ORIGINAL ARTICLE

Effects of the dual sodium–glucose linked transporter inhibitor, licogliflozin vs placebo or empagliflozin in patients with type 2 diabetes and heart failure

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Aims: Explore the efficacy, safety and tolerability of the dual sodium–glucose cotransporter (SGLT) 1 and 2 inhibitor, licogliflozin in patients with type-2 diabetes mellitus (T2DM) and heart failure.

Methods: This multicentre, parallel-group phase IIA study randomized 125 patients with T2DM and heart failure (New York Heart Association II–IV; plasma N-terminal pro b-type natriuretic peptide [NT-proBNP] >300 pg/mL) to licogliflozin (2.5 mg, 10 mg, 50 mg) taken at bedtime, empagliflozin (25 mg) or placebo (44 patients completed the study). The primary endpoint was change from baseline in NT-proBNP after 12 weeks. Secondary endpoints included change from baseline in glycated haemoglobin, fasting plasma glucose, weight, blood pressure, fasting lipid profile, high-sensitivity c-reactive protein, and safety and tolerability.

Results: Licogliflozin 10 mg for 12 weeks significantly reduced NT-proBNP vs placebo (Geometric mean ratio 0.56 [95% confidence interval: 0.33, 0.95], $P = .033$). A trend was observed with 50 mg licogliflozin (0.64 [95% confidence interval: 0.40, 1.03], $P = .064$), with no difference between licogliflozin and empagliflozin. The largest numerical decreases in glycated haemoglobin were with licogliflozin 50 mg (−0.58 ± 0.34%) and empagliflozin (−0.44 ± 1.18%) vs placebo (−0.04 ± 0.91%). The reduction in body weight was similar with licogliflozin 50 mg (−2.15 ± 2.40 kg) and empagliflozin (−2.25 ± 1.89 kg). A numerical reduction in systolic blood pressure was seen with licogliflozin 50 mg (−9.54 ± 16.88 mmHg) and empagliflozin (−6.98 ± 15.03 mmHg) vs placebo (−2.85 ± 11.97 mmHg). Adverse events (AEs) were mild, including hypotension (6.5%), hypoglycaemia (8.1%) and inadequate diabetes control (1.6%). The incidence of diarrhoea (4.9%) was lower than previously reported.

Conclusion: The reduction in NT-proBNP with licogliflozin suggests a potential benefit of SGLT1 and 2 inhibition in patients with T2DM and heart failure.

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1 | INTRODUCTION

Type-2 diabetes mellitus (T2DM) is associated with a high risk of cardiovascular (CV) disease and related complications, such as heart failure (HF). T2DM is associated with an increased incidence of HF and the risk of HF hospitalizations/mortality is higher in patients with the condition compared to those without.[1-3] HF is among the most common CV complications of T2DM, with an incidence greater than that of myocardial infarction (MI) or stroke.[4]

Selective sodium–glucose cotransporter (SGLT2) inhibitors have been developed as antidiabetes drugs and lead to a reduction in glycated haemoglobin (HbA$_{1c}$) of up to 1%.[5,6] A striking CV benefit of SGLT2 inhibitors has recently been demonstrated in patients with T2DM at high risk for CV events, where a significant reduction in the major adverse cardiac events endpoint (MACE, a composite of CV death, nonfatal MI and nonfatal stroke) and a reduction in HF hospitalizations was seen with empagliflozin and canagliflozin.[7,8] Further evidence was provided in a more recent study, which demonstrated a reduced risk of the composite of CV death or HF hospitalizations with dapagliflozin treatment,[9] a benefit driven by a reduction in HF hospitalizations. These findings are supported by the results of a recent, real-world evidence study.[10] The specific mechanisms underlying the benefit associated with SGLT2 inhibitors are unclear, but may be attributed to specific effects of SGLT2 inhibition on renal sodium and glucose handling,[11] which include the switch of cardiac metabolism from free fatty acid oxidation to β-hydroxybutyrate oxidation, enhanced oxygen supply due to haemoconcentration,[12] and inhibition of sodium-hydrogen exchange.[13] Since HF is the most frequent CV complication of T2DM, several large-scale trials have been designed to determine a potential benefit of SGLT2 inhibitors in patients with HF.[14-17]

Licogliflozin is a combined inhibitor of SGLT1 and SGLT2 and is hypothesized to further enhance the effects on renal sodium and glucose handling via inhibition of both cotransporter subtypes in the proximal renal tubule.[18] SGLT1 is also expressed in the small intestine, where it is required for glucose and galactose absorption. Enteric inhibition of SGLT1 has the potential of achieving weight loss through glucose and galactose malabsorption,[19] calorie wasting and other potential endocrine-based mechanisms.[18] Dual SGLT1 and 2 inhibitors have been shown to improve HbA1c in patients with T2DM[20] and to have beneficial effects on body weight in both patients with T2DM and patients with obesity.[18,20] SGLT1 receptors are also specifically expressed in the human heart, although the role of their expression in this tissue is not fully understood.[21,22]

The aim of this study was to assess the efficacy (including N-terminal pro b-type natriuretic peptide [NT-proBNP] measurement as a surrogate parameter for HF severity), safety and tolerability of licogliflozin in patients with T2DM, cardiac disease and HF.

