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Sponsor: Sanofi **Drug substance(s):** Tofogliflozin	**Study Identifiers:** U1111-1159-5316, NCT02201004 **Study code:** TOFOGL07061

Title of the study: A randomized, double-blind placebo controlled 2-arm parallel group, multicenter study with a 16-week treatment assessing the efficacy and safety, and 52-week long term safety including 36-week open-label extension of tofogliflozin with insulin treatment in type 2 diabetes mellitus

Study center(s): 30 centers in Japan

Study period:

Date first patient enrolled: 30/Jun/2014

Date last patient completed: 08/Oct/2016

Phase of development: Phase 4

Objectives:

Primary Objectives

- To assess the effects on glycemic control of tofogliflozin in comparison to placebo as an add-on treatment to insulin treatment in terms of hemoglobin A1c (HbA1c) reduction over a period of 16 weeks in Japanese patients with Type 2 Diabetes Mellitus (T2DM).
- To assess the safety of tofogliflozin as an add-on treatment to insulin treatment over 52 weeks.

Secondary Objectives

To evaluate the effects of tofogliflozin in comparison to placebo on:

1. Body weight;
2. Fasting plasma glucose (FPG);
3. Postprandial plasma glucose (PPG).

Methodology: This was a randomized, 2-arm parallel group, multicenter phase 4 study, with the 16-week double-blind, placebo controlled period followed by the 36-week open-label extension period, in Japanese patients with T2DM. This study comprised 3 periods: a 2-week screening period, a 52-week treatment period (16-week double-blind period and 36-week open-label period), and a 3-day follow-up period. Patients with T2DM were randomized in a 2:1 ratio to receive either tofogliflozin or placebo on top of insulin treatment for 16 weeks. In the double-blind period, either tofogliflozin 20 mg tablet or placebo tablet was administered once daily according to the treatment group. In the open-label extension period, tofogliflozin 20 mg tablet was administered once daily to all patients.

Number of patients:	Planned: 210 (tofogliflozin: 140, placebo: 70)
	Randomized: 211 (tofogliflozin: 141, placebo: 70)
	Treated: 210 (tofogliflozin: 140, placebo: 70)
Evaluated:	Efficacy: 210 (tofogliflozin: 140, placebo: 70)
	Safety: 210 (tofogliflozin: 140, placebo: 70)

Diagnosis and criteria for inclusion:

- Patients with T2DM insufficiently controlled with insulin treatment who meet any of the following criteria
  - Patients with T2DM insufficiently controlled with insulin treatment only
  - Patients with T2DM insufficiently controlled with combination therapy of basal insulin treatment and dipeptidyl peptidase-4 (DPP-4) inhibitor
- Patients treated for at least 3 months prior to screening visit with any of the following insulin treatments at stable dose of insulin (±20%)
  - Basal-bolus
  - Bolus
  - Premix (low and high)
  - Basal
- For basal insulin treatment, DPP-4 inhibitor can be allowed.
- No change dose of DPP-4 inhibitor for at least 3 months before screening.
- At screening: HbA1c ≥ 7.5% or ≤ 10.5%.
- At screening: FPG ≤ 220 mg/dL.
- At screening: Body mass index (BMI) ≥ 18.5 kg/m^2 or < 35.0 kg/m^2.
- Age ≥ 20 or ≤ 75 years (male or female).
- Signed written informed consent.

Study treatments

Investigational medicinal product(s):

Tofogliflozin 20 mg tablet

Formulation: containing 20 mg of tofogliflozin in one tablet

Route(s) of administration: oral administration

Dose regimen:

Double-blind period:

Tofogliflozin 20 mg tablet was administered orally once daily before or after breakfast.

Open-label period:

After the end of double-blind period, all patients took tofogliflozin 20 mg orally once daily.

Time of administration was not changed from before or after breakfast during the study.

