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ORIGINAL ARTICLE

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Efficacy of double *vs.* standard empagliflozin dose for METabolic syndromE tReatment (DEMETER — SIRIO 11) study. Rationale and protocol of the study

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ABSTRACT

Complex metabolic disorders associated with obesity and diabetes pose a serious therapeutic challenge. The DEMETER-SIRIO 11 study is a phase III, multicenter, randomized, open-label, investigator-initiated clinical trial with a 6-month follow-up aimed at performing a comparative evaluation of the effect of two empagliflozin doses (10 mg *vs.* 20 mg) on selected metabolic parameters in patients with metabolic syndrome. The primary hypothesis of the study is that a higher dose of empagliflozin will result in a significant reduction of BMI and HbA1c in patients with obesity and MS receiving empagliflozin 20 mg as compared to 10 mg. Sample size and power calculation were based on a superiority assumption for the primary efficacy endpoint (the difference in decrease of body weight by > 1.5 kg and HbA1c by > 0.4%) for the higher *vs.* standard dose arm at 6-months of follow-up. Therefore, a sample size of 79 patients per arm is required to provide 80% power to detect a higher decrease in BMI, and 85 patients per arm is required to provide 80% power to detect a higher decrease in HbA1c in the 20 mg versus 10 mg arm with a type I error rate of 0.05. Summing up, enrollment of a total of 200 patients (100 in each arm) is planned to compensate for the potential drop-out rate from the study of up to 15%. Prespecified subanalyses will be performed according to: 1) diabetes mellitus; 2) chronic kidney disease (GFR < 60 mL/min/1.73 m^2); 3) gender; and 4) age. A greater comprehensive improvement in biochemical, functional, and anthropometric parameters reflecting favorable metabolic changes is expected at the higher dose of empagliflozin compared to the standard dose.

Keywords: empagliflozin, metabolic syndrome, obesity, randomized clinical study

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Introduction

The reduction in glucose renal reabsorption induced by SGLT2 inhibitors is characterized by the rapid onset of glycosuria, the dose-dependent offset of action in the range of 24–48 hr, and the glycemia-dependent entity of glycosuria [1]. Glycosuria induced by SGLT2 inhibitors results in several further metabolic changes [2]. The extracellular space is partially emptied out of glucose, whereby plasma concentrations of glucose fall during fasting and postprandially. This fasting-like effect leads to a decrease in insulin-to-glucagon ratio, inducing endogenous fasting gluconeogenesis and ketogenesis [3–6], which are regulated by endogenous nutrient deprivation sensors SIRT1 (silent information regulator T1), PGC-1α (proliferator-activated receptor gamma co-activator 1-alpha), and FGF21 (fibroblast growth factor 21), which are known to exert cardioprotective effects in experimental models [6]. This metabolic theory based on experimental studies is consistent with the rapid onset of cardiovascular and renal benefits observed in the outcome trials [7–10].

The loss of glucose on SGLT2 inhibitors translates into a substantial whole-body energy deficit, ranging from 250 to 450 kcal/day. However, the weight loss observed in clinical trials was far less than expected from the negative calorie balance. This difference was due to an increase in calorie intake [11]. The weight loss induced by SGLT2 inhibitors could be strengthened by countering the compensatory increase in caloric intake, either through dietary counseling or by pharmacological appetite quenching [11, 12]. Moreover, SGLT2 inhibitors lead to an increase of LDL cholesterol and a decrease of triglyceride plasma levels, including due to delayed clearance of LDL cholesterol from the circulation along with increased plasma lipoprotein lipase activity [13]. The SGLT2 inhibitors have also been shown to reduce serum uric acid levels in a dose-dependent manner [14] and reduce urinary albumin excretion in patients with type 2 diabetes and prevalent micro- or macroalbuminuria [15]. Furthermore, the anti-inflammatory effect of SGLT2 inhibitors with a slight reduction in serum inflammatory markers: hsCRP, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) has been revealed [16] explaining the beneficial effect of SGLT2 inhibitors at the kidney and myocardium levels [2, 17, 18].

The metabolic effects of SGLT2 inhibitors are associated with hemodynamic changes caused by increased osmotic diuresis and consequently decreased plasma volume, followed by reduced preload and a reduction of interstitial fluid volume [12, 19, 20]. A concomitant decrease of arterial stiffness and blood pressure leads to an afterload reduction [12, 19]. The hemodynamic effects of SGLT2 inhibition were observed in both hyper- and euglycemic patients [1, 3]. These complex mechanisms of action of SGLT2 inhibitors make them an excellent therapeutic option for patients with HF, providing an additional nephroprotective effect [21–23]. The exceptional clinical benefits of SGLT2 inhibitors applied on top of the previously guideline-recommended treatment [24] in patients with chronic HFrEF, regardless of the coexistence of diabetes mellitus [21–23], led to fundamental changes in the recommended strategy of treatment [25, 26]. The new ESC guidelines emphasize the key role of the organization of HF management programs adapted to the local healthcare system, available resources, administrative policies, and tailored to the patient's needs [26]. Implementation of these recommendations implies the need to monitor readiness for discharge from the hospital, the implementation of the therapeutic plan, and functioning in chronic disease [27–36].

