Japanese study of tofogliflozin with type 2 diabetes mellitus patients in an observational study of the elderly (J-STEP/EL): A 12-week interim analysis

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ABSTRACT
Aims/Introduction: Sodium-glucose co-transporter 2 inhibitors are a promising treatment for type 2 diabetes mellitus, but are associated with concerns about specific adverse drug reactions. We carried out a 1-year post-marketing surveillance of tofogliflozin, a novel agent in this class, in Japanese elderly patients with type 2 diabetes mellitus and here report the results of a 12-week interim analysis, focusing on adverse drug reactions of special interest.

Materials and Methods: The present prospective observational study included all type 2 diabetes mellitus patients aged ≥65 years who started tofogliflozin during the first 3 months after its launch. Data on demographic and baseline characteristics, clinical course and adverse events were collected.

Results: Of 1,535 patients registered, 1,506 patients whose electronic case report forms were collected and who had at least one follow-up visit were included in the safety analysis at 12 weeks. A total of 178 of 1,506 patients (11.82%) had at least one adverse drug reaction to tofogliflozin. The incidence of adverse drug reactions of special interest (polyuria/pollakiuria, volume depletion-related events, urinary tract infection, genital infection, skin disorders and hypoglycemia) was 2.19, 2.32, 1.33, 1.13, 1.46 and 0.73%, respectively. No new safety concerns were identified. Among those evaluable for clinical effectiveness, the mean (standard deviation) glycated hemoglobin decreased from 7.65% (1.35%) at baseline to 7.25% (1.16%) at 12 weeks by 0.39% (0.94%; \( P < 0.0001 \)).

Conclusions: This interim analysis characterized the safety profile of tofogliflozin in Japanese elderly patients with type 2 diabetes mellitus during the early post-marketing period.

INTRODUCTION
The Japanese type 2 diabetic and prediabetic population as of 2012 was estimated at approximately 20.5 million (approximately 9.5 million diabetes and approximately 11.0 million prediabetes)1. Sodium–glucose co-transporter 2 (SGLT2) inhibitors are a new class of oral antidiabetic agents that exert their antidiabetic effects by inhibiting reabsorption of glucose in the proximal renal tubule and thereby promoting urinary glucose excretion2. SGLT2 mediates the active transport of glucose into a cell using the sodium gradient across the cell membrane. This transporter is localized in the proximal renal tubule, and is responsible for approximately 90% of glucose reabsorption in the kidney. Inhibition of SGLT2 leads to a suppression of renal glucose reabsorption and an increase of urinary glucose excretion, resulting in decreased blood glucose levels. Because the effect of SGLT2 inhibitors is not insulin-dependent, they have a
low potential for inducing hypoglycemic events. Additional advantages of SGLT2 inhibitors include their ability to cause weight loss through urinary glucose excretion and their mild antihypertensive effect. Thus, they are drawing attention as a class of agents with ideal characteristics to achieve the prevention of diabetic complications.

SGLT2 inhibitors hold promise as a treatment with a novel mechanism of action and therefore, this drug class has been widely used in many countries as a treatment for diabetes. In the USA, SGLT2 inhibitors have been proposed as second-line agents in the treatment of type 2 diabetes in the 2015 Standards of Medical Care in Diabetes.

However, physicians refrain from use of SGLT2 inhibitors in Japan because of concerns about the safety, especially adverse drug reactions that are recognized as the class effects of SGLT2 inhibitors, such as urinary tract and genital infections, ketoacidosis, dehydration, and events resulting from dehydration. These concerns led to the issue of ‘Recommendations on the proper use of SGLT2 inhibitors’ by an expert group after the first agent was launched in April 2014. This statement recommends that information should be collected on adverse drug reactions usually seen with antidiabetic agents in general (e.g., hypoglycemia), as well as adverse drug reactions specific to SGLT2 inhibitors, including urinary tract and genital infections, ketoacidosis, dehydration, cerebral infarction and dermatological symptoms. It also emphasizes that SGLT2 inhibitors should be used with care in elderly patients when considering their eligibility for the treatment.

Tofogliflozin is a novel, highly selective SGLT2 inhibitor developed in Japan for the treatment of type 2 diabetes. According to the recommendation statement and to the risk management plan for tofogliflozin, we initiated a post-marketing special drug use surveillance of tofogliflozin in elderly patients with type 2 diabetes. This surveillance was carried out according to the agreement with the regulatory agency in order to investigate the safety and effectiveness of the drug in elderly patients in routine clinical practice during the early post-marketing period. The surveillance registered all elderly patients (whenever possible) who started treatment with tofogliflozin during the early post-marketing period. Patients enrolled were followed up for 1 year from the date of treatment initiation, and we carried out an interim analysis when the first 12 weeks of data became available. Here, we report the safety and effectiveness results from this interim analysis.