What is already known about this subject

- Sodium–glucose cotransporter (SGLT2) inhibitors have been associated with reduced cardiovascular risk, including reduction in heart failure hospitalizations. However, the mechanism underlying these effects remains unclear. There are also limited data on the effect on N-terminal pro b-type natriuretic peptide (NT-proBNP), a biomarker of cardiac wall stress that is commonly elevated in patients with heart failure.
- SGLT1 and 2 inhibition with licogliflozin has shown beneficial effects on glucose handling in patients with type-2 diabetes mellitus (T2DM) and on body weight in patients with obesity
- However, the effects of SGLT1 and 2 inhibition in patients with T2DM and heart failure are unknown

What this study adds

- This is the first study to evaluate the effects of SGLT1 and 2 inhibition on NT-proBNP in patients with T2DM and heart failure, with results showing significant reductions in NT-proBNP with licogliflozin vs placebo
- Secondary analyses suggest reductions in glycated haemoglobin, body weight and systolic blood pressure following treatment with licogliflozin, in line with previously published data
- Licogliflozin treatment was safe and well-tolerated, with no new safety findings reported

2 | METHODS

2.1 | Study design and oversight

This multicentre, double-blind, double-dummy, parallel-group phase II study randomized patients to 1 of 3 doses of licogliflozin, placebo or empagliflozin (Figure 1). The trial was conducted in 55 centres across 21 countries. Patients meeting all the eligibility criteria at screening were entered into the placebo run-in period, where they received single blind placebo medication for 2 weeks (to familiarize with the study-drug intake schedule and to allow correction of any hypovolaemia). Eligible patients were then randomized to either licogliflozin (2.5, 10 or 50 mg once daily [qd], taken at bedtime), empagliflozin (up-titrated from 10 to 25 mg qd after 2 weeks to minimize potential adverse effects—taken in the morning) or their
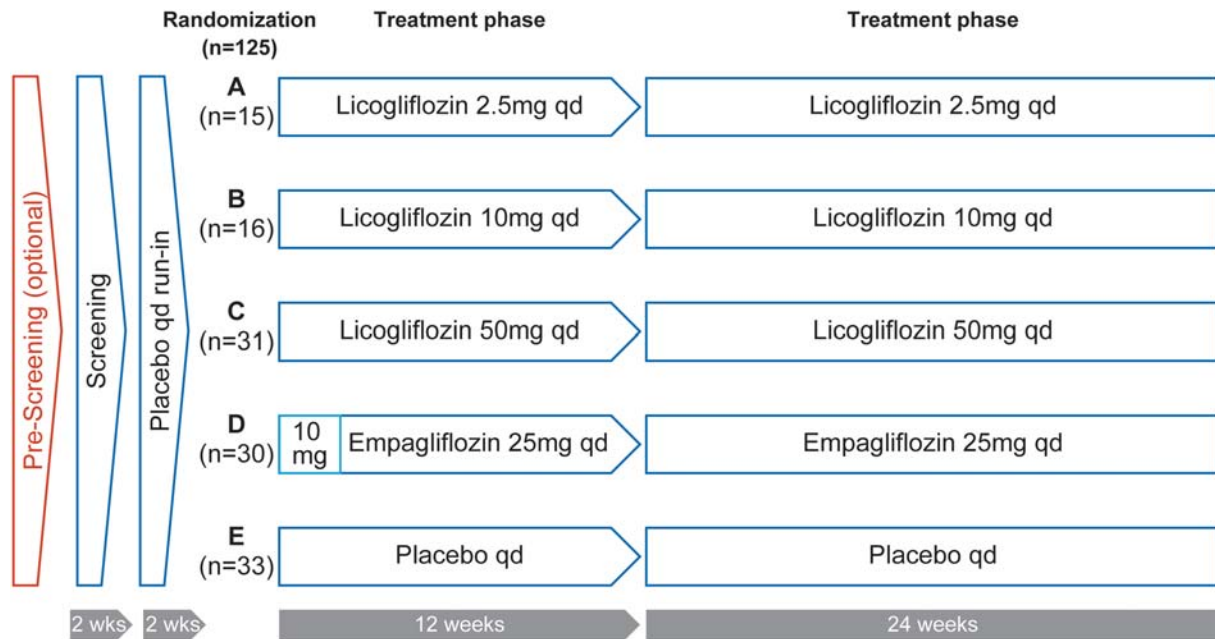
FIGURE 1 Study design. qd, once a day

corresponding placebo (morning or night). Licogliflozin 50 mg was chosen as the highest dose in this study, based on the previous proof of concept study, in which a urinary glucose excretion (UGE) over 24 hours of ~100 g was observed following once daily dosing with licogliflozin 15 mg in patients with T2DM.[18] Gastrointestinal tolerability was also better with lower doses of licogliflozin (30 mg qd vs 150 mg qd).[18] Empagliflozin was included as a comparator due to its known CV benefit in patients with T2DM.[8]

Following randomization, patients attended the study site again at 12 weeks for the evaluation of efficacy (change in NT-proBNP), safety and tolerability. Following the last study visit at week 12, patients continued with the same assigned treatment for a further 24 weeks. Long-term efficacy, tolerability and safety were planned for evaluation. This study was prematurely discontinued due to slow enrolment. Only a limited number of patients had completed the core 12-week period of the study when the study was stopped (n = 44), with just 1 patient completing the originally planned 24-week follow-up period. Therefore, the interpretation of the data presented is mainly descriptive and limited to the main study period, i.e. the first 12 weeks.