Rationale

The cluster of metabolic factors that include abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol levels is defined as the metabolic syndrome (MS) [37]. The complex mechanisms of action of SGLT2 inhibitors make them an optimal response to the health needs of patients with MS and its complications [2]. Both the EMPA-REG OUTCOME study, a high-scale randomized trial [38], and the meta-analysis assessing dose-ranging effects of SGLT2 inhibitors in patients with type 2 diabetes [39] showed insignificantly stronger effect of higher empagliflozin dose (25 mg) as compared to standard dose (10 mg) in terms of HbA1c and weight reduction. Moreover, the EMPA-REG OUTCOME study also showed a higher increase of HDL-Cholesterol with a higher empagliflozin dose [38]. A number of other, smaller studies compared the effects of different doses of SGLT2 inhibitors, but none of these studies included exclusively patients with MS, and none of them performed a comprehensive assessment of metabolic effects [40–47]. Therefore, we have designed a randomized clinical trial to perform a comparative evaluation of the effect of two empagliflozin doses (10 mg *vs.* 20 mg) on selected metabolic parameters in patients with MS.

Material and methods

Study design and population

The DEMETER-SIRIO 11 study is a phase III, multicenter, randomized, open-label, investigator-initiated clinical trial with a 6-month follow-up (ClinicalTrials.gov Identifier: NCT05905965). The study population will include 200 subjects with a diagnosis of MS.

MS is defined as a cluster of comorbid conditions, including the presence of obesity [waist circumference ≥ 88 cm in women; ≥ 102 cm or body mass index (BMI) ≥ 30 kg/m^2] and two of the three following criteria:
— high blood pressure (systolic blood pressure — in-office measurement: ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg or systolic blood pressure, ambulatory measurement: ≥ 130 and/or diastolic blood pressure ≥ 80 mm Hg) or on anti-hypertensive treatment;
— impaired glucose metabolism (fasting glucose ≥ 100 mg/dL or ≥ 140 mg/dL after 120 min in oral glucose tolerance test or HbA1c ≥ 5.7%) or on glucose-lowering drug treatment;
— elevated non-high-density lipoprotein (non-HDL ≥ 130 mg/dL) cholesterol level (atherogenic dyslipidemia) or on lipid-lowering drug treatment [48].

All enrolled patients will receive optimal, personalized therapy as defined by the European Society of Cardiology guidelines including [49–51]:
— education and motivation;
— optimal lipid-lowering treatment;
— optimal hypertension treatment;
— optimal antihyperglycemic treatment.

The exclusion criteria include: on treatment with SGLT2 inhibitors, chronic kidney disease with estimated glomerular filtration rate (eGFR) < 30 mL/min or on dialysis; severely impaired liver function; age < 18 and ≥ 85 years; known hypersensitivity to the active empagliflozin or to any of the excipients contained in Jardiance; history of ketoacidosis; diabetes treated with insulin; pregnancy; decompensated heart failure; acute coronary syndrome; active thromboembolic disease; currently treated for neoplastic disease; active inflammatory disease within 1 month prior to enrollment; expected lifetime < 1 year, non-cooperative patients.

All enrolled patients (nn = 200) will be randomly assigned in 1:1 ratio to one of the two study arms:
— Empagliflozin 20 mg — experimental arm;
— Empagliflozin 10 mg — control arm.

All study participants will be provided free of charge with study drugs according to the randomized allocation. Special care will be applied with regard to adherence to the study treatment (tablets counting at follow-up visits and the Adherence in Chronic Diseases Scale) [27–29, 52–59].

The primary co-endpoints of the study include BMI and HbA1c. Secondary endpoints include: LDL-C, triglycerides, CRP, NT-proBNP, LVEF (echocardiography), body composition, VO_2max (ergospirometry), waist-hip ratio (WHR), liver steatosis assessment (LSA) by computed tomography (CT), major adverse cardiovascular events — MACE (based on medical history: heart attack, stroke, death), cardiovascular hospitalizations. Other variables that are scheduled to be analyzed are: central arterial pressure, pulse wave propagation speed, ABPM (ambulatory blood pressure monitoring), endothelial function assessment by Endopath, autonomic nervous system assessment (ANSA) by Task Force Touch CARDIO (TFTC), exercise tolerance, thickness of the adipose tissue (skin fold), blood samples: blood count, serum creatinine and eGFR, ALT, AST, GGTP, total cholesterol, HDL-C, uric acid, plasma concentration of calcium, phosphate, parathormone, 25-OH-D3, cystatin C, erythropoietin; morning urine: N-acetyl-beta-D-glucosaminidase, sodium/creatinine ratio, calcium/creatinine ratio, albumin/creatinine ratio. Moreover, functioning in chronic disease and adherence to medication and diet will be assessed with dedicated questionnaires (FCIS, ACDS, ACDS diet) [54–57].

