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Received: 21 December 2025 | Revised: 17 January 2026 | Accepted: 20 January 2026

DOI: 10.1111/dom.70520

ORIGINAL ARTICLE

WILEY

Effects of sotagliflozin on markers of volume status and sodium handling in patients with type 1 diabetes: A biomarker analysis of the inTandem3 clinical trial

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Funding information
Lexicon Pharmaceuticals, Inc

Abstract

Aims: Sotagliflozin, an inhibitor of sodium-glucose co-transporter (SGLT)-1 and 2, reduces albuminuria, slows GFR decline, and may have diuretic and osmoregulatory effects. The effect of sotagliflozin added to insulin was assessed on markers of neurohormone activation and volume homeostasis in patients with type 1 diabetes (T1D).

Materials and Methods: This is a post-hoc analysis of the randomised, double-blinded, placebo-controlled inTandem3 trial, which assessed efficacy of sotagliflozin 400 mg/d versus placebo as an adjunct to insulin. The present biomarker analysis included 362 participants (26%) who had biological samples collected at baseline and week 24. Plasma renin, copeptin, serum N-terminal pro b-type natriuretic peptide (NT-proBNP), and markers of tubular injury, inflammation, haematopoiesis, and iron homeostasis were measured at baseline and following week 24 treatment; fractional excretion of lithium (FE_{Li}) and glucose ($FE_{Glucose}$) were calculated.

Results: Participants were 46 years of age (60% female) with a mean eGFR and median UACR of 88.4 mL/min/1.73 m^2 and 7.5 mg/g, respectively. Sotagliflozin increased copeptin, FE_{Li}, and $FE_{Glucose}$ by 33%, 14%, and 60-fold, respectively (all $p < 0.01$), but did not change renin or NT-proBNP (both $p \geq 0.11$) compared to placebo. Further, urinary kidney injury molecule-1 decreased by 19% ($p = 0.03$). Haemoglobin and haematocrit increased (both $p < 0.01$), without altering inflammatory, erythropoietic, or iron biomarkers (all $p \geq 0.11$).

Conclusions: In this T1D population, sotagliflozin increased copeptin levels, FE_{Li}, and $FE_{Glucose}$ without altering renin, reflecting adaptive mechanisms that preserve sodium and fluid balance and protect against volume depletion. Sotagliflozin also decreased markers of kidney injury and increased haematocrit.

KEYWORDS
biomarkers, inflammation, neurohormones, sotagliflozin, tubular injury, type 1 diabetes

1 | INTRODUCTION

Sotagliflozin, a dual inhibitor of sodium-glucose co-transporter (SGLT)-1 and SGLT-2, lowers albuminuria and the rate of glomerular filtration rate (GFR) decline in people with type 1 diabetes (T1D) with and without chronic kidney disease (CKD).[1–4] These kidney protective effects are associated with attenuated proximal tubular glucose and sodium reabsorption.[5] This partially restores tubuloglomerular feedback, which in turn lowers intraglomerular capillary pressure and filtration rate, thereby reducing physical stress on the glomerular filtration barrier, tubular exposure to albumin and nephrotoxic compounds, and oxygen demand for reabsorbing the filtered load.[6] The immediate clinical manifestation of this physiological cascade is an acute, reversible reduction in GFR, followed by long-term preservation of kidney function. Additionally, consistent reductions in haemoglobin A1c, estimated plasma volume, body weight, and blood pressure following treatment have supported the notion that SGLT inhibition attenuates proximal tubular sodium and glucose reabsorption, thereby increasing sodium, glucose, and electrolyte-free water excretion.[4,7,8]

SGLT inhibition may also impact intrarenal physiology in response to changes in intravascular volume. The SGLT inhibitor-induced natriuresis and diuresis are almost immediately limited and increasingly attenuated by downstream tubular responses (e.g., via NKCC2-mediated Na-reabsorption), neurohormonal activity (including renin and vasopressin), and modest lowering in arterial blood pressure.[9] The redistribution of tubular transport from the proximal tubule to downstream segments helps spread the transport workload more uniformly across the nephron, potentially preserving tubular function and integrity to reduce stress on the proximal tubule. This redistribution also raises oxygen demand and transfers metabolic stress from the renal cortex to the more vulnerable outer medulla, which could account for the observed upregulation of stress markers such as haeme oxygenase-1 and the increase in erythropoietin production. Overall, SGLT inhibitors may improve urinary biomarkers of tubular stress, injury, and fibrosis most likely due to reduced glucotoxicity and improved mitochondrial metabolism, subclinical indices that provide insight into mechanisms leading to kidney protection, prior to effects on clinical measures such as eGFR and albuminuria.[10–13] However, the extent to which markers of neurohormonal activation and tubular injury are engaged in people with uncomplicated T1D treated with an SGLT inhibitor remains unclear.[14–16]

In an exploratory analysis of the inTandem3 trial evaluating sotagliflozin added to insulin in people with T1D, we sought to evaluate the effects of sotagliflozin on markers of volume status, tubular activity (principally sodium handling), neurohormonal activation, and tubular injury. Based on prior observations in type 2 diabetes, we hypothesised that 24 weeks of sotagliflozin treatment would increase markers of neurohormonal activation, as a compensatory mechanism to preserve fluid balance, while also improving urinary biomarkers of kidney function—together demonstrating intact kidney mechanisms of SGLT inhibition in T1D.

