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Safety and effectiveness of tofogliflozin in Japanese patients with type 2 diabetes mellitus: Results of 24-month interim analysis of a long-term post-marketing study (J-STEP/LT)

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ABSTRACT

Aims/Introduction: Tofogliflozin is a potent and highly selective sodium–glucose cotransporter 2 inhibitor, and is currently used to treat patients with type 2 diabetes mellitus. We designed a 3-year study of tofogliflozin in patients with type 2 diabetes mellitus to evaluate the safety and effectiveness in routine clinical practice. The 3- and 12-month interim analysis showed tofogliflozin was well-tolerated, safe and clinically effective. Here, we report the results of the 24-month interim analysis.

Materials and Methods: This is a 3-year prospective, observational and multicenter post-marketing study (Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients/Long Term).

Results: Of the 6,897 patients enrolled, 6,712 and 6,461 patients were analyzed for the safety and effectiveness of tofogliflozin, respectively. During the 24-month observation period, the incidence rates of adverse drug reactions (ADRs) and serious adverse drug reactions were 11.25 and 1.21%, respectively. As to adverse drug reactions of special interest, the incidence rates of hypoglycemia, polyuria/pollakiuria, volume depletion-related events, urinary tract infections and genital infection were 0.83, 1.28, 1.46, 1.18 and 1.62%, respectively. Renal disorders, and cardiovascular and cerebrovascular disorders occurred in 0.63 and 0.76% of the patients, respectively. Glycated hemoglobin A1c and bodyweight decreased significantly by −0.70% ($P < 0.0001$) and −2.95 kg ($P < 0.0001$), respectively, from baseline to week 104 (last observation carried forward).

Conclusions: Significant safety concerns have not been observed, and clinical benefit including a long-term reduction in glycated hemoglobin A1c over a 104-week (24 months) observation period with weight loss was suggested in this 24-month interim analysis of the 3-year Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients/Long Term in routine clinical practice.

INTRODUCTION

Tofogliflozin is a potent and highly selective sodium–glucose cotransporter 2 (SGLT2) inhibitor[1–3], and is currently used for the treatment of patients with type 2 diabetes mellitus in Japan[4,5]. SGLT2 inhibitors exert their antidiabetic effects by inhibiting SGLT2, which is localized in the proximal renal tubule and is responsible for approximately 90% of glucose reabsorption in the kidney[6]. Suppression of renal glucose

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reabsorption and a subsequent increase in urinary glucose excretion results in decreased blood glucose levels[7].

In phase III and long-term clinical trials, once-daily oral administration of tofogliflozin for 24–52 weeks achieved clinically relevant improvements in glycemic control and weight loss[8–10]. In these trials, tofogliflozin was well-tolerated and most adverse drug reactions (ADRs) were mild or moderate in severity. The common adverse events (AEs) of tofogliflozin observed in the clinical trials were increase in blood ketone body level, hyperketonemia, thirst and pollakiuria, which are known as class effects of SGLT2 inhibitors[10]. The studies showed that the risk of hypoglycemia was low as long as tofogliflozin was administered as monotherapy[8–10]. However, these findings are mainly based on clinical trials that investigated a limited number of patients who met strict eligibility criteria for a duration not exceeding 1 year.

We, therefore, designed a 3-year post-marketing study of tofogliflozin in patients with type 2 diabetes mellitus to evaluate the safety and effectiveness in routine clinical practice. The 3-month[11] and 12-month[12] interim analyses showed that tofogliflozin was well-tolerated, safe and clinically effective. Here, we report the 24-month results of the interim analysis.

METHODS

Study design

The details of the present study have been reported elsewhere[12]. In brief, this Japanese Study of Tofogliflozin with Type 2 Diabetes Mellitus Patients in an Observational/Long-Term (J-STEP/LT) was a prospective, observational and multicenter post-marketing study co-sponsored by the manufacturers to evaluate the safety and effectiveness of two tofogliflozin hydrate products, Deberza® 20-mg tablet (Kowa Company, Ltd., Nagoya, Japan) and Apleway® 20-mg tablet (Sanofi K.K., Tokyo, Japan). The plan was to carry out the study from September 2014 to May 2019. The study was carried out in accordance with the Japanese regulatory requirements stipulated in the Good Post-Marketing Study Practice.

Participants and assessment

Tofogliflozin-naïve patients with type 2 diabetes mellitus were enrolled in this study without limitation in age, glycated hemoglobin (HbA1c), concomitant medications and disease history. The patients were instructed to take tofogliflozin 20 mg once daily before or after breakfast. A central registration system was used, and clinical data recorded in electronic case report forms included demographic and baseline characteristics, details of tofogliflozin treatment, concomitant antidiabetic treatment, clinical course (vital signs, HbA1c, fasting plasma glucose, laboratory tests), and AEs.

Safety was assessed based on the incidences of ADRs and ADRs of special interest, renal disorders, and cardiovascular and cerebrovascular disorders. An ADR was defined as an AE considered to be related to tofogliflozin administration. ADRs of special interest were defined as polyuria/pollakiuria, volume depletion-related events, urinary tract infection, genital infection, hypoglycemia and skin disorders. ADRs and ADRs of special interest were stratified by patient characteristics and baseline parameters.

Statistical analysis

ADRs were categorized according to the Medical Dictionary for Regulatory Activities/Japanese edition version 21.1. The population for safety analysis was defined as all patients from whom electronic case report forms were collected, excluding those with no follow-up visits after baseline. The population for effectiveness analysis included all patients for the safety analysis, but those who did not have any efficacy data. Effectiveness was assessed by mean changes ± standard deviation in HbA1c levels and bodyweight. The changes in HbA1c levels and bodyweight were further stratified by baseline estimated glomerular filtration rate (eGFR; <30, 30 to <45, 45 to <60, 60 to <90 or ≥90 mL/min/1.73 m^2) and body mass index (BMI; <22, 22 to <25, 25 to <30 or ≥30 kg/m^2).

Vital signs and clinical laboratory tests were also assessed and summarized.

