

**Supplemental Material for  
Metabolic, Intestinal, and Cardiovascular Effects of Sotagliflozin Compared With  
Empagliflozin in Patients with Type 2 Diabetes: a Randomized, Double-Blind Study**

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## **Inclusion and Exclusion Criteria**

### *Inclusion Criteria*

1. Male or female patients with T2DM (diagnosed at least 1 year before screening visit), between 18 and 74 years of age, inclusive, with:
  - Hypertension Grades 1 or 2 as defined by the European Society of Hypertension and the European Society of Cardiology (23) at screening. SBP was in the range of 140-179 mmHg (after 10 minutes resting in supine position; measurement in triplicate with each measurement was to be within this range at screening). If the BP range was not met at screening, 1 repeat measurement at another occasion was allowed prior to inclusion into the study.
  - HbA1c at screening was between 6.5% and 11%.
2. On a stable treatment with metformin (ie, no change in dose regimen or in dose levels in the last 3 months prior to screening and until randomization).
3. On a stable treatment with an ACE inhibitor or an ARB (ie, no change in dose regimen or in dose levels in the last 4 weeks prior to screening and until randomization).
4. On a stable treatment with an ACE inhibitor or an ARB after switching from beta-blockers and/or thiazides for eligible patients after screening (ie, no change in dose regimen and in dose levels in the last 4 weeks prior to run-in phase and until randomization).
5. Body weight between 50.0 kg and 130 kg, inclusive, if male, and between 40.0 kg and 110 kg, inclusive, if female; BMI between 18.0 and 38.0 kg/m<sup>2</sup>, inclusive.
6. Normal heart rate (HR) at screening after 10 minutes resting in supine position: 50 bpm < HR < 100 bpm.
7. Standard 12-lead electrocardiogram (ECG) parameters after 10 minutes resting in supine position without any clinically significant abnormalities as judged by the PI based on age, gender, and medical history of the individual patient.
8. Female patients must have used a double contraception method including a highly effective method of birth control, except if she had undergone sterilization at least 3 months earlier or was postmenopausal. The accepted double contraception methods included the use of intrauterine device or hormonal contraception in addition to 1 of the following contraceptive options: (1) condom; (2) diaphragm or cervical/vault cap; (3) spermicide. Menopause was defined as being amenorrheic for at least 2 years with plasma follicle-stimulating hormone in the laboratory's range for postmenopausal phase.
9. Male patients, whose partners were of childbearing potential (including lactating women), must have accepted to use, during sexual intercourse, a double contraception method according to the following algorithm: (condom) plus (intrauterine device or hormonal contraceptive) from the inclusion into the study up to 3 months after the last dosing.
10. Male patients, whose partners were pregnant, must have used, during sexual intercourse, a condom from the inclusion up to 3 months after the last dosing.
11. Male patients had agreed not to donate sperm from the inclusion up to 3 months after the last dosing.
12. Had given written informed consent prior to undertaking any study-related procedure.
13. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

14. Not under any administrative or legal supervision or under institutionalization due to regulatory or juridical order.
15. Estimated GFR (as calculated with Modification of Diet in Renal Disease formula) at screening must have been 60 mL/min/1.73m<sup>2</sup> or higher.

#### *Exclusion Criteria*

1. Patients with severe anemia, severe cardiovascular, gastrointestinal, respiratory, neurological, osteomuscular, psychiatric, or active malignant tumor or other major systemic disease or patients with infectious disease, signs of acute illness, or short life expectancy which made implementation of the protocol or interpretation of the study results difficult (as evaluated by detailed medical history and complete physical and laboratory examination).
2. Patients with renal impairment Stage III or higher.
3. Heart failure New York Heart Association III/IV.
4. Any clinically significant abnormality in echocardiography performed at screening as judged by the PI based on age, gender, and medical history of the individual patient.
5. History of myocardial infarction within the last 12 months prior to screening.
6. Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol (eg, long-term systemic glucocorticoids) and refusal or inability to take alternative treatment.
7. Type 1 diabetes.
8. Secondary hypertension of any etiology (eg, renovascular disease, pheochromocytoma, Cushing's syndrome).
9. Clinically significant pulmonary hypertension, in particular World Health Organization (WHO) Classes IV (pulmonary hypertension due to chronic thromboembolic pulmonary hypertension) and V (miscellaneous).
10. Diabetic retinopathy.
11. History of diabetic ketoacidosis or non-ketotic hyperosmolar coma within 12 weeks prior to the screening visit.
12. History of severe hypoglycemia which resulted in hospitalization or unconsciousness/seizures within 6 months prior to the screening visit.
13. History of prior gastric or intestinal surgical procedure which included gastric banding within 3 years before the screening visit. Any gastrointestinal surgery with removal of part of the bowels or the stomach.
14. Presence at screening or recurrent occurrence of cholelithiasis within 12 months prior to first dosing.
15. Cholecystectomy within 12 months prior to first dosing.
16. History of unexplained pancreatitis, chronic pancreatitis, stomach/gastric surgery, or inflammatory bowel disease.
17. Patients with hepatic impairment of Child-Pugh Class B or C.
18. Aspartate aminotransferase and/or alanine aminotransferase: >3 times the upper limit of the normal (ULN) laboratory range.
19. Total bilirubin: >1.5 times the ULN laboratory range (except in case of Gilbert's syndrome).
20. Amylase and/or lipase >3 time the ULN.
21. Hemoglobin <10.0 g/dL and/or neutrophils <1,500/mm<sup>3</sup> and/or platelets <100,000/mm<sup>3</sup>.

