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Impact of the SGLT2 inhibitor empagliflozin on urinary supersaturations in kidney stone formers (SWEETSTONE trial): protocol for a randomised, double-blind, placebo-controlled cross-over trial

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ABSTRACT

Introduction Kidney stones are a global healthcare problem. Given high recurrence rates and the morbidity associated with symptomatic stone disease, effective medical prophylaxis is clearly an unmet need. Explanatory analyses of randomised controlled trials with sodium/glucose cotransporter isoform 2 inhibitors indicated a 30%–50% reduced rate of stone events in patients with diabetes. Underlying mechanisms remain unclear. We aim to determine the effect of empagliflozin on urinary supersaturations in non-diabetic kidney stone formers to evaluate their therapeutic potential for recurrence prevention. We will provide first clinical trial evidence on whether urinary supersaturations are affected by empagliflozin in kidney stone formers.

Methods and analysis The SWEETSTONE trial is a randomised, double-blind, placebo-controlled, cross-over, exploratory study to assess the impact of empagliflozin on urinary supersaturations of calcium oxalate, calcium phosphate and uric acid in kidney stone formers. We plan to include 46 non-diabetic adults (18–74 years) with ≥1 past kidney stone event and stone composition with ≥80% of calcium or ≥80% of uric acid. Patients with secondary causes of kidney stones or chronic kidney disease will be excluded. Eligible individuals will be randomised in equal proportions to receive either a 14-day treatment with 25 mg empagliflozin followed after the 2–6 weeks wash out period by a 14-day treatment with a matching placebo or the reverse procedure. Secondary outcomes will include electrolyte concentrations, renal function, mineral metabolism and glycaemic parameters, urinary volume and safety.

Results will be presented as effect measures (95% CIs) with p values and hypothesis testing for primary outcomes (significance level 0.02).

Ethics and dissemination The SWEETSTONE trial was approved by the Swiss ethics committee and Swissmedic. First results are expected in the fourth quarter of 2022.

Trial registration number NCT04911660; Pre-results.

Strengths and limitations of this study

- First study that investigates the effect of empagliflozin on urinary supersaturations in kidney stone formers.
- Randomised, double-blind, placebo-controlled, cross-over study design.
- Preliminary data will be key to establish the relevance for larger trials assessing the prophylactic potential of empagliflozin in kidney stone disease.
- Single centre exploratory approach including 46 participants.

INTRODUCTION

Kidney stones constitute a worldwide healthcare challenge with a current lifetime risk of ~18.8% in men and ~9.4% in women in Western civilisations.[1–3] Recurrence rates are high, up to 40% and 75% at 5 and 10 years, respectively.[4 5] Hospitalisations, surgery and lost work time associated with kidney stones cause enormous healthcare-related expenditures.[6]

The presence of a solute at a concentration above its own solubility, a phenomenon called supersaturation, is the driving force of kidney stone formation. Relevant supersaturations for kidney stone disease in humans include calcium oxalate, brushite (calcium phosphate) and uric acid.[7] At a supersaturation >1 crystals form, at a supersaturation <1 crystals dissolve.[8] Urinary supersaturations calculated from ambulatory 24-hour urine collections accurately reflect long-term average supersaturation values in urine and are highly correlated with the kidney stone composition[9 10] encountered in kidney stone formers.[7] Treatments that reduced stone

events in randomised controlled trials (RCTs) were highly correlated with reductions in urinary supersaturations.[9 11] A recent analysis of a large 5-year kidney stone RCT revealed that as early as 1 week after randomisation, every 10% reduction of urinary calcium oxalate supersaturation from baseline was associated with an 8% reduction in the risk of stone recurrence during follow-up.[10]

Although kidney stone disease is traditionally considered an isolated renal disorder, there is overwhelming evidence that it is in fact a systemic disease. Arterial hypertension,[12 13] obesity,[14 15] diabetes mellitus,[16 17] gouty diathesis, dyslipidaemia, cardiovascular disease,[18] chronic kidney disease[19] and low bone mass[20] are much more prevalent in kidney stone formers than in non-stone formers. It is currently unknown if kidney stone disease is a cause or a consequence of these comorbidities. Clearly, however, these comorbidities contribute significantly to stone-related morbidity and mortality.[14–20]

