47.2 ± 65.8 (n = 4082)	− 7.9 ± 29.9* (n = 2990)	− 9.2 ± 40.0* (n = 4308)	− 10.6 ± 40.6* (n = 3655)	− 10.9 ± 42.2* (n = 3493)
Total cholesterol (mg/dL)	196.8 ± 40.0 (n = 3732)	192.5 ± 34.8 (n = 2750)	− 4.8 ± 28.8* (n = 2018)	− 1.9 ± 28.6* (n = 2941)	− 0.8 ± 30.9 (n = 2457)	− 2.5 ± 30.7* (n = 2309)
LDL-C (mg/dL)	114.6 ± 31.9 (n = 5349)	110.1 ± 28.5 (n = 4073)	− 3.3 ± 23.1* (n = 2937)	− 1.7 ± 24.5* (n = 4238)	− 2.4 ± 26.0* (n = 3631)	− 4.0 ± 26.7* (n = 3436)
HDL-C (mg/dL)	50.8 ± 13.6 (n = 5592)	53.9 ± 14.7 (n = 4239)	0.3 ± 7.0* (n = 3152)	1.4 ± 8.3* (n = 4498)	3.1 ± 8.8* (n = 3867)	2.9 ± 9.2* (n = 3660)
Triglyceride (mg/dL)	197.0 ± 184.3 (n = 5861)	175.5 ± 164.9 (n = 4411)	− 18.1 ± 156.2* (n = 3321)	− 16.6 ± 156.2* (n = 4722)	− 18.9 ± 143.1* (n = 4070)	− 16.3 ± 143.2* (n = 3847)
Uric acid (mg/dL)	5.3 ± 1.3 (n = 5191)	5.0 ± 1.2 (n = 3905)	− 0.35 ± 0.91* (n = 2809)	− 0.29 ± 0.90* (n = 4077)	− 0.32 ± 0.93* (n = 3461)	− 0.29 ± 0.95* (n = 3297)
Hematocrit (%)[a]	43.1 ± 4.3 (n = 6078)	45.1 ± 4.3 (n = 4711)	1.0 ± 2.2* (n = 3176)	1.6 ± 2.6* (n = 4609)	1.9 ± 2.7* (n = 3907)	1.9 ± 2.8* (n = 3753)
BUN (mg/dL)[a]	14.8 ± 4.5 (n = 5853)	16.0 ± 4.4 (n = 4497)	0.7 ± 3.5* (n = 3125)	0.8 ± 3.6* (n = 4491)	1.0 ± 3.7* (n = 3781)	1.2 ± 3.7* (n = 3645)

Table 3 continued

Parameters	Actual value		Change from baseline			
	Baseline	12 months	1 month	3 months	6 months	12 months
Serum Cr (mg/dL)[a]	0.74 ± 0.22 (n = 6757)	0.75 ± 0.23 (n = 5232)	0.03 ± 0.09* (n = 3620)	0.02 ± 0.09* (n = 5300)	0.02 ± 0.10* (n = 4462)	0.02 ± 0.10* (n = 4292)

Results are presented as the mean ± standard deviation (number of patients)

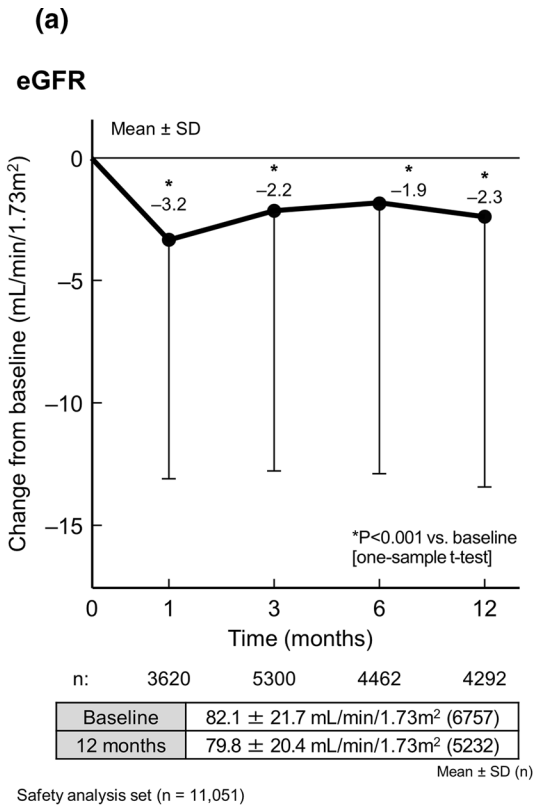
ALT alanine aminotransferase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *Cr* creatinine, *DBP* diastolic blood pressure, *γ-GTP* γ-glutamyl transpeptidase, *GOT* glutamic oxaloacetic transaminase, *GPT* glutamate-pyruvate transaminase, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *SBP* systolic blood pressure

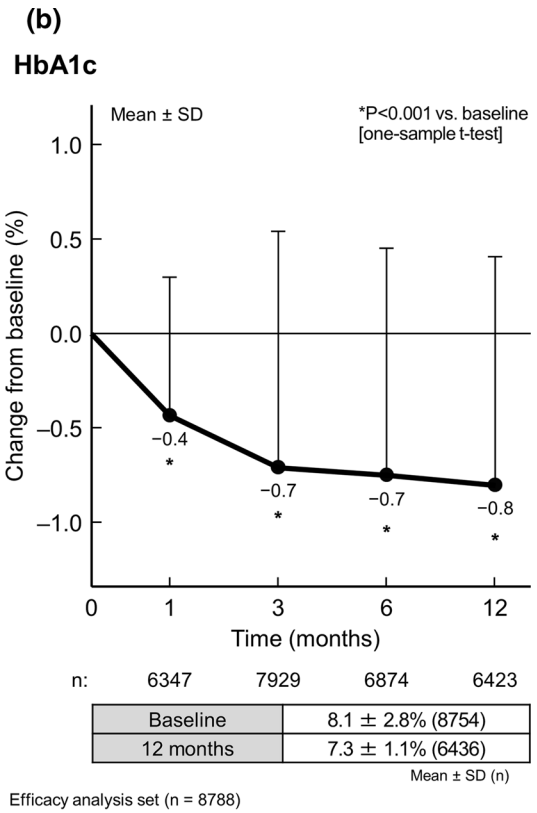
*$P < 0.05$ vs. baseline (paired t test)