2 | METHODS

2.1 | Study cohort

The current study is a post-hoc analysis of the randomised, double-blinded, placebo-controlled inTandem3 trial (NCT02531035), which enrolled 1402 people with T1D who were 18 years of age or older, had T1D for at least 1 year, and a HbA1c between 7.0% and 11.0% while on a stable basal dose of insulin. Participants were randomly assigned to receive sotagliflozin (400 mg per day) or placebo for 24 weeks.[1] The present analysis includes 362 (26%) participants from the United States who participated in a separate biomarker sub-study.

2.2 | Experimental protocol and analysis

Participants had biological samples collected at baseline and following 24 weeks of treatment of sotagliflozin or placebo. Blood samples were collected for subsequent analysis of high-sensitivity c-reactive protein (hs-CRP), interleukin-6 (IL-6), N-terminal pro B-type natriuretic peptide (NT-proBNP), C-terminal proendothelin-1 (CT-proET), renin, copeptin, haemoglobin, haematocrit, erythropoietin, iron, ferritin, and hepcidin. Assay methods are provided in Table S1. Plasma and serum samples were stored at −80°C for 104 months (range: 93–116 months) and 96 months (range: 87–107 months), respectively.

Urine samples were also collected at congruent timepoints to measure urinary kidney injury molecule-1 (KIM-1), urinary epidermal growth factor (EGF), and urinary monocyte chemotactic protein-1 (MCP-1). KIM-1, a transmembrane glycoprotein primarily expressed by renal proximal tubular cells, is a sensitive and specific urinary biomarker of proximal tubular injury[10,11]; EGF, expressed by tubular epithelial cells, represents functional tubular mass and is inversely associated with interstitial fibrosis and tubular atrophy[13]; and MCP-1, expressed by a variety of different cell types in the kidney, is associated with the presence of tubulointerstitial lesions.[12] Assay methods are provided in Table S1. Urine samples were stored at −80°C for 95 months (range: 86–105 months). All urinary tubular injury markers were normalised to urinary creatinine.

Serum (S) and urine (U) creatinine (Cr) and lithium (Li) were measured at baseline and week 24 and subsequently used for the calculation of fractional excretion of lithium (FE_{Li}), a surrogate marker for proximal tubular natriuresis. FE_{Li} (%) was calculated as: $(U_{Li} \times S_{Cr})/(S_{Li} \times U_{Cr}) \times 100$. The fractional excretion of glucose ($FE_{Glucose}$) was similarly calculated as: $(U_{Glucose} \times S_{Cr})/(S_{Glucose} \times U_{Cr}) \times 100$. Plasma volume was estimated using the validated Strauss equation.[17,18]

2.3 | Statistical analysis

Statistical analyses were performed using SAS 9.4. Biomarker outcomes were expressed as the geometric mean percentage changes (i.e., log10[change from baseline/value at baseline]) from baseline to week 24. Original values were first log-transformed—except for eGFR,

haematocrit, and haemoglobin—and the treatment effects were assessed using analysis of covariance (ANCOVA). ANCOVA models utilised the geometric mean percentage changes as the dependent variable, the randomisation stratum of body mass index at screening (<25 vs. ≥25 kg/m^2), randomisation stratum of HbA1c at week 2 (≤9 vs. >9%), and randomisation stratum of use of continuous subcutaneous insulin infusion at screening (yes versus no) as fixed categorical effects, and log10(baseline) and log10(baseline)-by-treatment interaction as a covariate. Further, secondary subset analyses were performed to determine if the use of renin-angiotensin system inhibitors (RASi) at baseline modified the effect of sotagliflozin on neurohormone, fractional excretion, and kidney injury markers. The ANCOVA model described above was replicated with the addition of RASi use at baseline as an additional fixed categorical effect. Lastly, correlational analyses were performed using the Spearman Rank correlation to determine associations among changes in biomarkers with sotagliflozin treatment. Continuous data is presented as Mean ± SD or Median (IQR), and discrete data presented is presented as count (percentage). Significance was defined as $p < 0.05$.

3 | RESULTS

Baseline characteristics are presented in Table 1. Mean age and diabetes duration were 46 ± 15 years and 23 ± 14 years, respectively. Body mass index was 29.2 ± 5.5 kg/m^2, and 60% of participants were female. Further, 12% of participants had a history of CVD, 46% were on a background RASi, 11% were on a background diuretic, 9% had an eGFR <60 mL/min/1.73 m^2, and 14% had a UACR ≥30 mg/g. In the current subset of participants, 24 weeks of sotagliflozin lowered HbA1c (placebo: 7.9 to 7.6 vs. sotagliflozin: 8.0 to 7.2%; $p < 0.01$), eGFR (placebo: 86.9 to 86.4 vs. sotagliflozin: 86.7 to 80.5 mL/min/1.73 m^2; $p = 0.02$), UACR (placebo: 6.9 to 7.2 vs. sotagliflozin: 8.3 to 7.3 mg/g; $p = 0.17$), systolic blood pressure (placebo: 120 to 121 vs. sotagliflozin: 121 to 117 mmHg; $p < 0.01$), and estimated plasma volume (placebo: +0.32% vs. sotagliflozin: −8.74%; $p < 0.01$), aligning with prior observations derived from the larger inTandem cohort.