Inhibitors of the sodium/glucose cotransporter isoform 2 (SGLT2) encoded by *SLC5A2* belong to a new class of oral hypoglycaemic drugs.[21] SGLT2 resides in the brush border membrane of proximal tubular cells in the kidney and reabsorbs ~90% of glucose filtered at the glomerulus.[22] SGLT2 inhibitors, such as empagliflozin, block the physiological glucose reabsorption in the proximal tubule from the glomerular filtrate, thereby inducing significant glucosuria accompanied by a reduction of blood glucose levels. Due to their unique mode of action, SGLT2 inhibitors induce weight loss, decrease blood pressure and increase urinary volume, the latter being a very effective measure to reduce stone recurrence.[8 9 23 24] Furthermore, empagliflozin has been proven to decrease cardiovascular mortality, death from any cause, hospitalisations for heart failure, decline of glomerular filtration rate and need for renal replacement therapy in patients with type 2 diabetes.[25 26] Some of these findings were also observed with two other SGLT2 inhibitors, canagliflozin[27] and dapagliflozin,[28] in large outcome trials.

Detailed analyses for kidney stone events in empagliflozin outcome trials have not been reported. However, in pooled analyses of phase I, II and III trials, the rate of kidney stone events tended to be 30%–50% lower in patients treated with 10 or 25 mg empagliflozin vs placebo.[29 30] This observation is remarkable as reported stone event rates in participants of these pooled empagliflozin trials (0.5–1/100 person years) were 10–100 fold lower compared with patients with established kidney stone disease.[31 32] Stone event rates in these pooled empagliflozin trials were similar to what has been observed in the general population in individuals with diabetes in three large prospective US cohorts (Nurses' Health Study I, the Nurses' Health Study II and the Health Professionals Follow-up Study).[16] RCTs testing dietary or pharmacologic measures for recurrence prevention typically included patients with stone event rates between 20 and 200 events/100 person-years.[33 34] Hence, if recurrence prevention of kidney stones by SGLT2 inhibitors will indeed prove effective and safe, individuals with high rates of stone formation would especially benefit from treatment.

Taken together, these observations strongly suggest that SGLT2 inhibitors could effectively reduce the risk of urinary supersaturations. However, while the effect of SGLT2 inhibitors on blood electrolyte and mineral metabolism parameters have been studied in detail in healthy volunteers and patients with diabetes, there is a lack of data on the impact of SGLT2 inhibition on urinary parameters, especially on parameters that influence the kidney stone formation rate. Also, to our knowledge, no studies have been conducted thus far with SGLT2 inhibitors specifically in kidney stone formers.

The SWEETSTONE clinical trial addresses the effect of SGLT2 inhibitors on urinary supersaturations in kidney stone formers. We plan to use empagliflozin, the clinically best characterised SGLT2 inhibitor to date with the most favourable side effect profile. Due to their pleiotropic effects, SGLT2 inhibitors are currently widely tested in non-diabetic populations (www.clinicaltrials.gov). Patients without diabetes constitute by far the largest group among kidney stone formers. Therefore, we decided to recruit non-diabetic stone formers in the SWEETSTONE trial to examine the largest target population.

As far as safety is concerned, therapy with SGLT2 inhibitors is generally well tolerated. An increased incidence of genital infections and (although rare) euglycaemic ketoacidosis are known side effects.[35] The latter is mainly observed in patients with type I diabetes and less frequently in those with type 2 diabetes. To the best of our knowledge, no cases of euglycaemic ketoacidosis in individuals without diabetes treated with SGLT2 inhibitors have been reported. In the large canagliflozin outcome study CANVAS, an increased incidence of lower extremity amputations at the level of the toe or metatarsal was noted.[27] This adverse effect, of which the mechanism is unknown, has not been reported with other SGLT2 inhibitors. However, caution is needed in patients at risk for amputation. Canagliflozin and dapagliflozin have been associated with an increased risk of bone fractures compared with placebo.[36 37] Canagliflozin increased serum phosphate, plasma fibroblast growth factor 23 (FGF23) and plasma parathyroid hormone (PTH) and decreased the level of 1,25-dihydroxyvitamin D in a short term study in healthy volunteers.[38] Similar results were obtained in individuals with diabetes treated with dapagliflozin (54). In contrast, pooled analyses of phase I, II and III trials of patients with type 2 diabetes treated with empagliflozin encompassing >15 000 patient-years of exposure did not reveal an increased rate of bone fractures, alterations of blood electrolytes, PTH, 25-dihydroxyvitamin D or bone turnover markers.[29 30 39]

In summary, SGLT2 inhibitors represent a promising new drug class for kidney stone formers. They may considerably decrease stone formation. In addition, kidney stone formers are likely to benefit from the metabolic and cardiovascular effects of SGLT2 inhibition. Clearly, there

is a direct need for clinical studies with SGLT2 inhibitors in kidney stone formers.