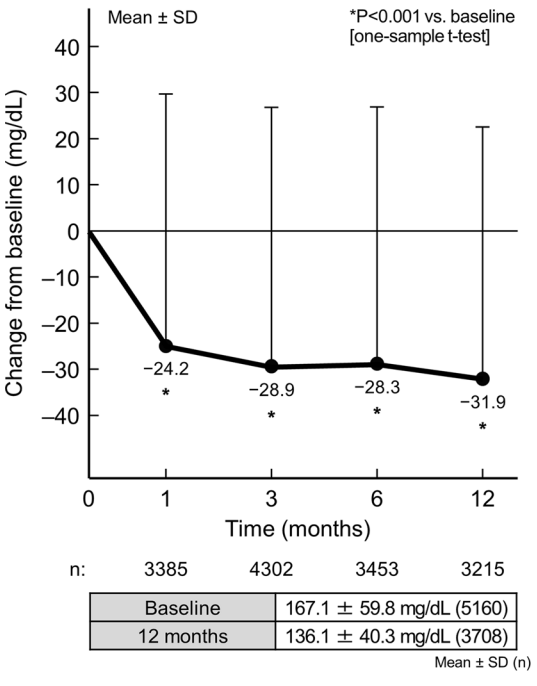
[a] Safety analysis set data; all other parameters were calculated on the basis of the efficacy analysis set data

Fig. 2 Changes in eGFR (**a**), HbA1c (**b**), fasting plasma glucose (**c**), and body weight (**d**) from baseline to 12 months. HbA1c glycated hemoglobin, eGFR estimated glomerular filtration rate, SD standard deviation

which two (0.02%) cases were considered serious. Genital infection-related ADRs included pruritus genital (40 ADRs, 0.36%), vulvovaginal candidiasis (28 ADRs, 0.25%), and female genital infection (20 ADRs, 0.18%). Urinary tract infection was reported in 115 patients (1.0%), of which five (0.05%) cases were considered serious. ADRs associated with urinary tract infection included cystitis (56 ADRs, 0.51%) and urinary tract infection (42 ADRs, 0.38%). Renal disorder was reported in 115 patients (1.0%), of which three (0.03%) cases were considered serious. Renal disorder-related ADRs included renal disorder (27 ADRs, 0.24%) and renal dysfunction (26 ADRs, 0.24%). Hepatic disorder was reported in 82 patients (0.74%), of which six (0.05%) cases were considered serious. ADRs associated with hepatic disorder included hepatic disorder (30 ADRs, 0. 27%) and hepatic dysfunction (28 ADRs, 0. 25%). Hypoglycemia was reported in 39 patients (0.35%), of which three (0.03%) cases were considered serious. ADRs associated with hypoglycemia included hypoglycemia (32 ADRs, 0.29%). Cardiovascular disease was reported in 30 patients (0.27%), of which 19 (0.17%) cases were considered serious. The most common ADRs associated with cardiovascular disease were acute myocardial infarction (five ADRs, 0.05%), myocardial infarction (five ADRs, 0.05%), angina pectoris (four ADRs, 0.04%), unstable angina pectoris (three ADRs, 0.03%), atrial fibrillation (three ADRs, 0.03%), and congestive heart failure (three ADRs, 0.03%). Cerebrovascular disease was reported in 23 patients (0.21%), of which 20 (0.18%) cases were considered serious. The most common ADRs associated with cerebrovascular disease were cerebral infarction (13 ADRs, 0.12%), lacunar infarction (three ADRs, 0.03%), transient ischemic attack (two ADRs, 0.02%), and cerebral hemorrhage (two ADRs, 0.02%). Malignant tumor was reported in 22 patients (0.20%), of which 19 (0.17%) cases were considered serious. ADRs associated with malignant


(a)
eGFR
Mean ± SD
Change from baseline (mL/min/1.73m²)
0
−5
−10
−15
*
−3.2
*
−2.2
*
−1.9
*
−2.3
*P<0.001 vs. baseline
[one-sample t-test]
0
1
3
6
12
Time (months)
n: 3620 5300 4462 4292
Baseline 82.1 ± 21.7 mL/min/1.73m² (6757)
12 months 79.8 ± 20.4 mL/min/1.73m² (5232)
Mean ± SD (n)
Safety analysis set (n = 11,051)


(b)
HbA1c
Mean ± SD
*P<0.001 vs. baseline
[one-sample t-test]
Change from baseline (%)
1.0
0.5
0.0
−0.5
−1.0
−0.4
*
−0.7
*
−0.7
*
−0.8
*
0
1
3
6
12
Time (months)
n: 6347 7929 6874 6423
Baseline 8.1 ± 2.8% (8754)
12 months 7.3 ± 1.1% (6436)
Mean ± SD (n)
Efficacy analysis set (n = 8788)


