Licogliflozin versus placebo in women with polycystic ovary syndrome: A randomized, double-blind, phase 2 trial

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Abstract
Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism and insulin resistance. The dual sodium-glucose co-transporter 1/2 inhibitor (SGLT1/2i) licogliflozin (LIK066) ameliorates hyperinsulinism in patients with diabetes and obesity. This study examines the effect of licogliflozin on androgens in women with PCOS. In a multicentre, randomized, placebo-controlled, double-blind, 2-week trial, patients with PCOS received licogliflozin 50 mg or placebo three times a day (TID). Changes in free testosterone (FT), other androgens and variables of insulin resistance were analysed. Concentration of FT did not change (TRLIK066:TRPCB [FT]: 0.88; 90% CI: 0.70-1.11; \( P = .353 \)). Licogliflozin reduced androstendione (A4) by 19% (TRLIK066:TRPCB [A4]: 0.81; 90% CI: 0.68-0.99; \( P = .089 \)) and dehydroepiandrosteron sulphate (DHEAS) by 24% (TRLIK066:TRPCB [DHEAS]: 0.76; 90% CI: 0.65-0.89; \( P = .008 \)). Hyperinsulinaemia was reduced by 70% by licogliflozin (highest insulin concentration [MAXI]; TRLIK066:TRPCB [MAXI]: 0.26; 90% CI:0.20-0.34; \( P < .001 \) and area under the curve insulin [AUCI]; TRLIK066:TRPCB [AUCI]: 0.32; 90% CI: 0.25-0.41; \( P < .001 \)). Diarrhoea and nausea occurred as common adverse events. Dual inhibition of SGLT1/2 ameliorates hyperinsulinaemia and hyperandrogenaemia in women with PCOS. Licogliflozin may represent a promising novel treatment option for PCOS.

Keywords
antidiabetic drug, clinical trial, drug mechanism, endocrine therapy, phase I-II study, SGLT2 inhibitor

INTRODUCTION
Polycystic ovary syndrome (PCOS), which affects 15% of women of fertile age, is characterized by hyperandrogenism and insulin resistance (IR) with compensatory hyperinsulinism. Androgen excess in PCOS leads to hirsutism, alopecia, acne and chronic anovulation, with a strong impact on quality of life and fertility. IR plays a pivotal role in the pathogenesis of PCOS, resulting not only in a higher risk of metabolic complications like diabetes, but also by promoting androgen synthesis and thereby aggravating the PCOS
phenotype. Intervention strategies aiming at amelioration of IR, such as the use of metformin, have shown effective reduction of hyperandrogenism in women with PCOS. Sodium-glucose co-transporter type 1 and 2 (SGLT1/2) play an important role in glucose homeostasis by acting on intestinal and renal glucose (re)absorption, and secondarily reducing hyperinsulinaemia and improving IR. SGLT2 inhibitors (SGLT2is) reduce blood glucose levels and are effective in the treatment of type 2 diabetes. Empagliflozin improves body composition in patients with PCOS, but has no effect on insulin or androgen levels compared with metformin. Licogliflozin (LIK066), a dual SGLT1/2 inhibitor (SGLT1/2i), significantly reduces postprandial glucose and insulin excursions, and induces weight loss in healthy volunteers and in patients with obesity. To date, there are no data on the effect of SGLT1/2is in patients with PCOS. We hypothesized that dual inhibition of SGLT1/2 targeting glucose (re)absorption may reduce hyperandrogenaemia by decreasing serum glucose and secondary hyperinsulinism, and therefore potentially broaden the therapeutic spectrum of PCOS.

2 | METHODS

2.1 | Study design

Details of the study design are provided in Appendix S1. In brief, this study was a randomized, placebo-controlled, double-blind, multicentre, phase 2 trial with participants recruited in Germany and the USA. PCOS patients fulfilled the Rotterdam criteria for phenotype A or B, were overweight or obese and insulin-resistant, and provided written informed consent before entering the study. Ethics approval was obtained locally. The trial was registered at ClinicalTrials.gov (NCT03152591) and EudraCT (2017-001373-16). Subjects were randomized by a centralized randomization process in a 1:1 ratio to licogliflozin or placebo.

2.2 | Study procedure

At baseline, fasting serial blood samples for glucose, free testosterone (FT), total testosterone (TT), androstenedione (A4), dehydroepiandrosterone sulphate (DHEAS) and DHEA were collected early in the morning and serially for FT, followed by the test meal with serial postprandial blood sampling over a 4-hour period. During the treatment period, patients received oral doses of 50 mg of licogliflozin or matching placebo three times a day (TID) for 14 days before meals. Safety, tolerability and compliance were checked on day 8. On day 15, the end of the treatment period, a mixed meal test was repeated as described. An end-of-study visit was performed on day 22. Androgen data of patients considered as having ovulated were not included in the data analysis to prevent bias because of the physiological increase of androgen levels during the luteal phase.