The Fisher's exact test was used to test the associations of the incidence of ADRs with patient characteristics or treatment at baseline. Data at baseline and after treatment were compared using the one-sample *t*-test or Cochran-Armitage test. The significance level was set at 5%. Missing data at week 104 were imputed with the last observation carried forward (LOCF) method, and the change from baseline to week 104 was calculated using LOCF data. All analyses were carried out using the statistical analysis software (SAS) release 9.4 (SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Patient disposition and characteristics

Of the 6,897 patients registered in 1,258 sites, 6,818 electronic case report forms were collected from 1,234 sites. The safety analysis population consisted of 6,712 patients after excluding those who did not return to the site after treatment initiation (n = 42), those ineligible under the criteria (n = 41) and others (n = 23). Of the 6,712 patients, the efficacy analysis population consisted of 6,461 patients after removal of 251 patients for whom no efficacy data were available (Figure 1). In total, 2,212 patients (33.0%) were withdrawn from the study during the 24-month observation period. Loss to follow up was the most common reason for treatment discontinuation (n = 760; 11.3%), and other reasons included AEs (n = 427; 6.4%), insufficient or no effect (n = 301, 4.5%), patient's request (n = 330, 4.9%), improvement in diabetes (n = 106, 1.6%) and the convenience of the study site or investigator (n = 176, 2.6%). The mean observation period was 578.0 ± 257.2 days, and the mean number of administration days was 575.3 ± 260.2 days. Patient characteristics are shown in Table 1. Of the 6,712 patients in safety analysis, 60.8% were men. The mean age ± standard deviation was 56.9 ± 12.2 years. The mean BMI was

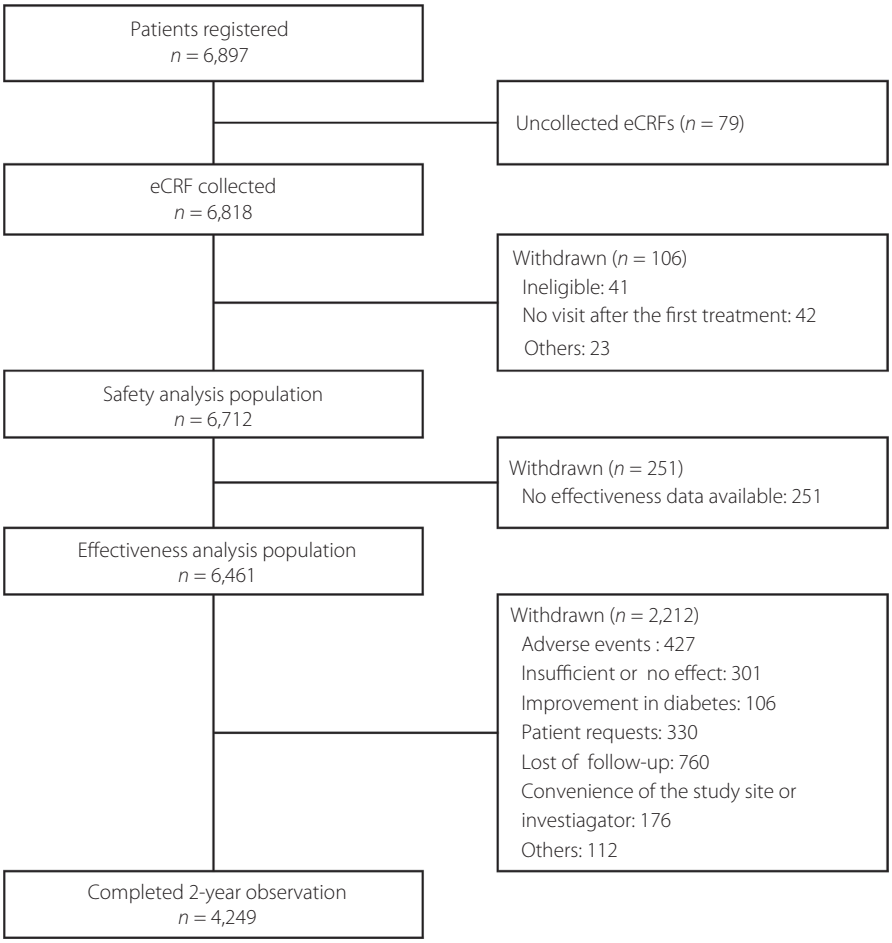

Figure 1 | Patient disposition. eCRF, electronic case report form.

28.7 ± 5.0 kg/m^2. The mean duration of diabetes, baseline HbA1c and eGFR were 8.2 ± 6.4 years, 8.0 ± 1.5% and 82.5 ± 22.5 mL/min/1.73 m^2, respectively. Diabetic nephropathy (21.1%), diabetic neuropathy (9.3%) and diabetic retinopathy (8.0%) were reported as diabetes complications. Overall, 80.5% of patients received concomitant antidiabetics, and the most commonly used oral antidiabetic drugs were dipeptidyl peptidase-4 inhibitors (59.6%), biguanides (45.5%) and sulfonylureas (28.4%). The mean number of oral antidiabetics was 2.0 ± 1.0. Insulin products and glucagon-like peptide-1 receptor agonists were used in 11.9 and 5.0% of patients, respectively. Diuretics were used in 448 patients (6.7%; Table 1).

Safety

Among 6,712 patients, 952 ADRs occurred in 755 patients (11.25%), and 103 serious ADRs were observed in 81 patients (1.21%) during the 104 weeks (24 months). A total of 659 AE events in 467 patients (6.96%) were determined to have no causal relationship to tofogliflozin use. The incidence of ADRs is shown in Table S1. serious ADRs were observed in 1.21% of patients, including nervous system disorders (17 patients, 0.25%), cardiac disorders (15 patients, 0.22%), and infections and infestations (12 patients, 0.18%). Diabetic ketoacidosis occurred in one patient (0.01%) as a serious ADR. The incidence of ADRs stratified by patient characteristics is shown in Table S2. A total of 12 deaths were reported during this observation period, of which one case (lung cancer) was considered to be related to tofogliflozin, whereas the remaining 11 were deemed to be unrelated to treatment.

