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ORIGINAL RESEARCH

Safety and Effectiveness of Ipragliflozin in Elderly Versus Non-elderly Japanese Patients with Type 2 Diabetes: Subgroup Analysis of STELLA-LONG TERM

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ABSTRACT

Introduction: STELLA-LONG TERM is a post-marketing surveillance study evaluating the safety and effectiveness of ipragliflozin in Japanese patients with type 2 diabetes mellitus.
Methods: Patients were classified by age at ipragliflozin initiation (< 65 and ≥ 65 years), and elderly patients were subclassified by baseline body mass index (BMI) < 25.0 or ≥ 25.0 kg/m^2. Incidence of adverse drug reactions (ADRs) and effectiveness were evaluated over 3 years.
Results: Among 11,051 patients, 7894 (71.4%) were aged < 65 years and 3157 (28.6%) ≥ 65 years. The 3-year ADR incidence was similar in patients aged ≥ 65 (19.04%) and < 65 years (19.36%; $P = 0.701$). Serious ADRs were more frequent in the subgroup ≥ 65 years (2.79% vs 1.55%; $P < 0.001$). In terms of ADRs of special interest, a significantly greater proportion of elderly patients had skin complications (2.22% vs 1.62%, $P = 0.033$), renal disorders (2.28% vs 1.51%, $P = 0.005$), hypoglycemia (0.73% vs 0.43%, $P = 0.048$), or malignant tumors (1.01% vs 0.24%, $P < 0.001$), while the incidence of polyuria/pollakiuria (5.97% vs 4.47%, $P = 0.002$) and hepatic disorders (1.39% vs 0.73%, $P = 0.004$) was significantly higher in non-elderly than elderly patients. In patients aged ≥ 65 years, the incidence of ADRs was higher when baseline BMI was ≥ 25 kg/m^2 versus < 25 kg/m^2 (24.40% vs 17.68%; $P < 0.001$). Glycosylated hemoglobin, fasting blood glucose, and body weight significantly decreased from baseline in both age groups at each evaluation up to 3 years (all $P < 0.001$).
Conclusions: Ipragliflozin was well tolerated and effective for 3 years in routine clinical use in elderly and non-elderly patients, although elderly patients had a higher rate of serious ADRs. No new safety concerns were identified.
Clinical Trial Registration: ClinicalTrials.gov identifier NCT02479399.

Keywords: Elderly; Ipragliflozin; Japan; Post-marketing surveillance; Sodium-glucose cotransporter 2 inhibitor; Type 2 diabetes mellitus

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Key Summary Points
Why carry out this study?
The STELLA-LONG TERM observational study investigated the safety and effectiveness of ipragliflozin in Japanese patients with type 2 diabetes during 3 years of real-world use.
This prespecified subgroup analysis investigated outcomes in STELLA-LONG TERM among patients aged < 65 years and ≥ 65 years, since elderly people represent a high proportion of the Japanese population.
What was learned from this study?
Long-term ipragliflozin therapy was well tolerated and effective in all elderly patients, including those in the 75 years and older age group and those with a baseline body mass index < 25 kg/m^2.
No new safety concerns were identified, but the incidence of serious adverse drug reactions was significantly higher in elderly than non-elderly patients.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14124275.

INTRODUCTION

Ipragliflozin was the first sodium–glucose cotransporter 2 (SGLT2) inhibitor to be approved in Japan for the treatment of patients with type 2 diabetes mellitus [1]. The approval was based on several randomized controlled trials in which ipragliflozin, as monotherapy or in combination with other antidiabetic agents, improved glycemic control [1–7].

The average age of patients with diabetes in Japan is increasing. In a 2018 survey, 72.5% of patients who were strongly suspected of having diabetes were aged ≥ 65 years and 33.5% were aged ≥ 75 years [8]. Given the high proportion of elderly people in Japan, and concerns raised regarding the safety of SGLT2 inhibitors in elderly patients, it was deemed necessary to confirm the safety of ipragliflozin in elderly Japanese patients [9]. The STELLA-ELDER study showed that 16.9% of patients aged ≥ 65 years who were receiving ipragliflozin during routine clinical practice developed adverse drug reactions (ADRs) over 1 year of treatment, with most of these events developing within the first 30 days of treatment [9, 10].

STELLA-LONG TERM (*S*pecified drug use resul*T*s surv*E*y of iprag*L*if*L*ozin tre*A*tment in type 2 diabetic patients: LONG-TERM use) was a 3-year post-marketing surveillance study designed to investigate the safety and effectiveness of long-term ipragliflozin therapy in routine clinical practice in Japan. Several subgroup analyses were conducted, including the comparison of effectiveness and safety in elderly (aged ≥ 65 years) versus non-elderly patients.

Subgroup analyses of STELLA-LONG TERM using 3- and 12-month interim data showed significant decreases from baseline in mean glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and body weight with ipragliflozin in both elderly and non-elderly patients [11, 12]. The incidence of ADRs was similar in the two age groups (≥ 65 and < 65 years); however, significantly more elderly than non-elderly patients experienced a serious ADR at 3 months (0.8% vs 0.5%, $P = 0.019$) [12] and 12 months (1.4% vs 0.8%, $P = 0.002$) [11], and no new safety concerns were identified compared with pre-approval clinical trials.

Here, we report the subgroup analysis of the safety and effectiveness of ipragliflozin in elderly versus non-elderly Japanese patients from the final, 3-year results of the STELLA-LONG TERM study.

METHODS

STELLA-LONG TERM was a 3-year, observational, multicenter post-marketing surveillance study in Japanese patients with type 2 diabetes mellitus (ClinicalTrials.gov identifier NCT02479399). The study design and methods have been previously described [13]. Briefly, data from patients who were first prescribed ipragliflozin between July 17, 2014 and October 16, 2015 at participating clinical sites were included. Patients received ipragliflozin 50 mg once daily, before or after breakfast. Increasing the dose to 100 mg once daily was permitted if the treating physician judged the efficacy of the lower dose to be insufficient. A lower dose was also permitted, with caution advised in patients with severe hepatic impairment.

This study was conducted in compliance with Japanese Good Post-marketing Study Practice (GPSP) regulations and the study protocol was approved by the Ministry of Health, Labour and Welfare of the Japanese government. All medical institutions that agreed to provide data signed a contract with Astellas Pharma Inc. The review board that approved the study waived the need for consent, as anonymous data were collected via electronic survey forms from clinical settings.

Assessments

Data in this analysis were compared in two age categories: elderly ($\geq$ 65 years) versus non-elderly ($<$ 65 years), and non-elderly versus two elderly subgroups (65 to $<$ 75 years and $\geq$ 75 years). Data were also compared between patients with a baseline body mass index (BMI) of $<$ 25 versus $\geq$ 25 kg/m^2. Safety data collected included the incidence of ADRs [categorized according to Medical Dictionary for Drug Regulatory Activities—Japanese translation (MedDRA/J) version 22.0] and ADRs of special interest during treatment, with ADRs defined as adverse events (AEs) for which a causal relationship to ipragliflozin could not be excluded.

In addition, changes in vital signs and laboratory parameters were monitored in the safety analysis population, including heart rate, white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, blood urea nitrogen (BUN), serum albumin, serum creatinine, sodium, chloride, potassium, calcium, phosphorus, magnesium, serum ketone body levels, fasting C-peptide, estimated glomerular filtration rate (eGFR), pH, urinary albumin, and urinary creatinine levels.