3.1 | Effect of sotagliflozin on neurohormones and fractional excretions

Copeptin, renin, and NT-proBNP, $FE_{Glucose}$, and FE_{Li} at baseline and following 24 weeks of placebo or sotagliflozin are presented in Table 2. Following 24 weeks of sotagliflozin, FE_{Li} was increased by 14% ($p < 0.01$), while $FE_{Glucose}$ increased by 60-fold compared to placebo ($p < 0.01$). Similarly, plasma copeptin increased by 33% following 24 weeks of sotagliflozin ($p < 0.01$). However, the 15% increase in renin and 12% increase in NT-proBNP were not statistically significant (both $p \geq 0.11$). In subset analysis, the effects of sotagliflozin on copeptin and FE_{Li} were not modified based on background use of RASi (both $P_{interaction} \geq 0.27$). RASi users tended to present with increases in renin (31% vs. 0%; $P_{interaction} = 0.04$) and NT-proBNP (17% vs. 4%; $P_{interaction} < 0.01$) with sotagliflozin compared to non-RASi users.

3.2 | Effect of sotagliflozin on kidney injury biomarkers

Urinary creatinine decreased by 17% following 24 weeks of sotagliflozin ($p < 0.01$) compared to placebo. Urinary KIM-1, EGF, and MCP-1 normalised to urinary creatinine at baseline and following 24 weeks of placebo and sotagliflozin are presented in Table 3. Following 24 weeks, normalised urinary KIM-1 decreased by 19% ($p < 0.01$), while normalised urinary MCP-1 increased by 23% ($p < 0.01$) with sotagliflozin compared to placebo. In contrast, the 5% increase in normalised urinary EGF was not significantly different ($p = 0.36$). In subset analysis, the effects of sotagliflozin on normalised urinary KIM-1 and MCP-1 were not modified based on background use of RASi (both $P_{interaction} \geq 0.54$). However, RASi users tended to present with decreases in normalised urinary EGF (−5% vs. 16%; $P_{interaction} < 0.01$) with sotagliflozin compared to non-RASi users.

3.3 | Effect of sotagliflozin on inflammation and haematological and iron biomarkers

Inflammatory (hs-CRP, IL-6, and CT-proET), haematopoietic (haemoglobin, haematocrit, and erythropoietin), and iron (Fe, ferritin, and hepcidin) biomarkers at baseline and following 24 weeks of placebo and sotagliflozin are presented in Table 4. The change in hs-CRP ($p = 0.46$), IL-6 ($p = 0.69$), and CT-proET ($p = 0.62$) was not different following 24 weeks of sotagliflozin compared to placebo. As expected, haemoglobin and haematocrit were both significantly increased with sotagliflozin vs. placebo ($p < 0.01$), while the change in erythropoietin ($p = 0.51$), Fe ($p = 0.26$), ferritin ($p = 0.11$), and hepcidin ($p = 0.39$) were not different between treatments following 24 weeks (Table 4). In participants that received sotagliflozin, we observed a negative association between changes in haematocrit and plasma volume ($R^2 = 0.84$, $p < 0.01$), and a modest negative association between changes in haematocrit and erythropoietin (R^2: 0.05; $p < 0.01$).

4 | DISCUSSION

Our current analysis evaluated the effect of sotagliflozin on tubular function (proximal sodium and glucose handling), neurohormonal activation, and urinary biomarkers of kidney function in people with T1D. Following 24 weeks of treatment, we found that fractional excretion of lithium and glucose, surrogates for proximal tubular natriuresis and glucosuria, increased by 14% and 60-fold, respectively, whereas copeptin, a surrogate for vasopressin release, increased by 33%,

TABLE 1 Participant characteristics.

Variable	Placebo ($n = 193$)	Sotagliflozin ($n = 169$)	Total ($n = 362$)
Demographics			
Age, years	45 ± 14	46 ± 15	46 ± 15
Sex, female	117 (60.6)	100 (59.2)	217 (59.9)
Height, cm	170 ± 19	170 ± 16	170 ± 18
Weight, kg	84.8 ± 19.0	83.5 ± 16.1	84.2 ± 17.7
Body mass index, kg/m^2	29.4 ± 5.8	29.1 ± 5.2	29.2 ± 5.5
History of CVD, *n* (%)	23 (11.9%)	20 (11.8%)	
Smoking status, *n* (%)			
Current	19 (9.8)	19 (11.2)	38 (10.5)
Former	44 (22.8)	34 (20.1)	78 (21.5)
Never	130 (67.4)	116 (68.6)	246 (68.0)
Diabetes duration, years	22.1 ± 13.8	24.2 ± 13.7	23.1 ± 13.8
HbA1c, %	8.05 ± 0.85	8.22 ± 0.95	8.13 ± 0.90
Use of CSII, *n* (%)	82 (42.5)	65 (38.5)	147 (40.6)
Medication			
Diuretics, *n* (%)	21 (10.9)	22 (13.0)	43 (11.9)
RASi, *n* (%)	89 (46.1)	83 (49.1)	172 (47.5)
Beta blockers, *n* (%)	19 (9.8)	18 (10.7)	37 (10.2)
Calcium channel blockers, *n* (%)	15 (7.8)	8 (4.7)	23 (6.4)
Other anti-hypertensive agents, *n* (%)	2 (1.0)	1 (0.6)	3 (0.8)
Statins, *n* (%)	93 (48.2)	72 (42.6)	165 (45.6)
Insulin use			
Daily total insulin dose, IU/day	61.2 ± 31.7	56.8 ± 31.3	59.2 ± 31.6
Daily basal insulin dose, IU/day	32.2 ± 16.6	30.7 ± 16.2	31.5 ± 16.4
Daily bolus insulin dose, IU/day	29.1 ± 20.5	26.1 ± 20.0	27.7 ± 20.3
Lipid profile			
Total cholesterol, mmol/L	4.64 ± 0.92	4.56 ± 0.89	4.60 ± 0.91
HDL cholesterol, mmol/L	1.72 ± 0.54	1.65 ± 0.45	1.69 ± 0.50
LDL cholesterol, mmol/L	2.45 ± 0.76	2.45 ± 0.76	2.45 ± 0.76
Haemodynamics			
Systolic blood pressure, mmHg	121 ± 14	121 ± 14	121 ± 14
Diastolic blood pressure, mmHg	77 ± 9	77 ± 9	77 ± 9
Heart rate, bpm	75 ± 11	75 ± 11	75 ± 11
Kidney function			
GFR, mL/min/1.73 m^2	88.7 ± 21.0	88.0 ± 22.3	88.4 ± 21.6
<60 mL/min/1.73 m^2	17 (8.8)	15 (8.9)	32 (8.8)
≥60 mL/min/1.73 m^2	176 (91.2)	154 (91.1)	330 (91.2)
UACR, mg/g	6.9 (4.6, 14.1)	8.3 (5.0, 20.0)	7.50 (4.7, 15.0)
<30 mg/g	162 (83.9)	134 (79.3)	296 (81.8)
≥30 mg/g	24 (12.4)	26 (15.4)	50 (13.8)