This study was designed and implemented in accordance with ICH Harmonized Tripartite Guidelines for Good Clinical Practice and according to the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board/Independent Ethics Committee of each centre where patients were recruited. All patients provided written informed consent for participation prior to randomization. Site monitoring was carried out by Novartis. The study investigator (or a designated staff member) was responsible for data collection and reporting. The study sponsor had access to the trial database and performed statistical analyses. All authors had full access to the study data

and had the final responsibility for the decision to submit this manuscript for publication.

2.2 | Participants

The goal was to randomize approximately 496 patients, with 125 randomized before early study termination. Patients (≥ 18 years) with T2DM, with HbA1c ≥ 6.5% and ≤ 10%, and a body mass index of ≥22 kg/m^2 at screening were included in this study. Eligible patients were also required to have an estimated glomerular filtration rate ≥45 mL/min/1.73m^2, plasma NT-proBNP >300 pg/mL and documented symptomatic chronic HF (New York Heart Association [NYHA] II–IV) at screening. Those receiving angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, angiotensin receptor–neprilysin inhibitors and/or β-blockers were required to be on stable doses.

Patients with type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury or secondary forms of diabetes were excluded from this study. Other key exclusion criteria included a history of ketoacidosis, recent MI or CV intervention, or low blood pressure (BP; systolic BP ≤ 100 mmHg). The full list of inclusion and exclusion criteria can be found in the Appendix.

2.3 | Study procedures

At the end of the run-in period, participants were randomized to either licogliflozin (2.5 mg, 10 mg or 50 mg qd in a 1:1:2 ratio), empagliflozin (:2 ratio) or placebo (:2 ratio). Randomization was performed with the help of a centralized computer system (Interactive

Response Technology) with patients stratified according to geographical region and left ventricular ejection fraction (LVEF: <45% vs ≥45%). All doses of licogliflozin (tablets), empagliflozin (over-encapsulated tablet) or corresponding placebo were administered orally twice daily. In the licogliflozin treatment arm, 1 licogliflozin tablet was taken at bedtime and the corresponding empagliflozin placebo (capsule) was taken in the morning (with or without food). In the empagliflozin arm, 1 empagliflozin capsule was taken in the morning and the corresponding licogliflozin placebo was taken at bedtime. Patients in the corresponding placebo arm took 1 capsule in the morning and 1 tablet at bedtime (double-dummy design).

For assessment of efficacy, NT-proBNP was evaluated at baseline and following 12 weeks of treatment. Other efficacy parameters included HbA1c, fasting plasma glucose (FPG), lipids, high-sensitivity C-reactive protein (hsCRP), body weight, body mass index, blood pressure (SBP, DBP) and NYHA class. Left atrial size and volume were assessed by echocardiography at week −2 (run-in) and week 12. All assessments were completed and analysed at a central laboratory.

Safety assessments included collection of all adverse events (AEs) and serious AEs along with their severity and relationship to study drug, and pregnancies. Haematology, blood chemistry and urine as well as vital signs, physical condition and body weight were regularly monitored. Suspected cases of ketoacidosis were reviewed by a Ketoacidosis Adjudication Committee.

2.4 | Study endpoints

The primary endpoint was the change from baseline in NT-proBNP relative to placebo following 12-weeks of treatment. Secondary endpoints included the effects of licogliflozin vs placebo at 12 weeks on HbA1c, FPG, weight, BP, lipids, hsCRP, urinary glucose and sodium excretion, echocardiography and NYHA class, and the effects of licogliflozin vs empagliflozin on the same. Safety and tolerability over 12-weeks were also assessed. Key exploratory endpoints included comparison of licogliflozin vs empagliflozin at 12 weeks on change from baseline in NT-proBNP, echocardiographic parameters and NYHA class.

2.5 | Statistical analysis

The study was designed to randomize 496 patients in total, aiming to provide sufficient power to detect a dose response signal in NT-proBNP (based on log-transformed ratio of NT-proBNP at week 12 compared to baseline), using Multiple Comparison Procedure-Modelling (MCP-MOD).[23,24] Due to early study termination and a smaller sample size than originally planned, a mixed effect model of repeated measures was performed in place of the MCP-MOD, as an exploratory analysis for NT-proBNP. The change from baseline in log-transformed NT-proBNP was used as the outcome variable. The model included LVEF at baseline (<45% vs ≥45%), treatment group (licogliflozin 2.5, 10 or 50 mg qd, empagliflozin, or placebo), visit and

treatment group-by-visit interaction as fixed-effect factors, baseline log-transformed NT-proBNP as a covariate, and an unstructured, within-subject covariance. NT-proBNP data up to week 12 were included in the model. The adjusted mean differences (back-transformed as ratios) for each treatment group at week 4 and week 12 were estimated from this model. A P-value <.05 (2-sided) was considered statistically significant. Statistical comparisons between the secondary endpoint data were not tested due to the limited sample sizes. Patient disposition, demographics, and primary and secondary efficacy analyses are described using summary statistics.