Tofogliflozin placebo tablet

Formulation: Placebo tablet unidentifiable in appearance with tofogliflozin 20 mg tablet

Route(s) of administration: oral administration

Dose regimen:

Double-blind period:

Tofogliflozin placebo tablet was administered orally once daily before or after breakfast.

Time of administration was not changed from before or after breakfast during the study.

Noninvestigational medicinal product(s): Insulin

Formulation: injection

Route(s) of administration: subcutaneous injection

Dose regimen: In principle, the insulin was at stable dose and regimen during the first 16 weeks. The insulin dose was to be reduced when development of hypoglycemia occured or prevention of hypoglycemia was necessary.

Duration of treatment: 52 weeks

Duration of observation: Approximately 54 weeks including 2 weeks screening, 52 weeks treatment, and 3 days follow-up.

Criteria for evaluation:

Efficacy:

Primary Endpoint:

- Change in HbA1c from baseline to Week 16.

Secondary Endpoints:

- Change in body weight, FPG, PPG, blood pressure and uric acid between tofogliflozin group and placebo group from baseline to Week 16.
- Change in HbA1c, body weight and FPG from baseline to Week 52.
- Change in lipid parameter from baseline to Week 16 and Week 52.
- Change in insulin dose from baseline to Week 16 and from Week 16 to 52.
- Proportion of patients who achieved HbA1c < 7.0% at Week 16 and 52.
- Proportion of patients who achieved HbA1c ≤ 6.5% at Week 16 and 52.

Safety:

Safety over 16 weeks (double-blind period) and over 52 weeks (double-blind and open-label period) were assessed by hypoglycemia (severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, and nocturnal hypoglycemia), urinary tract infections or genital infection, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, clinical laboratory, and 12-lead electrocardiogram.

Statistical methods:

Efficacy analysis

The primary efficacy population was the modified intention-to-treat (mITT) population, which includes patients randomized and exposed to at least one dose of the investigational medicinal product (IMP), and had both a baseline measurement and at least one post-baseline measurement of any efficacy variables. All efficacy analyses were performed by randomized treatment group (i.e., tofogliflozin and placebo).

Efficacy variables compared to placebo including the primary endpoint (change in HbA1c from baseline to Week 16) were analyzed using the mixed model with repeated measurements (MMRM) with treatment groups, visit, treatment group-by-visit interaction, randomization stratum of screening HbA1c (< 8.0%, ≥ 8.0%), randomization stratum of insulin regimen (Basal-bolus, Bolus, Premix, Basal) and randomization stratum of screening estimated glomerular filtration rate (eGFR) (≥ 90 mL/min/1.73 m^2, ≥ 60 - < 90 mL/min/1.73 m^2, ≥ 30 - < 60 mL/min/1.73 m^2) as fixed effects, baseline HbA1c, baseline HbA1c-by-visit interaction as covariates. The least squares (LS) mean changes in each variable from baseline to week 16 for each treatment group were provided in the framework of this model, as well as the difference between treatment groups and the 95% confidence interval (CI) for the least squares (LS) mean. The statistical test for the efficacy variables were at a (two-sided) 5% significance level. Descriptive statistics and graphs for each variable were also provided over 16 weeks and 52 weeks.

For the primary efficacy endpoint (change in HbA1c from baseline to Week 16), sensitivity analyses were performed with imputed value by method of last observation carried forward (LOCF), using analysis of covariance (ANCOVA) model and with the data including data collected after rescue therapy using the MMRM model. Sub-group analyses were also performed using

the MMRM model.

Each responder rate (proportion of subjects who achieved HbA1c < 7.0% and proportion of subjects who achieved HbA1c ≤ 6.5%) at Week 16 was summarized by treatment group and Cochran-Mantel-Haenszel (CMH) test stratified on randomization stratum of screening HbA1c (< 8.0%, ≥ 8.0%), randomization stratum of insulin regimen (Basal-bolus, Bolus, Premix, Basal) and randomization stratum of screening eGFR (≥ 90 mL/min/1.73 m^2, ≥ 60 - < 90 mL/min/1.73 m^2, ≥ 30 - < 60 mL/min/1.73 m^2). Providing p-value and 95% CI was performed to compare tofogliflozin and placebo. The responder rates at Week 52 were also provided.