Note: Discrete data presented as count (percentage) and continuous data presented as Mean ± SD or Median (IQR).
Abbreviations: CSII, continuous subcutaneous insulin infusion; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RASi, renin-angiotensin-aldosterone synthase inhibitor; UACR, urinary albumin-to-creatinine ratio.

compared to placebo. Renin and NT-proBNP did not significantly change with sotagliflozin. However, in the subgroup of patients receiving RASi, there was a trend towards increased renin. Furthermore, urinary KIM-1, a biomarker of proximal tubular injury, decreased by 19%, while urinary MCP-1, a biomarker of tubulointerstitial lesions, increased by 23%. Lastly, haemoglobin and haematocrit

TABLE 2 Changes in neurohormones and fractional excretions from baseline following 24-weeks of sotagliflozin treatment.

Variable	Placebo	Sotagliflozin	Difference in LS mean change between placebo and sotagliflozin (95% CI)	*p*-value
Neurohormones				
Renin, ng/L				
Baseline	10.7 (5.9, 20.5)	10.5 (5.7, 21.2)		
Week 24	9.8 (5.6, 20.6)	12.9 (6.0, 22.4)		
LS mean change (95% CI)	0.98 (0.84,1.13)	1.13 (0.97,1.30)	1.15 (0.97, 1.37)	0.11
Copeptin, pmol/L				
Baseline	4.1 (2.8, 7.4)	5.2 (3.0, 8.4)		
Week 24	4.3 (2.8, 7.5)	6.5 (3.7, 11.8)		
LS mean change (95% CI)	1.01 (0.92, 1.12)	1.34 (1.21, 1.48)	1.33 (1.18, 1.49)	<0.01
NT-proBNP, ng/L				
Baseline	29.0 (10.5, 71.5)	36.0 (13.0, 84.0)		
Week 24	26.0 (11.0, 68.0)	38.0 (15.0, 88.0)		
LS mean change (95% CI)	0.97 (0.86, 1.10)	1.09 (0.97, 1.24)	1.12 (0.97, 1.30)	0.13
Fractional excretion				
$Fe_{Glucose}$, %				
Baseline	0.11 (0.05, 1.65)	0.15 (0.06, 2.49)		
Week 24	0.10 (0.05, 0.79)	28.80 (14.42, 39.16)		
LS mean change (95% CI)	0.91 (0.63, 1.32)	56.14 (38.61, 81.34)	61.46 (39.83, 94.83)	<0.01
Fe_{Li}, %				
Baseline	11.2 (8.7, 13.6)	10.4 (7.9, 13.3)		
Week 24	11.1 (8.6, 13.4)	12.0 (9.2, 15.0)		
LS mean change (95% CI)	1.01 (0.94, 1.08)	1.15 (1.07, 1.24)	1.14 (1.05, 1.24)	<0.01

Note: Data at baseline and week 24 presented as median (IQR). Least squared (LS) within-group and between-group change presented as mean (95% confidence interval [CI]). Baseline value is defined as the last value collected prior to the first dose of double-blind study medication. Post-baseline LS means and *p*-values are obtained from ANCOVA model using log10(change from baseline/value at baseline) with treatment, randomisation stratum of BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), randomisation stratum of Week −2 HbA1C (≤9%, >9%), randomisation stratum of Use of CSII at Screening (Yes, No) as fixed categorical effects, and log10(baseline) and log10(baseline)-by-treatment interaction as a covariate.

increased, while erythropoietin and markers of iron homeostasis were not altered by sotagliflozin at 24 weeks. These observations collectively align with observations from cohorts of type 2 diabetes, demonstrating intact kidney mechanisms associated with SGLT inhibition in people with T1D.