METHODS AND ANALYSIS

Study objectives

Overall objective

The SWEETSTONE trial aims to evaluate whether empagliflozin has therapeutic/prophylactic potential in non-diabetic kidney stone formers.

Primary objective

To determine the effect of empagliflozin on urinary supersaturations as an indicator of the therapeutic /prophylactic potential of this drug in kidney stone formers.

Secondary objectives

To determine the impact of SGLT2 inhibition on urinary and blood parameters.

Safety objectives

Even though the small sample size does not allow for a conclusive safety profiling, we will collect and analyse vital signs, serious adverse events (SAEs) and adverse events of special interest (AESIs).

Study outcomes

Primary outcome

We will address the primary objective by evaluating three primary outcomes. We will assess each of these outcomes separately as they reflect different mechanisms and are of potential (clinical) relevance for later trials.

i. Calcium oxalate supersaturation.
ii. Brushite (calcium phosphate) supersaturation.
iii. Uric acid supersaturation.

Urinary supersaturations will be calculated by the Equil-2 programme.[7 33]

Secondary outcomes

We will assess the following parameters relevant to the secondary objectives:

i. Blood: sodium, potassium, chloride, calcium total and ionised, magnesium, phosphate, osmolality, glucose, albumin, creatinine, urea, uric acid, blood gas analysis, 25 hydroxy and 1,25 dihydroxy vitamin D, PTH, FGF23, hemoglobin A1c, lipid panel, thyroid-stimulating hormone.
ii. Twenty-four-hour urine: sodium, potassium, chloride, calcium, magnesium, phosphate, osmolality, glucose, protein, albumin, creatinine, urea, uric acid, oxalate, citrate, sulfate, ammonium, titratable acidity (TA), pCO2, pH, bicarbonate. Bicarbonate will be calculated by the Henderson-Hasselbalch equation, TA will be calculated by the Equil-2 programme.[7 33]

Safety outcomes

Safety will be described using the following parameters:

(1) SAEs:

We will collect, fully investigate and document all SAEs in the source documents and the electronic case report forms (eCRFs) for all participants from the date of signature of the informed consent form until the last protocol-specific procedure has been completed, including a safety follow-up period of 4 weeks. The definition on what constitutes an SAE follows standard definitions of International Council for Harmonisation guidelines.[40]

(2) Pre-specified adverse events of special interest (AESIs): We will not collect information on all adverse events as the general safety profile of empagliflozin is well known. Rather, we focus on events that we consider of importance for this patient population or where it is thought that there is an increased risk.

Hepatic injury: We define hepatic injury as an elevation of aspartate transferase (AST) and/or alanine transferase (ALT) ≥3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood sample or an isolated elevation of ALT and/or AST ≥5 fold ULN. These findings will constitute a hepatic injury alert and the patients will be followed up according to medical judgement. In case of clinical symptoms of hepatic injury without laboratory results (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc), the investigator will make sure ALT, AST and total bilirubin are analysed, if necessary in an unscheduled blood test.

Decreased renal function: We define decreased renal function as a creatinine value showing a ≥2 fold increase from baseline and is above the ULN. For the AESI 'decreased renal function', the investigator shall collect an unscheduled laboratory sample for creatinine as soon as possible and initiate follow-up laboratory tests of creatinine according to medical judgement.

Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA): In case of metabolic acidosis, ketoacidosis and DKA, further investigations will be done according to the medical judgement and the clinical course until a diagnosis is made and/or the patient has recovered.

(3) Vital signs: We will assess vital signs (heart rate, systolic and diastolic blood pressure at the right arm after at least 5 min at rest) at visits 2, 3 and 4.

Study design

The SWEETSTONE trial is an investigator-initiated randomised, double-blind, placebo-controlled, cross-over, single-centre exploratory study. Forty-six participants will be randomised in equal proportions into two groups (23 participants per group), one group receiving 25 mg empagliflozin, the investigational medicinal product (IMP), as the first treatment, and a placebo in a form identical to empagliflozin as the second treatment, the other group receiving the same treatments in the opposite sequence. Study duration will be 2×14 days with a randomised crossover allocation and an interjacent wash out period of 2–6 weeks (figure 1).