Table 2 summarizes the incidence of ADRs of special interest. Hypoglycemia occurred in 56 patients (0.83%), and four patients (0.06%) were serious. Polyuria/pollakiuria (predominantly pollakiuria) occurred in 86 patients (1.28%), none of which was serious. Volume depletion-related events occurred in 98 patients (1.46%), including dehydration (29, 0.43%), constipation (25, 0.37%), blood urea increased (16, 0.24%), thirst (8, 0.12%) and cerebral infarction (8, 0.12%), as frequently observed ADRs. A total of 16 serious ADRs were reported in this category, which were cerebral infarction (7 patients, 0.10%), myocardial infarction (3 patients, 0.04%) and

Table 1 | Patients characteristics at baseline (safety analysis population)

Variables	*n*	% or mean ± SD
Total no. patients	6,712	100.0
Sex		
Male	4,083	60.8
Female	2,629	39.2
Age (years)		
Mean ± SD	6,712	56.9 ± 12.2
Duration of diabetes (years)		
Mean ± SD	3,968	8.2 ± 6.4
Bodyweight (kg)		
Mean ± SD	5,980	77.5 ± 16.8
BMI (kg/m^2)		
Mean ± SD	5,538	28.7 ± 5.0
eGFR (mL/min/1.73 m^2)		
Mean ± SD	4,950	82.5 ± 22.5
HbA1c (%)		
Mean ± SD	6,411	8.0 ± 1.5
Complications		
Diabetic complications		
Yes	1,884	28.1
Diabetic retinopathy	535	8.0
Diabetic nephropathy	1,415	21.1
Diabetic neuropathy	622	9.3
Other	11	0.2
Cardiovascular and cerebrovascular complications		
Yes	696	10.4
Cardiovascular diseases	558	8.3
Cerebrovascular diseases	159	2.4
Cardiac failures	159	2.4
Concomitant antidiabetic treatment		
No	1,232	18.4
Yes	5,405	80.5
Unknown	75	1.1
Oral antidiabetics		
Yes	5,263	78.4
Biguanide	3,052	45.5
Sulfonylurea	1,903	28.4
DPP-4 inhibitor	4,001	59.6
SGLT2 inhibitor	1	0.01
Rapid-acting insulin secretagogues	411	6.1
α-Glucosidase inhibitor	846	12.6
Thiazolidinediones	958	14.3
Other	1	0.01
No. concomitant oral antidiabetics		
Mean ± SD	5,028	2.0 ± 1.0
Insulin products		
Yes	796	11.9
GLP-1 receptor agonists		
Yes	333	5.0
Concomitant use of diuretics		
Yes	448	6.7

BMI, body mass index; DDP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2.

dehydration (3 patients, 0.04%). Urinary tract infection-related ADRs included cystitis (40 patients, 0.60%) and urinary tract infection (26 patients, 0.39%), of which acute pyelonephritis (3 patients, 0.04%), urinary tract infection, sepsis shock and pyelonephritis (each 2 patients, 0.03%) were serious. These ADRs were ameliorated after discontinuation of tofogliflozin. Genital infection-related ADRs included pruritus genital (38 patients, 0.57%), vulvovaginal candidiasis (18 patients, 0.27%) and genital infection (18 patients, 0.27%), none of which was serious. Rash (11 patients, 0.16%) and pruritus (10 patients, 0.15%) were observed as ADRs in skin disorders, of which cellulitis and skin ulcer (each 1 patient, 0.01%) were serious.

Incidences of ADRs of special interest were stratified by age, sex and eGFR at baseline. In the age subgroups (≥65 vs <65 years), the incidence of polyuria/pollakiuria (1.79 vs 1.08%) and volume depletion-related events (2.00 vs 1.25%) were significantly higher in the patients aged ≥65 years than those <65 years (Figure 2a). In the sex subgroups (male vs female), urinary tract infections (0.32 vs 2.51%), genital infections (0.47 vs 3.42%) and skin disorders (0.56 vs 1.10%) occurred more frequently in women than in men, whereas cardiovascular and cerebrovascular disorders (0.98 vs 0.42%) occurred more frequently in men than in women (Figure 2b). In the eGFR subgroups (eGFR of 30 to <45, 45 to <60, 60 to <90 and ≥90 mL/min/1.73 m^2), there were significant differences in relation to polyuria/pollakiuria and volume depletion-related events (Figure 2c).

From the population for safety analysis (6,712 patients), cardiovascular and cerebrovascular disorders occurred in 51 patients (0.76%). Cardiovascular disorders that occurred more than twice were tachycardia (9 patients, 0.13%), acute myocardial infarction (7 patients, 0.10%), myocardial infarction (4 patients, 0.06%), atrial fibrillation (3 patients, 0.04%), palpitations (3 patients, 0.04%), angina pectoris (2 patients, 0.03%) and cardiac failure (2 patients, 0.03%). Cerebrovascular disorders that occurred more than twice were cerebral infarction (8 patients, 0.12%), lacunar infarction (3 patients, 0.04%), cerebral hemorrhage (2 patients, 0.03%) and transient ischemic attack (2 patients, 0.03%).

Changes in effectiveness-related laboratory variables

HbA1c levels (mean ± standard deviation) significantly decreased from 8.00 ± 1.48% (6,238 patients) at baseline to 7.31 ± 1.22% (6,373 patients) at LOCF, with a mean change of −0.70 ± 1.31% ($P < 0.0001$; Table 3; Figure 3a). A significant reduction in HbA1c level was observed in patients with baseline eGFR of ≥30 mL/min/1.73 m^2 ($P < 0.0001$), but not if eGFR was <30 mL/min/1.73 m^2 (Figure S1a). The HbA1c levels significantly decreased irrespective of the baseline BMI ($P < 0.0001$; Figure S1b). The mean reduction in fasting plasma glucose level was −32.67 ± 62.53 mg/dL ($P < 0.0001$). Mean bodyweight decreased from 77.84 ± 16.71 kg at baseline (5,385 patients) to 74.88 ± 16.46 kg (5,595 patients) at LOCF, with a mean change of −2.95 ± 4.40 kg ($P < 0.0001$; Table 3).

