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Study Protocol

Multicenter, Open Label, Randomized Controlled Superiority Trial for Availability to Reduce Nocturnal Urination Frequency: Study Protocol for a TOP-STAR Study

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Abstract: Nocturia is a common disease in patients with type 2 diabetes mellitus that can reduce the quality of life. Sodium glucose co-transporter 2 (SGLT2) inhibitors increase the urine volume and are often discontinued when polyuria occurs, although tofogliflozin, which has a short half-life in the blood, may improve nocturia by managing hyperglycemia and hypertension, without aggravating nocturia. As excessive sodium intake worsens nocturia and increases urine volume, sodium restriction is also effective in managing nocturia. This multicenter, open-label, randomized parallel-group trial will examine 80 patients with type 2 diabetes who experienced nocturia. After the baseline examination, the patients are randomly stratified into two groups and receive tofogliflozin treatment with or without sodium restriction for 12 weeks. The primary outcome is nocturia frequency at 12 weeks. The secondary outcomes are the frequency of daytime urine, changes in urine volume, and changes in home blood pressure.

Keywords: type 2 diabetes; sodium glucose co-transporter 2 (SGLT2) inhibitors; nocturia; sodium intake

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1. Introduction

1.1. Background and Rationale

Nocturia is a condition of waking up at night to urinate one or more times during the night [1]. The frequency of nocturia in Japan increases with age, reaching 83.8% in men and

76.6% in women in their 60s [2]. Nocturia is caused by several factors, including nocturnal polyuria, cystourethral disturbance, sleep disturbance, and cardiovascular disease, and either one or a combination of these factors may be involved. In addition to age, diabetes mellitus, hypertension, stroke, heart disease, and obesity have been associated with nocturia [3–8]. Approximately 40% of patients with diabetes arise more than twice at night to void [9]. In our KAMOGAWA-DM cohort study [10], according to a questionnaire survey on the frequency of nocturia conducted in 396 patients, 80% had nocturia more than once, while 40% had nocturia more than twice. Nocturia is a common condition in patients with diabetes.

In addition, Hashimoto et al. [11] reported that sleep disorders were a major cause of poorer quality of life (QOL) in Japanese patients with type 2 diabetes (T2D), and more than half of them were frequently awakened by the urge to void. Nocturia is a risk factor for fractures and decreases the survival rate [12].

Sodium glucose co-transporter 2 (SGLT2) inhibitors can improve glycemic control, glycemic variability, and fat loss, as well as prevent heart and renal failure [13,14]. However, concerns have been raised regarding the adverse events of SGLT2 inhibitors, not only dehydration and urinary tract infection, but also polyuria [15]. In fact, frequent uri-nation and polyuria have been the primary reasons for the discontinuation of SGLT2 inhibitor treatment [16].

One SGLT2 inhibitor, tofogliflozin, which has a short half-life, promotes urinary glu-cose excretion during daytime without worsening nocturia [17] and may improve hyper-glycemia and hypertension. As sodium retention exacerbates nocturia by causing non-dipping nocturnal hypertension, SGLT2 inhibitors with a short half-life could im-prove nocturia by increasing the daytime excretion of sodium [18].

Therefore, to correct and prevent the worsening of nocturia, not only medication but also restriction of dietary salt intake should be considered. Reduction in sodium intake can decrease the frequency of nocturia, nocturnal urine volume, and nocturnal polyuria index; patients with nocturia accompanied by nocturnal polyuria should control their sodium intake.

The observational study in Japan, nocturia volume, the frequency of nocturia, and nocturnal polyuria index were evaluated after 12 weeks of dietary guidance in patients who experienced one episode of nocturia, exceeding the maximum daily salt intake (8 g for men and 7 g for women). This study reported that nocturia frequency, urine volume, and nocturnal polyuria index improved in the group of participants who had been successful in restricting salt intake [19,20].

As mentioned above, various factors constitute nocturia, such as nocturnal hyperglycemia, excessive salt intake, and nocturnal hypertension; in particular, non-dipper-type nocturnal hypertension and heart failure are the risk factors for nocturia [21–23].