Treatment with empagliflozin is generally well tolerated, but careful monitoring will be given for safety, particularly with regard to genital infections, urinary tract infections, ketoacidosis, hypoglycemia, dyslipidemia, bladder cancer, and amputations.

The study will be conducted in accordance with the principles contained in the Declaration of Helsinki, and the study sites received approval from the Ethics Committee to conduct the study (study approval reference number KB KB 240/2022). Each patient will provide written informed consent to participate in the study.

Prespecified subanalyses will be performed according to: 1) diabetes mellitus; 2) chronic kidney disease (GFR < 60 mL/min/1.73 m^2); 3) gender; and 4) age (Tab. 1).

Statistical analysis

Sample size and power calculation were based on a superiority assumption for the primary efficacy endpoint (the difference in decrease of body weight by > 1.5 kg and HbA1c by > 0.4%) for higher *vs.* standard dose arm at 6 moths of follow-up. Previously reported decrease of body weight was –2.93 (SE: 0.47) (95% CI –3.85, –2.01) $p < 0.0001$ and –2.11 (SE: 0.46) (95% CI –3.02, –1.21) $p < 0.0001$ in patients (with body weight > 90 kg at baseline) receiving 25 mg and 10 mg of empagliflozin, respectively, as compared with placebo [60]. The mean difference in weight reduction between study arms was 0.82 kg, with a standard error (SE) of 0.47 corresponding to a standard deviation (SD) of 3.76. Based on the analysis of candidates for the study in our outpatient department, we assume higher body weight at baseline (mean > 100 kg) expecting higher decrease and higher difference between both study arms of > 1.5 kg with similar SD. Therefore, a sample size of 79 patients per arm is required to provide 80% power to detect a higher decrease of BMI (directly proportional to body weight: BMI = body weight [kg])/height^2 [m]) in the 20 mg *vs.* 10 mg arm with a type I error rate of 0.05.

Table 1. DEMETER — SIRIO 11 — important activities and their respective time points during the study period in the cohort study

Action	**Enrolment**		**Observation**	
Visit (V)	Screening	V1	V2	V3
Time Point (d)	< –1 week	0	3 months	6 months
Enrolment				
Eligability Screen	X			
• Body weight	X			
• Patient's height	X			
• Waist circumference	X			
• Blood pressure	X			
• Fasting glucose	X			
• HbA1c	X			
• Non-HDL-C	X			
Informed Consent	X			
Pseudonymisation	X			
Randomization	X			
Assessments				
Blood sampling		X		X
Urine sampling		X		X
BMI		X	X	X
WHR		X	X	X
Skin fold measure		X	X	X
Body composition		X	X	X
Echocardiography		X		X
Ergospirometry		X		X
Central arterial pressure		X		X
Pulse wave propagation speed		X		X
LSA — CT		X		X
Ambulatory BP monitoring		X		X
Endothelial function — Endopath		X		X
ANSA — TFTC		X		X
Questionnaires		X		X
Tablets counting			X	X
Outcome assessment				
Endpoints				X
Side effects monitoring			X	X

BMI — body mass index, WHR — waist hip ratio, LSA–CT — lenticulostriate arteries computed tomography, ANSA–TFTC — autonomic nervous system assesment – task force touch cardio

The observed decrease of HbA1c was –0.97 (SE: 0.15) (95% CI –1.26, –0.68) $p < 0.0001$ and –0.73 (SE: 0.14) (95% CI –1.01, –0.46) $p < 0.0001$ in patients (with initial HbA1c ≥ 8.5% at baseline) receiving 25 mg and 10 mg of empagliflozin, respectively, as compared with placebo [60]. The mean difference in HbA1c reduction between study arms was 0.24% with SE of 0.15 corresponding to the standard deviation (SD) of 1.05. Based on the analysis of candidates for the study in our outpatient department, we assume higher HbA1c at baseline (mean > 9.5%) expecting higher decrease and higher difference between both study arms of > 0.4% with similar SD. Therefore, a sample size of 85 patients per arm is required to provide 80% power to detect a higher decrease in HbA1c.

Summing up, enrollment of a total of 200 patients (100 in each arm) is planned to compensate for the potential drop-out rate from the study of up to 15%.