2.6 | Role of the funding source

Novartis sponsored the study, designed the study and analysed the data.

2.7 | Data sharing statement

Novartis is committed to sharing, with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[25] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[26]

3 | RESULTS

3.1 | Patient disposition and characteristics

Of the 142 patients enrolled in the run-in for this this study, 125 were randomized (1 was mis-randomized, never took any study drug and was excluded from data analyses) to study treatments: licogliflozin 2.5 mg (n = 15), licogliflozin 10 mg (n = 16), licogliflozin 50 mg (n = 31), empagliflozin 25 mg (n = 30) and placebo (n = 33; Figure S1). Of the 125 patients randomized in the study, 75 were discontinued due to early study termination, with 44 patients completing the 12-week study. Three patients permanently discontinued from study treatment due to AEs. Two patients died (one death in each of the licogliflozin 10 mg and placebo groups—not considered to be study-

drug related) while a third patient discontinued from the empagliflozin group due to increased blood creatinine levels.

The median age of the patients was 70.0 years (interquartile range: 62.0–74.0) and most were male (71.8%), Caucasian (91.1%) and enrolled in Europe (70.2%; Table 1). An LVEF of <45% was observed in approximately 25% of patients. Baseline NT-proBNP was comparable in all groups with the exception of the licogliflozin 50 mg group, where the median baseline value was substantially lower (605 pg/mL 50 mg licogliflozin vs >890 pg/mL in all other groups). For full details on smoking status, comorbidities, concomitant medications and anti-diabetic medications by treatment group, see Appendix (Tables S1, S2).

3.2 | Effect of licogliflozin, placebo or empagliflozin on NT-proBNP following 12-weeks of treatment

A numerical reduction in NT-proBNP from baseline was seen over time in both licogliflozin and empagliflozin groups vs placebo, which was apparent at week 4 and continued up to week 12 (Table S3). Due to early study termination, limited data were available.

The greatest overall effect on NT-proBNP was observed at week 12 for all licogliflozin groups vs placebo or empagliflozin (Figure 2). However, statistical significance was only observed for the licogliflozin 10 mg group vs placebo at week 12 (geometric mean ratio 0.56 [95% confidence interval: 0.33, 0.95]; P = .033). An apparent reduction in NT-proBNP from baseline was also seen in the 50 mg licogliflozin group compared to placebo at week 12, but this failed to reach statistical significance (geometric mean ratio 0.64 [95% confidence interval: 0.40, 1.03]; P = .064; Table S3). These results were derived from the mixed effect model of repeated measures, as described in the statistical analysis section.

3.3 | Effect of licogliflozin, placebo or empagliflozin on secondary endpoints after 12-weeks of treatment

A summary of the descriptive analysis of the 12-week change from baseline in secondary endpoints of main interest is shown in Table 2, with the remaining secondary endpoint data shown in Table S4.

3.3.1 | Glycaemic parameters

Numerically, the greatest reduction in HbA1c was observed with licogliflozin 50 mg (change from baseline for licogliflozin 50 mg, empagliflozin, and placebo were −0.58 ± 0.34%; −0.44 ± 1.18%), and −0.04 ± 0.91%, respectively). A numerical reduction in FPG was observed in all licogliflozin treatment groups at week 12, an

effect that was also apparent in empagliflozin and placebo groups (Table 2).

3.3.2 | Body weight

Body weight numerically decreased by ~1 kg by week 4 in both licogliflozin and empagliflozin groups (change from baseline −0.60 ± 2.27 kg for licogliflozin 2.5 mg, n = 14; −0.99 ± 1.65 kg for licogliflozin 10 mg, n = 15; −1.38 ± 2.00 for licogliflozin 50 mg, n = 28; −1.44 ± 1.70 kg for empagliflozin, n = 26), with a slight increase in body weight in the placebo group (2.62 ± 15.22 kg; n = 31). Weight stabilized by week 12 in the licogliflozin 2.5 mg group, with additional weight reduction seen in the other active treatment groups. Body weight in the placebo group at week 12 was approximately the same as that at baseline (Table 2).

3.3.3 | Change in blood pressure

An almost 10 mmHg reduction in SBP was seen in the licogliflozin 50 mg group at 12 weeks (−9.54 ± 16.88), with reductions of −6.98 ± 15.03 mmHg and −2.85 ± 11.97 mmHg observed with empagliflozin and placebo. Similar effects were noted for DBP, with the greatest reduction in DBP seen in the licogliflozin 50 mg group (−4.46 ± 11.24) vs empagliflozin (−1.81 ± 10.42 mmHg) and placebo (−2.00 ± 8.60 mmHg; Table 2).

3.3.4 | Fasting lipid profile and hsCRP

No consistent pattern was observed for change from baseline to week 12 for any of the lipid parameters or hsCRP across the active treatment groups.

Triglyceride levels were numerically increased from baseline at week 12 across all groups with the exception of licogliflozin 2.5 mg and placebo (Table S4). With the exception of the licogliflozin 10 mg group, total cholesterol increased across all groups at week 12. High-density lipoprotein–cholesterol increased in all treatment groups at week 12, except for the licogliflozin 10 mg group and placebo. Low-density lipoprotein–cholesterol also increased in all groups with the exception of the placebo group, which showed a small decrease at week 12 (Table S4).