(c)
Fasting plasma glucose
Mean ± SD
*P<0.001 vs. baseline
[one-sample t-test]
Change from baseline (mg/dL)
40
30
20
10
0
−10
−20
−30
−40
−24.2
*
−28.9
*
−28.3
*
−31.9
*
0
1
3
6
12
Time (months)
n: 3385 4302 3453 3215
Baseline 167.1 ± 59.8 mg/dL (5160)
12 months 136.1 ± 40.3 mg/dL (3708)
Mean ± SD (n)

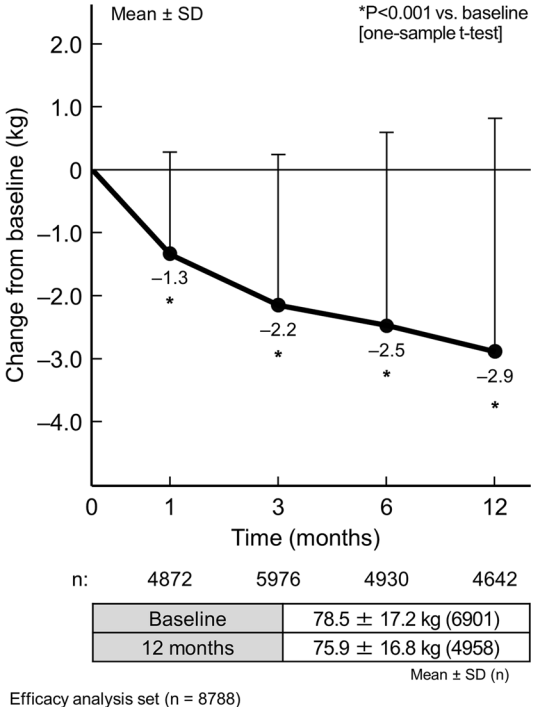

(d)
Body weight
Mean ± SD
*P<0.001 vs. baseline
[one-sample t-test]
Change from baseline (kg)
2.0
1.0
0
−1.0
−2.0
−3.0
−4.0
−1.3
*
−2.2
*
−2.5
*
−2.9
*
0
1
3
6
12
Time (months)
n: 4872 5976 4930 4642
Baseline 78.5 ± 17.2 kg (6901)
12 months 75.9 ± 16.8 kg (4958)
Mean ± SD (n)
Efficacy analysis set (n = 8788)

Table 4 Adverse drug reactions reported during the survey period

	STELLA-LONG TERM	Pre-approval clinical trials
Number of patients	11,051	1669
Number of patients with ADRs	1616	549
Number of ADRs	2239	887
Incidence rate ADRs	14.6%	32.9%
System organ class		
Infections and infestations	201 (1.8)	64 (3.8)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	25 (0.23)	4 (0.24)
Blood and lymphatic system disorders	9 (0.08)	8 (0.48)
Immune system disorders	1 (0.01)	0
Endocrine disorders	1 (0.01)	0
Metabolism and nutrition disorders	161 (1.5)	20 (1.2)
Psychiatric disorders	9 (0.08)	3 (0.18)
Nervous system disorders	74 (0.67)	42 (2.5)
Eye disorders	8 (0.07)	17 (1.0)
Ear and labyrinth disorders	1 (0.01)	5 (0.30)
Cardiac disorders	31 (0.28)	10 (0.60)
Vascular disorders	34 (0.31)	7 (0.42)
Respiratory, thoracic, and mediastinal disorders	11 (0.10)	7 (0.42)
Gastrointestinal disorders	100 (0.90)	101 (6.1)
Hepatobiliary disorders	70 (0.63)	8 (0.48)
Skin and subcutaneous tissue disorders	147 (1.3)	48 (2.9)
Musculoskeletal and connective tissue disorders	23 (0.21)	13 (0.78)
Renal and urinary disorders	644 (5.8)	176 (10.6)
Reproductive system and breast disorders	88 (0.80)	25 (1.5)
General disorders and administration site conditions	72 (0.65)	101 (6.1)
Investigations	205 (1.9)	133 (8.0)
Injury, poisoning, and procedural complications	10 (0.09)	0

Data are presented as number of events (%)
Coded using MedDRA/J Ver.20.1
ADR adverse drug reaction, *MedDRA* Medical Dictionary for Regulatory Activities

Table 5 Serious adverse drug reactions reported during the survey period

	STELLA-LONG TERM	Pre-approval clinical trials
Number of patients with serious ADRs	107	14
Number of serious ADRs	121	15
Incidence rate of serious ADRs	0.97%	0.84%
System organ class		
MedDRA preferred term		
Infections and infestations	9 (0.08)	2 (0.12)
Escherichia sepsis	1 (0.01)	0
Liver abscess	1 (0.01)	0
Peritonsillar abscess	1 (0.01)	0
Pneumonia	1 (0.01)	0
Pyelonephritis	0	2 (0.12)
Pyelonephritis acute	2 (0.02)	0
Urinary tract infection	3 (0.03)	0
Genital herpes simplex	1 (0.01)	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	20 (0.18)	3 (0.18)
Colon cancer	5 (0.05)	1 (0.06)
Metastases to lymph nodes	1 (0.01)	0
Pancreatic carcinoma	6 (0.05)	0
Pancreatic carcinoma metastatic	1 (0.01)	0
Squamous cell carcinoma of skin	1 (0.01)	0
Uterine cancer	0	1 (0.06)
Breast cancer female	2 (0.02)	0
Lung neoplasm malignant	1 (0.01)	0
Prostate cancer	1 (0.01)	1 (0.06)
Lung neoplasm	1 (0.01)	0
Thyroid cancer	1 (0.01)	0
Intraductal proliferative breast lesion	1 (0.01)	0
Blood and lymphatic system disorders	0	1 (0.06)
Hemolytic anemia	0	1 (0.06)
Endocrine disorders	1 (0.01)	0
Hypothyroidism	1 (0.01)	0