Study organisation

The Steering Committee of the DEMETER-SIRIO 11 study is responsible for the scientific content of the protocol, oversees the study steps, and checks adherence to "Good Clinical Practice" and the study protocol as well as performance. The Endpoint Adjudication Committee will adjudicate clinical endpoints based on data provided by the clinical trial sites. Patient data are collected systematically online. Data quality and completeness is of prime importance in SYSTEMI. Upon formal request, according to our internal SOP, access to primary data can be granted.

Discussion

Complex metabolic disorders associated with obesity and diabetes pose a serious therapeutic challenge, and due to the huge scale of this phenomenon, they are also a social problem. According to the US National Diabetes Statistics Report, more than 50% of patients with T2D have a BMI higher than 30 kg/m^2 [61].

The primary hypothesis of the DEMETER-SIRIO 11 study is that a higher dose of empagliflozin will result in a significant reduction of BMI and HbA1c in patients with obesity and metabolic syndrome receiving empagliflozin 20 mg as compared to 10 mg. A greater comprehensive improvement in biochemical, functional, and anthropometric parameters reflecting favorable metabolic changes is expected at the higher dose of empagliflozin compared to the standard dose.

Previously, greater reductions of both HbA1c and body weight at higher baseline values were observed [60, 62, 63], therefore even greater mean reduction of these parameters should be expected in patients with a diagnosis of obesity and metabolic syndrome than in the population of patients with T2 diabetes, only some of whom met the definition of obesity. Moreover, the dose-dependent effect of empagliflozin regarding these variables was reported [60]. Weight reduction has been shown to improve weight-related quality of life and satisfaction with physical and emotional health [63]. This effect is expected to improve adherence to the investigated treatment [64–70]. Better glycemic control and weight loss were associated with a marked reduction in systolic blood pressure (SBP). A significantly greater SBP reduction was observed in patients with higher baseline values [70].

Consistent benefits of SGLT2 inhibitors in patients with diabetes, heart failure, and chronic kidney disease have been shown in large-scale randomized clinical trials [8, 21, 23, 67–70]. However, a better understanding of the metabolic effects of SGLT2 inhibitors may help to introduce individual patient-centered care. Therefore, a comprehensive metabolic analysis of two different empagliflozin doses is planned in the DEMETER-SIRIO 11 study.

Article information

Data availability statement: *The data support the results will be available on request from the corresponding author, after completion of the study. Moreover, the data will also be available in the Nicolaus Copernicus repository RUMAK (https://repozytorium.umk.pl).*

Ethics statement: *The study will be conducted in accordance with the principles contained in the Declaration of Helsinki, and the study sites received approval from the Ethics Committee to conduct the study (study approval reference number KB KB 240/2022). Each patient will provide written informed consent to participate in the study.*

Author contributions: *Jacek Kubica — primary investigator, study design, writing of the manuscript; Aldona Kubica — study design, writing of the manuscript; Zofia Grąbczewska — study design, coordination of the study conduction — cardiological noninvasive tests, critical evaluation of the manuscript; Paweł Stróżecki — co-primary investigator, study design, coordination of the study conduction — renal tests, critical evaluation of the manuscript; Piotr Adamski — investigator, critical evaluation of the manuscript; Andrzej Brymora — investigator, critical evaluation of the manuscript; Rafał Donderski — investigator, critical evaluation of the manuscript; Tomasz Fabiszak — investigator, critical evaluation of the manuscript; Mariusz Flisiński — investigator, critical evaluation of the manuscript; Robert Gajda — primary site investigator, critical evaluation of the manuscript; Beata Januszko-Giergielewicz — study design, coordination of the study conduction — liver tests, critical evaluation of the manuscript; Michał Kasprzak — statistical analysis, critical evaluation of the manuscript; Agata Kosobucka — investigator, critical evaluation of the manuscript; Ewa Laskowska — investigator, echocardiographic analysis, critical evaluation of the manuscript; Przemysław Magielski — investigator, coordination of data collection, critical evaluation of the manuscript; Piotr Michalski — investigator, critical evaluation of the manuscript; Gavino Casu — investigator, critical evaluation of the manuscript; Eliano Pio Navarese — primary site investigator, critical evaluation of the manuscript; Piotr Niezgoda — investigator, critical evaluation of the*

manuscript; Małgorzta Ostrowska — investigator, critical evaluation of the manuscript; Łukasz Pietrzykowski — investigator, critical evaluation of the manuscript; Grzegorz Skonieczny — primary site investigator, critical evaluation of the manuscript; Beata Sulikowska — investigator, critical evaluation of the manuscript; Łukasz Szarpak — primary site investigator, critical evaluation of the manuscript; Paweł Szymański — primary site investigator, critical evaluation of the manuscript; Julia Maria Umińska — investigator, critical evaluation of the manuscript; Paweł Zalewski — study design, coordination of the study conduction — autonomic system tests, critical evaluation of the manuscript.

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