Nocturia should be managed with both medication and salt intake restriction in order to correct and prevent the exacerbation of nocturia; however, no study has evaluated the effect of a combination of salt intake restriction and SGLT2 inhibitor treatment on nocturia. It would be significant to examine the effect of tofogliflozin, an SGLT2 inhibitor with the shortest half-life, on nocturia in patients with T2D, and whether tofogliflozin treatment could be effective in combination with sodium restriction.

1.2. Objectives

1.2.1. Primary Objectives

The primary aim of this study is to evaluate the effect of tofogliflozin on nocturia in patients with T2D and to examine the efficacy of tofogliflozin with or without dietary sodium restriction on nocturia at 12 weeks after interventions.

1.2.2. Secondary Objectives

The secondary aim of this study is to assess below items at 12 weeks after interventions.

1. Frequency of urination during the day
2. Change in ratio of urinary volume at night to 24 h
3. Change in urine volume at night

4. Change in urine volume during the day
5. Change in total urinary sodium excretion and other urinalysis
6. Change in the results of blood tests
7. Change in home blood pressure at night
8. Change in body composition test
9. Change in questionnaire score (The Diabetes Treatment Satisfaction Questionnaire, status version, DTSQs score; Diabetes Diet-Related Quality of Life Revised, DDRQOL-R; Brief-type Self-administered Diet History Questionnaire, BDHQ; Core Lower Urinary Tract Symptoms score, CLSS)
10. Incidence of adverse events and diseases

2. Methods

2.1. Trial Design

This is a multicenter, open-label, randomized parallel group trial [Efficacy of dual therapy of TOfogliflozin and dietary instruction of sodium restriction in T2D patients with nocturia: A multicenter open-label randomized controlled superiority trial of the availability to reduce nocturnal urination frequency (TOP-STAR Study)] (Figure 1). Eighty patients with T2D and nocturia will be included in the study and randomly stratified into two groups.