Table 5 continued

	STELLA-LONG TERM	Pre-approval clinical trials
Metabolism and nutrition disorders	6 (0.05)	0
Dehydration	2 (0.02)	0
Hyperglycemia	1 (0.01)	0
Hyperphagia	1 (0.01)	0
Hypoglycemia	2 (0.02)	0
Psychiatric disorders	2 (0.02)	0
Depression	2 (0.02)	0
Nervous system disorders	21 (0.19)	1 (0.06)
Cerebral hemorrhage	2 (0.02)	0
Cerebral infarction	11 (0.10)	1 (0.06)
Depressed level of consciousness	1 (0.01)	0
Dizziness	1 (0.01)	0
Somnolence	1 (0.01)	0
Transient ischemic attack	1 (0.01)	0
Lacunar infarction	3 (0.03)	0
Putamen hemorrhage	1 (0.01)	0
Eye disorders	3 (0.03)	0
Diabetic retinopathy	1 (0.01)	0
Retinal hemorrhage	2 (0.02)	0
Ear and labyrinth disorders	1 (0.01)	0
Sudden hearing loss	1 (0.01)	0
Cardiac disorders	19 (0.17)	2 (0.12)
Acute myocardial infarction	5 (0.05)	1 (0.06)
Angina pectoris	2 (0.02)	0
Angina unstable	3 (0.03)	1 (0.06)
Atrial fibrillation	1 (0.01)	0
Cardiac failure congestive	2 (0.02)	0
Cardiovascular disorder	1 (0.01)	0
Coronary artery disease	1 (0.01)	0
Myocardial infarction	5 (0.05)	0
Vascular disorders	3 (0.03)	0
Hypertension	2 (0.02)	0

Table 5 continued

	STELLA-LONG TERM	Pre-approval clinical trials
Varicose vein	1 (0.01)	0
Gastrointestinal disorders	3 (0.03)	1 (0.06)
Duodenal ulcer	1 (0.01)	0
Gastric ulcer hemorrhage	1 (0.01)	0
Gastroesophageal reflux disease	1 (0.01)	0
Pancreatitis acute	1 (0.01)	0
Upper gastrointestinal hemorrhage	0	1 (0.06)
Hepatobiliary disorders	7 (0.06)	0
Cholecystitis	2 (0.02)	0
Cholecystitis acute	1 (0.01)	0
Cholelithiasis	1 (0.01)	0
Hepatic cirrhosis	2 (0.02)	0
Jaundice cholestatic	1 (0.01)	0
Liver disorder	1 (0.01)	0
Skin and subcutaneous tissue disorders	4 (0.04)	0
Drug eruption	1 (0.01)	0
Eczema	1 (0.01)	0
Skin ulcer	1 (0.01)	0
Urticaria	1 (0.01)	0
Renal and urinary disorders	6 (0.05)	3 (0.18)
Hematuria	1 (0.01)	0
Nephrolithiasis	0	1 (0.06)
Neurogenic bladder	1 (0.01)	0
Renal disorder	2 (0.02)	1 (0.06)
Renal vessel disorder	1 (0.01)	0
Ureterolithiasis	1 (0.01)	1 (0.06)
Reproductive system and breast disorders	1 (0.01)	0
Prostatitis	1 (0.01)	0
General disorders and administration site conditions	1 (0.01)	2 (0.12)
Death	0	1 (0.06)
Pain	0	1 (0.06)
Thirst	1 (0.01)	0

Table 5 continued

	STELLA-LONG TERM	Pre-approval clinical trials
Investigations	1 (0.01)	0
Gamma-glutamyl transferase increased	1 (0.01)	0
Injury, poisoning, and procedural complications	4 (0.04)	0
Fall	1 (0.01)	0
Femoral neck fracture	1 (0.01)	0
Foot fracture	1 (0.01)	0
Ligament sprain	1 (0.01)	0
Road traffic accident	1 (0.01)	0
Subarachnoid hemorrhage	1 (0.01)	0
Contusion	1 (0.01)	0
Brain contusion	1 (0.01)	0

Data are presented as number of events (%)
The numbers of patients under each system organ class (SOC) category do not necessarily add up to the total number of patients for each SOC category because some patients experienced more than one ADR
Coded using MedDRA/J Ver.20.1
ADR adverse drug reaction, *MedDRA* Medical Dictionary for Regulatory Activities

tumors included pancreatic carcinoma (six ADRs, 0.05%) and colon cancer (five ADRs, 0.05%). Ketoacidosis (events related to ketone-body increase) was reported in three patients (0.03%); none of the cases were considered serious. ADRs associated with ketoacidosis included diabetic ketoacidosis (two ADRs, 0.02%) and ketosis (one ADR, 0.01%). Fracture was reported in two patients (0.02%), of which one case was considered serious (0.01%). ADRs associated with fracture included ankle fracture, femoral neck fracture, and foot fracture (one ADR each, 0.01% each). No serious ADRs occurred in at least 1% of patients.

The time to onset of ADRs of special interest is shown in Table 7.The cumulative proportion of ADRs that occurred within 90 days from the start of treatment was 64.6% for all events (1447/2239 events), 89.4% for polyuria/pollakiuria (701/784 events), 74.7% for skin complications (127/170 events), 64.3% for hypoglycemia (27/42 events), and 61.4% for genital infection (86/140 events).