Table 2 | Incidence of drug adverse reactions of special interest (safety analysis population)

System organ class Preferred term	All *n* (%)	Serious *n* (%)
Total no. patients	6,712	
Hypoglycemia	56 (0.83)	
Hypoglycemia	56 (0.83)	4 (0.06)
Polyuria/pollakiuria	86 (1.28)	
Nocturia	13 (0.19)	–
Pollakiuria	64 (0.95)	–
Polyuria	6 (0.09)	–
Urine output increased	3 (0.04)	–
Volume depletion-related events	98 (1.46)	
Blood urea increased	16 (0.24)	–
Cerebral infarction	8 (0.12)	7 (0.10)
Constipation	25 (0.37)	–
Dehydration	29 (0.43)	3 (0.04)
Depressed level of consciousness	1 (0.01)	1 (0.01)
Dry mouth	1 (0.01)	–
Hematocrit increased	5	(0.07)
Hemoconcentration	1 (0.01)	–
Myocardial infarction	4 (0.06)	3 (0.04)
Polycythemia	3 (0.04)	–
Thirst	8 (0.12)	–
Heat illness	2 (0.03)	1 (0.01)
Acute kidney injury	1 (0.01)	1 (0.01)
Urinary tract infection	79 (1.18)	
Bacteriuria	1 (0.01)	–
Cystitis	40 (0.60)	1 (0.01)
Pyelonephritis	2 (0.03)	2 (0.03)
Pyelonephritis acute	3 (0.04)	3 (0.04)
Sepsis	1 (0.01)	1 (0.01)
Sepsis shock	2 (0.03)	2 (0.03)
Urethritis	5 (0.07)	–
Urinary tract infection	26 (0.39)	2 (0.03)
Cystitis-like symptom	2 (0.03)	–
Cystitis bacterial	1 (0.01)	–
Genital infection	109 (1.62)	
Balanitis candida	1 (0.01)	–
Balanoposthitis	9 (0.13)	–
Genital candidiasis	3 (0.04)	–
Genital herpes	1 (0.01)	–
Penile ulceration	1 (0.01)	–
Prostatitis	1 (0.01)	–
Pruritus genital	38 (0.57)	–
Vaginal infection	4 (0.06)	–
Vulvitis	4 (0.06)	–
Vulvovaginal candidiasis	18 (0.27)	–
Genital infection	18 (0.27)	–
Vulvovaginal pruritus	5 (0.07)	–
Genital infection female	1 (0.01)	–
Vulvar erosion	5 (0.07)	–
Candida infection	3 (0.04)	–
Skin disorders	52 (0.77)	
Alopecia areata	1 (0.01)	–
Cellulitis	1 (0.01)	1 (0.01)
Dermatitis	2 (0.03)	–
Drug eruption	1 (0.01)	–
Eczema	8 (0.12)	–
Erythema	1 (0.01)	–
Folliculitis	1 (0.01)	–
Herpes zoster	2 (0.03)	–
Palmoplantar keratoderma	1 (0.01)	–
Pruritus	10 (0.15)	–
Rash	11 (0.16)	–
Rash erythematous	2 (0.03)	–
Rash generalized	2 (0.03)	–
Rash pruritic	2 (0.03)	–
Seborrheic dermatitis	1 (0.01)	–
Skin disorder	1 (0.01)	–
Skin erosion	1 (0.01)	–
Skin infection	1 (0.01)	–
Skin ulcer	1 (0.01)	1 (0.01)
Tinea pedis	1 (0.01)	–
Urticaria	1 (0.01)	–
Pruritus generalized	2 (0.03)	–
Renal disorders	42 (0.63)	
Albumin urine present	2 (0.03)	–
Azotemia	1 (0.01)	–
Blood creatinine increased	5 (0.07)	–
Blood urea increased	16 (0.24)	–
Glomerular filtration rate decreased	1 (0.01)	1 (0.01)
Proteinuria	2 (0.03)	–
Renal disorder	2 (0.03)	–
Renal failure	1 (0.01)	–
Protein urine present	3 (0.04)	–
Urine albumin/creatinine ratio increased	1 (0.01)	–
Diabetic nephropathy	2 (0.03)	1 (0.01)
Urinary sediment abnormal	1 (0.01)	–
Renal impairment	7 (0.10)	3 (0.04)
Acute kidney injury	1 (0.01)	1 (0.01)
Cardiovascular and cerebrovascular disorders	51 (0.76)	
Acute myocardial infarction	7 (0.10)	7 (0.10)
Angina pectoris	2 (0.03)	1 (0.01)
Angina unstable	1 (0.01)	1 (0.01)
Arrhythmia	1 (0.01)	–
Atrial fibrillation	3 (0.04)	1 (0.01)
Brain stem infarction	1 (0.01)	1 (0.01)
Cardiac failure	2 (0.03)	1 (0.01)
Cardiac failure congestive	1 (0.01)	1 (0.01)
Cerebral hemorrhage	2 (0.03)	2 (0.03)
Cerebral infarction	8 (0.12)	7 (0.10)
Myocardial infarction	4 (0.06)	3 (0.04)
Palpitations	3 (0.04)	–
Prinzmetal angina	1 (0.01)	–
Subarachnoid hemorrhage	1 (0.01)	1 (0.01)
Tachycardia	9 (0.13)	–
Transient ischemic attack	2 (0.03)	–
Ventricular extrasystoles	1 (0.01)	–
Lacunar infarction	3 (0.04)	3 (0.04)

Medical Dictionary for Regulatory Activities/Japanese edition version 21.1.

Bodyweight reduction was higher in higher BMI subgroups, but independent of eGFR except eGFR <30 mL/min/1.73 m^2 (Figure S1C), and dependent on increase of BMI (Figure S1D). Changes over time in HbA1c level, fasting plasma glucose level and bodyweight are shown in Figure 3.