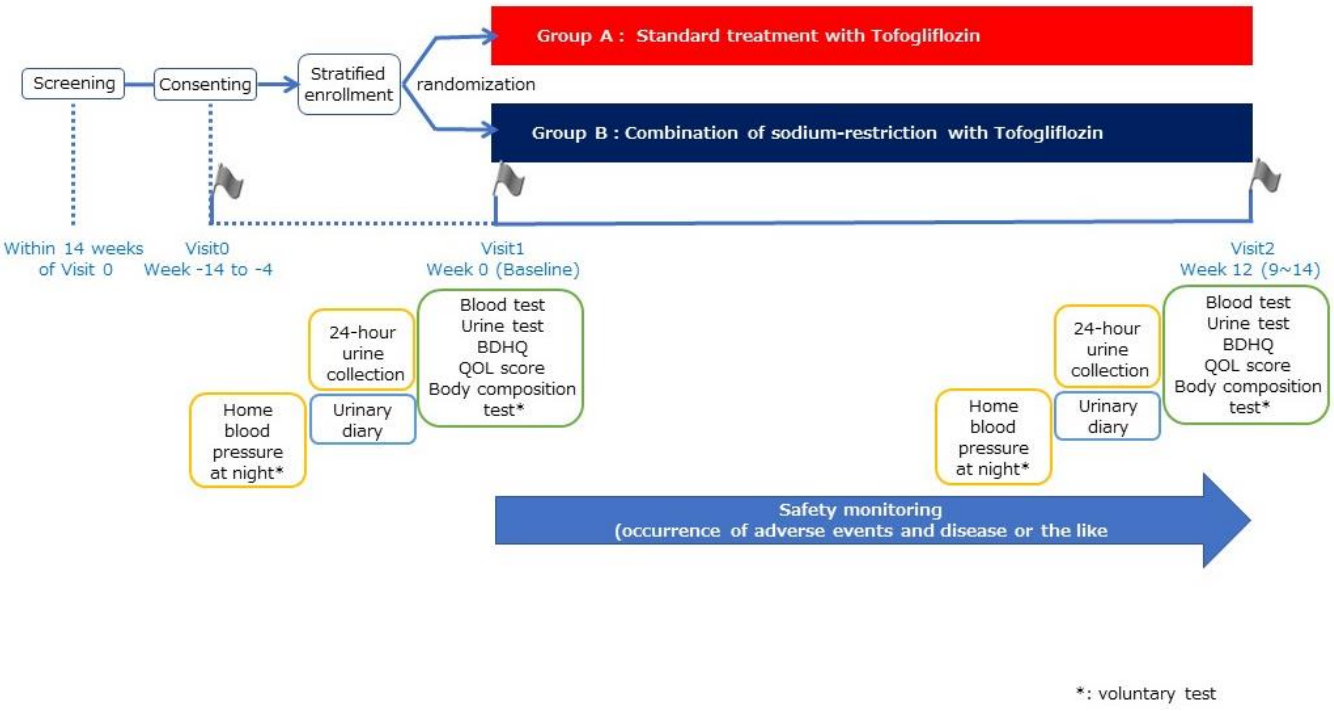

Figure 1. Study design of TOP-STAR study.

2.2. Eligibility Criteria, Recruitment, and Sample Size

Inclusion and exclusion criteria were established according to the study objectives and to ensure participant safety (Table 1).

This study will be conducted in 18 research institutions. In the previous study [20], the frequency of nocturia improved from 2.3 ± 0.9 times per day at baseline to 1.4 ± 1.0 times per day after 12 weeks in the group of participants who were successful in restricting salt intake. In the group of participants who were not successful in restricting salt intake, the frequency of nocturia did not improve (from 2.3 ± 1.1 days at baseline to 2.7 ± 1.1 days after 12 weeks). In this study, the frequency of nocturia was 2.3 ± 1.0 days in both groups at baseline, it remained unchanged (2.3 ± 1.0 days) in the tofogliflozin monotherapy group, and it was 1.3 ± 1.0 days in the combination group that received sodium restriction

guidance after 12 weeks. Under these conditions and at a significance level of 5% in both groups, 10,000 tests were required to determine the differences in nocturia frequency between the groups after 12 weeks as shown in the results of Poisson regression analysis using data assuming a Poisson distribution. Therefore, the minimum number of patients required for this study was 36 patients per group. In addition, assuming a dropout rate of 10% during the study period, the target number of participants to be enrolled in this study was 40 patients per group or 80 patients in two groups.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	
Patients with all of the following criteria will be considered	
1	Patients with type 2 diabetes
2	Patients with nocturia more than once
3	Male and female between the ages of 20 and 90 at the time of obtaining consent
4	Patients who provide their consent in a written form
Exclusion criteria	
Patients who meet any of the following criteria are not eligible to the study	
1	Patients who use SGLT2 inhibitor at least 3 months prior to giving their content
2	Patients who have already been instructed by a nutritionist of sodium-restriction
3	Patients with an estimated sodium intake of less than 6 g/day by urinalysis at the time of obtaining consent
4	Patients for whom tofogliflozin is contraindicated
5	Patients whose HbA1c is 10.5% or higher within 3 months
6	Patients with eGFR less than 15 mL/min/1.73 m^2 or serum creatinine higher than 3.5 mg/dL or with hemodialysis
7	Patients with low blood pressure (less than 100/60 mmHg)
8	Patients with unstable hypertension
9	Patients with activities of daily living (ADL) of PS2 or higher
10	Patients with heart failure classified as New York Heart Association (NYHA) category III or IV
11	Patients being pregnant or planning to become pregnant.
12	Patients suffering from cancer. However, the treatment has been completed and/or the cancer has not recurred and/or is becoming apparent
13	Patients with anemia (Hb is 10 g/dL or less) caused by primary diseases other than diabetic nephropathy
14	Patients with hypoalbuminemia (serum albumin is 3.5 g/dL or less) caused by primary diseases other than diabetic nephropathy
15	Patients with nephrotic syndrome (less than 3.0 g/dL of serum albumin and more than 3.5 g/day of urinary protein) due to primary disease except diabetic nephropathy
16	Patients judged to be non-adherent by the attending physician
17	Patients who require substitute to obtain consent
18	Patients deemed inappropriate by the attending physician