3.3.5 | Echocardiography and change in NYHA class

Changes in LVEF from baseline at week 12 were small and inconsistent, while no significant changes in left atrial size and volume were observed at week 12 (Table S4).

NYHA class improved for ~6–13% of patients across treatment groups by week 4, with the exception of the licogliflozin 2.5 mg group. At the same time, 2 of the patients (~8%) worsened in the

TABLE 1 Key patient baseline characteristics

Characteristic	Licogliflozin 2.5 mg n = 15	Licogliflozin 10 mg n = 16	Licogliflozin 50 mg n = 30	Empagliflozin 25 mg n = 30	Placebo n = 33
Age					
Median	70.0	72.5	66.0	68.5	71.0
IQR	62.0–75.0	66.0–75.5	60.0–71.0	62.0–74.0	59.0–74.0
Female, n (%)[a]	1 (6.7)	4 (25.0)	6 (20.0)	10 (33.3)	14 (42.4)
Race, n (%)[a]					
Caucasian	14 (93.3)	14 (87.5)	28 (93.3)	28 (93.3)	29 (87.9)
Black	0	0	0	0	1 (3.0)
Asian	1 (6.7)	2 (12.5)	2 (6.7)	1 (3.3)	3 (9.1)
Native American	0	0	0	0	0
Pacific islander	0	0	0	0	0
Unknown	0	0	0	0	0
Other	0	0	0	1 (3.3)	0
Weight (kg)					
Median	99.0	90.0	94.0	87.4	87.3
IQR	77.5–114.9	78.8–106.2	87.0–104.2	76.0–107.4	79.0–97.2
BMI[b] (kg/m^2)					
Median	33.3	31.9	32.0	31.2	31.3
IQR	28.1–37.5	29.2–35.9	29.1–37.7	28.8–34.7	28.4–34.2
SBP (mmHg)					
Median	134.3	134.2	130.8	131.0	128.0
IQR	125.0–138.7	121.0–143.3	117.3–138.7	120.7–139.7	119.3–134.7
DBP (mmHg)					
Median	75.7	78.7	75.7	76.3	73.3
IQR	72.3–85.0	73.7–83.3	70.0–82.0	73.0–80.3	64.7–79.0
eGFR (mL/min/1.73m^2)					
Median	76.3	61.3	69.8	63.5	66.5
IQR	50.7–91.3	58.6–72.2	53.6–77.8	56.9–73.1	55.5–78.8
LVEF (%; n)	14	16	30	27	30
Median	52.4	55.7	56.2	53.9	55.4
IQR	43.5–63.1	42.0–69.8	45.3–66.6	45.4–63.7	43.4–61.8
LVEF group, n (%)[a]					
<45%	5 (33.3)	4 (25.0)	6 (20.0)	7 (23.3)	8 (24.2)
≥45%	10 (66.7)	12 (75.0)	24 (80.0)	23 (76.7)	25 (75.8)
NYHA class, n (%)[a]					
I	0	0	0	0	0
II	13 (86.7)	14 (87.5)	26 (86.7)	22 (73.3)	25 (75.8)
III	2 (13.3)	2 (12.5)	3 (10.0)	8 (26.7)	8 (24.2)
IV	0	0	1 (3.3)	0	0
NT-proBNP (pg/mL)					
Median	1129.0	945.0	605.0	978.5	894.0
IQR	682.0–1891.0	577.5–1725.5	518.0–927.0	649.0–1292.0	477.0–1447.0

All baseline characteristics were assessed at baseline unless otherwise indicated;

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; n, number; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide; SBP, systolic blood pressure; IQR, interquartile range.