**MATERIALS AND METHODS**

This surveillance was a prospective observational study designed to investigate 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), in real-world patients with type 2 diabetes aged 65 years and older during the early post-marketing period, co-sponsored by the manufacturers. All institutions that received a supply of a tofogliflozin hydrate product and started to use the product in elderly patients during the first 3 months after its launch were invited to participate in the surveillance whenever possible. This surveillance was carried out from 23 May 2014 to 31 October 2015, in accordance with the ministerial ordinance on Good Post-marketing Study Practice.

**Participants**

The surveillance registered type 2 diabetes patients aged ≥65 years who started treatment with tofogliflozin during the period from 23 May to 22 August 2014 (all patients whenever possible) using a central registration system. Each patient was followed up for 1 year (52 weeks) from the date of treatment initiation.

**Data collection and assessments**

Data on demographic and baseline characteristics, details of tofogliflozin treatment, previous antidiabetic treatment and concomitant antidiabetic and non-antidiabetic treatment, clinical course (vital signs, glycated hemoglobin [HbA1c], fasting blood glucose, laboratory tests), and adverse events were recorded in electronic case report forms (eCRFs) and submitted to the sponsors in two separate times after data had been collected for 0–12 weeks and 13–52 weeks after treatment initiation, respectively. The safety variables to be assessed included the type, severity, and incidence of adverse drug reactions and adverse drug reactions of special interest (polyuria/pollakiuria, volume depletion-related events, urinary tract infection, genital infection, hypoglycemia and skin disorders), and changes in laboratory parameters and bodyweight. Adverse drug reactions were also examined according to age and the level of renal function. The effectiveness variable was the effect on glycemic control (change in HbA1c from baseline). An electronic data capture system was used for patient registration and data collection.

**Statistical analysis**

Data for 0–12 weeks after treatment initiation were included in this interim analysis. The actual follow-up period was up to 126 days, because a maximum of a 6-week (42-day) delay was allowed for the assessment at 12 weeks (84 days). The safety analysis set was defined as all patients for whom eCRFs were collected, excluding those with no follow-up visits after baseline. The effectiveness analysis set was defined as patients with effectiveness data among the safety analysis set. The Fisher’s exact test or the Cochran–Armitage trend test were used to investigate the association of the incidence of adverse drug reactions with age and renal impairment. Measurements at baseline and after treatment were compared using the paired Student’s t-test. The significance level was two-sided 5%. Adverse drug reactions were coded using the Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J) version 18.0. Missing data at 12 weeks were imputed with the last observation carried forward (LOCF) method, and the change from baseline to
12 weeks was calculated using LOCF data (the value at 12 weeks with LOCF minus the value at baseline).

RESULTS
Patient disposition
A total of 1,535 patients from 597 institutions were registered, and eCRFs were collected from 1,510 patients. For the remaining 25 patients, eCRFs could not be retrieved because of facility closure after enrollment or lack of cooperation by the physicians. After excluding four patients with no follow-up visits after baseline, 1,506 patients were included in the safety analysis set. Of these, effectiveness data were not available for 111 patients, and thus the effectiveness analysis set comprised 1,395 patients (Figure 1).

Among 1,506 patients in the safety analysis set, the mean (standard deviation) follow-up period was 88.6 days (26.2 days). In total, 279 patients (18.53%) discontinued tofogliflozin within the first 12 weeks of treatment. Adverse events were the most common reason for treatment discontinuation (120 patients; 7.97%), and other reasons included limited or no response (67 patients; 4.45%), patient request (40 patients; 2.66%) and failure to attend scheduled visits (19 patients; 1.26%).

Patient characteristics
Patient characteristics are presented in Table 1. The mean age of the patients was 72.4 years, with 66.7% aged ≥65 to <75 years, and 47.7% being men. At baseline, the mean HbA1c was 7.65%, the mean body mass index (BMI) was 26.8 kg/m² (≥25.0 to <30.0 kg/m² for 32.4%) and 39.0% had an estimated glomerular filtration rate (eGFR) of ≥60 to <90 mL/min/1.73 m². A total of 11.5% had received no previous pharmacological treatment, and 18.6% started to receive tofogliflozin as monotherapy at the beginning of the surveillance.

The status of antidiabetic treatment at the time of tofogliflozin initiation was as follows: one or more agents in the previous treatment were replaced by tofogliflozin in 420 patients; the previous treatment was continued without dose reduction and combined with tofogliflozin in 878 patients; the previous treatment was continued with dose reduction and combined with tofogliflozin in 25 patients; no previous treatment had been given in 173 patients; status unknown or unclassified for 10 patients. A total of 80 patients discontinued sulfonylurea therapy on tofogliflozin initiation. The use of insulin or meglitinide therapy was similar before and after the initiation of tofogliflozin.