SGLT inhibition attenuates glomerular hyperfiltration in people with T1D by reducing proximal tubular sodium and glucose reabsorption, thereby increasing NaCl and fluid delivery to the downstream macula densa. This activates tubuloglomerular feedback and lowers GFR via combined constriction of the afferent arteriole and dilation of the efferent arteriole.[6] This functional haemodynamic response can be observed at the onset of treatment and can persist throughout the duration of treatment, evident by the rebound in GFR observed following SGLT discontinuation. Prior work in people with T1D on background RASi found that the SGLT2 inhibitor empagliflozin increased FE_{Li} following 4 weeks of treatment.[8] In line with these prior observations, the current study found that 24 weeks of sotagliflozin also caused an increase in FE_{Li}. Given that most, but not all, of lithium reabsorption occurs within the proximal tubule,[19] these observations could be interpreted to reflect a decrease in proximal tubular reabsorption of sodium, collectively supporting the notion that increased proximal tubular natriuresis activates tubuloglomerular feedback, leading to an acute reduction in GFR. However, because fractional sodium excretion was not assessed in the current study, the translation towards total natriuresis remains uncertain, and although FE_{Li} provides mechanistic insight into proximal tubular function, it does not fully capture sodium handling along the entire nephron. Notably, there is growing recognition that the natriuretic and diuretic responses to SGLT inhibition may reflect an acute physiological response that diminishes within several days of continuous SGLT inhibitor treatment. This adaptive response is mediated by the upregulation of several tubular counter-regulatory mechanisms, including NKCC2-mediated NaCl reabsorption in the thick ascending limb, which act to re-establish sodium and fluid balance caused by the perturbation to homeostatic set-points governing volume control, thereby reducing the risk of significant volume depletion.[9] In patients

TABLE 3 Changes of kidney function and urinary biomarkers of renal injury from baseline following 24-weeks of sotagliflozin treatment.

Variable	Placebo	Sotagliflozin	Difference in LS mean change between placebo and sotagliflozin (95% CI)	*p*-value
Kidney function				
Urinary creatinine, mg/dL				
Baseline	101 (59, 139)	104 (62, 147)		
Week 24	103 (57, 157)	77 (52, 109)		
LS mean change (95% CI)	0.95 (0.85, 1.06)	0.79 (0.71, 0.88)	0.83 (0.73, 0.95)	<0.01
Urinary albumin, mg/dL				
Baseline	0.6 (0.3, 1.2)	0.8 (0.3, 1.8)		
Week 24	0.7 (0.3, 1.3)	0.5 (0.3, 1.1)		
LS mean change (95% CI)	1.04 (0.89, 1.21)	0.77 (0.66, 0.90)	0.74 (0.62, 0.89)	<0.01
Urinary pH				
Baseline	5.50 (5.50, 6.00)	5.50 (5.50, 6.00)		
Week 24	5.50 (5.50, 6.00)	5.50 (5.00, 5.50)		
LS mean change (95% CI)	1.00 (0.99, 1.01)	0.96 (0.95, 0.98)	0.96 (0.95, 0.98)	<0.01
eGFR, mL/min/1.73m^2[a]				
Baseline	86.9 (76.4, 98.0)	86.7 (73.1, 100.3)		
Week 24	86.4 (74.4, 96.3)	80.5 (72.5, 95.8)		
LS mean change (95% CI)	−2.77 (−4.50, −1.05)	−5.35 (−7.13, −3.57)	−2.6 (−4.8, −0.4)	0.02
UACR, mg/g				
Baseline	6.9 (4.6, 14.1)	8.3 (5.0, 20.0)		
Week 24	7.2 (4.6, 13.9)	7.3 (5.0, 14.3)		
LS mean change (95% CI)	1.10 (0.96, 1.26)	0.99 (0.86, 1.13)	0.90 (0.77, 1.05)	0.17
Tubular injury				
Normalised urinary KIM-1				
Baseline	7.80 (5.00, 13.13)	8.36 (4.83, 14.19)		
Week 24	7.23 (4.12, 13.33)	5.90 (3.21, 9.29)		
LS mean change (95% CI)	0.89 (0.75, 1.05)	0.72 (0.62, 0.85)	0.81 (0.67, 0.98)	0.03
Normalised urinary EGF				
Baseline	87.2 (59.1, 118.1)	90.2 (60.6, 119.5)		
Week 24	89.1 (63.8, 117.1)	91.4 (61.2, 120.4)		
LS mean change (95% CI)	0.99 (0.91, 1.07)	1.03 (0.95, 1.12)	1.05 (0.95, 1.15)	0.36
Normalised urinary MCP-1				
Baseline	1.10 (0.75, 1.62)	1.20 (0.84, 1.92)		
Week 24	1.10 (0.77, 1.57)	1.38 (0.87, 2.06)		
LS mean change (95% CI)	0.93 (0.83, 1.04)	1.14 (1.01, 1.28)	1.23 (1.07, 1.41)	<0.01

Note: Data at baseline and week 24 presented as median (IQR). Least squared (LS) within-group and between-group change presented as mean (95% confidence interval [CI]). Baseline value is defined as the last value collected prior to the first dose of double-blind study medication. Post-baseline LS means and *p*-values are obtained from ANCOVA model using log10(change from baseline/value at baseline) with treatment, randomisation stratum of BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), randomisation stratum of Week −2 A1C (≤9%, >9%), randomisation stratum of Use of CSII at Screening (Yes, No) as fixed categorical effects, and log10(baseline) and log10(baseline)-by-treatment interaction as a covariate.