22. Hemoglobinopathy or hemolytic anemia, receipt of blood or plasma products within 3 months prior to the time of screening.
23. Patient was unwilling to perform self-monitoring of plasma glucose (SMPG) and complete the patient's diary as required per protocol.
24. Contraindication to empagliflozin as per local labeling.
25. The participant worked a night (third) shift (defined as 11 PM [23:00] to 7 AM [07:00]).
26. Weight change of more than 5 kg during the 3 months preceding the screening visit.
27. Frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month).
28. Blood donation or any blood loss more than 300 mL within 2 months before inclusion.
29. Presence or history of drug hypersensitivity, or presence of rheumatic or autoimmune disease.
30. History or presence of drug or alcohol abuse (alcohol consumption more than 40 g per day on a regular basis).
31. If female, pregnancy (defined as positive beta-human gonadotrophin [ $\beta$ -HCG] blood test) or breastfeeding.
32. Any hypertensive treatment with drugs other than ACE inhibitors or ARBs in the last 4 weeks prior to screening (except patients who were on thiazides and/or beta-blockers and were switched to allow medications prior to run-in phase), spironolactone, loop diuretics.
33. Treatment with a glitazone, DPP-IV inhibitor, a sulfonylurea, a meglitinide (glinides), GLP-1 agonists, and/or an SGLT2 inhibitor within the last 3 months prior to screening.
34. Previous insulin use >1 month (at any time, aside from treatment of gestational diabetes).
35. On any medication that was metabolized by P-glycoprotein (eg, digoxin).
36. Patient who had taken other investigational drugs or prohibited therapy for this study within 3 months or 5 half-lives from screening or randomization, whichever was longer.
37. Use of systemic glucocorticoids (excluding topical or ophthalmic, application or inhaled forms) for more than 10 consecutive days within 90 days prior to the screening visit.
38. Any patient who, in the judgment of the PI, was likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.
39. Patients considered by the PI or any sub-investigator as inappropriate for this study for any medical, psychological, social, or geographical reason (eg, patients unable to fully understand the nature, scope, and possible consequences of the study; patients unable to fully understand patient's study documents; impossibility to meet specific protocol requirements, such as scheduled visits; being unable or unwilling to do self-pricking and blood glucose monitoring using the Sponsor-provided blood glucose meter at home; likelihood of requiring treatment with drugs not permitted by the clinical study protocol; night shift workers, etc).
40. Any patient in the exclusion period of a previous study according to applicable regulations.
41. Any patient who could not be contacted in case of emergency.
42. Any patient who was the PI or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study or any person dependent on study site, the PI, or the Sponsor.
43. Positive result on any of the following tests: hepatitis B surface antigen, anti-hepatitis C virus antibodies, anti-human immunodeficiency virus 1 and 2 antibodies.

44. Positive result on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
45. Positive alcohol test.
46. Urinary tract infection or genitourinary mycotic infections in the last 4 weeks prior to start of dosing.
47. Any antibiotic treatment in the last 6 months prior to dosing.
48. Any diarrhea at inclusion or a gastrointestinal infection in the last 4 weeks prior to start of dosing.
49. Presence or history of any chronic disease of the bowels or indigestions.
50. Patients who were vegan, a vegetarian, or had any other dietary restriction.
51. Presence of any contraindication to receive intravenous (IV) indocyanine-green (hypersensitivity of indocyanine-green/sodium iodide, iodine allergy, clinically manifest hyperthyreosis, autonomous thyroid adenoma, or focal and diffuse thyroid autonomy).
52. Known hypersensitivity to sotagliflozin, empagliflozin, or any excipient of these drug products.

## **Detailed Methods for In-House Assessments**

### *24-Hour Urine Collection*

The collection started after the first void on the morning of day -1/day 56 and continued until the first void on the morning of day 1/day 57. The 24-hour urine collection was fractionated for each meal of the day. The following parameters were analyzed: total volume, glucose, sodium, potassium, calcium, magnesium, phosphate, chloride, pH, creatinine, uric acid, urea, albumin, proteins, ketone bodies (total and  $\beta$ -hydroxybutyrate).

### *48-Hour Feces Collection*

Collections were performed over 48 hours prior to first drug intake and at week 8. Stools were weighed, put on dry ice, and kept at -80°C until analysis. The following parameters were measured: daily excretion of water, sodium, potassium, chloride, short-chain fatty acids (butyrate, propionate, acetate), glucose, pH, bicarbonate, and the Firmicutes:Bacteroidetes ratio.

### *CGM and SMBG Profiles*

During the 2 in-house periods, patients had their glucose recorded on all days with a continuous glucose monitoring (CGM) system (DexCom G4, San Diego, California, using a subcutaneous abdominal sensor); the last 3 days of each period were used for analysis. Patients were blinded to the CGM measurements. In addition, self-monitored plasma glucose (SMPG) measurements were taken during in-house days and at least twice weekly during the outpatient treatment period.

### *ABPM and Seated BP Profiles*

Blood pressure (BP) was measured continuously during the in-house periods using an ambulatory BP monitor (ABPM; OnTrak 90227, Spacelabs Healthcare, Snoqualmie, Washington). Measurements were obtained between 7:00 am and 11:00 pm (daytime) every 15 minutes and every 30 minutes between 11:00 pm and 7:00 am (nighttime). To be valid, the full 24-hour recording was to include a minimum of 80% of valid BP readings and not missing more than 2 hours of consecutive measures during daytime or 4 hours of consecutive measures during nighttime. Only the last 3 days of these periods were used for analysis.

Repetitive seated BP measurements were performed on Day -3 (Week -1) and on Day 54 (Week 8) to compare the effect size detectable with this method to ABPM measurements on an exploratory basis. On each of these 2 days, 5 measurements were performed over the day: 1 prior to breakfast (T0h), 1 prior to lunch (T5h), one 2 hours after lunch (T7h), 1 prior to dinner (T10h), and 1 at bedtime (T14h). For each seated BP measurement, the patient had 3 measurements taken while seated over 15 minutes (minimum 5 minutes between each reading). Prior to the first measurement, the patient remained seated at rest for at least 5 minutes. The value for analysis was the mean of these 3 measurements.

On further selected days, seated BP was measured only in the morning before breakfast, ie, on Day -1 (Week -1), Day 56 (Week 8). On Day 1 (Week -1) and Day 57 (Week 8), seated BP was measured in the morning predose/ before breakfast. Also, seated BP was measured on the outpatient visits (no diurnal profiles).

### *Pulse Wave Velocity*

Pulse wave velocity was assessed at baseline (day -2) and week 8 (day 55) at matching times of the day using a Sphygmocor XCEL device (AtCor, New South Wales, Australia) according to the manufacturer's specification. Parameters were carotid femoral pulse wave velocity and aortic augmentation index.

#### *Transthoracic Echocardiography*

Echocardiography (GE Vivid E9; GE Healthcare, Chicago, IL) was done during the in-house days at baseline and end of treatment at matching times of the day. Parameters included velocity time index (VTI) over left ventricular outflow tract (LVOT), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), tissue Doppler imaging (TDI), and the diastolic filling patterns (including E/e'). All recordings were done by a single assessor. At screening, echocardiography was used to exclude any significant cardiac disease or abnormality.