Safety analysis

Safety analyses were performed on the intention-to-treat (ITT) population, which was defined as all patients randomized and exposed to at least one dose of the double-blinded IMP. Safety analyses for the 16-week on-treatment period were performed by treatment group (i.e., tofogliflozin and placebo) in the ITT population. Safety analyses for the 52-week on-treatment period were performed in patients randomized to the tofogliflozin group. Safety analyses for the 36-week on-treatment period were performed on the intention-to-treat population for the open-label period (opITT) population, which was defined as patients randomized to the placebo group, completed the double-blind treatment period, and exposed to at least one dose of the open-label IMP (tofogliflozin). TEAEs during the on-treatment period were defined as adverse events (AE) that developed or worsened or became serious during the period from the first administration of the IMP up to 7 days after the last administration of the IMP. The summary of safety results during the 16-week on-treatment period (the period from the first dose of the double-blind IMP up to 7 days after the last dose of the double-blind IMP [for patients permanently discontinued during the double-blind treatment period] or the date of visit 6 [Week 16] [for patients who have completed the double-blind treatment period]) was descriptive and presented by each treatment group. The summary of safety results during the 36-week on-treatment period (the period from the next date of visit 6 [Week 16] up to 7 days after the last dose of the open-label IMP [tofogliflozin] in patients randomized to the placebo group), and the on-treatment period (the period from the first dose of the double-blind IMP up to 7 days after the last dose of the IMP during the whole treatment period) was descriptive and presented in the placebo group and the tofogliflozin group, respectively.

Summary:

Population characteristics:

A total of 320 patients with T2DM were screened and 211 patients were randomized in this study. Of them, 141 patients were randomized to the tofogliflozin group and 70 patients were randomized to the placebo group. One patient in the tofogliflozin group was randomized but not treated due to AE. All other patients (n= 210) received treatment as per randomization and were included in the ITT and mITT population. Sixty-eight (68) patients in the placebo group were included in the opITT population.

Three (3) patients (2.1%) in the tofogliflozin group and 2 patients (2.9%) in the placebo group prematurely discontinued treatment with IMP during the16-week double-blind treatment period. In the tofogliflozin group, the reasons of treatment discontinuation were due to withdrawal by patient in 1 patient and due to AE in 2 patients. In the placebo group, the reasons of treatment discontinuation were due to withdrawal by patient in 1 patient and due to out of selection criteria in 1 patient.

Nine (9) patients (6.4%) in the tofogliflozin group and 4 patients (5.7%) in the placebo group prematurely discontinued treatment with IMP during the 52-week study treatment period. In the tofogliflozin group, the reasons of treatment discontinuation were due to withdrawal by patient in 3 patients, due to AE in 5 patients and due to other reason in 1 patient. In the placebo group, the reasons of treatment discontinuation were due to withdrawal by patient in 2 patients, due to AE in 1 patient and due to out of selection criteria in 1 patient.

The demographic and baseline characteristics were not substantially different across the both groups except for age. The percentage of patients aged ≥ 65 years were higher in the tofogliflozin group compared to the placebo group (41.4% [58/140 patients] vs 24.3% [17/70 patients]). The mean age was 59.1 years in the tofogliflozin group and 56.4 years in the placebo group. The mean baseline HbA1c and eGFR were 8.53% and 79.8 mL/min/1.73m2 in the tofogliflozin group and 8.40% and 79.5 mL/min/1.73m2 in the placebo group. The body weight and the BMI at baseline were 68.84 kg and 25.79 kg/m2 in the tofogliflozin group and 72.24 kg and 26.89 kg/m2 in the placebo group