Safety results
Among 1,506 patients included in the safety analysis set, 178 patients (11.82%) had 254 adverse drug reactions to tofogliflozin (Table 2). The most common adverse drug reactions were pollakiuria (26 events; 1.73%), dehydration (15 events; 1.00%), hypoglycemia (11 events; 0.73%), cystitis (10 events; 0.66%) and nocturia (9 events; 0.60%).

Serious adverse drug reactions were reported in 16 out of 1,506 patients (1.06%). By system organ class, these included: nervous system disorders in nine patients (0.60%; cerebral infarction [3 events], loss of consciousness [2], lacunar infarction [2], altered state of consciousness [1] and depressed level of consciousness [1]), metabolism and nutrition disorders in four (0.27%; dehydration [3] and hyponatremia [1]), infections and infestations in three (0.20%; pyelonephritis [2], pneumonia [1] and muscle abscess [1]), cardiac disorders in two (0.13%;

Figure 1 | Patient disposition. eCRF, electronic case report forms.
Table 1 | Patient characteristics

| Characteristics | Safety analysis set | Characteristics | Safety analysis set |
|-----------------|---------------------|-----------------|---------------------|
|                 | n (%)               |                 | n (%)               |
| Total           | 1,506 (100.0)       | Liver disease   | 238 (15.8)          |
| Sex             |                     | Kidney disease  | 158 (10.5)          |
| Male            | 718 (47.7)          | CVD             | 324 (21.5)          |
| Female          | 788 (52.3)          | Heart failure   | 106 (7.0)           |
| Age (years)     |                     | Malignancy      | 21 (1.4)            |
| ≥65 to <75      | 1,005 (66.7)        | Urinary tract infection | 8 (0.5) |
| ≥75             | 501 (33.3)          | Genital infection | 0 (0.0)            |
| Mean ± SD       | 72.4 ± 6.0          | Hypertension    | 1,114 (74.0)        |
| Baseline BMI (kg/m²) |         | Dyslipidemia    | 1,058 (70.3)        |
| <22.0           | 131 (8.7)           | Gout            | 40 (2.7)            |
| ≥22.0 to <25.0  | 262 (17.4)          | Hyperuricemia   | 175 (11.6)          |
| ≥25.0 to <30.0  | 488 (32.4)          | Osteoporosis    | 171 (11.4)          |
| ≥30.0           | 220 (14.6)          | Previous antidiabetic treatment† | No 173 (11.5) |
| Unknown         | 405 (26.9)          |                 | Yes 1,324 (87.9)    |
| Mean ± SD       | 26.79 ± 4.47        | Oral antidiabetic drug | No 200 (13.3) |
| Duration of disease (years) |         |                 | Yes 1,297 (86.1)    |
| <1              | 44 (2.9)            | Biguanide       | 445 (296)           |
| ≥1 to <10       | 404 (26.8)          | Sulfonlurea     | 569 (37.8)          |
| ≥10             | 456 (30.3)          | DPP-4 inhibitor | 1,049 (69.7)        |
| Unknown         | 602 (40.0)          | SGLT2 inhibitor | 62 (4.1)            |
| Mean ± SD       | 108 ± 7.7           | Meglitinide     | 58 (3.9)            |
| Liver function at baseline |         | α-Glucosidase inhibitor | 258 (17.1) |
| Normal          | 1,240 (82.3)        | Insulin sensitizer | 333 (22.1) |
| Mild dysfunction| 202 (13.4)          | Insulin         | 168 (11.2)          |
| Moderate dysfunction | 17 (1.1)            | GLP-1 receptor agonist | 30 (2.0) |
| Severe dysfunction | 2 (0.1)            |                 |                     |
| Unknown         | 45 (3.0)            | Concomitant antidiabetic treatment‡ | No 280 (18.6) |
| Mean ± SD       | 7.65 ± 1.35         |                 | Yes 1,217 (80.8)    |
| Baseline HbA1c (%) |         | Oral antidiabetic drug | No 318 (21.1) |
| <6.5            | 232 (15.4)          |                 | Yes 1,179 (78.3)    |
| ≥6.5 to <7.0    | 241 (16.0)          | No. concomitant medications | Mean ± SD 20 ± 1.0 |
| ≥7.0 to <8.0    | 489 (32.5)          | Biguanide       | 468 (27.1)          |
| ≥8.0            | 443 (29.4)          | Sulfonlurea     | 500 (33.2)          |
| Unknown         | 101 (6.7)           | DPP-4 inhibitor | 930 (61.8)          |
| Mean ± SD       | 68.56 ± 20.22       | SGLT2 inhibitor | 0 (0.0)             |
| Baseline eGFR (mL/min/1.73 m²) |         | Meglitinide     | 52 (3.5)            |
| <30             | 19 (1.3)            | α-Glucosidase inhibitor | 210 (13.9) |
| ≥30 to <45      | 93 (6.2)            | Insulin sensitizer | 271 (18.0)          |
| ≥45 to <60      | 241 (16.0)          | Insulin         | 163 (10.8)          |
| ≥60 to <90      | 588 (39.0)          | GLP-1 receptor agonist | 24 (1.6)           |
| ≥90             | 134 (8.9)           | Concomitant diuretic therapy‡ | No 1,344 (89.2) |
| Unknown         | 431 (28.6)          |                 |                     |
| Mean ± SD       | 68.56 ± 20.22       | Oral antidiabetic drug | No 318 (21.1) |
| Past medical history |         |                 | Yes 1,179 (78.3)    |
| No              | 1,237 (82.1)        | No. concomitant medications | Mean ± SD 20 ± 1.0 |
| Yes             | 264 (17.5)          | Biguanide       | 468 (27.1)          |
| Unknown         | 5 (0.3)             | Sulfonlurea     | 500 (33.2)          |
| Liver disease   |                     | DPP-4 inhibitor | 930 (61.8)          |
| Yes             | 32 (2.1)            | SGLT2 inhibitor | 0 (0.0)             |
| Kidney disease  |                     | Meglitinide     | 52 (3.5)            |
| Yes             | 11 (0.7)            | α-Glucosidase inhibitor | 210 (13.9) |
| CVD             |                     | Insulin sensitizer | 271 (18.0)          |
| Yes             | 119 (7.9)           | Insulin         | 163 (10.8)          |
| Malignancy      |                     | GLP-1 receptor agonist | 24 (1.6)           |
| Yes             | 59 (3.9)            | Concomitant diuretic therapy‡ | No 1,344 (89.2) |
| Urinary tract infection |       |                 |                     |
| Yes             | 15 (1.0)            | Loop diuretic   | 65 (4.3)            |
| Genital infection |                   |                 |                     |
| Yes             | 3 (0.2)             | Thiazide        | 82 (5.4)            |
| Osteoporosis    |                     |                 |                     |
| Yes             | 9 (0.6)             | Aldosterone antagonist | 18 (1.2)        |
| Concurrent diseases |                 |                 |                     |
| No              | 91 (6.0)            | Mean daily dose of | <20 mg 112 (7.4)   |
| Yes             | 1,413 (93.8)        | tofogliflozin   | 1,394 (92.6)        |
| Unknown         | 2 (0.1)             |                 |                     |
| Diabetic complications |           |                 |                     |
| Yes             | 459 (30.5)          |                 |                     |
| Diabetic retinopathy |         |                 |                     |
| Yes             | 123 (8.2)           |                 |                     |
| Diabetic nephropathy |         |                 |                     |
| Yes             | 319 (21.2)          |                 |                     |
| Diabetic neuropathy |         |                 |                     |
| Yes             | 180 (12.0)          |                 |                     |