#### *Plasma Volume*

Plasma volume was estimated by means of the indocyanine-green method (1). On Days -3 and Day 54, patients were given an intravenous bolus injection of 0.25 mg/kg indocyanine-green into a large arm vein. Blood samples were collected from the contralateral arm every 30 seconds 2-5 minutes after the injection (7 samples). Plasma indocyanine-green concentrations were determined using a validated high-performance liquid chromatography analytical method (at MLM Medical Labs GmbH, Germany). The decline in indocyanine-green concentrations over time was back-extrapolated to the time immediately after injection (1 minute), and a physiologically based mathematical model was used to calculate plasma volume.

#### **Reference**

- Polidori D, Rowley C. Optimal back-extrapolation method for estimating plasma volume in humans using the indocyanine green dilution method. *Theor Biol Med Model*. 2014;11:33.

## Main Endpoints

- Urine
  - 24h urinary glucose excretion
  - Further 24h urine parameters:  
urine volume, electrolytes (sodium, potassium, calcium, magnesium, phosphate), pH, creatinine, uric acid, urea; albumin, proteins, ketones ( $\beta$ -hydroxybutyrate, total ketone bodies)
- Feces (collection period 48h):
  - Fecal sodium, potassium, chloride
  - SCFAs (butyrate, propionate, acetate) and glucose excretion
  - Also average volume and weight/day (incl. water contents)
  - pH/bicarbonate
  - Firmicutes:Bacteroidetes ratio
- 14 hour plasma profiles of glucose/insulin/intact pro-insulin/C-peptide/glucagon/GLP1 (active and total), PYY and pancreatic polypeptide (PP) over 14 hours after standardized meals (MMTT) at breakfast, lunchtime and dinner, performed at baseline and on the last day of treatment

## Further Endpoints

- Average mean, systolic and diastolic 24h blood pressure from ABPM, change from baseline
- Pulse wave velocity:
  - Carotid-radial pulse wave velocity
  - Carotid-femoral pulse wave velocity
  - Radial augmentations index
- Echocardiography:
  - Velocity time index (VTI) over left ventricular outflow tract (LVOT)
  - Left ventricular end-diastolic diameter (LVEDD)
  - Left ventricular ejection fraction (LVEF)
  - Tissue Doppler imaging (TDI) with (E/e') ratio and (E/A) ratio
  - Diastolic filling patterns
- Cardiovascular laboratory panel (serum/plasma):
  - PRA (plasma renin activity), AT1/2 (angiotensin 1/2), aldosterone
  - NT-proBNP, CT-pro vasopressin (Copeptin)
  - -Erythropoetin, hematology
- Fasting metabolic laboratory panel (serum/plasma):
  - FPG, plasma insulin + intact proinsulin, C-peptide, glucagon
  - Plasma acetate, propionate; triglycerides, FFA
  - $\beta$ -hydroxybutyrate, total ketone bodies
- Average mean, av. systolic and av. diastolic blood pressure (ABPM) at daytime (6 am until 11 pm) and during night (11 pm until 6 am)
- Seated SBP/DBP diurnal profile under in-house conditions; on Day -3 and Day 54
- Seated SBP/DBP single measurement on out-patients visits and on the mornings of Day -1, Day 1, Day 56, and Day 57
- Plasma volume (by indocyanine-green method)

- Following parameters from fractionated 24h urine collection:
  - Urinary glucose excretion
  - Urine volume, electrolytes (sodium, potassium, calcium, magnesium, phosphate), pH
  - Creatinine, uric acid, urea
  - Albumin, proteins
  - Ketones ( $\beta$ -hydroxybutyrate, total ketone bodies)
- SMPG diurnal profile on Days -1 and 56; at least once per week during out-patients treatment period
- Fasting SMPG on all in house days (beyond Days -1 and 56 who have a 5-point profile) and at least twice per week during out-patients treatment period
- CGM: average diurnal glucose

Further CGM parameters:

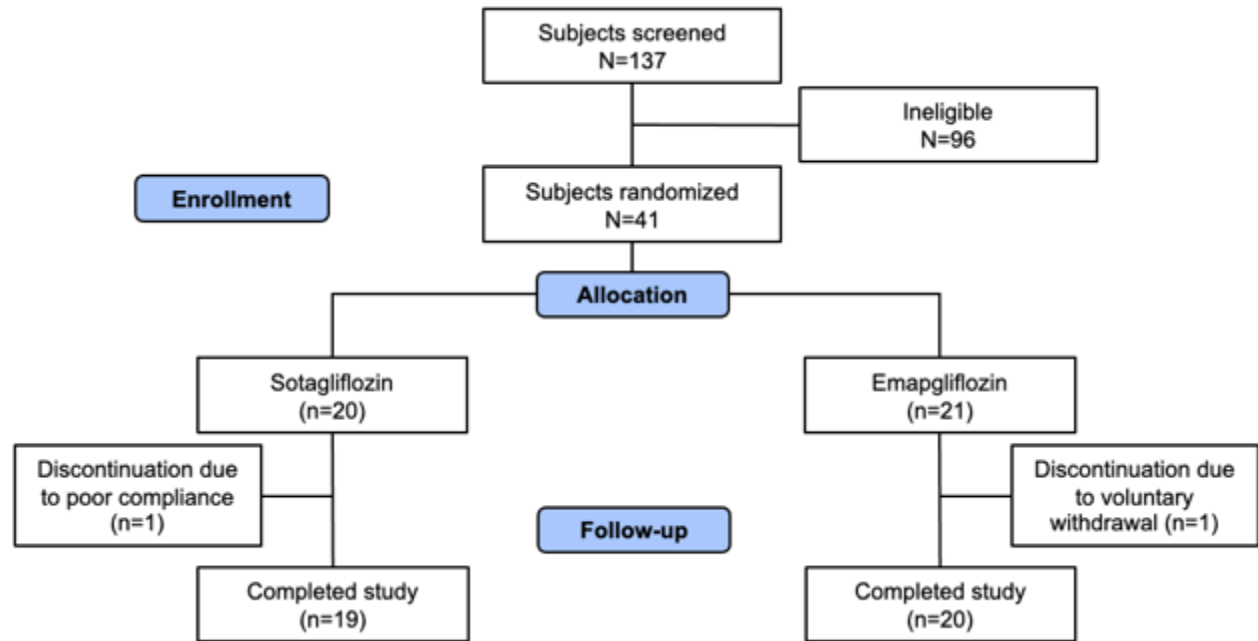
- Percent (%) of time in plasma glucose range of 80-140 mg/dL (4.4-7.8 mmol/L)
- Percent time above the upper limit ( $>140$  mg/dL;  $>7.8$  mmol/L) of glycemic range (%time in hyperglycemia)
- Percent time below the lower limit ( $<80$  mg/dL;  $<4.4$  mmol/L) of glycemic range (%time in hypoglycemia)
- Further CGM based parameters may be derived and full details will be specified in the Statistical Analysis Plan (SAP)

Additional PD parameters may be added if needed to evaluate the objectives of the study.