The disease characteristics at screening or baseline were also similar across the both groups. Diabetic sensory or motor neuropathy were higher in the tofogliflozin group compared to the placebo group (28.6% [40/140 patients] vs 18.6% [13/70 patients]) and diabetic autonomic neuropathy were higher in the tofogliflozin group compared to the placebo group (6.4% [9/140 patients] vs 0% [0 patient]). The proportion of patients who used insulin regimen (Basal-bolus, Bolus, Premix, and Basal, respectively) at screening/baseline was 24.3% (34 patients), 11.4% (16 patients), 16.4% (23 patients) and 47.9% (67 patients) in the tofogliflozin group and 24.3% (17 patients), 11.4% (8 patients), 15.7% (11 patients) and 48.6% (34 patients) in the placebo group.

Mean treatment duration (standard deviation [SD]) during the 16-week double-blind treatment period was 111.8 (11.5) days in the tofogliflozin group and 112.0 (7.1) days in the placebo group. Mean treatment compliance during the 16-week double-blind treatment period were 99.50% (1.00) in the tofogliflozin group and 99.02% (2.51) in the placebo group.

Mean treatment duration (SD) during the 36-week open-label treatment period was 243.3 (35.3) days in the tofogliflozin group and 247.7 (18.0) days in the placebo group. Mean treatment compliance during the 36-week open-label treatment period were 98.75% (8.58) in the tofogliflozin group and 99.20% (1.87) in the placebo group.

Mean treatment duration (SD) during the 52-week study treatment period was 349.8 (56.9) days in the tofogliflozin group and 352.6 (50.7) days in the placebo group. Mean treatment compliance during the 52-week study treatment period were 99.38% (1.50) in the tofogliflozin group and 99.16% (1.67) in the placebo group.

Efficacy results:

Treatment with tofogliflozin resulted in a statistically significant decrease in HbA1c from baseline to Week 16 compared to treatment with placebo in the analysis using MMRM. The LS mean changes in HbA1c from baseline to Week 16 excluding measurements after receiving the rescue therapy using MMRM were -0.59% for the tofogliflozin group and 0.48% for the placebo group (LS mean difference: -1.07%, p-value: < 0.0001).

LS mean changes in HbA1c from baseline to Week 16 (LOCF) using ANCOVA were -0.56% for the tofogliflozin group and 0.48% for the placebo group (LS mean difference: -1.05%, p-value: < 0.0001). LS mean changes in HbA1c from baseline to Week 16 including measurements after receiving the rescue therapy using MMRM were -0.59% for the tofogliflozin group and 0.50% for the placebo group (LS mean difference: -1.09%, p-value: < 0.0001). Sub-group analyses of LS mean changes in HbA1c from baseline to Week 16 using MMRM were -0.51% for the tofogliflozin group and 0.62% for the placebo group in age category <65 years (LS mean difference: -1.14%, p-value: < 0.0001) and were -0.59% for the tofogliflozin group and 0.32% for the placebo group in age category ≥65 years (LS mean difference: -0.90%, p-value: < 0.0001).

At the end of the double-blind period, the result of the analyses using ANCOVA and the result of MMRM including measurements after receiving the rescue therapy were similar with the result of the primary efficacy analysis.

At the end of the double-blind period, comparatively with placebo, treatment with tofogliflozin also resulted in a decrease of LS mean in body weight (-1.35 kg and 0.05 kg in the tofogliflozin group and the placebo group, respectively), a reduction of LS mean in FPG (23.3 mg/dL and 8.8 mg/dL), PPG (-62.9 mg/dL and 4.7 mg/dL), diastolic blood pressure (-2.1 mmHg and 0.8 mmHg) and uric acid (-0.14 mg/dL and 0.15 mg/dL). No statistical difference in the LS mean changes from baseline to Week 16 in systolic blood pressure was observed between the treatment groups (-3.6 mmHg and -1.5 mmHg in the tofogliflozin group and the placebo group, respectively).