[a]Percentages were calculated from the total number of patients in each treatment group.
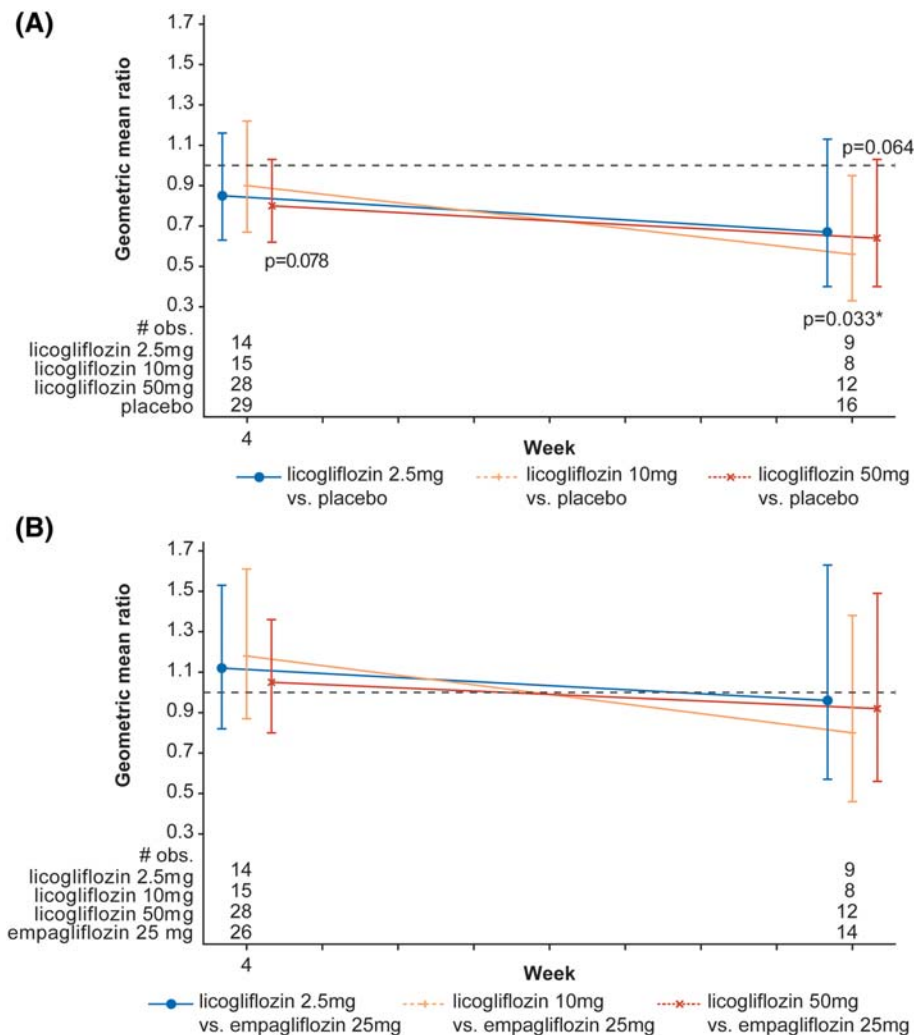
[b]Assessed at screening.

FIGURE 2 Change from baseline in N-terminal pro b-type natriuretic peptide (NT-proBNP; geometric mean ratio) following 4 weeks and 12 weeks' treatment. A, NT-proBNP ratio *vs* placebo, B, NT-proBNP ratio *vs* empagliflozin. Values are expressed as ratios (licogliflozin *vs* placebo or empagliflozin) of endpoint/baseline geometric means ±95% confidence interval; *P < .05. #obs., number of observations used in the model (for a given time-point)

licogliflozin 50 mg treatment group. Similar results were seen at week 12 (Table S4), although the sample size was smaller compared to baseline or week 4.

3.4 | Safety

The safety profile of licogliflozin in this study is in line with previous reports, with the exception that the rate of diarrhoea (4.9% in the pooled licogliflozin groups) was lower than previously observed.[18] The overall incidence of AEs was comparable between the licogliflozin and placebo groups, with a numerically higher incidence of AEs reported in the empagliflozin group (at least 1 AE was reported in 73, 53 and 42% of the empagliflozin 25 mg, licogliflozin 50 mg and placebo groups, respectively). Hypotension (6.5%), hypoglycaemia (8.1%), and inadequate diabetes control (1.6%) were the most common adverse events reported. Hypotension occurred in all treatment groups with the exception of the licogliflozin 10 mg group. Four patients (one per group, except licogliflozin 50 mg) experienced at least 1 clinically significant hypoglycaemic event (plasma glucose <3.0 mmol/L). No ketoacidosis events were reported. The incidence of bone fractures was low (reported in 1 patient in the licogliflozin 50 mg group, and in

1 patient in the empagliflozin group). Genital mycotic infection was reported in only 1 patient in the licogliflozin 10 mg group. Urinary tract infections were reported in 3 patients; 1 patient in the licogliflozin 2.5 mg group, 1 in the licogliflozin 10 mg group and 1 in the placebo group. The incidence of serious AEs was slightly higher in the empagliflozin group than the placebo or licogliflozin groups (Table 3).

No obvious changes in biochemistry or urinalysis markers were seen between licogliflozin, empagliflozin and placebo treatment arms. The change from baseline in key laboratory evaluations at week 12 is shown in Table S5.

4 | DISCUSSION

Coinhibition of SGLT1 and 2 with licogliflozin for 12 weeks in patients with T2DM and HF led to reductions in NT-proBNP, a biomarker of cardiac wall stress with an established relationship to HF severity and prognosis.[27-29] A significant effect was only observed with 10 mg licogliflozin, although a nonsignificant trend (P = .064) was also seen with the 50 mg dose. Due to the small sample sizes, our results cannot be considered conclusive. Larger studies are therefore required to

TABLE 2 The effect of 12-weeks treatment with licogliflozin (change from baseline) on key efficacy parameters (secondary endpoint) *vs* empagliflozin and placebo

Parameter[a], n mean (SD)	Licogliflozin 2.5 mg	Licogliflozin 10 mg	Licogliflozin 50 mg	Empagliflozin 25 mg	Placebo
HbA1c %, n	9	8	12	14	18
Mean (SD)	−0.29 (0.84)	−0.01 (0.51)	−0.58 (0.34)	−0.44 (1.18)	−0.04 (0.91)
FPG mmol/L, n	8	6	12	13	15
Mean (SD)	−1.02 (1.04)	−2.04 (4.98)	−0.43 (2.15)	−1.30 (2.44)	−1.19 (3.97)
Body weight kg, n	9	8	13	14	18
Mean (SD)	−0.78 (2.73)	−1.83 (1.40)	−2.15 (2.40)	−2.25 (1.89)	−0.34 (2.12)
BP mmHg, n	9	8	13	14	18
Mean SBP (SD)	5.15 (13.48)	0.17 (15.37)	−9.54 (16.88)	−6.98 (15.03)	−2.85 (11.97)
Mean DBP (SD)	−2.00 (6.58)	4.50 (12.75)	−4.46 (11.24)	−1.81 (10.42)	−2.00 (8.60)

BP, blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose, HbA1c, glycated haemoglobin, SBP, systolic blood pressure; SD, standard deviation.