ADRs of special interest according to treatment status are shown in Table 8. The incidence rate of ADRs was highest among patients with continued treatment status (61.0%), followed by patients with interruption or discontinuation of treatment due to an ADR (38.5%). For all other treatment status categories, the incidence rate of ADRs was less than 4%. Among patients with interruption or discontinuation of treatment due to the event, the incidence rate of skin complications was 81.3% (135/166 patients); ketoacidosis was 66.7% (2/3 patients); genital infection was 57.0% (77/135 patients); and fracture was 50% (1/2 patients). The outcomes of ADRs of special interest are shown in Table 9.

Effectiveness

The changes in HbA1c, fasting plasma glucose, and body weight from baseline to 12 months are shown in Fig. 2b–d, respectively. The baseline value of HbA1c was 8.1 ± 2.8% and that of fasting plasma glucose was 167.1 ± 59.8 mg/dL. The

Table 6 Adverse drug reactions of special interest

	STELLA-LONG TERM (safety analysis set *n* = 11,051)						Pre-approval clinical trials
	Total number of patients experiencing an ADR		Serious		Non-serious		Total (*n* = 1669)
All ADRs	1616	(14.6)	107	(0.97)	1539	(13.9)	(32.9)
ADRs of special interest							
Polyuria/pollakiuria	571	(5.2)	1	(0.01)	570	(5.2)	(10.0)
Volume depletion-related events, including dehydration	196	(1.8)	9	(0.08)	189	(1.7)	(4.5)
Skin complications	166	(1.5)	4	(0.04)	162	(1.5)	(4.0)
Genital infection	135	(1.2)	2	(0.02)	133	(1.2)	(2.0)
Urinary tract infection	115	(1.0)	5	(0.05)	110	(1.0)	(1.8)
Renal disorder	115	(1.0)	3	(0.03)	112	(1.0)	(4.8)
Hepatic disorder	82	(0.74)	6	(0.05)	78	(0.71)	(1.0)
Hypoglycemia	39	(0.35)	3	(0.03)	36	(0.33)	(1.4)
Cardiovascular disease[a]	30	(0.27)	19	(0.17)	11	(0.10)	(1.0)
Cerebrovascular disease[b]	23	(0.21)	20	(0.18)	3	(0.03)	(0.2)
Malignant tumor	22	(0.20)	19	(0.17)	3	(0.03)	(0.2)
Ketoacidosis, events related to ketone-body increase	3	(0.03)	0	(0.00)	3	(0.03)	(1.0)
Fracture	2	(0.02)	1	(0.01)	1	(0.01)	0

Data are presented as number of events (%), unless otherwise indicated

ADR adverse drug reaction

[a] Incidence of cardiovascular disease was 4.4/1000 person-years [34] and 9.59/1000 person-years [35] in the JDDM and JDCS studies, respectively

[b] Incidence of cerebrovascular disease was 3.1/1000 person-years [34] and 7.45/1000 person-years [35] in the JDDM and JDCS studies, respectively

improvement in glycemic control was statistically significant (both $P < 0.001$ vs. baseline) at 12 months, with sustained mean reductions from baseline in HbA1c (− 0.8 ± 1.2%) and fasting plasma glucose (− 31.9 ± 54.7 mg/dL). Statistically significant sustained reductions ($P < 0.001$ vs. baseline) in body weight (− 2.9 ± 3.7 kg) were also observed. A significant sustained decrease ($P = 0.002$ vs. baseline) in serum fasting insulin was observed, from 15.0 ± 20.0 μU/mL at baseline to 12.2 ± 10.8 μU/mL at 12 months (change − 4.9 ± 22.2 μU/mL).

Liver Function

Changes in AST and ALT from baseline to 12 months in patients with normal and abnormal liver function are shown in Fig. 3a, b, respectively. In patients with normal liver function at baseline, no clinically significant changes in AST and ALT were observed. In patients with abnormal liver function at baseline, clinically and statistically significant changes in AST (− 9.0 ± 19.0 U/L) and ALT

Table 7 Time to onset of adverse drug reactions of special interest

	< 7 days	7–< 15 days	15–< 30 days	30–< 45 days	45–< 60 days	60–< 90 days	90–< 180 days	180–< 270 days	270–< 360 days	360–< 720 days	Unknown
All ADRs (2239 events)	448 (20.0)	212 (9.5)	315 (14.1)	195 (8.7)	101 (4.5)	176 (7.9)	317 (14.2)	201 (8.0)	185 (7.4)	72 (3.5)	30 (1.3)
ADRs of special interest											
Hypoglycemia (42 events)	7 (16.7)	6 (14.3)	3 (7.1)	1 (2.4)	3 (7.1)	7 (16.7)	3 (7.1)	4 (9.5)	5 (11.9)	3 (7.1)	0
Genital infection (140 events)	14 (10.0)	15 (10.7)	21 (15.0)	10 (7.1)	9 (6.4)	17 (12.1)	23 (16.4)	17 (12.1)	11 (7.9)	3 (2.1)	0
Urinary tract infection (117 events)	3 (2.6)	9 (7.7)	23 (19.7)	4 (3.4)	7 (6.0)	16 (13.7)	30 (25.6)	15 (12.8)	9 (7.7)	1 (0.9)	0
Polyuria/pollakiuria (784 events)	320 (40.8)	97 (12.4)	142 (18.1)	86 (11.0)	31 (4.0)	25 (3.2)	46 (5.9)	17 (2.2)	10 (1.3)	4 (0.5)	6 (0.8)
Volume depletion (238 events)	33 (13.9)	7 (2.9)	40 (16.8)	30 (12.6)	8 (3.4)	27 (11.3)	42 (17.6)	19 (8.0)	12 (5.0)	11 (4.6)	9 (3.8)
Renal disorder (123 events)	1 (0.8)	5 (4.1)	17 (13.8)	11 (8.9)	7 (5.7)	16 (13.0)	27 (22.0)	16 (13.0)	10 (8.1)	12 (9.8)	1 (0.8)
Hepatic disorder (87 events)	1 (1.1)	1 (1.1)	12 (13.8)	10 (11.5)	6 (6.9)	9 (10.3)	22 (25.3)	10 (11.5)	7 (8.0)	8 (9.2)	1 (1.1)
Fracture (3 events)	0	0	0	0	0	1 (33.3)	0	1 (33.3)	1 (33.3)	0	0
Malignant tumor (23 events)	0	0	0	0	0	1 (4.3)	5 (21.7)	7 (30.4)	3 (13.0)	2 (8.7)	5 (21.7)
Cardiovascular disease (32 events)	1 (3.1)	0	3 (9.4)	1 (3.1)	4 (12.5)	2 (6.3)	4 (12.5)	5 (15.6)	8 (25.0)	4 (12.5)	0
Cerebrovascular disease (23 events)	0	2 (8.7)	0	1 (4.3)	1 (4.3)	3 (13.0)	5 (21.7)	4 (17.4)	5 (21.7)	2 (8.7)	0
Skin complications (170 events)	48 (28.2)	31 (18.2)	18 (10.6)	5 (2.9)	9 (5.3)	16 (9.4)	22 (12.9)	11 (6.5)	7 (4.1)	1 (0.6)	2 (1.2)
Ketone body-related events (3 events)	0	0	1 (33.3)	0	0	0	0	1 (33.3)	1 (33.3)	0	0