At the end of the double-blind period, no statistical difference between the treatment groups was observed in LS mean changes from baseline to Week 16 in total cholesterol (2.1 mg/dL and 0.3 mg/dL in the tofogliflozin group and the placebo group, respectively), HDL-cholesterol (3.2 mg/dL and 0.6 mg/dL), LDL-cholesterol (3.9 mg/dL and 2.2 mg/dL) and triglycerides (-25.6 mg/dL and -35.7 mg/dL). For triglycerides, median changes from baseline to Week 16 were -7.0 mg/dL for the tofogliflozin group and 2.0 mg/dL for the placebo group. Mean changes from baseline to Week 16 of post hoc sensitivity analysis for triglycerides using a nonparametric model were -31.1 mg/dL in the tofogliflozin group and 3.9 mg/dL in the placebo group. The results of post hoc sensitivity analysis for triglycerides using a nonparametric model were similar with the result of the analysis using parametric model.

The required insulin dose decreased in the tofogliflozin group compared to the placebo group (LS mean change from baseline to Week 16; -1.2 U in the tofogliflozin group and 0.1 U in the placebo group).

Proportion of patients who achieved HbA1c < 7.0% at Week 16 were 12.1% and 1.4% in the tofogliflozin group and the placebo group, respectively. Additionally, 4.3% in the tofogliflozin group reached HbA1c ≤6.5% at Week 16. No patient in the placebo

group reached HbA1c ≤6.5% at Week 16. Differences of proportion taking into account of the three randomization strata for each category were 10.75% for HbA1c < 7.0% and 6.86% for HbA1c ≤ 6.5%, respectively.

No patient in the tofogliflozin group and 2 patients (2.9%) in the placebo group required rescue therapy during the 16-week on-treatment period.

After Week 16, all patients in both groups received the open-label tofogliflozin and the insulin dose could be modified. Mean changes from baseline to Week 52 decreased in HbA1c (-0.76% and -0.73% in the tofogliflozin group and the placebo group, respectively), body weight (-1.52 kg and -2.13 kg), FPG (-29.3 mg/dL and -24.6 mg/dL), systolic blood pressure (-5.5 mmHg and -6.5 mmHg), diastolic blood pressure (2.0 mmHg and 2.4 mmHg), uric acid (0.14 mg/dL and 0.27 mg/dL), triglycerides (43.4 mg/dL and 6.8 mg/dL) and insulin dose (1.27 U and 0.58 U). Mean changes from baseline to Week 52 were 4.9 mg/dL and 1.6 mg/dL in total cholesterol, 2.6 mg/dL and 2.0 mg/dL in HDL-cholesterol, and 7.1 mg/dL and 1.0 mg/dL in LDL-cholesterol in the tofogliflozin group and the placebo group, respectively.

For mean changes from Week 16 to Week 52, treatment with tofogliflozin resulted in a decrease in the required insulin dose (-0.34 U in the tofogliflozin group and -0.43 U in the placebo group).

Proportion of patients who achieved HbA1c < 7.0% at Week 52 in the tofogliflozin group was 15.0%. Proportion of patients who achieved HbA1c ≤ 6.5% at Week 52 in the tofogliflozin group was 3.6%.

No patient in the tofogliflozin group and 2 patients (2.9%) in the placebo group were required rescue therapy during the 52-week on-treatment period.

Safety results:

In the 16-week double-blind on-treatment period, TEAEs were reported in 95 patients (67.9%) in the tofogliflozin group and 49 patients (70.0%) in the placebo group. The most common TEAEs during the 16-week on-treatment period in the tofogliflozin group compared to the placebo group (TEAEs in system organ class [SOC] which occurred ≥ 5% more frequently in the tofogliflozin group than in the placebo group) were metabolism and nutrition disorders SOC (46 patients [32.9%] in the tofogliflozin group and 17 patients [24.3%] in the placebo group), renal and urinary disorders SOC (14 patients [10.0%] in the tofogliflozin group and no patient [0%] in the placebo group) and general disorders and administration site conditions SOC (10 patients [7.1%] in the tofogliflozin group and 1 patient [1.4%] in the placebo group). In preferred term (PT), hypoglycaemia (43 patients [30.7%] in the tofogliflozin group and 15 patients [21.4%] in the placebo group) and thirst (9 patients [6.4%] in the tofogliflozin group and no patient [0%] in the placebo group) were ≥ 5% more frequently observed in the tofogliflozin group than in the placebo group.