CVD, cardiovascular/cerebrovascular disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; SD, standard deviation; SGLT2, sodium–glucose co-transporter 2. †Within 3 months before the initiation of tofogliflozin. ‡During the treatment with tofogliflozin.
atrial fibrillation [2]), musculoskeletal and connective tissue disorders in one (0.07%; muscle weakness [1]), and renal and urinary disorders in one (0.07%; chronic kidney disease [1]). Of these 21 events, five (23.8%) occurred within the first 4 weeks of treatment, three (14.3%) occurred at 4–8 weeks and 13 (61.9%) occurred after 8 weeks.

The three patients who developed cerebral infarction were a 67-year-old man, an 84-year-old man and a 76-year-old man, all with no past or present cardiovascular or cerebrovascular disease. The cerebral infarction occurred at 12 and 18 days, and 3 weeks after treatment initiation, and resolved 7, 15 and 18 days later, respectively. The two patients who developed lacunar infarction were an 80-year-old woman and a 68-year-old man, both with no past or present cardiovascular or cerebrovascular disease. The lacunar infarction occurred at 16 and 6 weeks after treatment initiation and resolved 9 and 57 days later, respectively.

Two deaths occurred during the follow-up period. The causal relationship with tofogliofilozin was denied by the physician. The first patient was a 92-year-old woman with pancreatic cancer and chronic heart failure, and she died of pancreatic cancer on an unknown date. The second patient, an 84-year-old man with cerebral infarction, had died suddenly at 101 days after treatment initiation.

Adverse drug reactions of special interest are summarized in Table 3. Polyuria/pollakiuria occurred in 33 patients (2.2%), within the first 4 weeks for 15 patients (45.5%), at 4–8 weeks for nine patients (27.3%) and after 8 weeks for nine patients (27.3%). Among them, three patients with pollakiuria had received diuretic therapy (loop diuretic for all of them), and none of those with polyuria had received diuretic therapy.