Effectiveness outcomes included changes from baseline in HbA1c, FPG, and body weight. Changes in HbA1c were also compared in patients with a baseline level of $<$ 8% versus $\geq$ 8%. Additionally, changes in vital signs and laboratory parameters, including fasting insulin, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, uric acid, and total bilirubin were analyzed in the effectiveness analysis population.

Data were collected at baseline and 1, 3, 6, 12, 24, and 36 months after treatment was initiated.

Statistical Analysis

The rationale for sample size calculations for the primary analysis has been defined previously [13]. The safety analysis population included patients who received at least one dose of ipragliflozin, had no registration violations, and had data available for at least one visit after baseline. The effectiveness analysis set was the safety population excluding patients who were noncompliant with treatment, had unclear efficacy assessment data or missing baseline or post-baseline data for HbA1c, serum fasting insulin, or FPG.

Categorical variables are presented as number and proportions (%) and continuous variables as mean $\pm$ standard deviation (SD). Patient demographic and clinical data for the different age groups or BMI categories were compared using the chi-squared test, two-sample *t* test, or one-way analysis of variance as

appropriate. Changes from baseline in laboratory variables were analyzed using the one-sample *t* test. For descriptive purposes only, baseline demographic and ADR data were compared with those from STELLA-ELDER [9].

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Patient Disposition

A total of 11,424 patients were registered from 2431 medical institutions, and survey forms were collected for 11,289 patients. The safety analysis set included 11,051 patients, while the effectiveness analysis set included 8763 patients. Details of reasons for exclusion from the two analysis populations are described in the final report of the overall STELLA-LONG TERM study [14].

Patient Characteristics

In the safety analysis set, 7894 patients were aged < 65 years (mean age 51.2 years) at baseline; 3157 were aged ≥ 65 years (mean age 71.3 years; Table 1) and of these, 752 were aged ≥ 75 years (Supplementary Table S1). Compared with the elderly group (≥ 65 years), a significantly higher proportion of non-elderly patients (< 65 years) were men (63.6% vs 53.5% of elderly patients; $P < 0.001$), and significantly fewer had HbA1c < 8% (50.1% vs 59.5% of elderly patients; $P < 0.001$; Table 1). In the effectiveness analysis set, the mean HbA1c at baseline was 8.17% in patients aged < 65 years and 7.77% in patients aged ≥ 65 years ($P < 0.001$).

Elderly patients had a longer mean duration of diabetes (10.16 vs 7.22 years; $P < 0.001$), and a significantly higher proportion of elderly patients had complications at baseline (87.5% vs 83.6%; $P < 0.001$). Non-elderly patients had a significantly higher mean body weight (81.92 vs 67.57 kg; $P < 0.001$), BMI (29.90 vs 26.76 kg/m^2; $P < 0.001$), and eGFR (85.56 vs 70.56 mL/min/1.73 m^2; $P < 0.001$) than elderly patients.

Baseline characteristics from STELLA-ELDER [9] are provided in Table 1 for comparison.

Safety

In the safety analysis set, 2129 patients (19.27%) had at least one ADR (Table 2).

In the first age category analysis (< 65 vs ≥ 65 years), the incidence of ADRs was similar between non-elderly and elderly patients (19.36% vs 19.04%, $P = 0.701$). A significantly greater proportion of elderly than non-elderly patients had a serious ADR (2.79% vs 1.55%, $P < 0.001$). When assessing ADRs of special interest, a significantly greater proportion of elderly patients had skin complications (2.22% vs 1.62%, $P = 0.033$), renal disorders (2.28% vs 1.51%, $P = 0.005$), hypoglycemia (0.73% vs 0.43%, $P = 0.048$), or malignant tumors (1.01% vs 0.24%, $P < 0.001$). The incidence of polyuria/pollakiuria (5.97% vs 4.47%, $P = 0.002$) and hepatic disorders (1.39% vs 0.73%, $P = 0.004$) was significantly higher in non-elderly than elderly patients.

ADR data from STELLA-ELDER are provided in Table 3 for comparison [9].

Supplementary Table S2 summarizes the ADRs and ADRs of special interest according to the second age category analysis (patients aged < 65, 65 to < 75, and ≥ 75 years). The incidence of any ADR was lower in patients aged ≥ 75 years than in those aged < 65 or 65 to < 75 years ($P = 0.035$), while the incidence of serious ADRs was significantly higher in patients aged 65 to < 75 or ≥ 75 years than in those aged < 65 years ($P < 0.001$).

Elderly patients (≥ 65 years) with a BMI < 25 kg/m^2 had a significantly lower incidence of ADRs than those with a BMI ≥ 25 kg/m^2. In the ≥ 65 years age group, the incidence of ADRs was 17.68% in patients with a BMI of < 25 kg/m^2 and 24.40% in those with a BMI of ≥ 25 kg/m^2 ($P < 0.001$); respective values were 19.81% and 25.27% ($P = 0.017$) in the 65 to < 75 years age group, and 11.43% and 20.60% ($P = 0.014$) in the ≥ 75 years group. Among patients with a baseline BMI < 25 kg/m^2, a

Table 1 Patient baseline characteristics in the safety analysis population (first age category analysis) of STELLA-LONG TERM and in STELLA-ELDER

	STELLA-LONG TERM			STELLA-ELDER [9]
	< 65 years	≥ 65 years	*P* value[a]	
All, *n*	7894	3157		8505
Sex, *n* (%)				
Male	5023 (63.6)	1690 (53.5)	(1) < 0.001	4181 (49.2)
Female	2871 (36.4)	1467 (46.5)		4324 (50.8)
Age, years				
Mean ± SD	51.2 ± 9.0	71.3 ± 5.5		72.3 ± 5.9
Median (range)	52.0 (14–64)	70.0 (65–95)		
65 to < 75, *n* (%)	–	2405 (76.2)		5800 (68.2)
≥ 75, *n* (%)	–	752 (23.8)		2705 (31.8)
Body weight, kg, mean ± SD (*n*)	81.92 ± 17.35 (6015)	67.57 ± 12.01 (2157)	(2) < 0.001	67.5 ± 12.9
BMI, kg/m^2				
Mean ± SD (*n*)	29.90 ± 5.44 (5548)	26.76 ± 4.07 (1944)	(2) < 0.001	27.0 ± 4.56
< 25.0, *n* (%)	883 (11.2)	690 (21.9)	(1) < 0.001	1762 (20.7)
≥ 25.0, *n* (%)	4665 (59.1)	1254 (39.7)		3306 (38.9)
Unknown	2346 (29.7)	1213 (38.4)		3437 (40.4)
Duration of diabetes, years				
Mean ± SD (*n*)	7.22 ± 5.74 (5417)	10.16 ± 7.79 (1831)	(2) < 0.001	10.6 ± 7.52
< 5, *n* (%)	2124 (26.9)	469 (14.9)	(1) < 0.001	1177 (13.8)
≥ 5, *n* (%)	3293 (41.7)	1362 (43.1)		4150 (48.8)
Unknown, *n* (%)	2477 (31.4)	1326 (42.0)		3178 (37.4)
Complications, *n* (%)				
Yes	6603 (83.6)	2762 (87.5)	(1) < 0.001	6917 (81.3)
No	1232 (15.6)	367 (11.6)		1477 (17.4)
Unknown	59 (0.7)	28 (0.9)		111 (1.3)
eGFR, mean mL/min/1.73 m^2 ± SD (*n*)	85.56 ± 19.35 (4762)	70.56 ± 17.96 (1935)	(2) < 0.001	69.7 ± 19.4