**Table S1.** Reasons for ineligibility at screening

<b>Reason</b>	<b>n</b>
Did not meet inclusion criteria	
BP not within range	61
BMI too high	6
HbA1c <6.5	5
Heart rate not within range	4
Weight criteria not met	2
GFR <60ml/min/1.73 m <sup>2</sup>	1
No stable dose regimen in the last 3 months; no double contraception method	1
HbA1c >11%	1
Met exclusion criteria	
Second hypertensive medication	2
Noncompliant	2
Inappropriate for this study for medical reasons	2
Intestinal surgery	1
History of alcohol abuse	1
Gained 8 kg in the last 3 months	1
Presence of rheumatic or autoimmune disease	1
Treatment with DPP-4 inhibitor	1
Other	
Withdrawal of consent due to personal reason	2
Out of screening window	2
Total	96

**Figure S1.** Patient disposition.



**Table S2.** Patient characteristics

	<b>Sotagliflozin 400 mg (n=20)</b>	<b>Empagliflozin 25 mg (n=21)</b>	<b>All (N=41)</b>
Sex, male/female, n	16/4	17/4	33/8
Age, years	61.0 ± 8.4	61.3 ± 8.1	61.2 ± 8.2
BMI, kg/m <sup>2</sup>	30.3 ± 3.1	28.9 ± 3.9	29.6 ± 3.6
HbA1c, % (mmol/mol)	7.7 ± 0.8 (61 ± 8.3)	7.4 ± 0.8 (57 ± 8.2)	7.6 ± 0.8 (59 ± 8.3)
Age at diabetes onset, years	54.0 ± 6.6	53.9 ± 6.6	53.9 ± 6.5
eGFR (mL/min/1.73 m <sup>2</sup> )	86.6 ± 12.5	88.6 ± 15.5	87.6 ± 14.0
Duration of diabetes, years	7.7 ± 4.5	8.3 ± 6.4	8.0 ± 5.5
Duration of metformin treatment, years	6.7 ± 5.0	5.5 ± 5.1	6.1 ± 5.0
Total daily dose of metformin, mg	1645 ± 533	1435 ± 584	1538 ± 563
Diabetic retinopathy, n (%)	0	0	0
Diabetic neuropathy, n (%)	3 (15.0)	0	3 (7.3)
Diabetic nephropathy, n (%)	0	0	0
Duration of hypertension, years	6.5 ± 4.1	8.1 ± 8.5	7.3 ± 6.7
Currently on ACEi, n (%)	11 (55.0)	14 (66.7)	25 (61.0)
Duration of ACEi treatment, years	5.4 ± 4.7	3.7 ± 3.1	4.4 ± 3.9
Currently on ARB, n (%)	9 (45.0)	7 (33.3)	16 (39.0)
Duration of ARB treatment, years	5.2 ± 4.0	6.5 ± 6.0	5.8 ± 4.8
Seated SBP at baseline (mmHg)*	142.2 ± 10.4	141.1 ± 14.5	141.6 ± 12.6
Seated DBP at baseline (mmHg)*	79.2 ± 7.4	82.1 ± 7.4	80.7 ± 7.4

Data are mean ± SD unless noted otherwise.

\*For seated SBP and DBP, baseline is the average of 5 measurements taken on Day -3.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SEM, standard error of the mean.

**Table S3.** Effects on incremental and absolute changes in AUC during the 10- and 14-hour intervals after breakfast.

Parameter	Interval	LS mean change from baseline (95% CI); <i>P</i> value		LS mean difference, sotagliflozin vs empagliflozin (95% CI); <i>P</i> value
		Sotagliflozin	Empagliflozin	
Incremental changes				
Glucose, h•mmol/L	0-10 h	-5.6 (-8.6 to -2.6); 0.0006	-3.3 (-6.2 to -0.4); 0.0294	-2.4 (-6.5 to 1.8); NS
	0-14 h	-5.7 (-10.1 to -1.4); 0.0117	-4.1 (-8.3 to 0.2); 0.0580	-1.6 (-7.7 to 4.5); NS
Insulin, h•pmol/L	0-10 h	-804 (-1162 to -444); <0.0001	-568 (-927 to -209); 0.0029	-235 (-744 to 273); NS
	0-14 h	-894 (-1407 to -381); 0.0012	-765 (-1277 to -252); 0.0047	-130 (-856 to 596); NS
Proinsulin, h•pmol/L	0-10 h	-43 (-56 to -30); <0.0001	-40 (-51 to -28); <0.0001	-3 (-21 to 15); NS
	0-14 h	-53 (-70 to -36); <0.0001	-62 (-78 to -47); <0.0001	9 (-14 to 32); NS
C-peptide, h•nmol/L	0-10 h	-2.5 (-3.5 to -1.4); <0.0001	-1.6 (-2.6 to -0.6); 0.0038	-0.9 (-2.3 to 0.6); NS
	0-14 h	-2.4 (-3.9 to -0.9); 0.0024	-1.9 (-3.4 to -0.4); 0.0136	-0.5 (-2.6 to 1.6); NS
aGLP-1, h•ng/L	0-10 h	13 (-1 to 27); 0.0590	-13 (-26 to 1); 0.0662	<b>26 (7 to 45); 0.0102</b>
	0-14 h	23 (3 to 42); 0.0233	-8 (-28 to 11); 0.3807	<b>31 (4 to 58); 0.0273</b>
tGLP-1, h•ng/L	0-10 h	75 (15 to 134); 0.0154	-40 (-100 to 19); 0.1769	<b>115 (31 to 199); 0.0091</b>
	0-14 h	86 (2 to 169); 0.0448	-24 (-108 to 60); 0.5582	110 (-8 to 228); NS
PYY, h•ng/L	0-10 h	159 (-10 to 328); 0.0639	85 (-79 to 249); 0.2978	74 (-163 to 311); NS
	0-14 h	178 (-49 to 404); 0.1197	150 (-70 to 370); 0.1747	28 (-289 to 346); NS
GIP, h•ng/L	0-10 h	-567 (-756 to -378); <.0001	-278 (-467 to -89); 0.0052	<b>-289 (-559 to -19); 0.0370</b>
	0-14 h	-619 (-844 to -394); <.0001	-385 (-609 to -160); 0.0014	-235 (-556 to 87); NS
Absolute changes				
Glucose, h•mmol/L	0-10 h	-18 (-22 to -13); <.0001	-16 (-21 to -12); <.0001	-1.3 (-7.7 to 5.1); NS
	0-14 h	-23 (-30 to -17); <.0001	-23 (-29 to -16); <.0001	-0.4 (-9.5 to 8.7); NS
Insulin, h•pmol/L	0-10 h	-891 (-1359 to -423); 0.0005	-676 (-1144 to -208); 0.006	-215 (-882 to 452); NS
	0-14 h	-986 (-1635 to -337); 0.004	-961 (-1610 to -312); 0.0049	-24 (-947 to 898); NS
Proinsulin, h•pmol/L	0-10 h	-55 (-73 to -37); <.0001	-57 (-74 to -41); <.0001	3 (-22 to 27); NS
	0-14 h	-70 (-94 to -46); <.0001	-88 (-110 to -65); <.0001	18 (-15 to 50); NS
C-peptide, h•nmol/L	0-10 h	-3.2 (-4.4 to -2.0); <.0001	-2.1 (-3.3 to -0.9); 0.0014	-1.2 (-2.9 to 0.6); NS
	0-14 h	-3.5 (-5.0 to -2.0); <.0001	-2.8 (-4.2 to -1.3); 0.0007	-0.7 (-2.9 to 1.4); NS
aGLP-1, h•ng/L	0-10 h	8.2 (-5.8 to 22.3); 0.2429	-6.7 (-20.7 to 7.4); 0.3406	14.9 (-5.1 to 34.9); NS