2.3. Interventions

2.3.1. Random Grouping and Intervention Description

The participants are randomly assigned in different groups [Group A: standard treatment group]. Randomisation will be provided by a computer-generated program at the EviPRO Holdings Inc. (Tokyo, Japan). The study participants are administered with tofogliflozin 20 mg orally once a day before or after breakfast. The duration of tofogliflozin administration is 12 weeks (9–14 weeks) [Group B: group with dietary sodium restriction]. In addition to the oral administration of 20 mg of tofogliflozin once a day before or after breakfast, a nutritionist provides instructions on sodium restriction. The duration of tofogliflozin treatment is 12 weeks (9–14 weeks). SGLT2 inhibitor treatment is initiated on

day 0 of the observation period. The study participants are requested to visit the research institutions at weeks 0 and 12, in addition to the date of obtaining consent.

2.3.2. Details of Instruction on Sodium Restriction

The nutritionist provided dietary instructions, with a target sodium intake of 6 g/day. In addition, for both groups, the target weight and amount of energy and protein in the diet were based on the nutritional guidelines that the patients received.

2.3.3. Details of Other Dietary Instruction

In both groups, the patients are instructed to stay properly hydrated to prevent dehydration (avoid excessive drinking or excessive water conservation).

Energy level: 25–35 kcal/kg/day for physical activity multiplied by the target weight.

Protein restriction: 0.8–1.0 g/kg/day (stage 3 diabetic nephropathy) and 0.6–0.8 g/kg/day (stage 4 diabetic nephropathy).

2.3.4. Observation Items

A baseline examination will be conducted prior to the intervention. The observations and schedules are presented in Tables 2 and 3. Generally, research participants will visit the research institution and undergo blood and urine tests at every visit.

Table 2. Observation items.

1. Eligibility information	
Observation point	At consenting and enrollment
Observation item	Inclusion criteria, exclusion criteria, gender, age, date of giving consent
2. Background information	
Observation point	At consenting, enrollment, or week 0
Observation item	Gender, age, height, weight, body mass index, duration of diabetes, presence of comorbidities (presence/absence of macrovascular/microvascular complications, renal disease, hepatic disease, hypertension, dyslipidemia), and history of illness (history of cardio-cerebrovascular disease)
3. Medication information	
Observation point	Week 0 and week 12
Observation item	Medications for diabetes, daily dosage, and other concomitant medication
4. Blood tests (fasting)	
Observation point	Week 0 and week 12
Observation item	Red blood cell count, white blood cell count, hematocrit, hemoglobin, estimated plasma volume, blood platelet count, hepatic enzymes (AST, ALT, serum albumin, LDH, gamma-GTP, ALP), UA, BUN, Cre, eGFR, T-Chol, HDL, LDL, TG, serum Na/K/Cl, HbA1c (or glycoalbumin), and plasma glucose
5. Special blood tests (fasting, using residual sample of "6 blood tests")	
Observation point	Week 0 and week 12
Observation item	Total ketone body, beta-hydroxybutyric acid, acetoacetic acid, and plasma metabolome^{++}
6. Urine tests (total)	
Observation point	Week 0 and week 12
Observation item	Specific gravity, pH, protein, glucose, ketone body, occult blood, bilirubin, urobilinogen, u-mAlb, U-Cre, and U-Na/K/Cl
7. Body composition test (optional test)	
Observation point	Week 0 and week 12
Observation item	Skeletal muscle mass, skeletal muscle mass to total body weight ratio, and fat mass