To convert values for HbA1c to mmol/mol, multiply by 10.93 and then subtract 23.50.

[a]Change from baseline.

TABLE 3 Treatment emergent serious adverse events (SAEs) by primary system organ class and preferred term

Primary system organ class preferred term	Licogliflozin 2.5 mg n (%) n = 15	Licogliflozin 10 mg n (%) n = 16	Licogliflozin 50 mg n (%) n = 30	Empagliflozin 25 mg n (%) n = 30	Placebo n (%) n = 33
Number of patients with at least 1 SAE	2 (13.3)	2 (12.5)	3 (10.0)	5 (16.7)	3 (9.1)
Cardiac disorders	1 (6.7)	1 (6.3)	1 (3.3)	2 (6.7)	2 (6.1)
Angina pectoris	0	0	0	1 (3.3)	0
Atrial fibrillation	0	0	0	1 (3.3)	0
Cardiac failure	1 (6.7)	0	0	0	1 (3.0)
Cardiac failure chronic	0	0	1 (3.3)	0	0
Cardiac failure congestive	0	0	0	0	1 (3.0)
Coronary artery disease	0	1 (6.3)	0	1 (3.3)	0
General disorders and administration site conditions	0	1 (6.3)	0	0	0
Cardiac death	0	1 (6.3)	0	0	0
Infections and infestations	1 (6.7)	0	1 (3.3)	1 (3.3)	0
Diarrhoea infections	1 (6.7)	0	0	0	0
Gastroenteritis	0	0	0	1 (3.3)	0
Wound infection	0	0	1 (3.3)	0	0
Injury, poisoning and procedural complications	0	0	0	2 (6.7)	0
Hip fracture	0	0	0	1 (3.3)	0
Wound dehiscence	0	0	0	1 (3.3)	0
Nervous system disorders	0	0	1 (3.3)	0	0
Cerebral vascular occlusion	0	0	1 (3.3)	0	0
Reproductive system and breast disorders	0	0	0	1 (3.3)	0
Benign prostatic hyperplasia	0	0	0	1 (3.3)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (3.0)
Respiratory failure	0	0	0	0	1 (3.0)

confirm these findings. The beneficial effects of SGLT2 inhibitors on NT-proBNP have previously been reported in patients with T2DM following treatment with canagliflozin[30] and dapagliflozin,[31] although the treatment durations were longer than in the current study (104 and 24 weeks respectively) and the patient population was predominantly free from cardiac disease. Furthermore, canagliflozin did not lead to a reduction in NT-proBNP but prevented an increase in NT-proBNP that was seen in the placebo group at 2 years.[30] The effects on NT-proBNP levels observed with licogliflozin-associated SGLT1 and 2 inhibition is in line with these assertions.

While the significant CV benefits of SGLT2 inhibitors are well documented in the EMPA-REG OUTCOME, CANVAS and DECLARE studies,[7-9] it should be noted that very few patients with established HF were enrolled in either the EMPA-REG OUTCOME study or CANVAS program. The first study completed in patients with HF with reduced ejection fraction treated with the SGLT2 inhibitor, dapagliflozin (DAPA-HF) was recently reported, showing a 26% relative reduction in the composite of CV death, hospitalization for HF, or urgent HF visit (P < .001). When analysed separately, HF hospitalizations were reduced by 30%, while CV mortality was reduced by 18%. The DAPA-HF study provides the first compelling data that SGLT2 inhibition benefits patients with HFrEF, both in patients with and without T2DM.[32]

The results of other ongoing studies in HF (EMPEROR-Reduced, EMPEROR-Preserved and DELIVER) will provide further evidence on the potential efficacy of SGLT2 inhibitors in patients with this condition.[14,15,17] CV outcomes associated with SGLT1 and 2 inhibitor-associated reductions in NT-proBNP have not yet been assessed. However, ongoing trials are evaluating the effects of the SGLT1/2 inhibitor, sotagliflozin, on CV outcomes in high-risk patients with T2DM and renal impairment (SCORED)[33] and in patients with T2DM and worsening HF (SOLOIST-WHF).[34] Observations from phase II studies of NT-proBNP in HF suggest that a 12-week treatment duration is sufficient to reveal a significant change in this biomarker.[35] While the low patient numbers in our study precluded any assessment of dose response, the significant reduction from baseline in NT-proBNP at 12 weeks following treatment with licogliflozin 10 mg suggests that SGLT1/2 inhibitors could lead to potential CV benefits. However, larger studies with long follow-up are needed to evaluate their impact on CV outcomes. Previous studies have established a dose-effect relationship for licogliflozin on UGE in patients with T2DM[18] and on body weight in patients with obesity.[18,36] While a dose-effect of licogliflozin could not be established in this study, secondary effects of licogliflozin on HbA1c, UGE and body weight are consistent with previous reports where a dose-effect relationship was established.[18,36] A potential dose-effect in patients with T2DM and HF requires further investigation.