2.3 | Statistical analysis

The primary endpoint of the study was the treatment effect on the geometric mean of three serial FT samples. Sex steroids including TT, A4, DHEA, DHEAS and sex hormone binding globulin (SHBG), as well as free androgen index (FAI), served as secondary endpoints. The exploratory objectives included serum insulin and plasma glucose levels before and in response to a test meal (area under the curve of insulin [AUCI] and maximum peak of insulin [MAXI], area under the curve of glucose [AUCG] and maximum peak of glucose [MAXG], and homeostatic model assessment of IR [HOMA-IR]). For the intragroup treatment effect, the relative change from baseline at day 15 was assessed by calculating the treatment ratio (TRLIK066:TRPCB [x] = [x at day 15] / [x at baseline]) for each variable. Results less than 1 indicate a decrease and more than 1 an increase within a treatment group. The ratio of relative changes (TRLIK066:TRPCB) was used to evaluate the intergroup treatment effect. TRLIK066 and TRPCB with their associated P value and two-sided 90% confidence interval (CI) were analysed for all examined variables in a covariance model with treatment as a categorical factor and baseline weight as a covariate. With a two-sided test, a P value of .1 or less was regarded as statistically significant.

3 | RESULTS

From 4 October 2017 to 4 June 2018, 29 patients (age 27.6 ± 5.3 years, body weight 105.2 ± 18.7 kg, body mass index 38.1 ± 6.3 kg/m²) were randomly allocated to licogliflozin 50 mg TID (n = 15, 52%) or placebo (n = 14, 48%) (Figure S1). Nine subjects were excluded from the analysis of androgens as a result of evidence of ovulation and/or missing baseline values. Baseline demographics were balanced between groups (Table S1).

3.1 | Primary outcome

In the licogliflozin group, 9/10 patients had a decrease in FT concentration compared with 5/10 in the placebo group (P = .07; Figure S2). Comparing the treatment groups, there was a non-significant 12% lower ratio for licogliflozin (TRLIK066:TRPCB [FT]: 0.88; 90% CI: 0.70-1.11; P = .353; Figure 1).

3.2 | Secondary endpoints

Licogliflozin showed a statistically significant reduction of A4 and DHEAS after 2 weeks of treatment, with an effect size of 19% for A4 (TRLIK066:TRPCB [A4]: 0.81; 90% CI: 0.68-0.99; P = .089) and 24% for DHEAS levels (TRLIK066:TRPCB [DHEAS]: 0.76; 90% CI: 0.65-0.89; P = .008; Figure 1). Licogliflozin versus placebo led to a non-significant reduction of DHEA (TRLIK066:TRPCB [DHEA]: 0.69; 90% CI: 0.48-1.01; P = .109) by 31% and TT levels by 9% (TRLIK066:TRPCB
Licogliflozin treatment resulted in significant changes in glucose and insulin excursions (Figure 2). In the verum group, reductions in AUCG and MAXG were observed with an effect size of 11% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [AUCG]: 0.89; 90% CI: 0.82-0.95; \(P \leq 0.001\) and 30% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [MAXG]: 0.70; 90% CI: 0.61-0.80; \(P \leq 0.001\), respectively. Licogliflozin versus placebo lowered AUCI by 68% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [AUCI]: 0.32; 90% CI: 0.25-0.41; \(P \leq 0.001\), MAXI by 74% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [MAXI]: 0.26; 90% CI: 0.20-0.34; \(P \leq 0.001\)) and HOMA-IR by 30% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [HOMA-IR]: 0.70; 90% CI: 0.58-0.84; \(P \leq 0.001\)).

3.3 Exploratory objectives

Licogliflozin treatment resulted in significant changes in glucose and insulin excursions (Figure 2). In the verum group, reductions in AUCG and MAXG were observed with an effect size of 11% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [AUCG]: 0.89; 90% CI: 0.82-0.95; \(P \leq 0.001\)) and 30% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [MAXG]: 0.70; 90% CI: 0.61-0.80; \(P \leq 0.001\)), respectively. Licogliflozin versus placebo lowered AUCI by 68% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [AUCI]: 0.32; 90% CI: 0.25-0.41; \(P \leq 0.001\)), MAXI by 74% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [MAXI]: 0.26; 90% CI: 0.20-0.34; \(P \leq 0.001\)), and HOMA-IR by 30% (TR\textsubscript{LIK066}:TR\textsubscript{PCB} [HOMA-IR]: 0.70; 90% CI: 0.58-0.84; \(P \leq 0.001\)).
Body weight before and after treatment was stable in both groups (Figure S3). The results are presented in detail in Table S2.

3.4 Safety and tolerability

In 15 (100%) and 10 (71.4%) patients treated with licogliflozin compared with placebo, adverse events (AEs) occurred mostly as diarrhoea and nausea of mild intensity (Table S3). Eunomenorrhoea/hypomenorrhoea was documented in 4/2 and in 2/1 subjects treated with licogliflozin and placebo, respectively. By the common terminology criteria for adverse events (CTCAE), no grade 3-5 AEs or AERelated study discontinuation occurred.