Table 2. *Cont.*

8. QOL score (questionnaire to whom the participants directly answer)	
Observation point	Week 0 and week 12
Observation item	• The Diabetes Treatment Satisfaction Questionnaire, status version (DTSQs) score. DTSQs are questionnaires used for measuring the patients' satisfaction to treatments specific for diabetes mellitus, are implemented worldwide, and consists of 8 questions. • Diabetes Diet-Related Quality of Life Revised (DDRQOL-R) This questionnaire consists of nine items. It is used to determine the diabetic patients' level of satisfaction regarding their diet and quality of life in relation to the changes in their dietary habits. • Brief-type Self-administered Diet History Questionnaire (BDHQ) A questionnaire designed to quantitatively and precisely examine the status of nutrients and food intake. • Core Lower Urinary Tract Symptoms score (CLSS). It is a 10-item questionnaire developed in Japan to investigate significant urinary tract symptoms.
9. Other items that the participants should measure on their own: Urinary diary	
Observation point	Week 0: conducted within 7 days after obtaining consent until the observation period week 0. Urine volume will be measured for 3 days; week 12: conducted within 7 days before observation point week 12. Urine volume will be measured for 3 days.
Observation item	Time of going to bed, time of waking up, time of urination, frequency of urination, volume of urine, and alcohol consumption The study participants store urine using a measuring cup.
10. 24 h urine collection test	
Observation point	Week 0 (24 h before the observation point) and week 12 (24 h before the observation point)
Observation item	Time of going to bed, time of waking up, volume of urine, volume of urine at night, plasma glucose, urinary creatinine excretion for 24 h, and urinary sodium excretion for 24 h The study participants store urine using a measuring cup and dispense a small portion of this urine into a spit.
11. Home blood pressure at night	
Observation point	Week 0 (5 days before observation point. Urine volume will be measured 3 times a day for 3 days), week 12 (conducted within 7 days before observation point week 12, 3 times each day) Conducted in a period that is different from the urinary diary period
Observation item	Home blood pressure at night: The participants measure their blood pressure three times at night using an upper arm blood pressure monitor (Omron HEM-9601T) (automatic measurement). The participants record the results in their diaries.
12. Adherence to research medication regimen and sodium restriction	
Observation point	Week 12
Observation item	The research physician conducts an interview to collect data regarding the patient's medication status and adherence with sodium restriction, and record the collected data in the CRF.

Additionally, nocturnal home blood pressure measurements will be taken three times a day for five days. Next, the urinary frequency will be recorded for 7 days, and urine volume will be measured using a measuring cup for 3 days. In addition to the blood and urine tests, scores on the Japanese version of the Diabetes Treatment Satisfaction Questionnaire, status version (DTSQs) score, Diabetes Diet-Related Quality of Life Revised (DDRQOL-R), Brief-type Self-administered Diet History Questionnaire (BDHQ), and Core Lower Urinary Tract Symptoms score (CLSS) will be assessed using a patient questionnaire. DTSQs are questionnaires used for measuring the patients' satisfaction to treatments specific for diabetes mellitus, are implemented worldwide, and consists of 8 questions [24]. DDRQOL-R consists of nine items. It is used to determine the diabetic patients' level of satisfaction

regarding their diet and quality of life in relation to the changes in their dietary habits [25]. BDHQ designed to quantitatively and precisely examine the status of nutrients and food intake [26]. CLSS is a 10-item questionnaire developed in Japan to investigate significant urinary tract symptoms [27].

Table 3. Observation schedule.

Observation Items	Enrollment	Baseline Week 0 *1	Week 12 (Week 9–14) or at Discontinuation *2
Obtaining consent	○		
① Eligibility information	○		
② Background information		○	
③ Medication information		○	○
④ Blood tests		○	○
⑤ Special blood tests		○	○
⑥ Urine tests		○	○
⑦ Body composition		▲	▲
⑧ Questionnaire		○	○
⑨ Urination log		○	○
⑩ 24 h urine collection		○	○
⑪ Nocturnal home blood pressure		▲	▲
⑫ Compliance with drug regimen/Compliance with sodium restriction			○
⑬ Adverse event and disease or the like		←○→	

○ Item is required to be observed at indicated observation. ▲ Item is optionally observed at indicated observation period/observation point. *1 The observation points at week 0 could be conducted on the same day as enrollment. However, it must be conducted prior to the initiation of the intervention and prior to the instruction on sodium restriction. *2 In the event of discontinuation, collect as much information as possible up to this point.

2.4. Criteria for Discontinuing or Modifying Allocated Interventions

2.4.1. Criteria and Coping Strategies for Study Discontinuation

If the investigator judges that it is difficult to continue the clinical trial for any of the following reasons, the investigator will immediately take necessary measures such as discontinuing the administration of the study drug. Patients' data will be used as data of a "study discontinuation case." The investigator will note the date, when the study started, the reason for withdrawal, and the process on the card and on the case report form (CRF). At the time of discontinuation, the necessary tests will be conducted. The efficacy and safety the procedure will be assessed at this point. Moreover, investigators will evaluate the efficacy and safety of the treatment, following up on the endpoints and analyzing the safety of the medical treatment received.