[a]This variable was not log-transformed and expressed in per unit change.

with type 2 diabetes, the SGLT2 inhibitor dapagliflozin did not significantly alter 24-h urinary sodium excretion,[20] even when sodium intake was rigorously controlled.[21]

In the current study, we also observed a 60-fold increase in the fractional excretion of glucose following 24 weeks of sotagliflozin treatment. While this reduction in glucose reabsorption is often accompanied by an increase in free-water clearance (i.e., osmotic diuresis), the activation of additional compensatory mechanisms also acts to minimise fluctuations in body fluid volume. One notable response is the reflex increase in copeptin,[22] a surrogate marker of vasopressin, which increases fluid intake and renal water reabsorption. This has been previously shown in animal models of type 2 diabetes,[23] and in people with type 2 diabetes,[16] T1D,[14] and heart failure[15] shortly following the initiation of SGLT2 inhibition. In support of these

TABLE 4 Changes of inflammatory and haematopoietic markers from baseline following 24-weeks of sotagliflozin treatment.

Variable	Placebo	Sotagliflozin	Difference in LS mean change between placebo and sotagliflozin (95% CI)	*p*-value
Inflammatory markers				
hs-CRP, mg/L				
Baseline	2.15 (0.86, 5.40)	2.13 (0.74, 5.13)		
Week 24	2.03 (0.92, 4.85)	2.25 (0.89, 4.77)		
LS mean change (95% CI)	1.01 (0.88, 1.17)	1.08 (0.94, 1.24)	1.07 (0.90, 1.26)	0.46
IL-6, ng/L				
Baseline	2.60 (1.80, 4.00)	2.50 (1.60, 4.50)		
Week 24	2.80 (1.80, 4.10)	2.70 (1.60, 4.40)		
LS mean change (95% CI)	1.06 (0.97, 1.16)	1.04 (0.96, 1.14)	0.98 (0.88, 1.09)	0.69
CT-proET, pmol/mL				
Baseline	45.1 (39.7, 54.4)	46.2 (38.7, 53.1)		
Week 24	46.0 (40.1, 54.9)	48.8 (40.7, 58.6)		
LS mean change (95% CI)	1.00 (0.91, 1.10)	1.03 (0.94, 1.13)	1.03 (0.92, 1.14)	0.62
Haematopoietic markers				
Haemoglobin, g/dL[a]				
Baseline	13.8 (12.9, 14.8)	13.8 (12.9, 14.8)		
Week 24	13.9 (13.0, 14.8)	14.3 (13.5, 15.3)		
LS mean change (95% CI)	0.12 (−0.03, 0.28)	0.61 (0.45, 0.77)	0.49 (0.31, 0.67)	<0.01
Haematocrit, %[a]				
Baseline	41 (39, 44)	41 (39, 44)		
Week 24	41 (39, 44)	43 (41, 46)		
LS mean change (95% CI)	−0.07 (0.58, 0.44)	1.92 (1.41, 2.44)	1.99 (0.39, 2.59)	<0.01
Erythropoietin, pg/mL				
Baseline	79.5 (61.0, 119.8)	90.0 (68.4, 130.0)		
Week 24	88.0 (61.0, 128.0)	94.0 (71.0, 120.0)		
LS mean change (95% CI)	1.05 (0.97, 1.13)	1.08 (1.00, 1.16)	1.03 (0.94, 1.12)	0.51
Iron metabolism				
Serum Fe, µmol/L				
Baseline	15.2 (11.6, 19.5)	14.8 (11.7, 19.4)		
Week 24	14.8 (11.2, 20.1)	15.0 (11.1, 19.3)		
LS mean change (95% CI)	1.05 (0.98, 1.12)	1.00 (0.94, 1.07)	0.96 (0.88, 1.03)	0.26
Serum Ferritin, µg/L				
Baseline	65.5 (36.0, 128.0)	80.0 (39.0, 131.0)		
Week 24	69.0 (34.0, 137.0)	71.0 (42.0, 119.0)		
LS mean change (95% CI)	1.04 (0.97, 1.12)	0.98 (0.91, 1.05)	0.94 (0.86, 1.02)	0.11
Plasma hepcidin, ng/mL				
Baseline	12.65 (4.95, 21.23)	12.19 (5.81, 23.50)		
Week 24	11.46 (4.66, 19.61)	11.55 (5.94, 21.62)		
LS mean change (95% CI)	0.95 (0.72, 1.25)	0.83 (0.63, 1.09)	0.87 (0.63, 1.20)	0.39

Note: Data at baseline and week 24 presented as median (IQR). Least squared (LS) within-group and between-group change presented as mean (95% confidence interval [CI]). Baseline value is defined as the last value collected prior to the first dose of double-blind study medication. Post-baseline LS means and *p*-values are obtained from ANCOVA model using log10(change from baseline/value at baseline) with treatment, randomisation stratum of BMI at Screening (<25 kg/m^2, ≥25 kg/m^2), randomisation stratum of Week −2 A1C (≤9%, >9%), randomisation stratum of Use of CSII at Screening (Yes, No) as fixed categorical effects, and log10(baseline) and log10(baseline)-by-treatment interaction as a covariate.

[a]This variable was not log-transformed and expressed in per unit change.

prior studies, the current study also observed a 33% increase in copeptin following 24 weeks of sotagliflozin treatment. In addition to the osmotic diuretic effect of SGLT inhibition, reductions in circulating blood volume—a non-osmotic stimulus for vasopressin—and potential initial mild reductions in blood pressure might contribute to reflex activation of vasopressin-mediated compensatory tubular mechanism aimed at maintaining fluid balance.