We will use stratified randomisation to assign participants to the different trial arms with stone composition

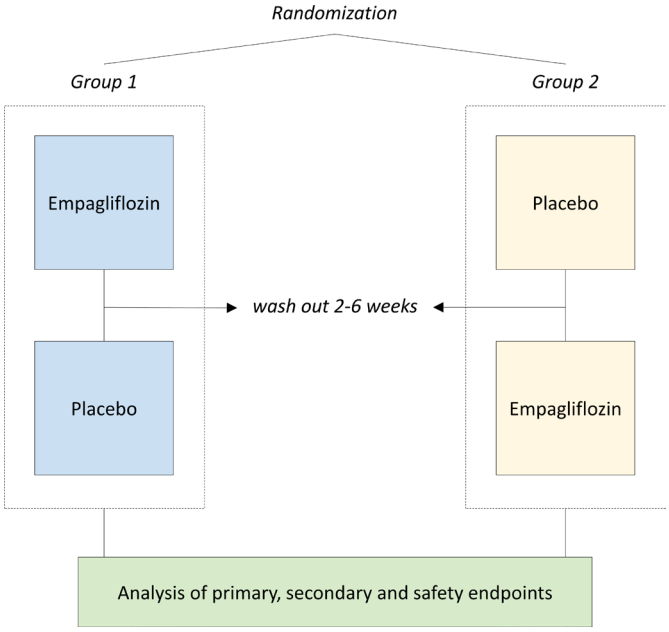

Figure 1 SWEETSTONE study design.

as stratification factor (50% of participants with calcium stones, 50% with uric acid stones). Randomisation lists will be generated by an independent statistician at the clinical trials unit (CTU) of the University of Bern. Envelops with the treatment allocation will be prepared by a person at Boehringer Ingelheim based on the randomisation list generated by CTU Bern personnel not otherwise involved in the study. If at screening, a patient is taking a medication outlined in box 1, the medication needs to be stopped and a 4-week wash out-period is required prior to randomisation. Before randomisation, a baseline 24 hours urine and a fasting blood sample will be obtained. Participants will remain on the assigned treatment for a period of 14 days. During day 13, participants will collect a 24-hour urine. On day 14, a fasting blood sample will be collected. If a study visit after exactly 14 days of intake is not possible, up to four additional intake days are allowed. The urine collection must be performed while the participant is still on treatment to avoid any effect fading. The following 14 days (days 15–28) will be a wash out period without any intake (can be extended by up to four further weeks, if necessary). On day 29 (or later according to the length of the wash out phase), the second period of 14 days treatment starts (empagliflozin or placebo, whichever was not received initially). During day 13 of this second treatment period, participants will collect again a 24-hour urine, and on day 14, a fasting blood sample will be collected. Remaining pills will be counted at each visit. All trial personnel but the statistician and data manager at CTU Bern preparing the randomisation list and the drug packs (who are not involved in enrolment and follow-up of participants), will be blinded to the assigned treatment. Values of urinary glucose will also be blinded to prevent apparent clues regarding treatment assignment. Blinding will be upheld until all analyses have been completed. Unblinding will only be permissible in situations where knowledge of the allocation is needed for the care of a patient (eg, suspected unexpected SAE). State-of-the-art non-pharmacological recommendations for stone prevention according to current American[21] and European[6] nephrolithiasis guidelines will be given to all participants as the standard medical care for stone formers. Recommendations will include increased fluid intake with circadian drinking to ensure daily urinary volumes of at least 2–2.5 L, a balanced diet rich in vegetables and fibres with normal calcium content (1–1.2 g/day) but limited sodium chloride (4–6 g/day) and animal protein (0.8–1 g/kg/day) content. Participants will be advised to retain a normal BMI, have adequate physical activity and balance excessive fluid loss.

Box 1 Eligibility criteria of the SWEETSTONE trial

Inclusion criteria

- Informed consent as documented by signature.
- Age between 18 and 74 years.
- One or more kidney stone event(s) in the past.
- Any past kidney stone containing ≥80% of calcium or ≥80% of uric acid.
- HbA1c <6.5%.