Other mechanisms have been proposed for the beneficial CV effects of SGLT2 inhibitors, including reduced insulin resistance and blood glucose levels, weight loss and reduced visceral fat, reduced blood pressure, reduced arterial stiffness, and reduced inflammation and oxidative stress.[37] SGLT2 inhibitors have been associated with reductions in HbA1c, blood pressure, body weight and other metabolic parameters.[38-41] While the effect differences between SGLT1 and 2 inhibition vs SGLT2 alone are uncertain, it has been suggested that dual inhibition would lead to a marked increase in UGE, with a further reduction in HbA1c.[37] The numerical changes from baseline at week 12 in HbA1c and body weight observed in the current study suggests that licogliflozin could lead to meaningful reductions in these parameters. These observations are supported by a previous study in patients with T2DM and in patients with obesity[18] and are also in line with earlier observations of a reduction in HbA1c and body weight in studies with SGLT2 inhibitors.[38-41] While reductions in HbA1c and body weight are not thought to be the leading factors responsible for the CV benefit seen in the EMPA-REG OUTCOME study, weight loss could potentially be a contributing factor to the progressive reduction in CV mortality and HF seen over 1–3 years.[8,37]

The numerical reduction in SBP with licogliflozin 50 mg also has potential benefit in this patient population and is consistent with the findings of a recent meta-analysis study with SGLT2 inhibitors, showing a 4 mmHg reduction in SBP and a 1.7 mmHg reduction in DBP.[41] The SBP reduction observed with licogliflozin 50 mg was numerically greater than that with empagliflozin, which is noteworthy. SBP was also reduced (~5 mmHg) in the EMPA-REG OUTCOME study, which could at least partly explain the beneficial CV outcome in this study.[8] The observation of SGLT1 expression in the heart, suggests detailed studies are needed to rule out any cardiac adverse effects of dual inhibition.[21,24] Human SGLT1 has more recently been associated with several extra-renal effects (including entero-endocrine and cardiac effects), which may provide CV benefit. However, the role of SGLT1 in these tissues remains to be determined.[20]

The most common AEs associated with SGLT2 inhibition or dual SGLT1 and 2 inhibition are mycotic infections (only reported in 1 patient in this study).[18,20,38-41] Gastrointestinal AEs are commonly reported following treatment with both sotagliflozin and licogliflozin,[18,20] while clinical trials with sotagliflozin have also raised concerns around the risk of hypoglycaemia and diabetic ketoacidosis.[43] No new safety signals were reported in this study, with most AEs limited and mild in nature. The licogliflozin dose was not taken around mealtime to minimize the risk of gastrointestinal adverse effects of SGLT1 inhibition in the gut, such as diarrhoea, as previously reported.[18] Clinically significant hypoglycaemic events were only reported in 4 patients, while no ketoacidosis events were reported. SGLT2 inhibitors are also associated with an increased risk of urinary tract infections (UTIs), volume depletion, fractures and amputations.[37] The incidence of hypotension, bone fractures and UTIs in the current study was low and numerically similar between treatment groups. The 2 deaths reported in the study were evaluated as not related to the study drug. Longer-term studies with larger groups are required to confirm these preliminary observations.

One of the major limitations of this study is the small sample size, which was caused by study early termination due to slow enrolment. A second limitation for a study of this size is patient randomization into 5 groups, with early study termination resulting in a mostly descriptive presentation of the results and preventing direct

comparison with the SGLT2 inhibitor, empagliflozin. For many outcome measures, the sample sizes at weeks 4 and 12 are significantly (up to 50%) smaller than those at baseline. Our findings should therefore be interpreted with caution. The early termination of this study also means that there is extremely limited data available at the longer-duration 36-week time point, which is therefore not reported.

In conclusion, treatment with licogliflozin, an SGLT1 and 2 inhibitor may have a positive impact on NT-proBNP in patients with T2DM and HF. Clearly, larger and longer trials with dual SGLT1 and 2 inhibitors would be required to validate if such drugs may have benefits in patients with T2DM and HF.

COMPETING INTERESTS

The UMCG, which employs R.A.d.B. has received research grants and/or fees from AstraZeneca, Abbott, Bristol-Myers Squibb, Novartis, Novo Nordisk, and Roche. R.A.d.B. has received speaker fees and travel expenses from Abbott, AstraZeneca, Novartis, and Roche. J.N. has received speaker fees and travel expenses from Novartis, AstraZeneca, Vifor Pharma and Boehringer Ingelheim. P.K., Y.W., P.P., and D.K. are employed by and own stock in Novartis.

CONTRIBUTORS

R.A.d.B., J.N., P.K. and D.K. were responsible for the concept and design of this study, with R.A.d.B., J.N., P.K. and P.P. responsible for the study conduct. Data collection was carried out by R.A.d.B, J.N., P.K. and P.P., while statistical analysis was carried out by Y.W. All authors contributed equally to the development and writing of this manuscript.

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SUPPORTING INFORMATION

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