Table 3

| Adverse drug reactions | Incidence (%) | Adverse drug reactions | Incidence (%) |
|------------------------|---------------|------------------------|---------------|
| Renal and urinary disorders | 42 (2.79) | Nervous system disorders | 18 (1.20) |
| Pollakiuria | 26 (1.73) | Dizziness | 6 (0.40) |
| Nocturia | 9 (0.60) | Cerebral infarction | 3 (0.20) |
| Polyuria | 6 (0.40) | Dizziness postural | 2 (0.13) |
| Renal impairment | 3 (0.20) | Loss of consciousness | 2 (0.13) |
| Infections and infestations | 28 (1.86) | Lacunar infarction | 2 (0.13) |
| Cystitis | 10 (0.66) | Gastrointestinal disorders | 17 (1.13) |
| Urinary tract infection | 6 (0.40) | Nausea | 7 (0.46) |
| Vulvovaginal candidiasis | 3 (0.20) | Constipation | 5 (0.33) |
| Pyelonephritis | 2 (0.13) | Abdominal discomfort | 3 (0.20) |
| Acute pyelonephritis | 2 (0.13) | Diarrhea | 3 (0.20) |
| Vulpitis | 2 (0.13) | General disorders and administration site conditions | 17 (1.13) |
| Genital infection | 2 (0.13) | Thirst | 6 (0.40) |
| Metabolism and nutrition disorders | 27 (1.79) | Abnormal sensation | 3 (0.20) |
| Dehydration | 15 (1.00) | Hunger | 2 (0.13) |
| Hypoglycemia | 11 (0.73) | Malaise | 2 (0.13) |
| Skin and subcutaneous tissue disorders | 23 (1.53) | Reproductive system and breast disorders | 9 (0.60) |
| Pruritus | 6 (0.40) | Genital pruritus | 7 (0.46) |
| Rash | 5 (0.33) | Balanoposthitis | 2 (0.13) |
| Urticaria | 3 (0.20) | Musculoskeletal and connective tissue disorders | 7 (0.46) |
| Drug eruption | 2 (0.13) | Muscle weakness | 3 (0.20) |
| Erythema | 2 (0.13) | Pain in extremity | 2 (0.13) |
| Pruritic rash | 2 (0.13) | Vascular disorders | 4 (0.27) |
| Generalized pruritus | 2 (0.13) | Hypotension | 2 (0.13) |
| Investigations | 19 (1.26) | Orthostatic hypotension | 2 (0.13) |
| Blood urea increased | 4 (0.27) | Hepatobiliary disorders | 3 (0.20) |
| Glycohemoglobin increased | 3 (0.20) | Hepatic function abnormal | 3 (0.20) |
| Loss of weight | 3 (0.20) | Cardiac disorders | 3 (0.20) |
| Blood pressure increased | 2 (0.13) | Atrial fibrillation | 2 (0.13) |
Table 3 | Adverse drug reactions by the category of adverse reactions of special interest

| No. adverse drug reactions (%) | Polyuria/pollakiuria | Volume depletion-related events | Urinary tract infection |
|-------------------------------|----------------------|--------------------------------|------------------------|
| Number of patients (%)        | 33 (2.19)           | 35 (2.32)                      | 20 (1.33)              |
| No. adverse drug reactions (%)| Pollakiuria          | Dehydration                     | Cystitis               |
|                               | 26 (1.73)           | 15 (1.00)                      | 10 (0.66)              |
|                               | Nocturia             | Thirst                          | Urinary tract infection|
|                               | 9 (0.60)            | 6 (0.40)                       | 6 (0.40)               |
|                               | Polyuria             | Constipation                    | Pyelonephritis         |
|                               | 6 (0.40)            | 5 (0.33)                       | 2 (0.13)               |
|                               |                     | Blood urea increased            | Acute pyelonephritis   |
|                               |                     | 4 (0.27)                       | 2 (0.13)               |
|                               |                     | Cerebral infection              | Hemorrhagic cystitis   |
|                               |                     | 3 (0.20)                       | 1 (0.07)               |
|                               |                     | Loss of consciousness           |                        |
|                               |                     | 2 (0.13)                       |                        |
|                               |                     | Lacunar infarction              |                        |
|                               |                     | 2 (0.13)                       |                        |
|                               |                     | Depressed level of consciousness|                        |
|                               |                     | 1 (0.07)                       |                        |
|                               |                     | Hemorrhocencentration           |                        |
|                               |                     | 1 (0.07)                       |                        |
|                               |                     | Heat stroke                     |                        |
|                               |                     | 1 (0.07)                       |                        |