The effects of SGLT inhibition on renin release from the juxtaglomerular cells are complex and driven by several competing mechanisms. SGLT inhibition can stimulate renin via reductions in renal perfusion pressure (through increased tubuloglomerular feedback–mediated afferent vasoconstriction, modest extracellular volume contraction, and lower blood pressure), whereas increased sodium delivery to the macula densa tends to suppress renin release. Despite these opposing signals, prior studies consistently report early increases in circulating renin, possibly reflecting transient activation of the systemic RAS. In type 2 diabetes, a non-randomised open-label, single arm study observed an ~77% increase in renin following 2 weeks of dapagliflozin and stringent control of sodium intake,[7] while a post hoc analysis of two double-blind placebo-controlled crossover studies observed an ~47% increase in renin following 6–12 weeks of dapagliflozin.[16] In people with T1D on background RASi, a cross-over study observed an ~30% increase in renin following 4 weeks of empagliflozin.[8]

The current study reported a nominal ~15% increase in renin that was not statistically significant following 24 weeks of sotagliflozin. Considering the longer follow-up (24 weeks) in the current study compared to prior studies, one potential reason for the divergent findings could pertain to diminished renin release over durations of treatment. This may reflect adaptive physiological mechanisms, such as enhanced water and sodium conservation, which could blunt the stimulus for renin activation despite ongoing treatment. Alternatively, the current study only included ~50% of participants on background RASi, whereas prior studies in type 2 diabetes enrolled participants on background RASi,[7,16] and prior work in T1D included a 4-week run-in period of RASi treatment.[8] In a secondary subset analysis, we observed that renin tended to increase in participants on background RASi but not in RASi naïve participants. This observation may suggest that chronic RASi removes angiotensin II–mediated short-loop negative feedback on juxtaglomerular cells, thereby sensitising renin secretion in response to the haemodynamic changes induced by SGLT inhibition. In addition, under RAS-blockade the balance of angiotensin-peptide signalling may shift towards activation of the protective ACE2/Ang-(1–7)/Mas receptor axis,[24] which could promote vasodilation to modulate renal vascular tone and further influence renin dynamics. Taken together, these findings suggest that the renin response to SGLT inhibition could be time-dependent or contingent on concomitant RAS inhibitor therapy. Finally, the current study found that 24 weeks of sotagliflozin has no impact on NT-proBNP. This observation appears consistent with prior studies in people with type 2 diabetes, where 6–12 weeks of dapagliflozin treatment had no effect on NT-proBNP,[16] and in people with heart failure, where 2–24 weeks of SGLT2 inhibition also had no effect.[25–27] In our subgroup analysis, we somewhat unexpectedly found that participants on background RASi experienced a modest increase in NT-proBNP in response to sotagliflozin. This may reflect a transient haemodynamic or volume-mediated compensatory effect, potentially unmasked by chronic inhibition of angiotensin II signalling, as discussed above. Alternatively, it could indicate altered myocardial or renal signalling in the context of combined RAAS- and SGLT2 inhibition. Given the exploratory nature of this analysis in a small subgroup, a chance finding cannot be excluded.

Previous urinary biomarkers analyses have shown that empagliflozin reduced urinary KIM-1 by ~34% following 6 months of treatment in 79 participants with type 2 diabetes.[28] These observations align with the significant 19% reduction in urinary KIM-1 following 24 weeks of sotagliflozin observed in the present study. Given that KIM-1 is a sensitive marker of proximal tubular injury, these findings collectively support the concept that SGLT inhibition protects the proximal tubule[10,11]—a key site of diabetes-related kidney injury—because this segment is responsible for reabsorbing a large fraction of glomerular filtrate, imposing high oxygen demand, particularly in the diabetic milieu. SGLT inhibition shifts a large portion of the glucose, sodium, and fluid reabsorption downstream, thereby more equally redistributing the transport workload along the nephron, which may help preserve tubular function and reduce long-term tubular stress. Moreover, prior studies have shown that SGLT inhibition can increase EGF expression in people with type 2 diabetes, a urinary biomarker for kidney distal tubular cell integrity.[29] However, this was not observed in the current study, potentially reflecting the redistribution of tubular workload towards the distal segments, described above. Somewhat unexpectedly, urinary MCP-1 normalised to creatinine increased following sotagliflozin; however, upon further review, we note that absolute urinary MCP-1 concentrations remained unchanged (data not shown). This suggests that the apparent rise in normalised urinary MCP-1 primarily reflects a reduction in urinary creatinine excretion with sotagliflozin, possibly due to altered tubular creatinine handling or other hitherto unidentified mechanisms, rather than indicating an increase in tubular inflammation. Finally, sotagliflozin significantly increased haemoglobin and haematocrit, accompanied by a reduction in estimated plasma volume, without meaningful changes in erythropoietin, iron, ferritin, or hepcidin, indicating that haemoconcentration rather than enhanced erythropoiesis was the primary driver. The strong negative correlation between changes in haematocrit and plasma volume ($R^2 = 0.84$, $p < 0.01$) reinforces the central role of volume contraction. Yet, the modest correlation between haematocrit and erythropoietin ($R^2 = 0.05$, $p < 0.01$) also suggests limited erythropoietin stimulation, likely reflecting a shift in tubular workload and oxygen demand from the cortex to the outer medulla, where local hypoxia can activate hypoxia-inducible factors and trigger adaptive erythropoietin secretion by corticomedullary interstitial cells.[30]