Parameter	Interval	LS mean change from baseline (95% CI); <i>P</i> value		LS mean difference, sotagliflozin vs empagliflozin (95% CI); <i>P</i> value
		Sotagliflozin	Empagliflozin	
tGLP-1, h•ng/L	0-14 h	15 (-4 to 35); 0.1116	0 (-19 to 19); 0.9904	15 (-12 to 42); NS
	0-10 h	94 (8 to 180); 0.0339	13 (-73 to 99); 0.7529	80 (-42 to 202); NS
	0-14 h	104 (-11 to 218); 0.0744	53 (-61 to 168); 0.3495	50 (-112 to 213); NS
PYY, h•ng/L	0-10 h	175 (-7 to 358); 0.0588	57 (-120 to 234); 0.5159	118 (-137 to 374); NS
	0-14 h	164 (-46 to 374); 0.1206	92 (-111 to 296); 0.3609	72 (-221 to 365); NS
GIP, h•ng/L	0-10 h	-563 (-753 to -373); <.0001	-271 (-461 to -81); 0.0065	<b>-292 (-564 to -20); 0.0365</b>
	0-14 h	-619 (-857 to -381); <.0001	-371 (-610 to -133); 0.0032	-248 (-589 to 93); 0.1491

Boldface highlights statistically significant differences.

aGLP-1, active glucagon-like peptide 1; AUC, area under the curve; GIP, glucose-dependent insulintropic polypeptide; NS, not significant; PYY, peptide YY; tGLP-1, total GLP-1.

**Table S4.** Effects on absolute changes in AUC during the 5-hour interval after breakfast.

Parameter	Time interval	LS mean change from baseline (95% CI); <i>P</i> value		LS mean difference, sotagliflozin vs empagliflozin (95% CI); <i>P</i> value
		Sotagliflozin	Empagliflozin	
Glucose, h•mmol/L	0-2 h	-3.4 (-4.5 to -2.2); <0.0001	-2.2 (-3.3 to -1.1); 0.0004	-1.2 (-2.8 to 0.5); NS
	0-3 h	-6.0 (-7.7 to -4.4); <0.0001	-4.5 (-6.1 to -2.9); <0.0001	-1.5 (-3.9 to 0.8); NS
	0-5 h	-8.2 (-11.0 to -5.7); <0.0001	-7.1 (-9.6 to -4.6); <0.0001	-1.2 (-4.7 to 2.4); NS
Insulin, h•pmol/L	0-2 h	-215 (-330 to -100); 0.0006	-110 (-225 to 5); 0.0610	-105 (-270 to 60); NS
	0-3 h	-414 (-570 to -258); <0.0001	-220 (-376 to -65); 0.0070	-194 (-416 to 29); NS
	0-5 h	-580 (-821 to -338); <0.0001	-278 (-519 to -36); 0.0257	-302 (-648 to 43); NS
Proinsulin, h•pmol/L	0-2 h	-6 (-9 to -3); 0.0002	-4 (-6 to -1); 0.0075	-2 (-6 to 2); NS
	0-3 h	-14 (-19 to -9); <0.0001	-8 (-13 to -4); 0.0011	-6 (-12 to 1); NS
	0-5 h	-23 (-35 to -12); 0.0003	-15 (-26 to -4); 0.0075	-8 (-24 to 8); NS
C-peptide, h•nmol/L	0-2 h	-0.5 (-0.8 to -0.1); 0.0082	0.1 (-0.3 to 0.4); NS	<b>-0.5 (-1.0 to -0.04); 0.0364</b>
	0-3 h	-1.1 (-1.6 to -0.6); 0.0001	-0.2 (-0.7 to 0.4); NS	<b>-1.0 (-1.7 to -0.22); 0.0131</b>
	0-5 h	-1.7 (-2.6 to -0.8); 0.0006	-0.4 (-1.3 to 0.6); NS	<b>-1.3 (-2.7 to -0.03); 0.0457</b>
aGLP-1, h•ng/L	0-2 h	6.6 (2.4 to 10.7); 0.0029	-1.9 (-6.0 to 2.3); NS	<b>8.4 (2.5 to 14.4); 0.0067</b>
	0-3 h	10.0 (4.5 to 15.5); 0.0008	-2.3 (-7.8 to 3.2); NS	<b>12.3 (4.5 to 20.2); 0.0031</b>
	0-5 h	13.9 (6.6 to 21.3); 0.0005	-2.5 (-9.8 to 4.9); NS	<b>16.4 (6.0 to 26.8); 0.0029</b>
tGLP-1, h•ng/L	0-2 h	41 (24 to 59); <0.0001	11 (-6 to 29); NS	<b>30 (5 to 55); 0.0203</b>
	0-3 h	62 (36 to 88); <0.0001	11 (-14 to 37); NS	<b>51 (14 to 87); 0.0084</b>
	0-5 h	104 (63 to 146); <0.0001	26 (-16 to 67); NS	<b>79 (20 to 138); 0.0102</b>
PYY, h•ng/L	0-2 h	26 (-11 to 62); NS	29 (-9 to 66); NS	-3 (-56 to 50); NS
	0-3 h	76 (28 to 124); 0.0030	31 (-18 to 80); NS	45 (-24 to 114); NS
	0-5 h	115 (27 to 202); 0.0124	74 (-16 to 165); NS	40 (-86 to 167); NS
GIP, h•ng/L	0-2 h	-201 (-254 to -149); <0.0001	-66 (-119 to -14); 0.0153	<b>-135 (-211 to -59); 0.0009</b>
	0-3 h	-272 (-346 to -198); <0.0001	-98 (-172 to -24); 0.0109	<b>-174 (-280 to -68); 0.0022</b>
	0-5 h	-325 (-431 to -219); <0.0001	-168 (-274 to -62); 0.0029	<b>-157 (-309 to -6); 0.0426</b>