| No. adverse drug reactions (%) | Genital infection | Skin disorders | Hypoglycemia |
|-------------------------------|-------------------|----------------|--------------|
| Number of patients (%)        | 17 (1.13)         | 22 (1.46)      | 11 (0.73)    |
| No. adverse drug reactions (%)| Genital pruritus  | Pruritus        | Hypoglycemia |
|                               | 7 (0.46)          | 6 (0.40)       | 11 (0.73)    |
|                               | Vulvovaginal candidiasis | Rash |              |
|                               | 3 (0.20)          | 5 (0.33)       |              |
|                               | Balanoposthitis   | Urinaria        |              |
|                               | 2 (0.13)          | 3 (0.20)       |              |
|                               | Vulvitis          | Drug eruption   |              |
|                               | 2 (0.13)          | 2 (0.13)       |              |
|                               | Genital infection | Erythema        |              |
|                               | 2 (0.13)          | 2 (0.13)       |              |
|                               | Genital infection fungal | Pruritic rash |              |
|                               | 1 (0.07)          | 2 (0.13)       |              |
|                               | Genital infection female | Generalized pruritus |          |
|                               | 1 (0.07)          | 2 (0.13)       |              |
|                               | Genital rash      | Eczema          |              |
|                               | 1 (0.07)          | 1 (0.07)       |              |
|                               | Vaginal inflammation | Miliaria |              |
|                               | 1 (0.07)          | 1 (0.07)       |              |
|                               |                   | Papule           |              |
|                               |                   | 1 (0.07)        |              |
|                               |                   | Rash scarlatiniform |          |
|                               |                   | 1 (0.07)        |              |
|                               |                   | Skin exfoliation  |              |
|                               |                   | 1 (0.07)        |              |

Adverse drug reactions were coded using Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J) version 18.0. Safety analysis set: 1,506 patients.

Changes in vital signs and laboratory tests are shown in Table S1. The mean bodyweight significantly decreased from 67.48 kg (12.54 kg) at baseline to 65.59 kg (12.23 kg) at 12 weeks (LOCF), and the mean change was −1.94 kg (2.43 kg) (P < 0.0001). Patients with a baseline BMI of <22 (n = 88), ≥22 to <25 (n = 183), ≥25 to <30 (n = 387) and ≥30 kg/m² (n = 181) had a mean change of −1.21 kg (1.56 kg), −1.60 kg (1.87 kg), −1.85 kg (1.95 kg) and −2.77 kg (3.94 kg), respectively. Thus, the reduction in bodyweight tended to be greater in patients with a higher baseline BMI, but even those with a baseline BMI of less than 22 kg/m² had a mean reduction of more than 1 kg.

The frequency of adverse drug reactions was examined according to age and the level of renal function. Among patients aged ≥65 to <75 years (n = 1,005) and those aged ≥75 years (n = 501), the number of patients who developed one or more adverse drug reactions was 124 (12.34%) and 54 (10.78%), respectively (Table S2). The corresponding number for serious adverse drug reactions was nine (0.90%) and seven (1.40%). When stratified by renal function, the number of patients who developed one or more adverse drug reactions was two (10.53%), 16 (17.20%), 31 (12.86%), 72 (12.24%), and 14 (10.45%) among those with a baseline eGFR of <30 (n = 19), ≥30 to <45 (n = 93), ≥45 to <60 (n = 241), ≥60 to <90 (n = 588) and ≥90 mL/min/1.73 m² (n = 134), respectively (Table S3). The corresponding number for serious...
adverse drug reactions was one (5.26%), two (2.15%), four (1.66%), four (0.68%) and two (1.49%).

**Effectiveness results**

The mean HbA1c decreased over time from 7.65% (1.35%) at baseline \( (n = 1,327) \) to 7.44% (1.24%), 7.21% (1.07%), and 7.25% (1.16%) at 4 weeks \( (n = 1,100) \), 12 weeks \( (n = 1,152) \) and 12 weeks with LOCF, respectively, and the mean change was −0.39% (0.94%; LOCF; \( P < 0.0001 \)).

Table 4 shows the changes in HbA1c and bodyweight stratified by baseline eGFR. The reduction in HbA1c was significant in groups with a baseline eGFR of ≥45 mL/min/1.73 m², and tended to be greater in groups with a higher baseline eGFR. The reduction in bodyweight was significant in all groups, and tended to be greater in groups with a higher baseline eGFR.