In the 36-week tofogliflozin on-treatment period in the placebo group, TEAEs were reported in 50 patients (73.5%). The most common TEAEs during the 36-week on-treatment period (TEAEs which occurred more than 30%) were Infections and infestations SOC (23 patients [33.8%]) and Metabolism and nutrition disorders SOC (21 patients [30.9%]). Hypoglycaemia (PT) was the most common TEAE (20 patients [29.4%]) observed during the 36-week on-treatment period of the placebo group.

In the 52-week on-treatment period in the tofogliflozin group, TEAEs were reported in 126 patients (90.0%). The most common TEAEs during the 52-week on-treatment period (TEAEs which occurred more than 30%) were Infections and infestations SOC (63 patients [45.0%]) and Metabolism and nutrition disorders SOC (64 patients [45.7%]). Hypoglycaemia (PT) was the most common TEAE (60 patients [42.9%]) during the 52-week on-treatment period of the tofogliflozin group.

In the 16-week double-blind on-treatment period, TEAEs related to IMP were reported in 58 patients (41.4%) in the tofogliflozin group and 16 patients (22.9%) in the placebo group. The most common TEAEs related to IMP during the 16-week on-treatment period was hypoglycaemia (PT) (38 patients [27.1%] in the tofogliflozin group and 11 patients [15.7%] in the placebo group). TEAEs related to non-investigational medicinal product (NIMP) were reported in 43 patients (30.7%) in the tofogliflozin group and 14 patients (20.0%) in the placebo group. The most common TEAE related to NIMP during the 16-week on-treatment period was hypoglycaemia (PT) (42 patients [30.0%] in the tofogliflozin group and 13 patients [18.6%] in the placebo group).

In the 36-week tofogliflozin on-treatment period in the placebo group, TEAEs related to IMP or NIMP during the 36-week on-treatment period were reported in 24 patients (35.3%) and 19 patients (27.9%), respectively. The most common TEAE related to IMP or NIMP during the 36-week on-treatment period was hypoglycaemia (PT) (18 patients [26.5%] and 19 patients [27.9%], respectively).

In the 52-week on-treatment period in the tofogliflozin group, TEAEs related to IMP or NIMP were reported in 77 patients (55.0%) and 61 patients (43.6%), respectively. The most common TEAE related to IMP or NIMP during the 52-week on-treatment period was hypoglycaemia (PT) (53 patients [37.9%] and 59 patients [42.1%], respectively).

No death occurred in both groups during the study.

During the 16-week on-treatment period, serious TEAEs were reported in 5 patients (1 patient [hypoglycaemic unconsciousness] in the tofogliflozin group and 4 patients [pneumonia in 1 patient, cerebellar infarction and cerebrovascular stenosis in 1 patient, and cataract in 2 patients] in the placebo group).

During the 36-week tofogliflozin on-treatment period in the placebo group, serious TEAEs were reported in 5 patients (gastroenteritis in 2 patients, cellulitis, cardiac failure and myocardial infarction in 1 patient each).

During the 52-week on-treatment period in the tofogliflozin group, serious TEAEs during the 52-week on-treatment period were reported in 4 patients (hypoglycaemic unconsciousness, coronary artery stenosis, spondylolisthesis and ankle fracture in 1 patient each).