Boldface highlights statistically significant differences.

aGLP-1, active glucagon-like peptide 1; AUC, area under the curve; GIP, glucose-dependent insulinotropic polypeptide; NS, not significant; PYY, peptide YY; tGLP-1, total GLP-1.

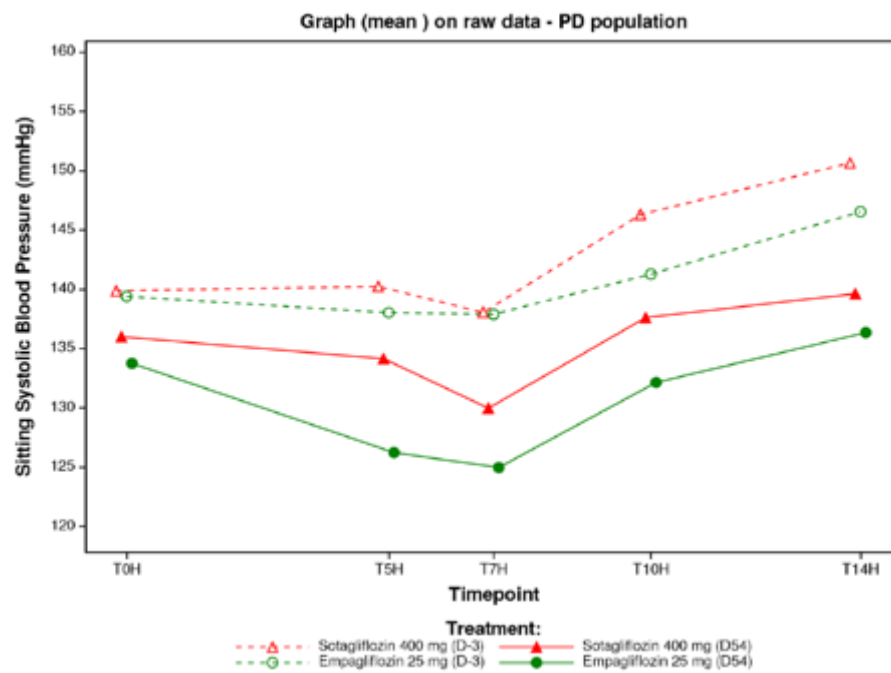
**Table S5.** Changes in fasting metabolites.

<b>Parameter</b>	<b>Sotagliflozin</b>	<b>Empagliflozin</b>	<b>LS mean difference, sotagliflozin vs empagliflozin (95% CI)</b>	<b><i>P</i> value</b>
Propionate, $\mu\text{mol/L}$				
Baseline	4.00 $\pm$ 0.95	4.21 $\pm$ 0.77		
Change from baseline	-0.08 (-0.49 to 0.32)	-0.04 (-0.43 to 0.36)	-0.05 (-0.61 to 0.52)	0.8721
Acetate, $\mu\text{mol/L}$				
Baseline	49.6 $\pm$ 11.5	55.9 $\pm$ 15.4		
Change from baseline	-0.8 (-8.2 to 6.5)	10.1 (3.0 to 17.2)	-11.0 (-21.3 to -0.6)	0.0385
Free fatty acids, $\text{mmol/L}$				
Baseline	0.57 $\pm$ 0.16	0.53 $\pm$ 0.16		
Change from baseline	0.04 (-0.006 to 0.09)	0.05 (0.002 to 0.1)	-0.007 (-0.07 to 0.06)	0.8428
Total ketones, $\mu\text{mol/L}$				
Baseline	270 $\pm$ 266	190 $\pm$ 102		
Change from baseline	249 (75 to 422)	285 (116 to 453)	-36 (-281 to 208)	0.7661
$\beta$ -hydroxybutyrate, $\mu\text{mol/L}$				
Baseline	178 $\pm$ 176	125 $\pm$ 73		
Change from baseline	179 (54 to 304)	203 (82 to 325)	-24.4 (-200 to 152)	0.7799

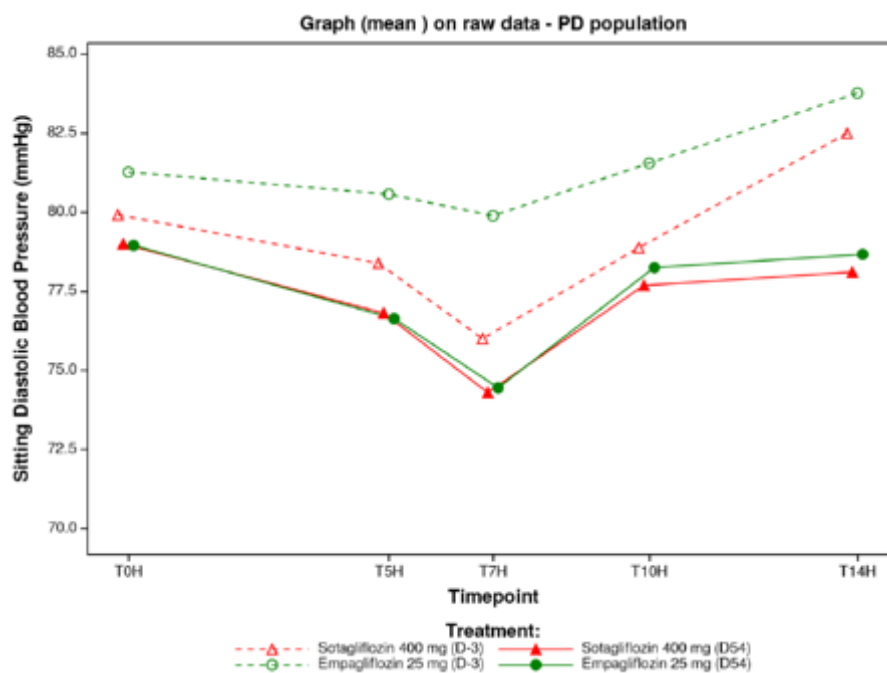
Baseline data are mean  $\pm$  standard deviation (SD). Change from baseline data within each group are least squares (LS) mean  $\pm$  standard error (SE).