Number of events (%). In patients who experienced a recurrence of an adverse drug reaction, the date of onset was defined as the first occurrence

Table 8 Adverse drug reactions of special interest according to treatment status

	Total number of patients experiencing an ADR	Ipragliflozin treatment status											
		Continued		Dose reduction		Interruption or discontinuation due to the event		Interruption or discontinuation for other reasons		Completion of treatment before ADR		Unknown	
All ADRs	1616	986	(61.0)	20	(1.2)	622	(38.5)	57	(3.5)	7	(0.4)	7	(0.4)
ADRs of special interest													
Skin complications	166	30	(18.1)	1	(0.6)	135	(81.3)	0	(0.0)	0	(0.0)	0	(0.0)
Ketoacidosis, events related to ketone-body increase	3	1	(33.3)	0	(0.0)	2	(66.7)	0	(0.0)	0	(0.0)	0	(0.0)
Genital infection	135	58	(43.0)	1	(0.7)	77	(57.0)	0	(0.0)	1	(0.7)	0	(0.0)
Fracture	2	2	(100.0)	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoglycemia	39	20	(51.3)	2	(5.1)	18	(46.2)	1	(2.6)	0	(0.0)	0	(0.0)
Urinary tract infection	115	64	(55.7)	0	(0.0)	53	(46.1)	1	(0.9)	0	(0.0)	0	(0.0)
Cerebrovascular disease	23	8	(34.8)	1	(4.4)	10	(43.5)	2	(8.7)	0	(0.0)	2	(8.7)
Cardiovascular disease	30	16	(53.3)	0	(0.0)	13	(43.3)	0	(0.0)	0	(0.0)	1	(3.3)
Volume depletion-related events, including dehydration	196	121	(61.7)	2	(1.0)	72	(36.7)	7	(3.6)	0	(0.0)	0	(0.0)
Polyuria/pollakiuria	571	413	(72.3)	10	(1.8)	132	(23.1)	19	(3.3)	0	(0.0)	0	(0.0)
Malignant tumor	22	14	(63.6)	0	(0.0)	4	(18.2)	1	(4.5)	1	(4.5)	2	(9.1)
Renal disorder	115	92	(80.0)	0	(0.0)	17	(14.8)	6	(5.2)	0	(0.0)	1	(0.9)
Hepatic disorder	82	65	(79.3)	0	(0.0)	11	(13.4)	5	(6.1)	2	(2.4)	1	(1.2)

Data are presented as number of events (%) unless otherwise specified. If a patient experienced two or more ADRs within the same category and the treatment status was different, they were counted into respective categories

ADR adverse drug reaction

Table 9 Outcomes of adverse drug reactions of special interest

	Total	Outcome											
		Resolved		Remission		Not recovered		Sequelae		Death		Unknown	
All ADRs	2239	1206	(53.9)	707	(31.6)	202	(9.0)	8	(0.4)	9	(0.4)	107	(4.8)
ADRs of special interest													
Hypoglycemia	42	38	(90.5)	4	(9.5)	0		0		0		0	
Genital infection	140	98	(70.0)	33	(23.6)	6	(4.3)	0		0		3	(2.1)
Urinary tract infection	117	96	(82.1)	19	(16.2)	1	(0.9)	0		0		1	(0.9)
Polyuria/pollakiuria	784	313	(39.9)	353	(45.0)	88	(11.2)	0		0		30	(3.8)
Volume depletion	238	152	(63.9)	70	(29.4)	10	(4.2)	1	(0.4)	0		5	(2.1)
Renal disorder	123	59	(48.0)	31	(25.2)	17	(13.8)	0		0		16	(13.0)
Hepatic disorder	87	43	(49.4)	12	(13.8)	16	(18.4)	0		1	(1.1)	15	(17.2)
Fracture	3	1	(33.3)	2	(66.7)	0		0		0		0	
Malignant tumor	23	4	(17.4)	6	(26.1)	3	(13.0)	0		5	(21.7)	5	(21.7)
Cardiovascular disease	32	15	(46.9)	11	(34.4)	3	(9.4)	0		2	(6.3)	1	(3.1)
Cerebrovascular disease	23	8	(34.8)	6	(26.1)	0		8	(34.8)	0		1	(4.3)
Skin complications	170	121	(71.2)	42	(24.7)	7	(4.1)	0		0		0	
Ketone body-related events	3	2	(66.7)	1	(33.3)	0		0		0		0	

Data are presented as number of events (%)

($-$ 14.7 $\pm$ 24.8 U/L) levels were observed ($P < 0.05$ vs. baseline).