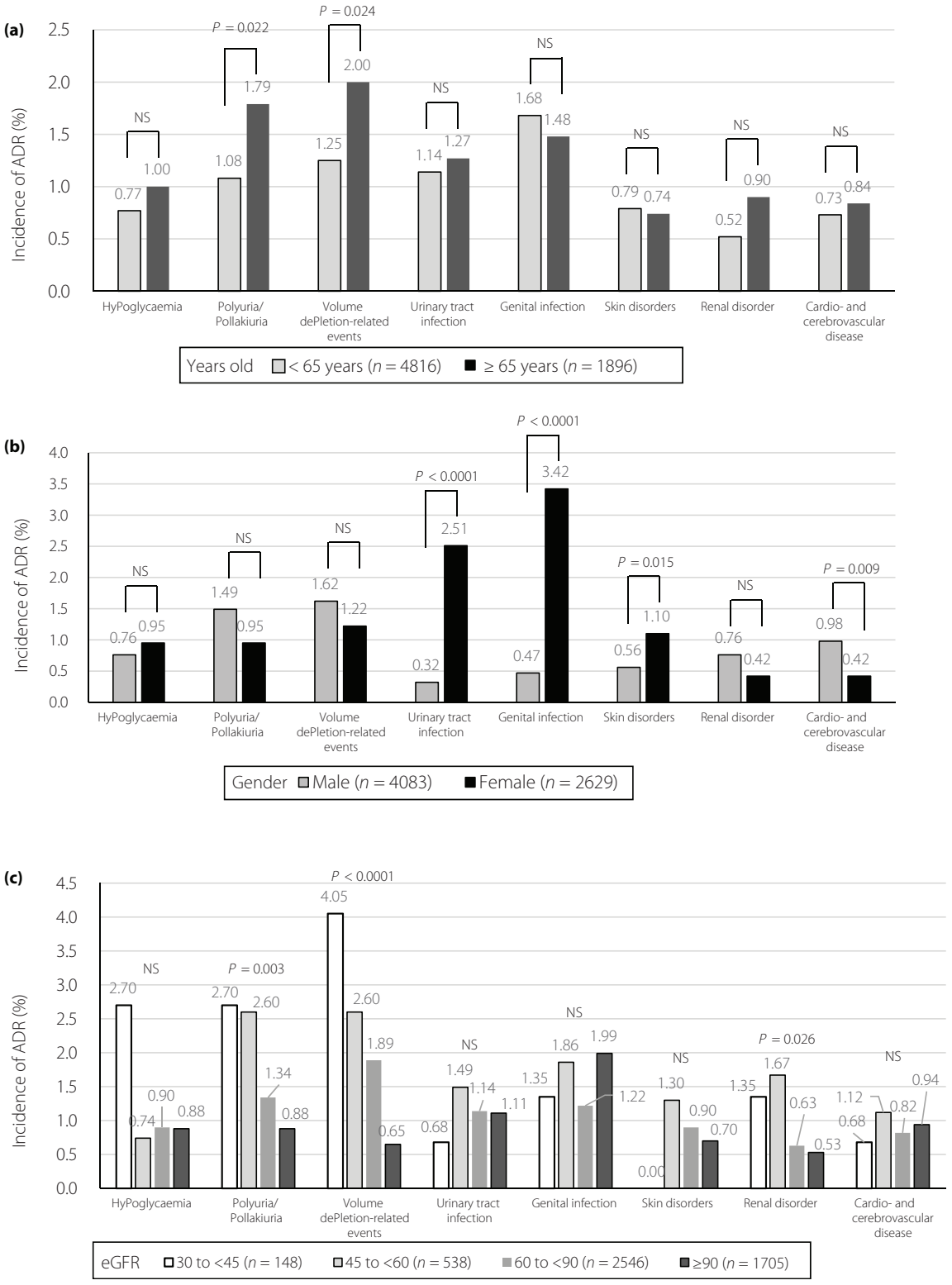

Figure 2 | Incidences of adverse drug reactions (ADRs) of special interest after 104 weeks of treatment with tofogliflozin, which is stratified by (a) age, (b) sex and (c) eGFR. Fisher's exact test is performed for (a) and (b), and Cochran-Armitage test for (c). Number of patients is provided in parentheses. There were no patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. NS, not significant.

Table 3 | Surrogate marker of effectiveness, vital signs and laboratory variables