Table 1 continued

	STELLA-LONG TERM			STELLA-ELDER [9]
	< 65 years	≥ 65 years	*P* value[a]	
HbA1c, %				
Mean ± SD (*n*)[b]	8.17 ± 1.51 (6413)	7.77 ± 1.24 (2313)	(2) < 0.001	7.84 ± 1.33 (6853)
< 8%, *n* (%)	3958 (50.1)	1877 (59.5)	(1) < 0.001	4381 (51.5)
≥ 8%, *n* (%)	3473 (44.0)	1009 (32.0)		2747 (32.3)
Unknown	463 (5.9)	271 (8.6)		1377 (16.2)
Initial dose of ipragliflozin, *n* (%)				
25 mg	879 (11.1)	541 (17.1)	–[c]	1152 (13.5)
50 mg	6999 (88.7)	2613 (82.8)		7344 (86.3)
100 mg	13 (0.2)	2 (0.1)		9 (0.1)
Other	3 (0.04)	1 (0.03)		0
Daily dose of ipragliflozin, mg, mean ± SD (*n*)	48.34 ± 8.39 (7894)	46.73 ± 9.91 (3157)	(2) < 0.001	
Dose changes during treatment, *n* (%)				
25 mg to 25 mg	602 (7.6)	419 (13.3)	(1) < 0.001	856 (10.1)
25 mg to 50 mg	242 (3.1)	102 (3.2)		263 (3.1)
50 mg to 50 mg	6765 (85.7)	2514 (79.6)		7168 (84.3)
50 mg to 100 mg	121 (1.5)	41 (1.3)		78 (0.9)
Other	164 (2.1)	81 (2.6)		140 (1.6)

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *SD* standard deviation

[a] *P* values across subgroups assessed by (1) chi-squared test or (2) two-sample *t* test; no statistical comparison between groups was made for specific complications

[b] Mean HbA1c values were from the effectiveness analysis set

[c] No *P* value was calculated when at least one element of the contingency table was < 10

significantly greater proportion of elderly vs non-elderly patients in the first age category analysis (≥ 65 vs < 65 years) had a serious ADR (2.75% vs 1.36%, $P = 0.048$; Table 3). Within the BMI < 25 kg/m^2 group, patients aged ≥ 75 years had a significantly lower incidence of ADRs than those aged < 65 or 65 to < 75 years ($P = 0.043$; Table 3).

Both non-elderly and elderly patients (< 65 vs ≥ 65 years; first age category analysis) in the safety analysis cohort showed significant decreases from baseline to 3 years in WBC count (− 275.0 ± 1447.8/μL and − 148.7 ± 1323.7/μL, both $P < 0.05$) and eGFR (− 3.18 ± 12.24 mL/min/1.73 m^2 and − 2.21 ± 10.74 mL/min/1.73 m^2, both $P < 0.001$; Table 4).

In both non-elderly and elderly patients, significant increases from baseline to 3 years were observed in mean RBC count (both $P < 0.001$), hemoglobin levels (both $P < 0.001$), hematocrit (both $P < 0.001$), BUN (both $P < 0.001$), serum creatinine (both $P < 0.001$), sodium (both $P < 0.001$), chloride (both $P < 0.001$), and phosphorus (both $P < 0.05$; Table 4).

When comparing the magnitude of change between the two age groups, WBC count ($P < 0.05$), and eGFR ($P < 0.05$) were

Table 2 Adverse drug reactions in the safety analysis population (first age category analysis) of STELLA-LONG TERM, in pre-approval clinical trials, and STELLA-ELDER

ADRs, *n* (%)	Pre-approval (*n* = 1669) [2–7]	STELLA-LONG TERM				STELLA-ELDER (*n* = 8505) [9]
		All (*n* = 11,051)	< 65 years (*n* = 7894)	≥ 65 years (*n* = 3157)	*P* value[a]	
Any ADR	549 (32.89)	2129 (19.27)	1528 (19.36)	601 (19.04)	0.701	1438 (16.9)
Serious ADR	14 (0.8)	210 (1.90)	122 (1.55)	88 (2.79)	< 0.001	127 (1.5)
ADRs of special interest						
Polyuria/ pollakiuria	168 (10.0)	612 (5.54)	471 (5.97)	141 (4.47)	0.002	170 (2.0)
Volume depletion	73 (4.5)	243 (2.20)	167 (2.12)	76 (2.41)	0.345	266 (3.1)
Skin complications	59 (4.0)	198 (1.79)	128 (1.62)	70 (2.22)	0.033	269 (3.2)
Renal disorder	76 (4.8)	191 (1.73)	119 (1.51)	72 (2.28)	0.005	118 (1.4)
Urinary tract infection	29 (1.8)	170 (1.54)	115 (1.46)	55 (1.74)	0.271	118 (1.4)
Genital infection	32 (2.0)	161 (1.46)	126 (1.60)	35 (1.11)	0.053	166 (2.0)
Hepatic disorder	17 (1.0)	133 (1.20)	110 (1.39)	23 (0.73)	0.004	19 (0.2)
Cardiovascular disease	16 (1.0)	67 (0.61)	50 (0.63)	17 (0.54)	0.562	24 (0.3)
Hypoglycemia	22 (1.4)	57 (0.52)	34 (0.43)	23 (0.73)	0.048	58 (0.7)
Malignant tumor	4 (0.2)	51 (0.46)	19 (0.24)	32 (1.01)	< 0.001	11 (0.1)
Cerebrovascular disease	4 (0.2)	48 (0.43)	29 (0.37)	19 (0.60)	0.090	36 (0.4)
Ketone body related events	11 (1.0)	7 (0.06)	6 (0.08)	1 (0.03)	–[b]	2 (0.02)
Fracture	0	4 (0.04)	4 (0.05)	0	–[b]	2 (0.02)
Lower limb amputation	0	0	0	0	–[b]	0

No. of patients (%) are shown
ADR adverse drug reaction
[a] Chi-squared test for difference between BMI subgroups
[b] No *P* value was calculated when at least one element of the contingency table was < 10

significantly more reduced in non-elderly (< 65 years) than in elderly patients (≥ 65 years; Table 4).

Changes from baseline in vital signs and laboratory parameters in patients aged 65 to

Table 3 Adverse drug reactions by BMI and age in the safety analysis population

	Elderly patients, by BMI category								
	≥ 65 years (n = 1944)			65 to < 75 years (n = 1536)			≥ 75 years (n = 408)		
	BMI		P value[a]	BMI		P value[a]	BMI		P value[a]
	< 25 kg/m^2 (n = 690)	≥ 25 kg/m^2 (n = 1254)		< 25 kg/m^2 (n = 515)	≥ 25 kg/m^2 (n = 1021)		< 25 kg/m^2 (n = 175)	≥ 25 kg/m^2 (n = 233)	
Any ADR	122 (17.68)	306 (24.40)	< 0.001	102 (19.81)	258 (25.27)	0.017	20 (11.43)	48 (20.60)	0.014
Serious ADR	19 (2.75)	47 (3.75)	0.247	15 (2.91)	39 (3.82)	0.362	4 (2.29)	8 (3.43)	–[b]

	Patients with a BMI < 25 kg/m^2, by age					
	< 65 years (n = 883)	≥ 65 years (n = 690)	P value[a]	65 to < 75 years (n = 515)	≥ 75 years (n = 175)	P value[a]
ADR	159 (18.01)	122 (17.68)	0.867	102 (19.81)	20 (11.43)	0.043
Serious ADR	12 (1.36)	19 (2.75)	0.048	15 (2.91)	4 (2.29)	–[b]

No. of patients (%) are shown

ADR adverse drug reaction, *BMI* body mass index

[a] Chi-squared test for difference between BMI subgroups

[b] No P value was calculated when at least one element of the contingency table was < 10

< 75 years and ≥ 75 years are shown in Supplementary Table S3.