Table 10 shows the correlation between changes in ALT and other parameters in patients with abnormal liver function. No obvious correlation was observed between the changes in ALT and changes in other parameters in patients with abnormal liver function.

Changes in the fatty liver index over time from baseline to 12 months are shown in Fig. 4. The fatty liver index decreased significantly from 64.4 $\pm$ 26.4 at baseline to 55.5 $\pm$ 27.9 at 12 months ($-$ 8.7 $\pm$ 12.7, $P < 0.001$ vs. baseline).

DISCUSSION

The STELLA-LONG TERM study is an ongoing 3-year post-marketing surveillance study. In this interim report, we present the safety and effectiveness results up to 12 months. Patient characteristics remained almost unchanged from those of the previous interim report for which 3-, 12-, and 24-month data were pooled [4]. Other antidiabetics were concomitantly used with ipragliflozin in many patients (81.5%). Drugs commonly used with ipragliflozin were DPP-4 inhibitors and metformin.

In the previous interim report [4], the incidence of ADRs was 10.7% (1184/11,053). However, in the present analysis conducted on the finalized data from all patients treated for 12 months, the incidence increased to 14.6% (1616/11,051). The incidence rates of ADRs were higher in clinical trials prior to ipragliflozin approval compared with those in the present survey for all SOC categories, except metabolism and nutrition disorders and hepatobiliary disorders.

The incidence rates of serious ADRs remained almost unchanged from those in the previous interim report [4]. There were 11 events of cerebral infarction and 6 events of pancreatic cancer, which was the most common

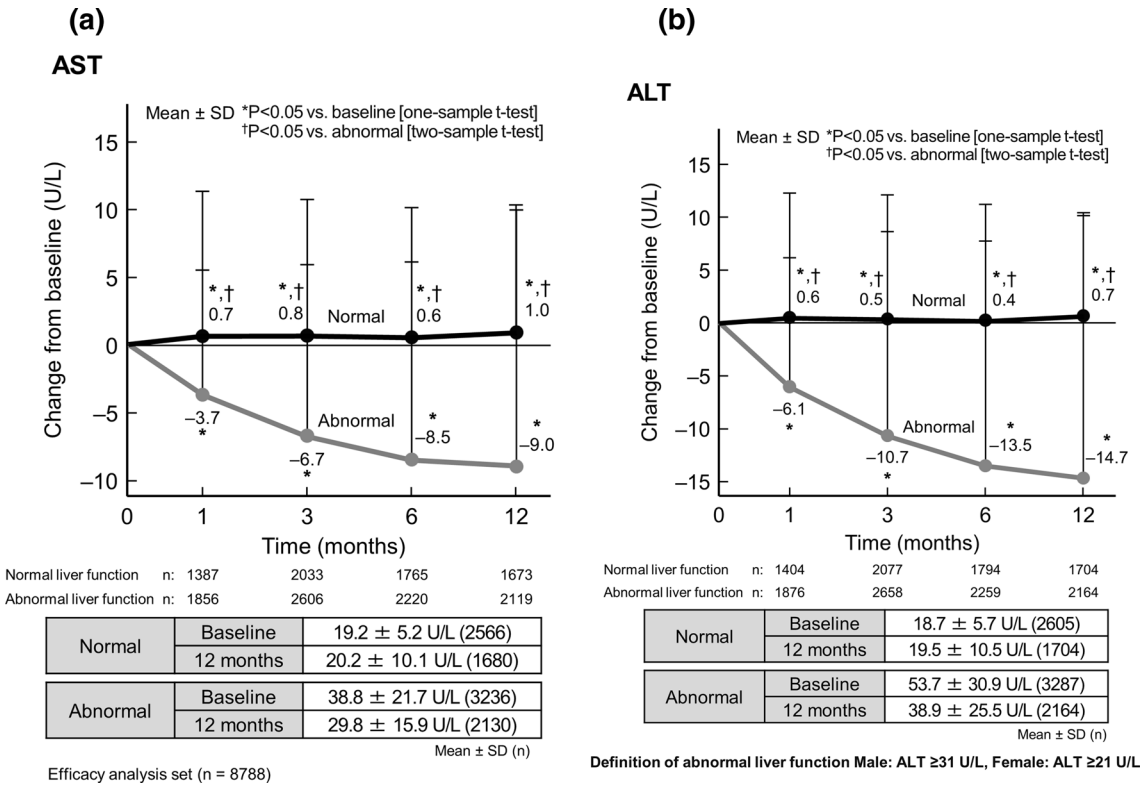


Fig. 3 Changes in AST (**a**) and ALT (**b**) from baseline to 12 months in patients stratified by liver function status. ALT alanine aminotransferase, AST aspartate aminotransferase, SD standard deviation

Table 10 Correlation between changes in ALT and other parameters in patients with abnormal liver function

	n	Pearson correlation coefficient	*P* value
Changes in HbA1c	2145	0.149	< 0.001
Changes in fasting plasma glucose	1198	0.106	< 0.001
Changes in fasting insulin	103	0.103	0.302
Changes in body weight	1837	0.206	< 0.001
Changes in waist circumference	351	0.006	0.918
Changes in systolic blood pressure	1886	0.032	0.171
Changes in diastolic blood pressure	1884	0.081	< 0.001
Changes in total bilirubin	904	0.102	0.002
Changes in triglycerides	2018	0.050	0.023

ALT alanine aminotransferase, *HbA1c* glycated hemoglobin

tumor type among the malignant tumors. No cases of serious ketoacidosis or lower limb amputation were observed.