2.4.2. Criteria for Discontinuation of Study in Each Participant

(1) A study participant voluntarily withdraws from the study or withdraws her or his consent.

(2) Discontinuation of the study is required due to the occurrence of adverse events and diseases.

(3) The continuous use of the study agent worsens the primary disease or causes complications.

(4) Patients have remarkably poor adherence with medication or sodium intake restrictions (the medication rate is estimated to be less than 60% or higher than 120% of the expected dosage).

(5) The study participant is found pregnant.

(6) A serious deviation from the research protocol occurs, which is judged to have a significant impact on the research results.

(7) The investigators have decided that the discontinuation of the study is appropriate due to other reasons.

2.4.3. Criteria for Discontinuation of Study

(1) When continuation of the study is difficult for any of the following reasons, the principal investigator will determine whether the study could be continued or not. When it is determined that continuation is inappropriate, the principal investigator shall inform the principal investigators of all collaborating institutions of the reasons for the discontinuation and how to deal with the participants, and have them take the necessary actions. The principal investigator shall inform the accreditation review committee in written form of the discontinuation of the study.

(1-1) Significant information regarding the efficacy, safety and quality of the study agent was obtained.

(1-2) Participant recruitment and the planned number of study participants were difficult to achieve.

(1-3) Protocol modification was instructed but was not executed.

(2) When discontinuing a study, the investigator should immediately discontinue the study and report the decision to the president of his/her institution. The principal investigator must also take appropriate action promptly and notify the participant of the decision to discontinue the study.

2.4.4. Coping with Adverse Events

SGLT2 inhibitors can cause dehydration, urinary tract infections, normoglycemic ketoacidosis, and polyuria, and we carefully explain the possibility of these side effects at the recruitment of previous study. If a study participant suffers an adverse event during the study which may or may not be attributable to the SGLT2 inhibitor, the investigator will promptly take appropriate medical treatment. Investigators should report the adverse event to the responsible investigator and director of the institution and document the necessary information on the medical carte and CRF according to the study protocol. If it is necessary to interrupt the administration of study drug or medical treatment due to an adverse event, the study participant should be briefed on how to manage serious adverse events [SAEs].

2.5. Deviation from the Protocol

The investigator shall document in the carte and CRF any deviation or modification from the study protocol that is necessary to avoid immediate risk to study participants or for other compelling medical reasons, and the details and reasons for such deviation or modification shall be stated in the Carte and CRF. Study participants will be followed up throughout the study. If the investigator is unable to follow the protocol exactly, he/she should continue to collect sufficient information for the study. Data handling will be determined by the data handling committee in a blinded situation.

2.6. Management of Incompatibility

Incompatibility refers to non-compliance with legal regulations or operational protocols, fabrication and falsification of test data. The management of incompatibility shall be performed as follows:

1. When the responsible investigator becomes aware of the incompatibility of present study, the responsible investigator must immediately report this fact to the principal investigator.
2. When the investigator becomes aware of the non-conformity of the study, the investigator immediately reports this fact to the responsible investigator.
3. When there are serious incompatibilities, the investigator must immediately ask the accreditation review committee members for their opinions.

2.7. Strategies to Improve Adherence to Interventions

2.7.1. Management of the Study Agent

No placebo will be used in this study. Both groups will use commercially available, approved drugs for the study. Additionally, this is an open-label study. Therefore, specific management of the study agent is not conducted, and the study agent is managed in the same manner as general drugs.

2.7.2. Outcomes

The investigators collect and enter the results of the examinations list in Table 2 in the CRF and send the CRF to the data center. Adverse events are considered as safety endpoints throughout the study. The items measured by the study participants themselves are recorded in specific documents and sent to the data center by the investigators.

2.8. Data Collection and Management

2.8.1. Plans for Assessment and Collection of Outcomes

Original Documents

The research institution preserves and manages the following information as original source documents, and responds to monitoring, audits, and certifying review committees' requests.