Effectiveness

Over the 3 years, mean HbA1c was significantly decreased from baseline ($P < 0.001$) at each time point in non-elderly and elderly patients for first age category analysis (Fig. 1a), as well as in the subcategories of elderly patients aged 65 to < 75 years and ≥ 75 years (Supplementary Fig. S1). At 3 years, the mean ± SD change from baseline in HbA1c was − 0.69 ± 1.30% in patients aged < 65 years, and − 0.60 ± 1.09% in patients aged ≥ 65 years. When analyzed by baseline HbA1c category, mean HbA1c was significantly decreased from baseline at each time point in patients with baseline HbA1c < 8% and ≥ 8%, in both non-elderly and elderly patients (Fig. 1b, c).

When data for elderly patients were analyzed according to baseline BMI (< 25 vs ≥ 25 kg/m^2), in both BMI categories, mean HbA1c was significantly ($P < 0.001$) reduced from baseline at each time point in patients aged ≥ 65 years (Fig. 2a), 65 to < 75 years (Fig. 2b), and ≥ 75 years (Fig. 2c). In patients aged ≥ 65 years, the mean ± SD change in HbA1c from baseline at 3 years was − 0.61 ± 1.05% in those with a baseline BMI < 25 kg/m^2 and − 0.58 ± 1.08% in those with a baseline BMI ≥ 25 kg/m^2.

Over the 3-year study, mean body weight was significantly ($P < 0.001$) reduced from baseline at each time point in patients aged < 65 and ≥ 65 years (Fig. 3a), and in those aged 65 to 75 years and ≥ 75 years (Supplementary Fig. S2a). After 3 years, the mean ± SD change in body weight was − 3.34 ± 4.54 kg in patients aged < 65 years and − 2.99 ± 3.55 kg in patients aged ≥ 65 years.

When analyzed by baseline BMI category, mean body weight was significantly reduced from baseline at all time points in patients with a baseline BMI < 25 kg/m^2 and ≥ 25 kg/m^2 across all age categories (< 65 and ≥ 65 years, Fig. 3b, c; and < 65, 65 to < 75 years and ≥ 75 years, Supplementary Fig. S2b and c).

Table 4 Changes from baseline to 3 years in vital signs and laboratory parameters in the safety analysis population

	< 65 years			≥ 65 years			*P* value for comparison between age groups[a]
	Mean value ± SD		Change from baseline ± SD	Mean value ± SD		Change from baseline ± SD	
	Baseline	3 years		Baseline	3 years		
Heart rate, BPM	79.2 ± 12.7 (*n* = 3715)	77.4 ± 11.7 (*n* = 2268)	− 0.9 ± 10.3** (*n* = 1814)	74.8 ± 10.9 (*n* = 1478)	74.1 ± 10.6 (*n* = 899)	− 0.1 ± 9.6 (*n* = 742)	0.081
WBC count, /μL	7259.1 ± 1995.1 (*n* = 4242)	6902.4 ± 1752.4 (*n* = 2519)	− 275.0 ± 1447.8** (*n* = 1991)	6517.8 ± 1667.5 (*n* = 1768)	6392.7 ± 1540.0 (*n* = 1053)	− 148.7 ± 1323.7* (*n* = 830)	0.031
RBC count, × 10^4/μL	489.8 ± 115.8 (*n* = 4238)	504.5 ± 47.8 (*n* = 2529)	17.3 ± 32.3** (*n* = 1988)	453.0 ± 46.4 (*n* = 1771)	471.0 ± 47.2 (*n* = 1057)	16.5 ± 31.4** (*n* = 836)	0.533
Hemoglobin, g/dL	14.67 ± 1.50 (*n* = 4239)	15.18 ± 1.43 (*n* = 2538)	0.53 ± 1.02** (*n* = 1998)	13.83 ± 1.42 (*n* = 1754)	14.39 ± 1.41 (*n* = 1052)	0.45 ± 0.99** (*n* = 835)	0.053
Hematocrit, %	43.80 ± 3.98 (*n* = 4246)	45.84 ± 3.94 (*n* = 2523)	2.03 ± 2.99** (*n* = 1979)	41.72 ± 3.94 (*n* = 1782)	43.85 ± 4.20 (*n* = 1060)	1.85 ± 3.14** (*n* = 835)	0.147
BUN, mg/dL	14.15 ± 4.11 (*n* = 4217)	15.56 ± 4.13 (*n* = 2512)	1.34 ± 3.65** (*n* = 2005)	16.58 ± 4.98 (*n* = 1639)	17.46 ± 4.85 (*n* = 950)	1.15 ± 3.98** (*n* = 747)	0.232
Serum albumin, g/dL	4.36 ± 0.37 (*n* = 2129)	4.36 ± 0.35 (*n* = 1285)	0.01 ± 0.30 (*n* = 907)	4.23 ± 0.44 (*n* = 863)	4.25 ± 0.36 (*n* = 512)	− 0.01 ± 0.33 (*n* = 359)	0.314
Serum creatinine, mg/dL	0.721 ± 0.204 (*n* = 4827)	0.734 ± 0.214 (*n* = 2854)	0.019 ± 0.122** (*n* = 2316)	0.780 ± 0.255 (*n* = 1936)	0.786 ± 0.257 (*n* = 1141)	0.021 ± 0.136** (*n* = 924)	0.764
Sodium, mmol/L	139.9 ± 2.5 (*n* = 3362)	140.5 ± 2.3 (*n* = 1901)	0.4 ± 2.6** (*n* = 1487)	140.5 ± 2.4 (*n* = 1371)	141.0 ± 2.4 (*n* = 779)	0.5 ± 2.6** (*n* = 594)	0.742
Chloride, mmol/L	102.4 ± 2.9 (*n* = 3268)	102.8 ± 2.7 (*n* = 1877)	0.4 ± 2.9** (*n* = 1457)	103.0 ± 2.8 (*n* = 1345)	103.4 ± 2.7 (*n* = 766)	0.4 ± 2.8** (*n* = 584)	0.899
Potassium, mmol/L	4.19 ± 0.40 (*n* = 3537)	4.22 ± 0.39 (*n* = 1955)	0.01 ± 0.39 (*n* = 1529)	4.30 ± 0.47 (*n* = 1503)	4.28 ± 0.42 (*n* = 811)	− 0.02 ± 0.42 (*n* = 616)	0.219