Exclusion criteria

- Patients with secondary causes of recurrent nephrolithiasis:
  - Severe eating disorders (anorexia or bulimia).
  - Chronic bowel disease, past intestinal or bariatric surgery.
  - Sarcoidosis.
  - Primary hyperparathyroidism.
  - Complete distal tubular acidosis.
- Patients with the following medications:
  - Antidiabetic treatment (insulin and non-insulin agents).
  - Patients not able or not willing to stop the following medication during the period of participation in the trial (including a time window of 4 weeks wash-out prior to randomisation):
    - Diuretics (thiazide and loop diuretics).
    - Carbonic anhydrase inhibitors (including topiramate).
    - Xanthine oxidase inhibitors.
    - Alkali, including potassium citrate or sodium bicarbonate.
    - Treatment with 1,25-(OH) vitamin D (calcitriol).
    - Calcium supplementation.
    - Bisphosphonates, denusomab, teriparatide.
    - Glucocorticoids.
- Obstructive uropathy, if not treated successfully.
- Genitourinary infection, if not treated successfully.
- Chronic kidney disease (CKD) (defined as CKD-epidemiology collaboration estimated glomerular filtration rate <60 mL/min per 1.73 m^2 body surface area).
- Kidney transplant.
- Pregnant and lactating women [urine pregnancy test to be performed for women of childbearing potential (defined as women who are not surgically sterilised/hysterectomised and/or who are postmenopausal for less than 12 months) or women of childbearing potential that refuse to use an effective contraceptive method (birth control pill or IUD).
- Inability to understand and follow the protocol.
- Known allergy to the study drug.
- Participation in another interventional clinical trial within 4 weeks prior to baseline and during the current trial.

Box 2

Criteria for withdrawal/discontinuation of participants

Discontinuation of study IMP

Study IMP must be permanently discontinued if any of the following occurs:

- Any exclusion criterion applies during the trial.
- The responsible study investigator feels that treatment with the study regimen is harmful to the participant's well-being.
- Participant is non-compliant with the study intervention as judged by the investigator.
- Pregnancy.

Discontinuation of study

Study participants must be withdrawn from the study:

- If the participant withdraws consent for further study participation.
- If the responsible investigator feels that continuation of the study would be harmful to the participant's well-being.

IMP, investigational medicinal product.

Study site

The SWEETSTONE trial will be performed at the Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Switzerland.

Study population

Eligibility criteria

We will recruit participants according to the eligibility criteria detailed in box 1.

Criteria for withdrawal/discontinuation of participants

Criteria of treatment discontinuation or study discontinuation are listed in box 2. Participants discontinuing study treatment will be replaced by new participants to reach a final number of 46 patients completing the study. This is justified given the pilot character of this trial. A study participant who discontinues study participation prematurely for any reason will be defined as dropout if the participant has already been randomised. A study participant who terminates the study before randomisation will be regarded as a screening failure. Any samples and data collected until study withdrawal will remain coded for the analysis. It will not be possible to anonymise the data and samples on withdrawal.

Study assessments

The target population consists of non-diabetic individuals with a history of kidney stones. Recruitment will take place among outpatients, referred to our stone clinic for metabolic stone work-up or that are already in regular follow-up at our clinic. With regard to scheduling of patient visits, lab analyses and imaging, the SWEETSTONE protocol strictly adheres to recommendations of the American and European guidelines on nephrolithiasis.[6 21] All blood analyses will be performed after at least 6 hours of fasting. Urine and blood analyses will be performed at the Central Laboratory of Bern University Hospital using standard laboratory methods according to recent recommendations.[41] Urine collections will be performed under paraffin oil with thymol as additive. Urine pH will be measured by an electrode pH metre that will be calibrated daily. Prior to randomisation, patients will undergo a screening visit to check their health status (including lab values), eligibility and determination of stone history. Two different groups of stone formers will be screened and recruited: (1) individuals with a past history of calcium containing kidney stones and (2) individuals with a past history of uric acid containing kidney stones. Only stone composition analysis results based on the two gold standard methods, infrared spectroscopy or X-ray diffraction, will be accepted.[42] If available medical history indicates eligibility for study participation, the individual will be informed in detail about the study by the responsible investigator. Inclusion will take place only on receipt of written informed consent and complete fulfilment of all eligibility criteria. No payment or compensation will be given to study participants. At randomisation and at all study visits thereafter, participants will receive state-of-the-art dietary recommendations for stone prevention according to current American and European nephrolithiasis guidelines including: increased fluid intake with circadian drinking to ensure daily urinary volumes of at least 2–2.5 L, a balanced diet rich in vegetables and fibres with normal calcium content (1–1.2 g/day) but limited sodium chloride (4–6 g/day) and animal protein (0.8–1 g/kg/day) content dosage.[43 44]

Investigational medicinal product

Tablets containing 25 mg empagliflozin and matching placebo tablets will be supplied by Boehringer Ingelheim, Basel, Switzerland according to applicable regulations. IMP tablets will be provided as bottles containing 30 tablets each and labelled with trial-specific labels according to 'Manufacturing of IMP' Volume IV of the EU guideline to Good Manufacturing Practice.[45] All IMPs will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Both, Empagliflozin and placebo tablets will be administered once daily per os in the morning.