1. Original documents for all data items (medical data, nurse records, drug records, laboratory data, subject logbooks, CRFs, QOL questionnaires, etc.).
2. Records of informed consent indicating the patient's agreement to the study participation.

2.8.2. Documents to Be Served as Source Documents

In addition to the original source documents, the research institution preserves and controls the information described below as source documents and provides them to the monitoring, accreditation review committees, and audit.

1. Withdrawal of consent form.
2. Medication adherence information.
3. Adverse event and disease information.

2.8.3. Data Management and Confidentiality

Central registry numbers will be used to identify study participants. When electronic data on subjects are transferred, the consent of the data management must be obtained. If data are transferred from an unsecured electronic network, encryption of the data must be performed at the source. If the data center needs to provide participant data to other research institutions, approval from the principal investigator and data management is required. Plan for collection, laboratory evaluation, and preservation of biospecimens for genetic or molecular analysis for the study/future use.

All involved individuals in this study are required to protect the personal information of the study participants. We will conduct this study in compliance with the Personal Information Protection Act and other applicable laws and regulations. Study participant's unique information (medical record number, initials) will be securely contained within the research institution, and information that would allow someone external to the research organization to recognize the study participant (name, phone number, address, etc.) will not be included in the CRF or registry database.

The researcher will use the correspondence table to identify the research participant (anonymization) and will maintain it privately. Correspondence sheets will be securely stored and appropriately managed by the researcher for the retention period specified by the Clinical Trials Act (until the day after five years have elapsed from the date of study completion) or the retention period specified by each research institute, whichever is later. Anonymized data acquired for analysis will be preserved for any future secondary research,

such as meta-analyses. Prior approval from the Ethics Review Committee is required before anonymized data will be used for further research.

Specific blood test samples will be assayed in laboratories made available by each research organization and will be disposed of after data acquisition under the responsibility and procedures of the respective companies.

2.9. Patient and Public Involvement Statement

Patients will not be included in the research design, selection of the study questions, or measurement of the results. No participants will be included in the analysis or publication of the results. Patients will receive a brief summary of the study results written in Japanese after the completion of the study.

2.10. Statistical Methods

2.10.1. Analysis of the Primary Endpoint

The primary and secondary endpoints are analyzed using the full analysis set and, if necessary, using the per-protocol set (PPS). The safety endpoints are analyzed in the safety analysis population. The two-sided significance level of the analysis was set at 5%. The person in charge of the statistical analysis is responsible for preparing a separate statistical analysis plan and specifying the details of the statistical method, including data handling. A statistical analysis plan is prepared prior to data fixation. If changes were made to the original analysis plan, the statistical analysis plan should be revised with a revision history, and the changes should be recorded.

The primary endpoint is the frequency of nocturia at 12 weeks, and the difference between groups is evaluated to determine its statistical significance. Poisson regression analysis (generalized linear model assuming a Poisson distribution) is performed with group as the fixed effect and the allocation adjustment factors and days of nocturnal voiding at baseline as covariates to test the following null hypothesis: that the days of nocturnal voiding in the two groups are equal. The summary statistics (number of cases, minimum, median, and maximum, mean, standard deviation) are calculated for each time point and each group.

2.10.2. Analysis of the Secondary Endpoints

With regard to the primary endpoint, the frequency of urination during the day is assessed for statistical significance using Poisson regression analysis with group as the fixed effect and the allocation adjustment factor and baseline value as covariates. For the other change endpoints, group differences are evaluated using analysis of covariance with the group as the fixed effect and allocation adjustment factors and baseline values as covariates. In addition, the summary statistics of the measurements and changes at each time point for each endpoint are calculated for each group. The incidence of adverse events and diseases are analyzed as part of the safety endpoints.

2.10.3. Methods for Additional Analyses (e.g., Subgroup Analyses)

For the primary and secondary endpoints, the combined salt intake restriction guidance group (tofogliflozin plus salt intake restriction guidance group) is subdivided into a successful salt reduction group and an unsuccessful salt reduction group, and the three groups are compared with the standard treatment group (tofogliflozin group). The details are described in a separate statistical analysis section.