Table 4 continued

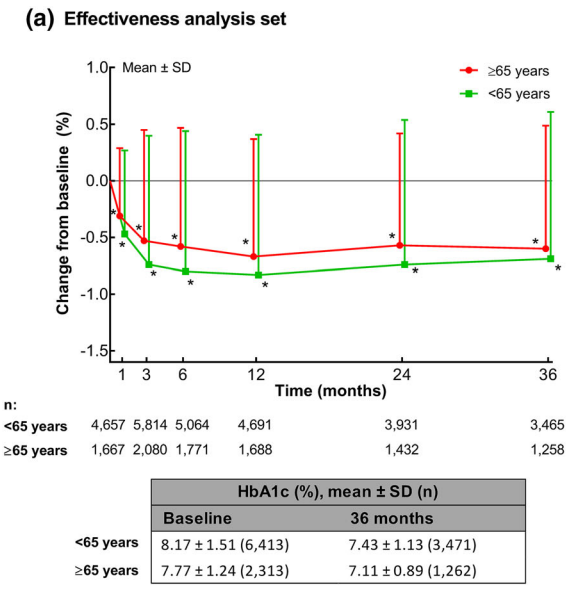
	< 65 years			≥ 65 years			*P* value for comparison between age groups[a]
	Mean value ± SD		Change from baseline ± SD	Mean value ± SD		Change from baseline ± SD	
	Baseline	3 years		Baseline	3 years		
Calcium, mmol/L	9.36 ± 0.45 (*n* = 1067)	9.31 ± 0.45 (*n* = 645)	− 0.05 ± 0.42* (*n* = 424)	9.29 ± 0.44 (*n* = 434)	9.23 ± 0.44 (*n* = 275)	0.00 ± 0.44 (*n* = 172)	0.146
Phosphorus, mg/dL	3.29 ± 0.69 (*n* = 574)	3.40 ± 0.56 (*n* = 348)	0.11 ± 0.51* (*n* = 211)	3.17 ± 0.55 (*n* = 221)	3.22 ± 0.56 (*n* = 144)	0.18 ± 0.58* (*n* = 75)	0.333
Magnesium, mg/dL	2.07 ± 0.24 (*n* = 171)	2.20 ± 0.22 (*n* = 165)	0.08 ± 0.22* (*n* = 51)	2.13 ± 0.22 (*n* = 91)	2.28 ± 0.23 (*n* = 89)	0.13 ± 0.22* (*n* = 24)	0.434
Serum ketone body, μmol/L	127.79 ± 124.83 (*n* = 112)	111.63 ± 174.35 (*n* = 86)	0.82 ± 78.22 (*n* = 28)	144.54 ± 184.88 (*n* = 28)	110.93 ± 99.43 (*n* = 29)	13.10 ± 101.09 (*n* = 9)	–[b]
Fasting C-peptide, ng/mL	3.595 ± 4.724 (*n* = 283)	2.791 ± 1.693 (*n* = 112)	− 0.848 ± 1.995* (*n* = 54)	3.046 ± 2.123 (*n* = 91)	2.981 ± 2.021 (*n* = 36)	− 0.478 ± 1.148 (*n* = 15)	0.496
eGFR, mL/min/1.73 m^2	85.56 ± 19.35 (*n* = 4762)	82.46 ± 18.71 (*n* = 2839)	− 3.18 ± 12.24** (*n* = 2289)	70.56 ± 17.96 (*n* = 1935)	69.05 ± 17.22 (*n* = 1140)	− 2.21 ± 10.74** (*n* = 922)	0.035
pH	5.99 ± 0.73 (*n* = 2904)	5.93 ± 0.71 (*n* = 1697)	− 0.05 ± 0.83* (*n* = 1310)	5.98 ± 0.76 (*n* = 946)	5.96 ± 0.77 (*n* = 559)	− 0.02 ± 0.87 (*n* = 421)	0.508
Urinary albumin, mg/g·Cr	115.66 ± 413.90 (*n* = 620)	81.76 ± 347.36 (*n* = 332)	− 22.31 ± 247.97 (*n* = 162)	89.14 ± 225.92 (*n* = 160)	64.78 ± 175.08 (*n* = 105)	− 38.57 ± 310.31 (*n* = 55)	0.695
Urinary creatinine, mg/dL	116.767 ± 139.480 (*n* = 472)	76.143 ± 57.129 (*n* = 254)	− 27.398 ± 72.246** (*n* = 116)	87.824 ± 99.304 (*n* = 150)	55.990 ± 37.936 (*n* = 96)	− 16.975 ± 52.858* (*n* = 46)	0.376

BUN blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *RBC* red blood cell, *SD* standard deviation, *WBC* white blood cell

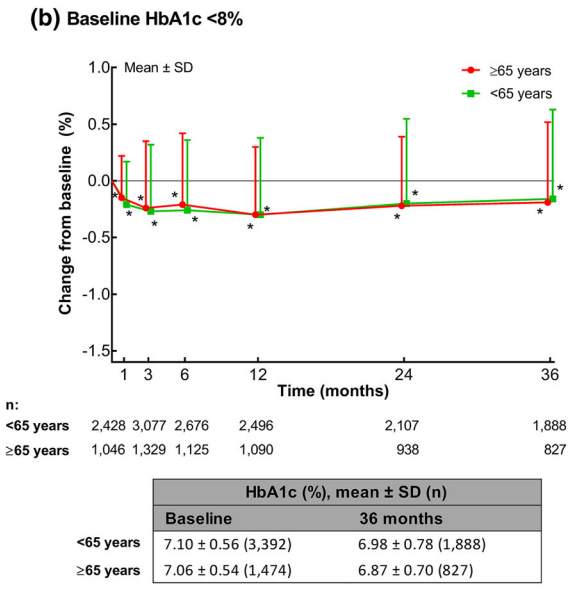
*$P < 0.05$, **$P < 0.001$ vs baseline (one-sample *t* test)

[a] Two-sample *t* test for the comparison of change from baseline between patients aged < 65 years and patients aged ≥ 65 years

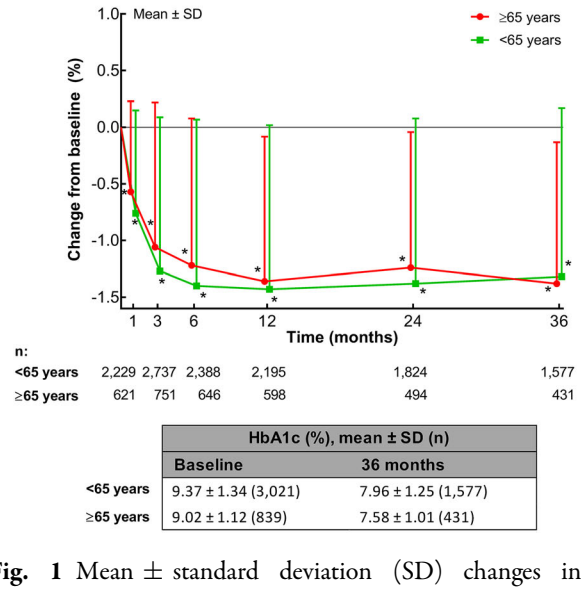
[b] No *P* value was calculated when at least one element of the contingency table was < 10



HbA1c (%), mean ± SD (n)		
	Baseline	36 months
<65 years	8.17 ± 1.51 (6,413)	7.43 ± 1.13 (3,471)
≥65 years	7.77 ± 1.24 (2,313)	7.11 ± 0.89 (1,262)



HbA1c (%), mean ± SD (n)		
	Baseline	36 months
<65 years	7.10 ± 0.56 (3,392)	6.98 ± 0.78 (1,888)
≥65 years	7.06 ± 0.54 (1,474)	6.87 ± 0.70 (827)



HbA1c (%), mean ± SD (n)		
	Baseline	36 months
<65 years	9.37 ± 1.34 (3,021)	7.96 ± 1.25 (1,577)
≥65 years	9.02 ± 1.12 (839)	7.58 ± 1.01 (431)

Fig. 1 Mean ± standard deviation (SD) changes in glycated hemoglobin (HbA1c) by age in **a** the effectiveness analysis population, **b** patients with baseline HbA1c < 8%, and **c** patients with baseline HbA1c ≥ 8%. Tables show the absolute mean ± SD values at baseline and 3 years. *$P < 0.001$ vs baseline (one-sample t test)