Variable	Baseline	Week 24	Week 52	Week 104	LOCF	Mean ± SD (*n*) Change from baseline to LOCF	*P*-value*
HbA1c (%)	8.00 ± 1.48 (6,238)	7.22 ± 1.07 (5,037)	7.14 ± 1.08 (4,903)	7.19 ± 1.06 (4,260)	7.31 ± 1.22 (6,373)	−0.70 ± 1.31 (6,170)	<0.0001
FPG (mg/dL)	170.06 ± 64.88 (3,310)	134.85 ± 41.27 (2,586)	134.49 ± 43.49 (2,501)	134.53 ± 40.97 (2,173)	137.26 ± 46.32 (4,208)	−32.67 ± 62.53 (3,143)	<0.0001
Bodyweight (kg)	77.84 ± 16.71 (5,385)	75.50 ± 16.30 (4,159)	75.10 ± 16.25 (3,972)	74.58 ± 15.51 (3,344)	74.88 ± 16.46 (5,595)	−2.95 ± 4.40 (5,215)	<0.0001
BMI (kg/m^2)	28.85 ± 5.00 (4,959)	27.98 ± 4.91 (3,824)	27.78 ± 4.86 (3,654)	27.58 ± 4.63 (3,045)	27.79 ± 4.96 (5,059)	−1.10 ± 1.61 (4,806)	<0.0001
Waist circumference (cm)	96.38 ± 11.58 (943)	93.48 ± 11.67 (627)	91.97 ± 11.13 (627)	92.31 ± 11.39 (514)	93.44 ± 12.05 (1,142)	−3.01 ± 5.33 (730)	<0.0001
Systolic blood pressure (mmHg)	132.5 ± 15.6 (5,836)	128.6 ± 13.8 (4,782)	128.3 ± 14.2 (4,608)	128.8 ± 13.6 (4,025)	128.9 ± 14.4 (6,135)	−3.6 ± 15.7 (5,773)	<0.0001
Diastolic blood pressure (mmHg)	78.1 ± 11.3 (5,834)	75.6 ± 10.1 (4,780)	75.3 ± 10.3 (4,607)	75.3 ± 9.9 (4,022)	75.6 ± 10.4 (6,135)	−2.4 ± 10.6 (5,771)	<0.0001
Heart rate (b.p.m.)	77.5 ± 12.5 (3,529)	76.0 ± 11.7 (2,963)	76.1 ± 11.7 (2,846)	76.3 ± 11.8 (2,496)	76.8 ± 12.1 (4,059)	−0.9 ± 10.5 (3,429)	<0.0001
Serum creatinine (mg/dL)	0.73 ± 0.22 (4,821)	0.75 ± 0.25 (3,777)	0.76 ± 0.24 (3,746)	0.75 ± 0.24 (3,232)	0.76 ± 0.27 (5,457)	0.02 ± 0.17 (4,587)	<0.0001
eGFR (mL/min/1.73 m^2)	82.44 ± 22.44 (4,821)	80.97 ± 22.65 (3,777)	80.39 ± 22.30 (3,746)	80.48 ± 22.14 (3,232)	80.68 ± 22.76 (5,457)	−1.99 ± 13.96 (4,587)	<0.0001
Serum albumin (g/dL)	4.60 ± 4.29 (1,985)	4.43 ± 1.65 (1,508)	4.53 ± 2.45 (1,511)	4.62 ± 4.07 (1,289)	4.74 ± 5.14 (2,643)	0.03 ± 3.42 (1,767)	0.7549
BUN (mg/dL)	14.86 ± 4.42 (4,049)	16.27 ± 4.55 (3,143)	16.14 ± 4.75 (3,118)	16.29 ± 4.54 (2,625)	16.26 ± 4.91 (4,726)	1.40 ± 4.31 (3,815)	<0.0001
AST, U/L (GOT)	30.74 ± 19.94 (4,826)	25.11 ± 14.47 (3,636)	25.54 ± 15.26 (3,598)	25.42 ± 13.51 (3,124)	25.63 ± 14.62 (5,439)	−4.81 ± 18.11 (4,546)	<0.0001
ALT, U/L (GPT)	38.59 ± 34.96 (4,884)	29.30 ± 21.45 (3,694)	29.69 ± 24.10 (3,666)	29.69 ± 22.11 (3,175)	30.00 ± 23.72 (5,484)	−8.18 ± 30.79 (4,614)	<0.0001
ALP (IU/L)	244.91 ± 85.05 (2,520)	234.02 ± 83.73 (1,949)	233.11 ± 86.42 (1,895)	232.47 ± 84.06 (1,577)	234.56 ± 86.29 (3,163)	−7.88 ± 63.15 (2,271)	<0.0001
γ-GTP (U/L)	57.57 ± 68.12 (4,428)	45.71 ± 60.28 (3,363)	46.08 ± 66.65 (3,346)	45.86 ± 69.17 (2,848)	45.69 ± 64.51 (5,116)	−11.46 ± 55.02 (4,143)	<0.0001
Total bilirubin (mg/dL)	0.64 ± 0.29 (2,128)	0.64 ± 0.28 (1,646)	0.64 ± 0.30 (1,586)	0.66 ± 0.30 (1,327)	0.65 ± 0.29 (2,653)	0.01 ± 0.24 (1,908)	0.3189
TC (mg/dL)	196.19 ± 39.39 (3,029)	195.07 ± 36.35 (2,295)	192.66 ± 35.38 (2,235)	192.29 ± 33.85 (1,844)	193.59 ± 36.73 (3,540)	−2.52 ± 33.21 (2,788)	<0.0001
HDL-C (mg/dL)	51.54 ± 13.74 (4,547)	53.86 ± 14.88 (3,503)	53.98 ± 14.44 (3,456)	54.23 ± 14.20 (2,992)	53.97 ± 14.79 (5,154)	2.69 ± 9.81 (4,282)	<0.0001
LDL-C (mg/dL)	114.25 ± 31.37 (4,526)	112.28 ± 29.60 (3,486)	110.56 ± 30.50 (3,497)	109.28 ± 28.34 (3,064)	110.91 ± 30.09 (5,192)	−3.44 ± 28.88 (4,277)	<0.0001
non HDL-C (mg/dL)	143.94 ± 40.46 (2,724)	140.43 ± 36.34 (2,078)	137.76 ± 34.72 (2,034)	137.85 ± 33.23 (1,700)	139.18 ± 36.29 (3,149)	−5.20 ± 33.41 (2,451)	<0.0001
TG (mg/dL)	172.11 ± 149.52 (2,187)	147.31 ± 106.66 (1,720)	149.57 ± 101.60 (1,662)	148.67 ± 98.04 (1,468)	154.04 ± 131.35 (3,144)	−19.67 ± 104.35 (1,916)	<0.0001
Hemoglobin (g/dL)	14.85 ± 12.68 (4,063)	15.60 ± 17.01 (3,129)	15.37 ± 13.85 (3,098)	15.53 ± 15.47 (2,682)	15.45 ± 15.07 (4,924)	0.49 ± 15.39 (3,809)	0.0484
Hematocrit (%)	43.46 ± 4.72 (4,154)	45.15 ± 4.51 (3,181)	45.28 ± 4.59 (3,149)	45.42 ± 4.48 (2,698)	45.29 ± 4.60 (5,000)	1.79 ± 3.46 (3,890)	<0.0001
Na (mmol/L)	139.75 ± 6.99 (2,973)	140.39 ± 5.42 (2,328)	140.38 ± 4.77 (2,276)	140.39 ± 4.00 (1,904)	140.25 ± 5.08 (3,717)	0.37 ± 6.48 (2,727)	0.0028
K (mmol/L)	4.59 ± 10.35 (3,239)	4.79 ± 12.24 (2,573)	4.34 ± 3.93 (2,528)	4.44 ± 4.77 (2,063)	4.42 ± 4.40 (4,040)	−0.12 ± 11.63 (2,990)	0.5656
Cl (mmol/L)	102.16 ± 4.97 (2,887)	102.49 ± 6.66 (2,283)	102.51 ± 7.11 (2,239)	102.23 ± 7.64 (1,868)	102.36 ± 7.44 (3,643)	0.19 ± 7.80 (2,644)	0.2066
Mg (mg/dL)	2.73 ± 7.64 (161)	3.42 ± 10.79 (172)	3.50 ± 10.94 (171)	3.31 ± 11.26 (148)	3.74 ± 12.30 (318)	0.15 ± 0.59 (141)	0.0030
Ca (mg/dL)	9.50 ± 4.62 (819)	9.42 ± 3.79 (650)	9.38 ± 3.44 (655)	14.21 ± 64.40 (541)	11.57 ± 43.97 (1,163)	2.23 ± 45.29 (713)	0.1884
P (mg/dL)	3.33 ± 0.76 (381)	4.10 ± 13.02 (320)	3.38 ± 0.58 (330)	5.10 ± 20.00 (270)	4.55 ± 16.40 (603)	0.09 ± 0.60 (326)	0.0058
Blood ketone body (μmol/L)	113.29 ± 131.62 (125)	139.47 ± 177.01 (117)	117.24 ± 129.93 (102)	126.40 ± 161.06 (83)	144.29 ± 240.16 (233)	22.26 ± 198.69 (107)	0.2492
Uric acid (mg/dL)	5.30 ± 1.36 (3,738)	5.00 ± 1.27 (2,841)	5.04 ± 1.31 (2,707)	5.05 ± 1.23 (2,238)	5.03 ± 1.27 (4,628)	−0.27 ± 1.04 (3,410)	<0.0001
Serum c-peptide (ng/mL)	3.74 ± 5.94 (424)	3.47 ± 5.13 (231)	4.74 ± 10.38 (204)	2.92 ± 2.17 (178)	4.06 ± 8.27 (579)	−0.10 ± 2.68 (230)	0.5576

*One-sample *t*-test. γ-GTP, γ-glutamyltranspeptidase; ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartic aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; Cl, chlorine; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GOT, •••; GPT, •••; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; K, potassium; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; Mg, magnesium; Na, sodium; P, phosphorus; SD, standard deviation; TC, total cholesterol; TG, triglyceride.