During the 16-week on-treatment period, TEAEs leading to permanent treatment discontinuation were reported in 3 patients (2.1%) in the tofogliflozin group (genital infection, diabetes mellitus and cold urticaria) and no patient (0%) in the placebo group. Genital infection and cold urticaria were considered to be related to tofogliflozin. One patient in the tofogliflozin group who experienced genital infection during the 16-week on-treatment period discontinued the IMP during the 36-week open-label treatment period.

During the 36-week on-treatment period in the placebo group, TEAE leading to permanent treatment discontinuation was reported in 1 patient (1.5%) (drug eruption). The event was considered to be related to tofogliflozin.

During the 52-week on-treatment period in the tofogliflozin group, TEAEs leading to permanent treatment discontinuation were reported in 5 patients (3.6%) (genital infection, diabetes mellitus, peripheral arterial occlusive disease, cold urticaria, and blood creatine phosphokinase increased). These TEAEs were considered to be related to tofogliflozin except diabetes mellitus and blood creatine phosphokinase increased.

In the 16-week on-treatment period, any hypoglycemia as per protocol definition (i.e., severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, nocturnal hypoglycemia) was reported in 44 patients (31.4%) in the tofogliflozin group and 15 patients (21.4%) in the placebo group. A total of 26 patients (18.6%) in the tofogliflozin group and 9 patients (12.9%) in the placebo group experienced documented symptomatic hypoglycemia. Severe hypoglycemia occurred in 1 patient (0.7%) in the tofogliflozin group and no patient (0%) in the placebo group. The rate of hypoglycemia in 100 person-year was 102.68 patients (410.73 events) in the tofogliflozin group, and 69.89 patients (232.97 events) in the placebo group.

In the 36-week on-treatment period of the placebo group, any hypoglycemia as per the protocol definition was reported in 20 patients (29.4%). A total of 12 patients (17.6%) experienced documented symptomatic hypoglycemia. Severe hypoglycemia occurred in 1 patient (1.5%) during the 36-week on-treatment period. The rate of hypoglycemia in 100 person-year was 43.37 patients (190.81 events).

In the 52-week on-treatment period of the tofogliflozin group, any hypoglycemia as per the protocol definition was reported in 61 patients (43.6%). A total of 38 patients (27.1%) experienced documented symptomatic hypoglycemia. Severe hypoglycemia occurred in 1 patient (0.7%) during the 52-week on-treatment period. The rate of hypoglycemia in 100 person-year was 45.49 patients (250.57 events).

As for other TEAEs by primary AE group, urinary tract infection (no patient [0%] and 1 patient [1.4%] in the tofogliflozin group and in the placebo group, respectively), genital infection (2 patients [1.4%] and no patient [0%]), skin and subcutaneous tissue disorders (7 patients [5.0%] and 2 patients [2.9%]), excessive urination (10 patients [7.1%] and no patient [0%]) and AEs related to volume depletion (11 patients [7.9%] and 1 patient [1.4%]) were observed during the 16-week on-treatment period.

In the 36-week on-treatment period in the placebo group, urinary tract infection (1 patient [1.5%]), skin and subcutaneous tissue disorders (7 patients [10.3%]), excessive urination (2 patients [2.9%]) and AEs related to volume depletion (5 patients [7.4%]) were observed as other TEAEs by primary AE group. Genital infection was not reported in the 36-week on-treatment period in the placebo group.

In the 52-week on-treatment period in the tofogliflozin group, urinary tract infection (3 patients [2.1%]), genital infection (3

patients [2.1%]), skin and subcutaneous tissue disorders (10 patients [7.1%]), excessive urination (10 patients [7.1%]) and AEs related to volume depletion (14 patients [10.0%]) were observed as other TEAEs by primary AE group. Few patients had post-baseline potentially clinically significant abnormalities (PCSAs) for the laboratory parameters in each treatment group during the 16-week, the 36-week and the 52-week on-treatment period. Only one patient had post-baseline PCSAs for the vital signs (≤ 50 bpm and decrease from baseline ≥ 20 bpm) in the tofogliflozin group during the 52-week on-treatment period.
Issue date: 21-Sep-2017