Statistical methods

Sample size

Based on the reduction observed in the kidney stone event rate in pooled phase I–III empagliflozin trials, we extrapolate reductions of 30%–60% in urinary supersaturations with empagliflozin compared with placebo. A reduction of ~15% in urinary calcium oxalate supersaturation has been found to confer a ~12% risk reduction of a recurrent stone event in a previous RCT.[46] There are no comparable data with respect to uric acid nephrolithiasis. We therefore set the effect we do not want to miss for this trial to a 15% reduction in any of the three urinary supersaturation ratios. The calculation of the sample size is based on the primary outcomes (urinary supersaturation) of intraindividual comparisons within the different groups using a crossover design. Sample size calculation

was done using Stata (Release V.16.1) based on a paired means test. To account for the multiple primary endpoints, we adjusted the significance level and fixed it at 0.02 (two sided).[47] Power was set to 85%. Assuming a common SD of 20% and an intraindividual correlation of 0.5 (crossover design), 23 patients will be needed to achieve the desired power. Based on this sample size calculation, we plan to include a total of 46 individuals in the study (23 calcium kidney stone formers and 23 uric acid kidney stone formers).

Statistical analysis

The statistical analysis will be done at CTU Bern by a statistician blinded to the allocated sequence. This process is defined in standard operating procedures. After start of the trial but before recruitment end, a statistical analysis plan will be written. The plan will include all necessary data preparation steps (eg, additional validations, generation of new variables), definitions (eg, analysis sets), and statistical analyses (eg, models, outputs such as tables and graphs). All statistical analyses will be presented as effect measure plus 95% CI. Analysis of the primary outcomes will be accompanied by p-values and hypothesis testing with a significance level of 0.02. Analyses will be done for both patients groups separately that is, calcium and uric acid kidney stone formers. All analyses will be done exclusively on the per-protocol group, that is, only compliant patients completing both treatment periods will be included. Non-compliance is defined as: (1) more than two non-consecutive or (2) at least two consecutive days with missed intake of the allocated tablet (ie, to be compliant, patients must take at least 12 tablets and are not allowed to miss intake on consecutive days); or (3) 1 day of missed intake after day 10 of the respective treatment period. The same criteria apply to both treatment periods separately. Datasets generated during the study will be made available on request after completion of all predefined analyses.

Primary analysis

Linear mixed effects model will be used for analysis. The mixed effects model will contain the baseline measurements, the 14-days measurements, and an indicator for the treatment and period as fixed effects to adjust for any period effects,[48] and a random effect for participants to account for within-participant correlation of repeated measurements. All primary and secondary endpoints will be analysed with this approach. It should be noted that we will not formally test for possible carry-over effects: (1) the long wash out period should prevent them by design and (2) such gate-keeper tests lead to inflated type I errors.[49]

Interim analyses

There is currently no reliable data on the correlation between the baseline and 14-days measurement and between the two different treatment periods for urinary supersaturations. Therefore, the sample size will be reassessed after 50% of patients have completed the trial to assure sufficient power (note: enrolment will not be interrupted). The reassessment of the sample size will only be based on the observed SD and correlations between baseline and follow-up values and between treatment periods. Observed changes within and between treatment periods will not be displayed. No formal testing will take place; therefore, the significance-level does not require adjustment.

Safety analysis

Safety endpoints to be analysed include vital signs, AESIs and SAEs. No formal statistical testing will be applied but data presented descriptively.

Quality assurance and control

Monitoring

For quality control of study conduct and data retrieval, the study site will be visited by appropriately trained and qualified Monitors. All source data and relevant documents will be accessible to Monitors and questions of Monitors are answered during site visits. Any findings and comments will be documented in site visit reports and communicated to the responsible stakeholders. All monitoring activities will be defined in a monitoring plan prior to study start (first participant enrolled).

Data management

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (secuTrial). The EDC system is activated for the trial only after successfully passing a formal test procedure. All data entered in the eCRF are stored on a Linux server in a dedicated Oracle database. Responsibility for hosting the EDC system and the database lies with Inselspital Bern. The server hosting the EDC system and the database is kept in a locked server room. Only the system administrators have direct access to the server. All data entered into the eCRF are transferred to the database using Transport Layer Security encryption. The sponsor investigator will keep the Trial Master File, the extracted data, the meta data and interim and final reports for at least 10 years.

Patient and public involvement

We did not involve patients or the public in designing the SWEETSTONE trial. The trial is registered at ClinicalTrials.gov and Swiss National Clinical Trials Portal. In addition, the trial is listed as ongoing research project on the website of the CTU of Bern University. Patients will be informed about the dissemination plans before they give their consent to participate. Results will be shared with each participants when all analyses will be completed.