**Figure S2.** Time-course of mean sitting systolic (*A*) and diastolic (*B*) blood pressure at baseline and after 8 weeks treatment with sotagliflozin 400 mg or empagliflozin 25 mg. Plots are mean  $\pm$  standard error of the mean (SEM).

A



B



**Table S6.** Vascular parameters.

<b>Parameter</b>	<b>Sotagliflozin</b>	<b>Empagliflozin</b>	<b>LS mean difference, sotagliflozin vs empagliflozin (95% CI)</b>	<b>P value</b>
Angiotensin I, ng/L				
Baseline	188 ± 170	104 ± 70		
Change from baseline	154 ± 72	258 ± 70	-104 (-312 to 104)	0.3167
Renin activity, ng/mL/h				
Baseline	1.9 ± 2.3	0.8 ± 0.6		
Change from baseline	4.2 ± 1.7*	3.0 ± 1.7	1.2 (-3.9 to 6.2)	0.6341
Aldosterone, ng/L				
Baseline	87 ± 32	73 ± 44		
Change from baseline	41 ± 9*	25 ± 9*	16 (-9 to 41)	0.2117
Copeptin, pmol/L				
Baseline	8.0 ± 3.8	7.7 ± 3.8		
Change from baseline	1.4 ± 0.8	2.5 ± 0.8*	-1.1 (-3.4 to 1.2)	0.3299
NT-proBNP, ng/L				
Baseline	68 ± 50	52 ± 28		
Change from baseline	-8 ± 6	-16 ± 5*	8 (-8 to 24)	0.2959
Velocity time index, s				
Baseline	26.1 ± 4.4	25.5 ± 4.6		
Change from baseline (mean ± SEM)	-0.5 ± 1.1	-2.2 ± 1.7	N/A	N/A
LVEDD, mm				
Baseline	50.1 ± 6.1	49.1 ± 6.5		
Change from baseline (mean ± SEM)	-0.9 ± 0.6	-0.9 ± 0.8	N/A	N/A
LVEF (%)				
Baseline	65 ± 10	71 ± 10		
Change from baseline (mean ± SEM)	5 ± 2	3 ± 3	N/A	N/A

Parameter	Sotagliflozin	Empagliflozin	LS mean difference, sotagliflozin vs empagliflozin (95% CI)	P value
E/e' ratio				
Baseline	8.3 ± 1.9	8.1 ± 1.3		
Change from baseline (mean ± SEM)	0.4 ± 0.6	-0.4 ± 0.4	N/A	N/A
E/A ratio				
Baseline	0.85 ± 0.22	0.76 ± 0.18		
Change from baseline (mean ± SEM)	0.01 ± 0.05	-0.005 ± 0.03	N/A	N/A
Aortic augmentation, %				
Baseline	26 ± 12	26 ± 9		
Change from baseline	0.5 ± 1.9	-0.1 ± 1.9	0.6 (-4.8 to 6.0)	0.8255
Pulse wave velocity, m/s				
Baseline	10.1 ± 1.9	10.2 ± 1.5		
Change from baseline	-0.2 ± 0.2	-0.8 ± 0.2*	0.6 (-0.5 to 1.2)	0.0710

Baseline data are mean ± standard deviation (SD). Change from baseline data within each group are least squares (LS) mean ± standard error (SE) except where noted.

\*Significant change from baseline.

CI, confidence interval; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; N/A, not applicable (statistical analysis not conducted); NT-proBNP, N-terminal pro-B-type natriuretic peptide.

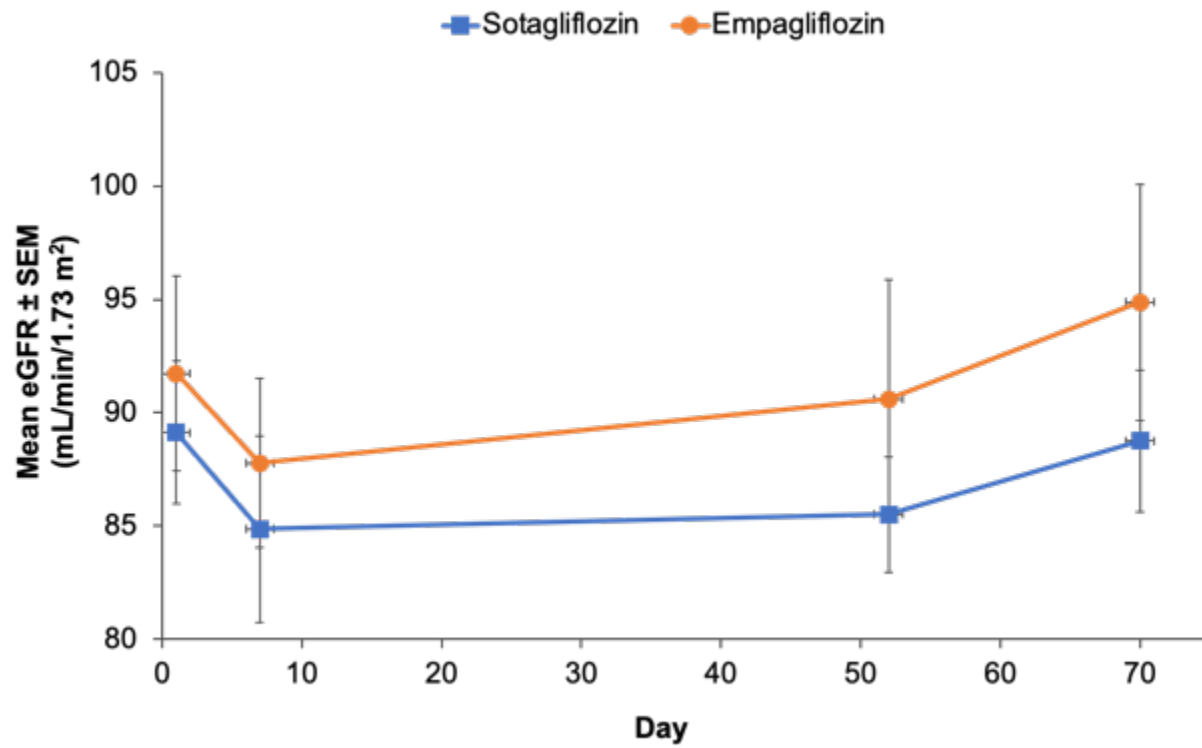
**Table S7.** 24-hour urine collection.