Methods used for analyzing the protocol nonadherence and any statistical methods used for handle missing data

Data on protocol non-compliance will not be part of the per-protocol population analysis, but will be part of the full analysis.

2.11. Ethics and Dissemination

2.11.1. Data Handling Committee

The data handling committee will be responsible for processing all data, both missing data and data departing from the protocol, in a blinded manner prior to statistical analysis. The committee consist of the principal investigator, responsible officer, and a biomedical statistics expert.

2.11.2. Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

Third-party institution (Evipro Holdings Corporation) will conduct the monitoring according to the standard operating procedures for monitoring. The responsible investigator will regularly monitor the persons in charge of data quality and investigate whether the study is being conducted in compliance with the research protocol, ethical guidelines for medicine, and the Clinical Trials Act, as well as the progress of the study by taking appropriate measures to ensure compliance with the protocol. Monitoring personnel is tasked to provide a monitoring report and submit it periodically to the principal investigator. The adverse events and diseases are monitored and promptly reported to ensure the safety of the study participants.

2.12. Adverse Event Reporting and Harms

2.12.1. Reporting of Adverse Events

Adverse events outside of SAEs will be reported by noting them on the CRF associated with those occurrences and sending it to the data center. The data center shall summarize the appropriate report and inform the responsible investigator and receive instructions on how to handle the event. The investigational drug manufacturer/distributor (Kowa Company, Ltd., Aichi Japan) will also be notified.

2.12.2. Frequency and Plans for Auditing Trial Conduct

EviPRO Holdings, a third-party institution, will conduct the audits. Audits will be performed according to the protocol and Standard Operating Procedures to ensure compliance with the study protocol. The results of the audit will be reported by the auditor to the investigator, other investigator.

2.12.3. Dissemination Plans

Results of the study will be reported in peer-reviewed international journals.

3. Discussion

This study was designed based on the hypothesis that SGLT2 inhibitors, which are anti-diabetic drugs with cardioprotective and renal protective effects, may relieve nocturia not only by improving hyperglycemia and hypertension, but also by increasing daytime sodium excretion, with a focus on managing polyuria and nocturia, which are common complaints of patients with type 2 diabetes. In addition, comparing the efficacy of SGLT2 inhibitors alone with that of salt restriction combined with SGLT2 inhibitors is meaningful as it will enable the researchers to examine the efficacy and superiority of each treatment for nocturia. In addition, the long-term intention of this study is to improve health quality of life through the improvement of nocturia, hoping that this will lead to an improvement in the overall health of the patients.

In this pilot study, the frequency of nocturia is the primary endpoint, while the frequency of urination during the day and change in urine volume as secondary endpoints, which provides insight into the effect of SGLT2 inhibitors and sodium restriction on urination frequency and volume. This finding will be essential for developing future randomized trials.

In previous observational studies, the frequency of nocturia, urine volume, and nocturnal polyuria index improved in patients who successfully restricted salt intake, but nocturia did not improve in patients with unsuccessfully restricted salt intake by nearly 70% of

the time. SGLT2 inhibitors are effective in preventing the progression of macrovascular disease and diabetic complications, and their use is expected to increase in the future. However, SGLT2 inhibitors have some disadvantages, such as nocturia; hence, we hope that this study will expand the possibilities of SGLT2 inhibitors. In previous observational studies, the frequency of nocturia, urine volume, and nocturnal polyuria index improved in patients who successfully restricted salt intake, but nocturia did not improve in patients with unsuccessfully restricted salt intake by nearly 70% of the time. SGLT2 inhibitors are effective in preventing the progression of macrovascular disease and diabetic complications, and their use is expected to increase in the future. However, SGLT2 inhibitors have some disadvantages, such as nocturia; hence, we hope that this study will expand the possibilities of SGLT2 inhibitors.

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Institutional Review Board Statement: This study was registered with the Japan Clinical Trial Registry (jRCTs051210212) and was approved by the ethics committees of the Kyoto Prefectural University of Medicine (CRB5200001). The TOP-STAR study is to be conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Written informed consent has been obtained from all the participants.

Data Availability Statement: Data will not be publicly available.

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