The overall incidence rate of ADRs in the present interim report (14.6%) was lower than that in clinical trials prior to ipragliflozin approval (32.9%) [19–24]. This was also the case for individual ADRs; the incidence rate of each ADR was lower than that of clinical trials prior to ipragliflozin approval [19–24]. Genital

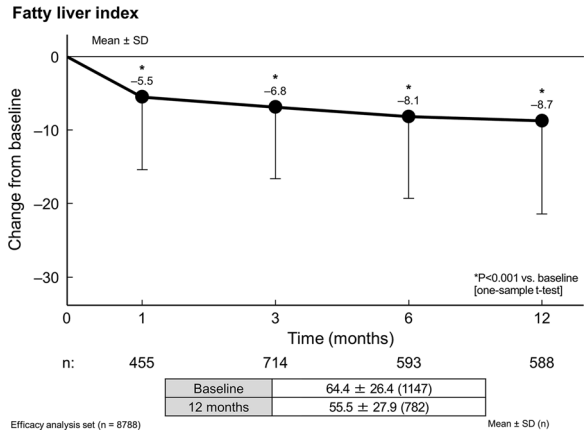


Fig. 4 Changes in fatty liver index from baseline to 12 months. SD standard deviation

infection is considered a class effect of SGLT2 inhibitors, although a recent meta-analysis reported that rates of genital mycotic infection were significantly higher in patients who received daily canagliflozin (100 or 300 mg) vs sitagliptin (100 mg), a DPP-4 inhibitor [25]. In the present study, 28 ADRs of vulvovaginal candidiasis were reported (0.25%), though it remains to be determined whether this is comparable with other SGLT2 inhibitors.

Regarding the time to onset of ADRs, approximately 65% of all ADRs occurred within 90 days of the start of the medication. Nearly 90% of polyuria/pollakiuria events and nearly 75% of skin complications occurred within 90 days. There was no particular trend in the onset time of fractures or malignant tumors.

In the present interim report, we investigated ADRs of special interest according to treatment status. In 81.3% of patients who experienced skin complications, treatment was interrupted or discontinued because of the event. This finding is likely related to the recommendations issued by experts advising caution with the use of SGLT2 inhibitors, especially in regard to skin problems [26].

Most ADRs resolved in the majority of patients. However, this did not apply to cases of malignant tumors and cerebrovascular/cardiovascular diseases. Regarding the incidence rate of ADRs by patient demographic and clinical characteristics, the incidences of ADRs were high, mainly in patients with long duration of disease, patients receiving increased doses of ipragliflozin, patients using many concomitant medications, and patients with higher baseline HbA1c levels.

The extent of decreases in HbA1c and fasting plasma glucose levels observed in the early phase of treatment were maintained for 12 months. The low rate of discontinuations due to "no improvement or worsening" (3.5%) and the use of concomitant medications and/or optimal dose modifications under the close supervision of the attending physician may be attributed to the favorable glycemic control.

Although statistically significant changes from baseline to 12 months in vital signs and all other laboratory parameters were observed, some of these changes may not be clinically significant and may have resulted from the large sample size. Favorable changes in blood pressure, lipids, plasma glucose, and uric acid suggest that a favorable effect on cardiovascular event risk may be expected, although this remains to be confirmed when the 3-year data become available. Statistically significant reductions from baseline to 12 months in AST and ALT were observed for patients with abnormal liver function status at baseline, while no clinically significant changes were shown in patients with normal liver function. This finding is consistent with that observed in a previous interim report of liver function of the STELLA-LONG TERM study [6]. Previous studies on other SGLT2 inhibitors have also reported an improvement in liver function-related parameters (AST and ALT) [27–30]. Taken together, these findings suggest that T2DM patients, especially those with abnormal liver function, may benefit from treatment with ipragliflozin.

No obvious correlation between ALT and change in each parameter was observed. This finding is consistent with that of a previous study on another SGLT2 inhibitor in which no correlation was found between HbA1c improvement and liver function [30].

The improvement in fatty liver index observed in the present study was consistent with that shown previously [31]. The fatty liver index is a surrogate marker of hepatic steatosis, which has been suggested to have a prognostic value for the risk of diabetes mellitus [32].

Future research on liver function will focus on the association between changes in fatty liver index values and other parameters and on comparing abnormal and normal fatty liver index subgroups.

The present study has some limitations. There was potential bias from incorrect completion of the survey report forms, which may have led to over- or under-representation of ADRs. The absence of a control group for comparison raises the possibility that the incidence of ADRs, as well as improvements in effectiveness variables, may be attributed to factors other than ipragliflozin (e.g., concomitant medications).

CONCLUSION

Ipragliflozin was effective and well tolerated in Japanese patients with T2DM over 12 months in a real-world clinical setting. Improvements in liver function parameters (AST and ALT) were observed in T2DM patients with abnormal liver function. The results reported here should be considered preliminary in nature and the results of further analyses are planned to be published as the data become available in the future.

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Compliance with Ethics Guidelines. This post-marketing surveillance study was in compliance with Good Post-marketing Study Practice. This study involved the collection of

anonymized data from a clinical setting as required by the regulatory body; therefore, informed consent was waived in compliance with the Japanese regulations for post-marketing surveillance studies. All of the medical institutions that agreed to provide data signed a contract with Astellas Pharma Inc.

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