ETHICS AND DISSEMINATION

The SWEETSTONE trial will be carried out in accordance with the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice issued by the International Council for Harmonisation of Technical Requirements

for Pharmaceuticals for Human Use (ICH), the Swiss Law and Swiss regulatory authority's requirements. The CEC and CA will receive safety and interim reports and will be informed about study stop/ end in agreement with local requirements.The study was approved by the CEC in Bern, Switzerland (EK BE) on 22 February 2021, EK approval # 2020_02679. Approval by the CA was obtained on 10 May 2021 (Swissmedic approval # 2021DR2077).

Patient recruitment started in July 2021 and at the time of submission, five participants have been recruited. The study will presumably end in June 2022 and first results are expected in the fourth quarter of 2022. No publications containing the results of this study have already been published or submitted to any journal.

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Contributors DF is the sponsor investigator of the trial. DF and LB conceived the study, wrote the initial study protocol and applied for funding. DF, LB, GC, FR and ST participated in finalising the study protocol and the statistical analysis plan. DF and GC coordinate the study. SS, NF, MbM, BV and DF participate in the execution of the study. SS, GC and DF drafted the first manuscript. All authors contributed to the manuscript and all authors read and approved the final version.

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Competing interests The SWEETSTONE trial is partially supported by Boehringer Ingelheim, Basel, Switzerland, who provided the IMP and granted SFr75000 supporting laboratory analyses. Boehringer Ingelheim will have the right to comment on any manuscript derived from this study but will have no right to interfere in the process of publishing results in any form deemed appropriate by the investigators.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Scales CD, Smith AC, Hanley JM, *et al*. Prevalence of kidney stones in the United States. *Eur Urol* 2012;62:160–5.
2 Yoshida O, Okada Y. Epidemiology of urolithiasis in Japan: a chronological and geographical study. *Urol Int* 1990;45:104–11.
3 Hesse A, Brändle E, Wilbert D, *et al*. Study on the prevalence and incidence of urolithiasis in Germany comparing the years 1979 vs. 2000. *Eur Urol* 2003;44:709–13.
4 Worcester EM, Coe FL. Clinical practice. calcium kidney stones. *N Engl J Med* 2010;363:954–63.
5 Uribarri J, Oh MS, Carroll HJ. The first kidney stone. *Ann Intern Med* 1989;111:1006–9.
6 Saigal CS, Joyce G, Timilsina AR, *et al*. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int* 2005;68:1808–14.
7 Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in nephrolithiasis. *Kidney Int* 1997;51:894–900.
8 Cheungpasitporn W, Rossetti S, Friend K, *et al*. Treatment effect, adherence, and safety of high fluid intake for the prevention of incident and recurrent kidney stones: a systematic review and meta-analysis. *J Nephrol* 2016;29:211–9.
9 Borghi L, Meschi T, Amato F, *et al*. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol* 1996;155:839–43.
10 Ferraro PM, Ticinesi A, Meschi T, *et al*. Short-Term changes in urinary relative supersaturation predict recurrence of kidney stones: a tool to guide preventive measures in urolithiasis. *J Urol* 2018;200:1082–7.
11 Borghi L, Schianchi T, Meschi T, *et al*. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 2002;346:77–84.
12 Madore F, Stampfer MJ, Willett WC, *et al*. Nephrolithiasis and risk of hypertension in women. *Am J Kidney Dis* 1998;32:802–7.
13 Madore F, Stampfer MJ, Rimm EB, *et al*. Nephrolithiasis and risk of hypertension. *Am J Hypertens* 1998;11:46–53.
14 Taylor EN, Curhan GC. Body size and 24-hour urine composition. *Am J Kidney Dis* 2006;48:905–15.
15 Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA* 2005;293:455–62.
16 Taylor EN, Stampfer MJ, Curhan GC. Diabetes mellitus and the risk of nephrolithiasis. *Kidney Int* 2005;68:1230–5.
17 Meydan N, Barutca S, Caliskan S, *et al*. Urinary stone disease in diabetes mellitus. *Scand J Urol Nephrol* 2003;37:64–70.
18 Liu Y, Li S, Zeng Z, *et al*. Kidney stones and cardiovascular risk: a meta-analysis of cohort studies. *Am J Kidney Dis* 2014;64:402–10.
19 Alexander RT, Hemmelgarn BR, Wiebe N, *et al*. Kidney stones and kidney function loss: a cohort study. *BMJ* 2012;345:e5287.
20 Sakhaee K, Maalouf NM, Kumar R, *et al*. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. *Kidney Int* 2011;79:393–403.
21 Maalouf NM, Sakhaee K, Parks JH, *et al*. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int* 2004;65:1422–5.
22 Kanai Y, Lee WS, You G, *et al*. The human kidney low affinity Na+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. *J Clin Invest* 1994;93:397–404.
23 Refardt J, Winzeler B, Meienberg F, *et al*. Empagliflozin increases short-term urinary volume output in artificially induced syndrome of inappropriate antidiuresis. *Int J Endocrinol* 2017;2017:1–8.
24 Seman L, Macha S, Nehmiz G, *et al*. Empagliflozin (BI 10773), a potent and selective SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Drug Dev* 2013;2:152–61.
25 Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–28.
26 Wanner C, Inzucchi SE, Lachin JM, *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323–34.
27 Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;377:644–57.
28 Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med Overseas Ed* 2019;380:347–57.
29 Kohler S, Zeller C, Iliev H, *et al*. Safety and tolerability of Empagliflozin in patients with type 2 diabetes: pooled analysis of phase I-III clinical trials. *Adv Ther* 2017;34:1707–26.
30 Kohler S, Salsali A, Hantel S, *et al*. Safety and tolerability of Empagliflozin in patients with type 2 diabetes. *Clin Ther* 2016;38:1299–313.
31 Rule AD, Lieske JC, Li X, *et al*. The ROKS nomogram for predicting a second symptomatic stone episode. *J Am Soc Nephrol* 2014;25:2878–86.