Several limitations should be considered when interpreting the results of this post-hoc analysis. First, this analysis represents a biomarker sub-study of the larger inTandem-3 trial, including 362 participants (26% of the full trial cohort) exclusively from the United States, which may limit generalizability to the broader T1D population. Compared with the overall inTandem-3 population, the biomarker subcohort was modestly older, included a higher proportion of women, and had a longer duration of T1D and a higher BMI (Table S2). However, the sub-study cohort demonstrated comparable changes in

HbA1c, eGFR, UACR, systolic blood pressure, and estimated plasma volume, supporting its representativeness of inTandem-3. Second, while the assessment after 24 weeks can capture tubular and neurohormonal responses to SGLT inhibition, we were not able to capture early, acute effects occurring within days, which often precede compensatory adaptations. Observing these acute responses would have provided a more complete understanding of the temporal dynamics of adaptation. Third, FE_{Li} and copeptin were employed as surrogate markers of proximal tubular sodium handling and vasopressin-mediated antidiuretic activity, respectively. While informative, these measures may not fully capture in vivo physiology. Fourth, dietary sodium and fluid intake were not controlled in this trial, potentially contributing to inter-individual variability in renal and neurohormonal responses.

In conclusion, in adults with T1D and generally preserved kidney function, sotagliflozin robustly increased copeptin levels and FE_{Li}, indicating dynamic compensatory mechanisms that tightly safeguard fluid and sodium balance and prevent volume depletion in response to SGLT inhibition. Sotagliflozin also increased haemoglobin and haematocrit through haemoconcentration rather than erythropoiesis, as evidenced by the strong inverse association with estimated plasma volume and only minimal correlation with erythropoietin.

AUTHOR CONTRIBUTIONS

All authors developed the concept and designed the analysis. Manon Girard performed the analysis. All authors reviewed the results and interpreted the findings. Massimo Nardone and Marcel H. A. Muskiet wrote the first draft of the manuscript. Erik Moedt, Hiddo J. L. Heerspink, Michael J. Davies, Manon Girard, and David Z. I. Cherney reviewed/edited the manuscript. All authors approved the final version of the manuscript. Michael J. Davies is the guarantor of the work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

ACKNOWLEDGEMENTS

The authors thank the inTandem-3 trial investigators, staff, and patients for their participation. Massimo Nardone is supported by a Banting and Best Diabetes Centre Postdoctoral fellowship at the University of Toronto. David Z. I. Cherney receives funding from the University of Toronto Department of Medicine Eliot Phillipson Clinician Scientist Training Program, the KRESCENT Postdoctoral Fellowship (co-sponsored by the Kidney Foundation of Canada, the Canadian Society of Nephrology, and the Canadian Institute of Health Research), the Banting and Best Diabetes Center Postdoctoral fellowship at the University of Toronto, and CIHR Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Research Award. David Z. I. Cherney is supported by a Department of Medicine, the University of Toronto Merit Award, and receives support from the Canadian Institutes of Health Research, Diabetes Canada, and the Heart and Stroke/Richard Lewar Center of Excellence in Cardiovascular Research. David Z. I. Cherney is also the recipient of a 5-year CIHR-Kidney Foundation of Canada Team Grant award, with additional support from JDRF. Marcel H. A. Muskiet is supported by a Professor Michaela Diamant Postdoctoral Fellowship Grant.

FUNDING INFORMATION

The inTandem programme was supported and conducted by Lexicon Pharmaceuticals, Inc.

CONFLICT OF INTEREST STATEMENT

Massimo Nardone and Erik Moedt declare no competing interests. Hiddo J. L. Heerspink reports funding to conduct clinical trials from AstraZeneca, Bayer AG, Boehringer Ingelheim, Janssen Research & Development, and Novo Nordisk A/S (all to the University of Groningen); consulting fees from AstraZeneca, Alexion Pharmaceuticals, Inc., Bayer AG, Boehringer Ingelheim, Chinook Therapeutics, CSL Behring, Dimerix Ltd., Eli Lilly and Company, Gilead Sciences, Janssen Research & Development, Novartis AG, Novo Nordisk A/S, and Travere Therapeutics; payment of honoraria for lectures from AstraZeneca, Bayer AG, and Novo Nordisk A/S; support for travelling to and attending the American Diabetes Association meeting and American Society of Nephrology meeting from AstraZeneca and Eli Lilly and Company (to Hiddo J. L. Heerspink and the University of Groningen); and receipt of the study drug from AstraZeneca, Bayer AG, Boehringer Ingelheim, Janssen Research & Development, and Novo Nordisk A/S. Michael J. Davies and Manon Girard are employees of Lexicon Pharmaceuticals, Inc. and may hold stock or stock options in the company. David Z. I. Cherney has received consulting fees, speaking honoraria, or both from Janssen, Bayer, Boehringer Ingelheim, Eli Lilly, AstraZeneca, Merck, Prometic, and Sanofi; and has received operating funds from Janssen, Boehringer Ingelheim, Eli Lilly, Sanofi, AstraZeneca, and Merck. Marcel H. A. Muskiet reports consulting fees, speaking honoraria, or both from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, and Novo Nordisk A/S (all honoraria to his institution).

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70520.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Lexicon Pharmaceuticals, Inc. but restrictions apply to the availability of these data and therefore are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Lexicon Pharmaceuticals, Inc.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Nardone M, Moedt E, Heerspink HJL, et al. Effects of sotagliflozin on markers of volume status and sodium handling in patients with type 1 diabetes: A biomarker analysis of the inTandem3 clinical trial. *Diabetes Obes Metab*. 2026;1-10. doi:10.1111/dom.70520