4 DISCUSSION

We present the first placebo-controlled, randomized trial with a dual SGLT1/2i in patients with PCOS showing a licogliflozin-mediated reduction in glucose and insulin, as well as A4 and DHEAS concentrations, after 2 weeks of treatment. In patients with obesity with and without diabetes, daily intake of 150 mg for 2 weeks compared with one single dose of 300 mg licogliflozin led to a reduction in AUCG of 21%-48% and in AUCI of 80%-93%.6 In patients with type 2 diabetes, treatment with 5-100 mg dapagliflozin for 2 weeks reduced AUCG by 17.6%-22.6% and FG by 11%-21.8%,7 and treatment with 2.5-100 mg empagliflozin for 1 week ameliorated FG by 4.5%-13.1%.8 Comparing these studies with our results, licogliflozin reduces glucose to a lesser and insulin to a similar extent in PCOS as in obesity with and without diabetes, and its effect size is comparable with 2.5-5 mg empagliflozin in diabetes.

Among the substance class of SGLTis, there is one published study in PCOS testing empagliflozin versus metformin in an open 12-week trial, which showed improvements in body composition, but not in hormonal or metabolic variables.5 Discrepancy between this study and our findings indicates that inhibition of SGLT1 in the gut may significantly contribute to the effects on insulin and androgens. SGLT1 plays a central role in intestinal glucose resorption, blocking glucose uptake in the upper intestine. By this, SGLT1 modulates the secretion of incretins such as glucagon-like peptide-1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP). Premeal intake of the SGLT1i GSK-1614235 has been shown to stimulate GLP1 and GIP secretion in healthy volunteers.9 Additionally, glucose shift from the proximal to the distal intestines may lead to glucose degradation by the gut microbiome and formation of short-chain fatty acids, further promoting GLP1 release.7 Based on their inhibitory effect on glucose absorption and influence on incretins, SGLTs with an affinity to the type 1 transporter may provide additional treatment effects compared with those with highly selective SGLT2 affinity.

The observed effect of licogliflozin, with reductions in A4 and DHEAS concentrations of 19% and 24%, respectively, suggests that correction of hyperinsulinaemia results in amelioration of ovarian hyperandrogenism, specifically reducing the pathological activity of 17,20-lyase. A4 has been proposed as a key androgen in PCOS that could be more sensitive than testosterone for the detection of PCOS-related androgen excess.10 Additionally, A4 has shown a higher association to IR and may better reflect the metabolic dysfunction of PCOS.11 Therefore, the treatment effect of licogliflozin with improvement of A4 may be of clinical relevance, despite its non-significant effects on FT concentrations.12

Interpreting the treatment effect of licogliflozin on FT, several aspects should also be taken into account. Firstly, PCOS is a highly heterogeneous disorder with a varying degree of metabolic risk among its subphenotypes. Clinical responses to insulin-sensitizing agents are not exclusively associated with the degree of underlying IR.13-15 Our patient cohort consisted of patients with PCOS type A and B, representing the most severe metabolic phenotypes. Hence, the absence of therapeutic effects on FT concentrations in these patients does not exclude a beneficial effect in patients with milder PCOS subphenotypes. Secondly, because of the physiological increase of androgens in the luteal phase, patients ovulating during the treatment period were excluded from androgen analysis. Four patients in the licogliflozin and two in the placebo arm ovulated during the treatment period. The study eligibility criteria selected for patients with a higher degree of chronic anovulation, and ovulation was not a prespecified objective. Therefore, the probability of observing ovulation in a severely diseased, small population under short-term treatment conditions may have been substantially low. Postulating that ovulation was induced by licogliflozin in terms of a clinical salutary effect, exclusion of ovulating women may have led to an underestimation of the real treatment effect.

In this short-term trial, licogliflozin showed no effect on body weight, but licogliflozin led to a 6% reduction in body weight in obese patients treated for 12 weeks.6 Therapeutic lifestyle changes with a comparable weight loss have been shown to improve ovarian function in obese patients with PCOS.16 In summary, SGLT1/2is may represent a novel therapeutic option for patients with PCOS. Further studies with a longer treatment duration considering milder PCOS phenotypes and clinical outcome variables such as ovulation rate are warranted to elucidate the full potential of dual SGLT1/2is in PCOS.

AUTHOR CONTRIBUTIONS

CTB, MZ, and NH and have made substantial contributions to conception and design, AD, DZ, JS, KD, SI, and ST have made substantial contributions to the acquisition of data. MP has made substantial contributions to analysis and CTB, MH, MZ, NH, ST and have made substantial contribution to the interpretation of data. ST and MH have been involved in drafting the manuscript and CTB, DF, MH, and MZ have revised it critically for important intellectual content. All authors have read and agree with content of the manuscript and given final approval of the version to be published. All authors participated in the writing process by making comments and suggestions and by
approving the manuscript, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DATA AVAILABILITY STATEMENT
Data sharing and data accessibility: Individual participant data from this study will be available in an anonymized form from the publication date of this manuscript for the following 24 months, on a collaborative basis for individual participant data meta-analyses. Proposals should be directed to Susanne Tan (susanne.tan@uk-essen.de).

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

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