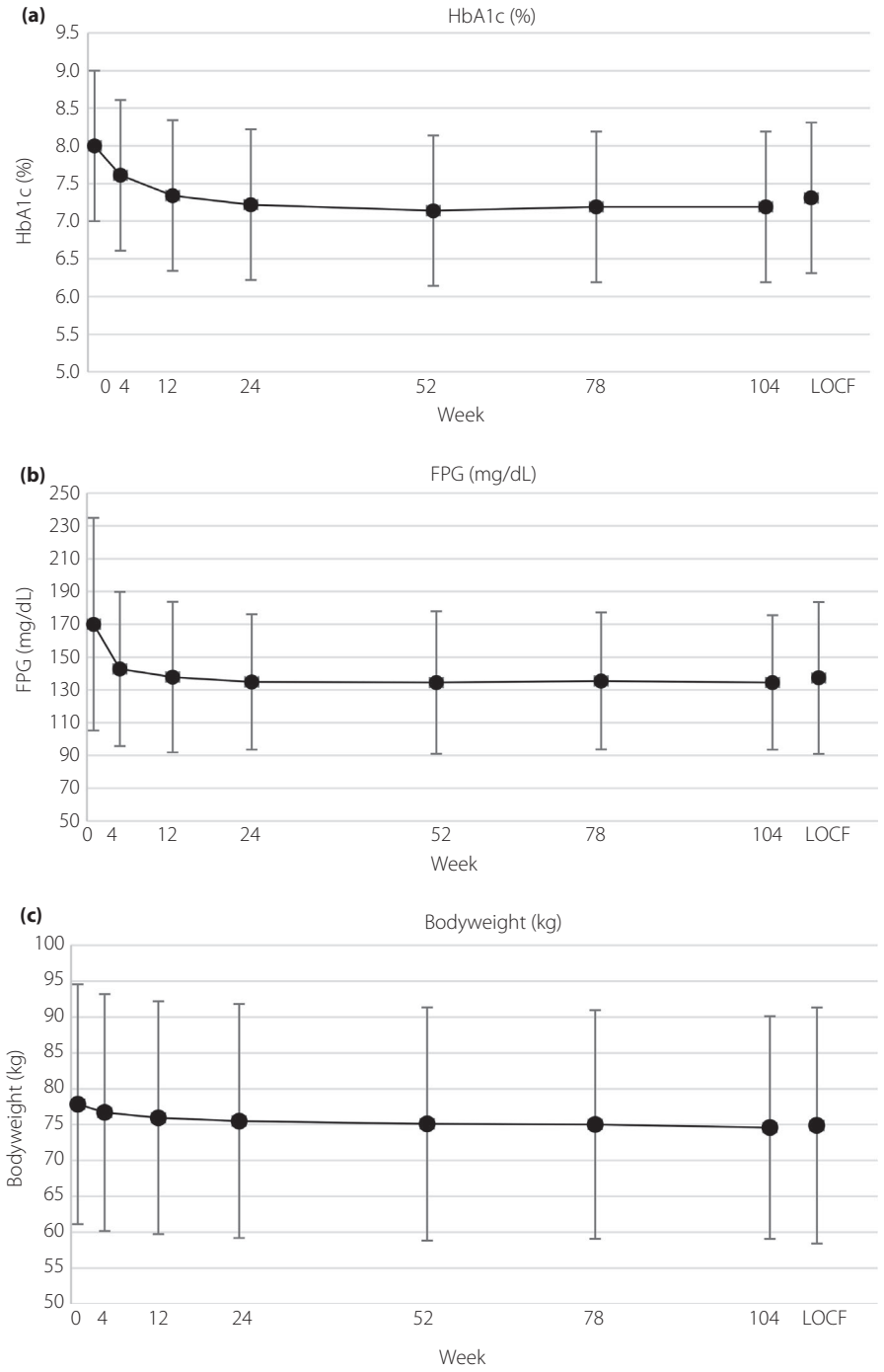

Figure 3 | Changes of (a) glycated hemoglobin (HbA1c; %), (b) fasting plasma glucose (FPG; mg/dL) and (c) bodyweight (kg) from baseline to week 104 (last observation carried forward). Data represent mean ± standard deviation.

Other clinical laboratory variables and vital signs

Changes in other laboratory variables and vital signs are summarized in Table 3. Significant decreases ($P < 0.0001$) were observed in BMI; waist circumference; systolic blood pressure; diastolic blood pressure; eGFR; liver function parameters, including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and γ-glutamyl transpeptidase; and lipid parameters, including total cholesterol, low-density lipoprotein cholesterol, triglyceride and uric acid, whereas significant increases ($P < 0.0001$) in serum creatinine, blood urea nitrogen,

high-density lipoprotein cholesterol and hematocrit were observed. A significant decrease of eGFR was observed during the observation period.

DISCUSSION

This report presents the results of the 104-week interim analysis of a 3-year post-marketing study of tofogliflozin in patients with type 2 diabetes mellitus to evaluate the safety and effectiveness of tofogliflozin (J-STEP/LT study). The tolerability, safety and effectiveness of tofogliflozin were maintained at 104-week treatment, and the results were compared favorably along with the findings from the 3-month[11] and 12-month[12] interim analyses.

The incidences of ADRs and serious ADRs increased slightly from the previous interim analyses: ADRs were 5.14, 9.12 and 11.25%, and serious ADRs were 0.45, 0.88 and 1.21% at 12, 52 and 104 weeks, respectively. The incidences of ADRs of special interest increased in a similar manner. The incidence of cancers was low (0.1%). It has been a concern that SGLT2 inhibitors increase the risk of euglycemic diabetic ketoacidosis, especially in patients with insulin insufficiency[13]. In the present study, only one patient showed diabetic ketoacidosis. This patient continued to receive tofogliflozin when unwell with acute bronchitis. Whether it was euglycemic was unknown because of a lack of blood glucose level information. However, the risk of diabetic ketoacidosis would be very low in type 2 diabetes mellitus patients receiving tofogliflozin. Although the Canagliflozin Cardiovascular Assessment Study (CANVAS) program has shown that treatment with canagliflozin is associated with an increased risk of lower limb amputation and bone fracture[14], these ADRs were not reported in the present patients.