In the first age category analysis, mean ± SD FPG was significantly ($P < 0.001$) reduced from baseline to 3 years by − 29.3 ± 50.5 mg/dL in patients aged < 65 years and − 27.5 ± 49.1 mg/dL in patients aged ≥ 65 years (Table 5). In both non-elderly and elderly patients in the first age category effectiveness analysis, there were also significant reductions from baseline in fasting insulin, BMI, waist circumference, SBP, DBP, uric acid, and liver function markers (AST, ALT, γ-GTP, and ALP), as well as significant improvements in lipid parameters (triglycerides, total cholesterol, LDL-C, and HDL-C; Table 5). The changes from baseline were significantly greater for patients aged < 65 years than ≥ 65 years for AST ($P < 0.05$) and ALT

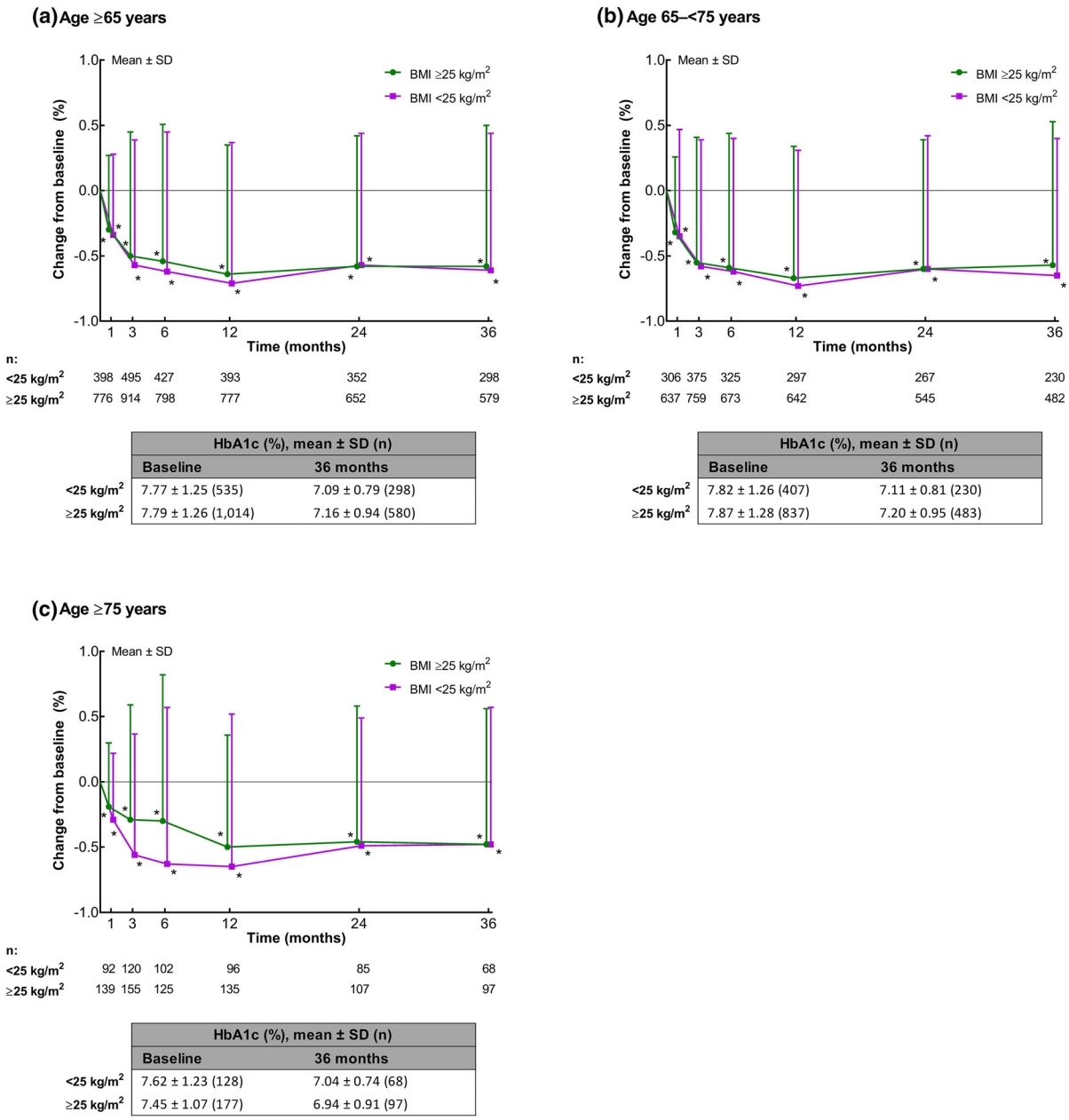


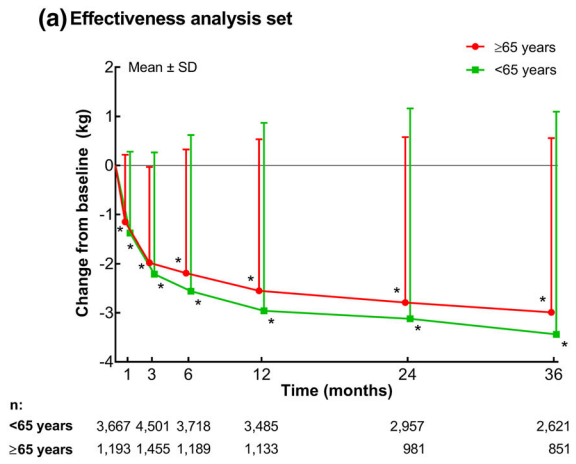
Fig. 2 Mean ± standard deviation (SD) changes in glycated hemoglobin (HbA1c) by BMI (< 25 vs ≥ 25 kg/m^2) in elderly patients: **a** patients aged ≥ 65 years, **b** patients aged 65 to < 75 years, and **c** patients aged ≥ 75 years. Tables show the absolute mean ± SD values at baseline and 3 years. *$P < 0.001$ vs baseline (one-sample t test)

($P < 0.001$); there were no other between-group differences.

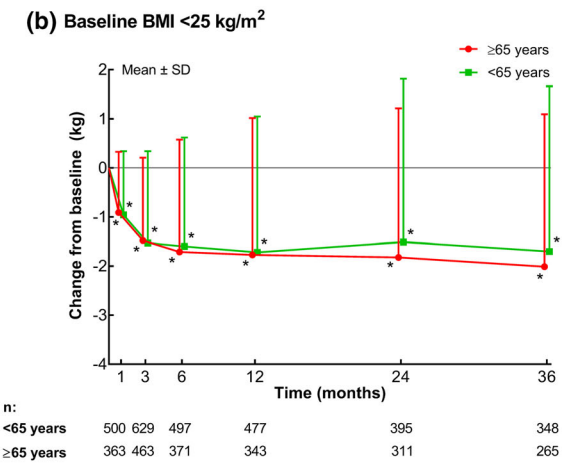
Changes in vital signs and laboratory markers in the effectiveness analysis population in patients aged 65 to < 75 years and ≥ 75 years are shown in Supplementary Table S4.