32 Vaughan LE, Enders FT, Lieske JC, *et al*. Predictors of symptomatic kidney stone recurrence after the first and subsequent episodes. *Mayo Clin Proc* 2019;94:202–10.
33 Fink HA, Wilt TJ, Eidman KE, *et al*. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of physicians clinical guideline. *Ann Intern Med* 2013;158:535–43.
34 Dhayat NA, Faller N, Bonny O, *et al*. Efficacy of standard and low dose hydrochlorothiazide in the recurrence prevention of calcium nephrolithiasis (NOSTONE trial): protocol for a randomized double-blind placebo-controlled trial. *BMC Nephrol* 2018;19:349.
35 Singh M, Kumar A. Risks associated with SGLT2 inhibitors: an overview. *Curr Drug Saf* 2018;13:84–91.
36 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;85:962–71.
37 Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. *Lancet Diabetes Endocrinol* 2015;3:8–10.
38 Blau JE, Bauman V, Conway EM, *et al*. Canagliflozin triggers the FGF23/1,25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized crossover study. *JCI Insight* 2018;3. doi:10.1172/jci.insight.99123. [Epub ahead of print: 19 04 2018].
39 Kohler S, Kaspers S, Salsali A, *et al*. Analysis of fractures in patients with type 2 diabetes treated with Empagliflozin in pooled data from placebo-controlled trials and a head-to-head study versus glimepiride. *Diabetes Care* 2018;41:1809–16.
40 Guideline ICHHT. Clinical safety data management: definitions and standards for expedited reporting E2A. In: *International Conference on harmonisation of technical requirements for registration of pharmaceuticals for human use*, 1994.
41 Williams JC, Gambaro G, Rodgers A, *et al*. Urine and stone analysis for the investigation of the renal stone former: a consensus conference. *Urolithiasis* 2021;49:1-16.
42 Basiri A, Taheri M, Taheri F. What is the state of the stone analysis techniques in urolithiasis? *Urol J* 2012;9:445–54.
43 Pearle MS, Goldfarb DS, Assimos DG, *et al*. Medical management of kidney stones: AUA guideline. *J Urol* 2014;192:316–24.
44 Turk C, Knoll T, Petrik A, European Association of U. EUA guidelines on urolithiasis 2014.
45 EudraLex TRGMPitEU. *Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13 - Investigational Medicinal Products, Brussels*, 2010.
46 Pak CYC, Sakhaee K, Moe O, *et al*. Biochemical profile of stone-forming patients with diabetes mellitus. *Urology* 2003;61:523–7.
47 Vickerstaff V, Omar RZ, Ambler G. Methods to adjust for multiple comparisons in the analysis and sample size calculation of randomised controlled trials with multiple primary outcomes. *BMC Med Res Methodol* 2019;19:129.
48 Dwan K, Li T, Altman DG, *et al*. Consort 2010 statement: extension to randomised crossover trials. *BMJ* 2019;366:l4378.
49 Freeman PR. The performance of the two-stage analysis of two-treatment, two-period crossover trials. *Stat Med* 1989;8:1421–32.