**DISCUSSION**

The present post-marketing special drug use surveillance was carried out to investigate the safety and effectiveness of tofogliflozin in elderly patients aged ≥65 years in routine clinical practice. According to the Japan Patient Survey 2011 by the Ministry of Health, Labor and Welfare, elderly patients aged ≥65 years comprise 63.4% of all diabetic patients treated in Japan. Given this situation, this surveillance focusing on the elderly patient population is relevant in clinical practice. In this surveillance, all type 2 diabetes patients aged ≥65 years who started treatment with tofogliflozin during the 3-month period from 23 May to 22 August 2014 in Japan were registered, and we carried out an interim analysis when the first 12 weeks became available for 1,510 patients (safety analysis on 1,506 and effectiveness analysis on 1,395 patients). Of note, although the surveillance included all elderly patients treated with tofogliflozin and did not select them based on special factors, the study population was selected to some extent as a population with characteristics suitable for treatment with SGLT2 inhibitors, with nearly half of the patients having a BMI of ≥25 kg/m². The present study population had a mean HbA1c of 7.65% and a mean BMI of 26.8 kg/m², and thus tended to be obese, suggesting that tofogliflozin might have been prescribed with the expectation of not only glycemic control, but also bodyweight reduction.

In the tofogliflozin clinical development program (before marketing approval), adverse drug reactions were reported in 397 of 1,060 patients (37.5%), and the most common events were blood ketone bodies increased \( (n = 117; 11.0\%) \), thirst \( (n = 80; 7.5\%) \) and polyuria/pollakiuria \( (n = 80; 7.5\%) \). In the present study, the overall incidence of adverse drug reactions was lower, but the type of adverse drug reactions was similar, with the most common events being polyuria/pollakiuria (26 events; 1.73%), dehydration (15 events; 1.00%), hypoglycemia (11 events; 0.73%), cystitis (10 events; 0.66%) and nocturia (9 events; 0.60%).

Hypoglycemia, polyuria/pollakiuria, volume depletion-related events, urinary tract infection and genital infection, which were defined as adverse drug reactions of special interest in the present study, are listed as important identifications on the proper use of SGLT2 inhibitors reported in the ‘recommendations on the proper use of SGLT2 inhibitors’ statement. Hypoglycemia occurred in 11 patients \( (0.7\%) \) in this surveillance. Of them, 10 patients had concomitant medications, and most patients were receiving a combination therapy with sulfonylurea or insulin. When an SGLT2 inhibitor is used in combination with sulfonylurea, it is important to consider the dose reduction of sulfonylurea, as recommended in the recommendation statement.

Polyuria/pollakiuria and volume depletion-related events occurred in 68 patients \( (4.52\%) \), and these were observed more frequently than other events because of the mechanism of the
action of this drug. Apart from thirst, which occurred at a lower incidence (0.4%), this trend is the same as that confirmed in the data before marketing approval. Of the 35 patients who developed volume depletion-related events, three were receiving diuretic therapy. Given the rate of the concurrent use of diuretics in the entire population (153/1,506), it is unlikely that the use of diuretics might have contributed to the occurrence of volume depletion-related events. Cerebral infarction or lacunar infarction developed in five patients. We could not determine whether the occurrence in five patients within the first 3 months was high or low, because this surveillance did not set the control group. If future cerebral infarction cases are accumulated, we will be able to assess patient characteristics that could predict the occurrence of the event in the final analysis.

Urinary tract and genital infections occurred more frequently in women than in men. No consistent trend was seen in the time to onset for either adverse drug reaction. The nature of urinary tract and genital infections observed in this surveillance was consistent with that observed for the class of SGLT2 inhibitors in Japan. Skin disorders, another category of adverse drug reactions of special interest, are recognized as the most common adverse drug reactions to the class of SGLT2 inhibitors in the recommendations on the proper use of SGLT2 inhibitors’ statement, and occurred in 22 patients (1.46%) in the present study. Although it is unknown whether skin disorders are class adverse effects, there seems to be cross-reactivity among SGLT2 inhibitors, and the statement recommends that patients developing skin rash should immediately consult a dermatologist.

For bodyweight, which was assessed as a safety parameter in this surveillance, but is also an efficacy parameter, there was a significant reduction. However, higher BMI was associated with a greater reduction in bodyweight, and patients with a normal BMI had little change in bodyweight, suggesting that the effect of tofogliflozin on bodyweight is not a safety concern. Nevertheless, attention should be paid to bodyweight reduction in patients with lower BMI, because even patients with a baseline BMI of less than 22 kg/m² had a mean reduction of more than 1 kg in bodyweight.

For effectiveness, a significant reduction was seen in HbA1c at 12 weeks of treatment. Although the target has not been reached yet (7.21% at 12 weeks), the mean value was gradually decreasing, and thus is expected to decrease further after 12 weeks. This trend was similar to that observed in long-term trials of tofogliflozin in Japanese patients, in which HbA1c gradually decreased during the first 3 months and was maintained at constant low levels thereafter.