DISCUSSION

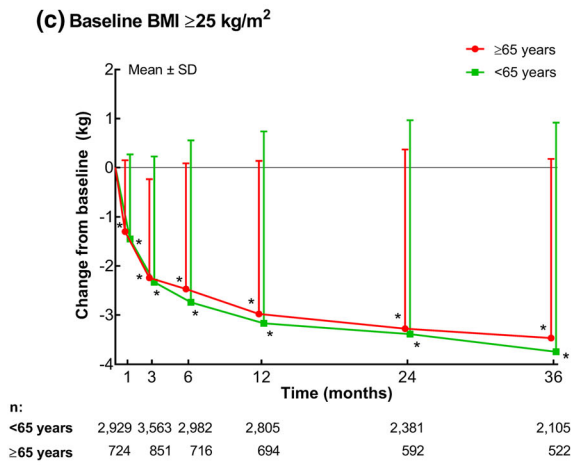
In this subgroup analysis of the large, 3-year STELLA-LONG TERM post-marketing surveillance study, ipragliflozin treatment was well



	Bodyweight (kg), mean ± SD (n)	
	Baseline	36 months
<65 years	82.06 ± 17.16 (5,163)	78.40 ± 15.97 (2,784)
≥65 years	67.91 ± 12.02 (1,722)	65.18 ± 11.61 (920)



	Bodyweight (kg), mean ± SD (n)	
	Baseline	36 months
<65 years	63.08 ± 7.93 (734)	61.69 ± 7.82 (348)
≥65 years	58.90 ± 7.79 (537)	56.89 ± 7.65 (265)



	Bodyweight (kg), mean ± SD (n)	
	Baseline	36 months
<65 years	85.76 ± 16.18 (4,037)	81.16 ± 15.34 (2,105)
≥65 years	72.85 ± 10.83 (1,015)	69.48 ± 10.82 (522)

Fig. 3 Mean ± standard deviation (SD) changes in body weight by age in **a** the effectiveness analysis population, **b** patients with a baseline BMI < 25 kg/m^2, and **c** patients with a baseline BMI ≥ 25 kg/m^2. Tables show the absolute mean ± SD values at baseline and 3 years. $^*P < 0.001$ vs baseline (one-sample t test)

tolerated and effective in both elderly and non-elderly Japanese patients with type 2 diabetes. Of the > 11,000 patients included in STELLA-LONG TERM, approximately 29% were aged ≥ 65 years. As may be expected, compared with non-elderly patients, elderly patients had a significantly longer duration of diabetes at baseline, were more likely to have complications, and had a significantly lower mean body weight, BMI, and eGFR. Additionally, a significantly greater proportion of elderly than non-elderly patients had an HbA1c < 8% at baseline.

Table 5 Changes from baseline to 3 years in vital signs and laboratory parameters in the effectiveness analysis population

	< 65 years			≥ 65 years			*P* value for comparison between age groups[a]
	Mean value ± SD		Change from baseline ± SD	Mean value ± SD		Change from baseline ± SD	
	Baseline	3 years		Baseline	3 years		
FPG, mg/dL	167.7 ± 59.6 (*n* = 3692)	136.3 ± 37.6 (*n* = 2038)	− 29.3 ± 50.5** (*n* = 1745)	164.7 ± 56.6 (*n* = 1455)	135.2 ± 37.6 (*n* = 788)	− 27.5 ± 49.1** (*n* = 700)	0.418
Fasting insulin, μU/mL	13.60 ± 9.51 (*n* = 411)	11.64 ± 8.58 (*n* = 181)	− 2.87 ± 8.24** (*n* = 96)	11.42 ± 9.60 (*n* = 151)	8.30 ± 4.38 (*n* = 85)	− 3.45 ± 8.30* (*n* = 44)	0.699
BMI, kg/m^2	29.93 ± 5.37 (*n* = 4771)	28.62 ± 4.97 (*n* = 2581)	− 1.27 ± 1.66** (*n* = 2453)	26.83 ± 4.08 (*n* = 1552)	25.82 ± 3.98 (*n* = 838)	− 1.19 ± 1.42** (*n* = 787)	0.203
Waist circumference, cm	98.75 ± 12.64 (*n* = 995)	94.27 ± 12.19 (*n* = 472)	− 2.82 ± 4.65** (*n* = 373)	92.83 ± 10.13 (*n* = 397)	89.88 ± 10.25 (*n* = 234)	− 2.99 ± 4.67** (*n* = 190)	0.666
SBP, mmHg	133.0 ± 15.2 (*n* = 5245)	128.8 ± 13.1 (*n* = 3031)	− 4.4 ± 14.7** (*n* = 2766)	134.3 ± 14.9 (*n* = 1899)	129.9 ± 13.0 (*n* = 1099)	− 4.2 ± 14.6** (*n* = 1011)	0.682
DBP, mmHg	79.5 ± 10.2 (*n* = 5178)	76.9 ± 9.4 (*n* = 3017)	− 2.8 ± 10.1** (*n* = 2731)	74.1 ± 9.8 (*n* = 1888)	72.0 ± 9.1 (*n* = 1093)	− 2.4 ± 9.9** (*n* = 1001)	0.342
AST, U/L	31.2 ± 20.3 (*n* = 4271)	25.7 ± 12.8 (*n* = 2440)	− 4.6 ± 14.9** (*n* = 2104)	27.2 ± 16.2 (*n* = 1542)	24.4 ± 13.6 (*n* = 906)	− 3.0 ± 15.6** (*n* = 771)	0.010
ALT, U/L	41.8 ± 31.1 (*n* = 4330)	31.9 ± 21.5 (*n* = 2460)	− 8.5 ± 22.6** (*n* = 2135)	28.0 ± 19.2 (*n* = 1552)	23.3 ± 14.8 (*n* = 909)	− 5.3 ± 16.2** (*n* = 778)	< 0.001
ALP, U/L	243.9 ± 83.3 (*n* = 2303)	228.7 ± 70.4 (*n* = 1338)	− 10.0 ± 54.4** (*n* = 1035)	248.6 ± 84.5 (*n* = 847)	234.6 ± 70.9 (*n* = 495)	− 12.9 ± 58.6** (*n* = 382)	0.380
γ-GTP, U/L	62.1 ± 72.8 (*n* = 3987)	46.7 ± 55.3 (*n* = 2286)	− 12.1 ± 47.8** (*n* = 1938)	49.2 ± 64.6 (*n* = 1435)	35.6 ± 39.7 (*n* = 835)	− 11.8 ± 39.0** (*n* = 709)	0.905
Total cholesterol, mg/dL	199.0 ± 40.1 (*n* = 2728)	192.8 ± 36.0 (*n* = 1455)	− 3.0 ± 33.9* (*n* = 1210)	190.4 ± 38.6 (*n* = 993)	187.6 ± 32.6 (*n* = 528)	− 2.9 ± 28.6* (*n* = 446)	0.944
LDL-C, mg/dL	116.2 ± 32.4 (*n* = 3913)	110.1 ± 28.4 (*n* = 2303)	− 5.8 ± 30.4** (*n* = 1882)	109.9 ± 29.9 (*n* = 1430)	106.0 ± 27.6 (*n* = 833)	− 4.6 ± 26.4** (*n* = 691)	0.347