Parameter	Sotagliflozin	Empagliflozin	LS mean difference, sotagliflozin vs empagliflozin (95% CI)	P value
Urine volume, L				
Baseline	1.69 ± 0.65	1.66 ± 0.64		
Change from baseline	0.20 ± 0.14	0.59 ± 0.14	-0.39 (-0.80 to 0.17)	0.0596
<b>Excretion</b>				
Sodium, mmol				
Baseline	118 ± 41	133 ± 41		
Change from baseline	-2.9 ± 9.8	6.0 ± 9.5	-8.9 (-36.9 to 19.2)	0.5240
Potassium, mmol				
Baseline	35 ± 12	36 ± 11		
Change from baseline	2.8 ± 2.6	0.9 ± 2.5	2.0 (-5.3 to 9.3)	0.5884
Calcium, mmol				
Baseline	5.7 ± 2.4	5.6 ± 2.4		
Change from baseline	1.1 ± 0.4*	0.07 ± 0.4	1.2 (0.002 to 2.3)	0.0496
Magnesium, mmol				
Baseline	2.5 ± 0.9	2.8 ± 0.9		
Change from baseline	1.1 ± 0.3*	0.3 ± 0.3	0.8 (0.03 to 1.5)	0.0412
Uric acid, mmol				
Baseline	2.2 ± 0.8	2.2 ± 0.8		
Change from baseline	0.07 ± 0.2	0.06 ± 0.2	0.01 (-0.5 to 0.5)	0.9711
Albumin, mg				
Baseline	18 ± 55	13 ± 20		
Change from baseline	-1.0 ± 1.7	-5.8 ± 1.6*	4.8 (0.1 to 9.5)	0.0476
β-hydroxybutyrate, μmol				
Baseline	65 ± 84	48 ± 119		
Change from baseline	500 ± 218*	101 ± 213	399 (-222 to 1019)	0.2005

Baseline data are mean ± standard deviation (SD). Change from baseline data within each group are least squares (LS) mean ± standard error (SE). CI, confidence interval.

\*Significant change from baseline.

**Figure S3.** Absolute change in estimated glomerular filtration rate (eGFR) over the course of the study, plotted as mean  $\pm$  standard error of the mean (SEM).



**Table S8.** 48-hour feces collection.

<b>Parameter</b>	<b>Sotagliflozin</b>	<b>Empagliflozin</b>	<b>LS mean difference, sotagliflozin vs empagliflozin (95% CI)</b>	<b>P value</b>
Fecal weight g/day				
Baseline	214 ± 105	243 ± 129		
Change from baseline	-3 ± 26	18 ± 29	-22 (-102 to 59)	0.5877
Fecal water, mL/day				
Baseline	121 ± 85	149 ± 96		
Change from baseline	-28 ± 16	8 ± 17	35 (-83 to 13)	0.1445
Glucose excretion, mmol/day				
Baseline	13 ± 12	15 ± 17		
Change from baseline	-2.4 ± 2.7	-1.1 ± 2.4	1.3 (-8.6 to 6.0)	0.7173
Sodium excretion, mmol/day				
Baseline	5 ± 5	6 ± 6		
Change from baseline	-1.2 ± 1.1	-0.4 ± 1.2	-0.8 (-4.2 to 2.6)	0.6274
Potassium excretion, mmol/day				
Baseline	10 ± 5	11 ± 5		
Change from baseline	-0.006 ± 1.4	1.6 ± 1.5	-1.6 (-5.9 to 2.6)	0.4456
Butyrate excretion, mmol/day				
Baseline	2.4 ± 1.7	2.6 ± 2.1		
Change from baseline	-0.3 ± 0.4	0.3 ± 0.4	-0.7 (-1.9 to 0.6)	0.2801
Propionate excretion, mmol/day				
Baseline	3.7 ± 2.5	4.3 ± 2.9		
Change from baseline	-0.7 ± 0.5	-0.1 ± 0.6	-0.6 (-2.2 to 1.0)	0.4330
Acetate excretion, mmol/day				
Baseline	9.6 ± 5.8	11.3 ± 6.8		
Change from baseline	-1.3 ± 1.4	1.1 ± 1.5	-2.4 (-6.6 to 1.8)	0.2562
Firmicutes/bacteroidetes ratio				
Baseline	207 ± 438	101 ± 236		
Change from baseline	-74 ± 37	-60 ± 41	-14 (-126 to 99)	0.8017

Baseline data are mean ± standard deviation (SD). Change from baseline data within each group are least squares (LS) mean ± standard error (SE). CI, confidence interval.

**Table S9.** Summary of key adverse events.

<b>Adverse event, n (%)</b>	<b>Sotagliflozin (n=20)</b>	<b>Empagliflozin (n=21)</b>
Any adverse event	16 (80.0)	13 (61.9)
Severe adverse event	0	0
Serious adverse event	0	0
Adverse event leading to treatment discontinuation	0	0
Events of special interest	4 (20.0)	1 (4.8)
Genital fungal infection	2 (10.0)	0
Urinary tract infection	1 (5.0)	0
Paraesthesia	1 (5.0)	1 (4.8)
Hypoglycemia	0	1 (4.8)*
Gastrointestinal disorders	4 (20.0)	3 (14.3)
Abdominal distension	1 (5.0)	0
Dry mouth	1 (5.0)	1 (4.8)
Feces discolored	1 (5.0)	0
Hemorrhoids	1 (5.0)	0
Nausea	1 (5.0)	0
Vomiting	1 (5.0)	0
Abdominal pain	0	1 (4.8)
Constipation	0	1 (4.8)
Diarrhea	0	1 (4.8)
Dyspepsia		1 (4.8)

\*No. events = 1.