The low risk of hypoglycemia induced by SGLT2 inhibitors is well known because of its insulin-independent mechanism of action[15]. In the present study, a total of 56 patients (0.83%) experienced hypoglycemia. Among them, just five patients receiving tofogliflozin as monotherapy experienced hypoglycemia, and most cases of hypoglycemia (51/56 patients) occurred in combination with other classes of antidiabetics, such as insulin products, glucagon-like peptide-1 receptor agonists, sulfonyl urease, α-glucosidase inhibitors and biguanides. Age, sex and eGFR were not found to be factors affecting the incidence of hypoglycemia. Regarding hypoglycemia, four cases were severe; one patient was treated with tofogliflozin and insulin product, and the other three patients received dipeptidyl peptidase-4 inhibitors, sulfonylureas, thiazolidinedione and/or α-glycosidase inhibitors as a concomitant antidiabetic. These severe hypoglycemia occurred within the first year, with onset on day 6, 16, 285 and 305 after the start of administration of tofogliflozin, as reported in the previous report of the 12-month analysis[12], but not reported during the observation period from 12 to 24 months. As observed in the present study, polyuria/pollakiuria and volume depletion-related events are often caused by SGLT2 inhibitors as a class effect due to their mild osmotic diuretic activity[6,16]. Among the serious ADRs of special interest, 16 patients experienced volume depletion-related events, including cerebral infarction (0.10%), dehydration and myocardial infarction (0.04%), depressed level of consciousness, heat illness, and acute kidney injury (each 0.01%). In the present study, these ADRs occurred at a significantly higher rate in the elderly, and it is quite important to guide patients receiving tofogliflozin, particularly the elderly, to ensure sufficient fluid intake[17].

Cardiovascular event risk reduction is one of the main goals of diabetic medical management, and it has been well recognized that some SGLT2 inhibitors reduce major adverse cardiovascular events, heart failure hospitalizations and worsening of kidney function independent of glycemic control[18,19]. Type 2 diabetes mellitus is frequently comorbid with chronic kidney disease[20], and is closely associated with an increased risk of cardiovascular disease[18,21]. In the present study, the incidence of renal disorders was low (0.63%), but change in eGFR from baseline to week 104 (LOCF) was 1.99 mL/min/1.73 m^2 ($P < 0.0001$). In patients with baseline eGFR ≥90 mL/min/1.73m^2, eGFR decline was within the normal range. Conversely, patients with baseline eGFRs of 30–60 mL/min/1.73 m^2 showed improved renal function. The previous study showed that tofogliflozin improved albuminuria and renal tubular function in patients with type 2 diabetes mellitus[22]. These results might represent no major problems with renal dysfunction, which is known to be a common risk for SGLT2 inhibitors indicated in their package inserts, but its renoprotective effect as reported[23,24] in other SGLT2 inhibitors cannot be concluded.

In the present study, the incidence of cardiovascular and cerebrovascular diseases was low (0.76%), with preference to male patients, but half (29/51) of them were serious. History of cardiovascular diseases or renal diseases as a complication are associated with a higher incidence rate. As whether tofogliflozin reduces the risks of cardiovascular and renal outcomes remains to be clarified, further clinical studies are required.

As for effectiveness of tofogliflozin, glycemic control and weight control concerns clinicians as treatment outcomes of type 2 diabetes mellitus. The present analysis showed both improvement of HbA1c (−0.70 ± 1.31%) and weight loss (−2.95 ± 4.40 kg) in people treated with tofogliflozin at week 104 (LOCF), consistent with the results of randomized placebo-controlled, double-blind trials[9]. HbA1c levels were reduced irrespective of BMI, but reduced renal function (eGFR of <30 mL/min/1.73 m^2) attenuated the glucose-lowering effects of tofogliflozin, similar to the clinical findings reported for other SGLT2 inhibitors[25].

The weight loss is thought to be caused by a combination of reduced body fat from caloric loss and fluid loss from osmotic diuresis[26]. Yoshida *et al.*[27] reported that weight loss with tofogliflozin is attenuated as a result of an improved antilipolytic effect of insulin on adipose tissue, which might be a mechanism underlying the slowing of lipolysis progression in the later phase of weight loss. Tofogliflozin improved insulin resistance by increasing glucose uptake, especially in

skeletal muscle, and accelerated lipolysis in the adipose tissue of male mice[28]. There is a concern that tofogliflozin could reduce body fat mass, skeletal muscle mass and skeletal muscle index (a marker of sarcopenia) in patients with type 2 diabetes mellitus[29]. However, the reduction was small, and their skeletal muscle index (a marker of sarcopenia) remained high enough above the cut-off values of the Asian sarcopenia criteria[30]. In the present study, bodyweight was reduced in patients with higher baseline BMI, but was more subtle in lean patients with lower baseline BMI, suggesting tofogliflozin can be used for a wide range of patients.

The present study had several limitations. First, this J-STEP/LT study is an observational study in routine clinical practice. Unlike randomized controlled trials, a variety of biases are unavoidable. Nevertheless, the data are indispensable in the understanding of actual clinical use and outcomes. Second, we could not determine the safety and efficacy of tofogliflozin because of the lack of a comparator. In particular, the risks/benefits of tofogliflozin associated with cardiovascular disease and renal disorders remain unclear. A placebo-controlled, long-term study with a large cohort is required.

In conclusion, the 104-week (24 months) interim data of our 3-year post-marketing study (J-STEP/LT) show that 24-month treatment with tofogliflozin is well-tolerated, safe and effective in Japanese patients with type 2 diabetes mellitus in clinical practice. There were no new clinically significant safety concerns, and clinical benefits including long-term reduction in HbA1c levels over the 104 weeks along with weight loss, were suggested.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Changes in glycated hemoglobin (HbA1c) and bodyweight from baseline to week 104 (last observation carried forward).

Table S1 | Incidence of adverse drug reactions (safety analysis population).

Table S2 | Incidence of adverse drug reactions stratified by patient characteristics (safety analysis population).