Table 5 continued

	< 65 years			≥ 65 years			*P* value for comparison between age groups[a]
	Mean value ± SD		Change from baseline ± SD	Mean value ± SD		Change from baseline ± SD	
	Baseline	3 years		Baseline	3 years		
HDL-C, mg/dL	49.9 ± 13.0 (n = 4132)	53.6 ± 16.3 (n = 2368)	3.2 ± 8.7** (n = 2018)	53.5 ± 14.7 (n = 1448)	56.1 ± 14.3 (n = 853)	3.0 ± 10.3** (n = 719)	0.580
Triglycerides, mg/dL	208.5 ± 198.9 (n = 4322)	183.2 ± 154.1 (n = 2475)	− 15.1 ± 148.9** (n = 2122)	163.5 ± 126.4 (n = 1532)	147.1 ± 79.0 (n = 893)	− 12.4 ± 86.9** (n = 759)	0.633
Uric acid, mg/dL	5.40 ± 1.31 (n = 3808)	5.12 ± 1.20 (n = 2199)	− 0.23 ± 1.01** (n = 1810)	5.17 ± 1.33 (n = 1369)	4.89 ± 1.21 (n = 795)	− 0.26 ± 1.03** (n = 655)	0.473
Total bilirubin, mg/dL	0.637 ± 0.256 (n = 1906)	0.650 ± 0.257 (n = 1145)	0.030 ± 0.208** (n = 891)	0.627 ± 0.238 (n = 764)	0.654 ± 0.228 (n = 452)	0.026 ± 0.185* (n = 351)	0.754

γ-GTP gamma-glutamyl transpeptidase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *BMI* body mass index, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HDL-C* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *SD* standard deviation, *SBP* systolic blood pressure

*$P < 0.05$, **$P < 0.001$ vs baseline (one-sample t test)

[a] Two-sample t test for the comparison of change from baseline between patients aged < 65 years and patients aged ≥ 65 years

In comparison with the 1-year STELLA-ELDER Japanese post-marketing study, elderly patients in STELLA-LONG TERM had a numerically similar baseline mean body weight, BMI, eGFR, duration of diabetes, and proportion of patients with an HbA1c $\geq$ 8%; whereas the proportion of patients with complications at baseline was numerically higher among elderly patients in the current study than those in STELLA-ELDER [10].

In the current study, the incidence of ADRs was similar in patients aged < 65 years (19.36%) and in those aged $\geq$ 65 years (19.0%). These proportions are greater than those reported in the 1-year interim results of this study, when 14.8% of non-elderly and 14.2% of elderly patients had at least one ADR [11]; the latter incidence in elderly patients was lower than that after 1 year of treatment in STELLA-ELDER [10]. A significantly greater proportion of elderly versus non-elderly patients had a serious ADR in both this final 3-year analysis (2.79% vs 1.55%) and the 1-year analysis (1.4% vs 0.8%) of STELLA-LONG TERM [11]. The most likely explanation for the difference in ADR rates between STELLA-ELDER and the current study lies in the timing of the two studies. Ipragliflozin was approved in Japan in April 2014 and the registration period for the STELLA-ELDER study was the first 3 months after ipragliflozin was introduced. The Japanese Diabetes Society (JDS) published recommendations on the proper use of SGLT2 inhibitors in June 2014 (updated again in 2020 [15]), after registration for STELLA-ELDER had begun. Patients were registered in the STELLA-LONG TERM between July 2014 and October 2015, after publication of the JDS recommendations, which probably influenced prescribing practices, particularly in elderly patients.

When assessing ADRs of special interest, in both this analysis and the 1-year analysis, the incidence of skin complications, renal disorder, and hypoglycemia was higher in elderly than in non-elderly patients, while polyuria/pollakiurua and hepatic disorders were more common in non-elderly patients [11].

In this final report, the incidence of malignant tumors was significantly higher in elderly patients, and the incidence was higher than that observed in the 1-year interim report [11]. Over 3 years in the overall safety analysis population, the incidence of malignant tumors reported as an ADR was 0.46%; 0.24% in patients aged < 65 years, and 1.01% in those aged $\geq$ 65 years ($P < 0.001$), whereas in the 1-year analysis, malignant tumors were diagnosed in 0.2% of patients aged < 65 years and 0.3% of those aged $\geq$ 65 years ($P = 0.079$) [11]. The increase in incidence from 1 to 3 years is not surprising, given that in the general population the incidence of malignant tumors increases with a longer period of observation. Although it is difficult to compare studies with different designs, the main report of the final STELLA-LONG TERM compared the incidence of malignant tumors in the safety population with that in the J-DOIT3 study [16] and found that it was lower in STELLA-LONG TERM than in Japanese patients receiving conventional standard care for type 2 diabetes [14].

The higher incidence of hypoglycemia in the elderly patients in this trial may possibly be explained by these patients having a lower BMI than non-elderly patients. Kidney function often deteriorates with age, which may explain the higher incidence of renal disorders in the elderly patients in this trial. On the other hand, data from international clinical trials suggest that SGLT2 inhibitors have renoprotective effects, which may benefit elderly patients [17–19]. Further research is warranted to confirm this effect in Japanese patients [19]. Such research should include a comparator agent so that the effect of SGLT2 inhibitors on renal function in elderly Japanese patients can be confirmed.

Compared with younger individuals, elderly patients are also more prone to particular skin conditions, such as pruritus, infections, and eczema [20, 21], and these may be exacerbated by medical comorbidities such as diabetes or by concomitant medications [20]. This may explain the higher incidence of skin complications in the elderly patients in this trial.

The treatment of frail older patients with diabetes must be carefully managed [22, 23]. Compared with elderly patients without diabetes, sarcopenia/muscle mass loss appears to be accelerated in elderly patients with diabetes

[24]; thus, we paid careful attention to older patients with a lower BMI. In elderly patients in this study, the incidence of ADRs was significantly lower in patients with a baseline BMI < 25 kg/m^2 than ≥ 25 kg/m^2. Among elderly patients with a BMI < 25 kg/m^2, the incidence of ADRs was significantly lower in patients aged ≥ 75 years than in those aged 65 to < 75 years, suggesting that there is no increased risk of ADRs among the older frail population.

Statistically significantly greater decreases in WBC and eGFR were observed in non-elderly compared with elderly patients in this study. However, in both cohorts, mean values at the study endpoint were still well above those that would indicate even mild renal impairment or leukopenia. Further, studies of some other SGLT2 inhibitors (empagliflozin [25], tofogliflozin [26]) in Japanese patients have also shown decreases in eGFR.

In addition to confirming the long-term safety of ipragliflozin in a real-world setting, this trial showed ipragliflozin to be effective in both elderly and non-elderly patients. Throughout 3 years of treatment, mean HbA1c and body weight were reduced from baseline at every measured time point in both age groups. These significant reductions in mean HbA1c were observed regardless of whether baseline HbA1c was $< 8\%$ or $\geq 8\%$. Significant reductions in mean HbA1c were also recorded in those aged ≥ 75 years, regardless of whether their baseline BMI was < 25 kg/m^2 or ≥ 25 kg/m^2.

This study was not without limitations. The main objective of post-marketing surveillance studies is to collect real-world data on the safety and effectiveness of a drug from as many patients as possible. As such as study, STELLA-LONG TERM had a single-arm, observational methodology and was carried out in routine clinical practice; therefore, it lacked a control arm and the results may have been influenced by variables other than the study treatment (such as the use of other antidiabetic drugs or selection bias in the use of ipragliflozin in elderly patients). Further, patients who completed or discontinued the study were not followed up, and these missing data need to be taken into account when interpreting our results. Finally, we did not specifically investigate factors relevant to sarcopenia or frailty in the elderly subgroup.

CONCLUSION

In this subgroup analysis of the final results of the 3-year STELLA-LONG TERM trial, ipragliflozin was well tolerated and effective in both elderly and non-elderly patients, and no new safety concerns were identified. The incidence of serious ADRs was significantly higher in elderly than non-elderly patients. Additionally, long-term ipragliflozin therapy was well tolerated and effective in all elderly patients, including those aged ≥ 75 years and with a baseline BMI < 25 kg/m^2.

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Data Availability. Researchers may request access to anonymized participant level data, trial level data, and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing, see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx

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