Subgroup analyses stratified by renal function showed that the effectiveness in reducing HbA1c and bodyweight was lower in patients with severe renal dysfunction (lower eGFR). It has been suggested that patients with renal impairment are less likely to respond to SGLT2 inhibitors, because urinary glucose excretion depends on eGFR, and for canagliflozin, it has been recommended that the drug should be used in patients with an eGFR ≥45 mL/min/1.73 m². The results of the subgroup effectiveness analyses are consistent with these previous reports. For safety, there was no clear relationship between the level of renal function and the incidence of adverse drug reactions. However, a study of dapagliflozin in patients with type 2 diabetes and chronic kidney disease showed that the incidence of genital infection, bone fractures, and volume depletion-related events was higher in dapagliflozin-treated patients than in placebo-treated patients. With this in mind, we are currently involved in the final analysis of data collected for 52 weeks to determine the safety of tofogliflozin in elderly patients with renal impairment.

The present analysis had some limitations. This was only an interim analysis of an observational study at 12 weeks after treatment initiation. The data presented are not definitive, and it is possible that new trends might become evident in the final analysis at 52 weeks. The results at 12 weeks might also be changed based on a review and correction of data, including physician’s assessment.

In conclusion, we present a 12-week interim analysis of a surveillance to investigate the safety and effectiveness of tofogliflozin in real-world elderly patients with type 2 diabetes aged ≥65 years. The analysis showed the adverse drug reaction profile during the early post-marketing period with respect to polyuria/pollakiuria, volume depletion-related events, urinary tract infection, genital infection, hypoglycemia and skin disorders. The final analysis at 52 weeks is currently underway.

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REFERENCES

1. Ministry of Health, Labour and Welfare Japan. The National Health and Nutrition Survey Japan 2012. Available from: http://www.mhlw.go.jp/stf/houdou/0000032074.html Accessed October 17, 2015 (in Japanese).
2. Japan Diabetic Society. Treatment Guide for Diabetes 2014–2015. Tokyo: Bunkodo, 2014 (in Japanese).
3. DeFronzo RA, Davidson JA, del Prato S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes Obes Metab* 2012; 14: 5–14.
4. List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. *Kidney Int Suppl* 2011; 120: S20–S27.
5. Poole RM, Prossler JE. Tofogliflozin: first global approval. *Drugs* 2014; 74: 939–944.
6. Committee on Proper Use of SGLT2 Inhibitors. Recommendations on the proper use of SGLT2 inhibitors. 2014 (in Japanese).
7. Rosenwasser RF, Rosenwasser JN, Sutton D, *et al.* Tofogliflozin: a highly selective SGLT2 inhibitor for the treatment of type 2 diabetes. *Drugs Today* 2014; 50: 739–745.
8. Japan Pharmaceutical Manufacturers Association. A guide for preparing risk management plans for drug products (provisional). August 2014 (in Japanese).
9. Kowa Company, Ltd. Risk management plan for Deberza 20 mg Tablet. June 2015 (in Japanese).
10. Sanofi KK. Risk management plan for Apleway 20 mg Tablet. June 2015 (in Japanese).
11. Ministry of Health, Labour and Welfare Japan. Summary of Patient Survey 2011. Available from: http://www.mhlw.go.jp/english/database/db-hss/sps_2011.html. Accessed October 17, 2015.
12. Kowa Company, Ltd. Package insert for Deberza 20 mg Tablet (in Japanese).
13. Sanofi KK Package insert for Apleway 20 mg Tablet (in Japanese).
14. Tanizawa Y, Kaku K, Araki E, *et al.* Long-term safety and efficacy of tofogliflozin, a selective inhibitor of sodium glucose cotransporter 2, as monotherapy or in combination with other oral antidiabetic agents in Japanese patients with type 2 diabetes mellitus: multicenter, open-label, randomized controlled trials. *Expert Opin Pharmacother* 2014; 15: 749–766.
15. Kasichayanula S, Chang M, Hasegawa M, *et al.* Pharmacokinetics and pharmacodynamics of dapagliflozin, a novel selective inhibitor of sodium-glucose co-transporter type 2, in Japanese subjects without and with type 2 diabetes mellitus. *Diabetes Obes Metab* 2011; 13: 357–365.
16. Khurana M, Vaidyanathan J, Marathe A, *et al.* Canagliflozin use in patients with renal impairment-Utility of quantitative clinical pharmacology analyses in dose optimization. *J Clin Pharmacol* 2015; 55: 647–656.
17. Kohan DE, Fioretto P, Tang W, *et al.* Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int* 2014; 85: 962–971.

**SUPPORTING INFORMATION**
Additional Supporting Information may be found in the online version of this article:

Table S1 | Mean changes in laboratory values.
Table S2 | Adverse drug reactions by age.
Table S3 | Adverse drug reactions by baseline estimated glomerular filtration rate.