Synopsis

Sponsor	Medical University of Warsaw Ul. Zwirki i Wigury 61 02-091 Warsaw, Poland
Principal Investigators **Sponsor's Representative**	Jolanta Siller-Matula MD, PhD, Associate Professor Marek Postuła, MD, PhD, Professor
Indication	Patients with acute/decompensated heart failure
Study design and phase	National, multicenter, randomized, double-blind, parallel-group, stratified by SGLT-2 inhibitor type, placebo-controlled trial, – a Phase III study.
Study Short Title	Empagliflozin and dapagliflozin in acute Heart failure (EMPATHY trial)
Keyword	SGLT-2 inhibition, dapagliflozin, empagliflozin, acute heart failure
Aims of the trial	*Primary objective:* 1. to investigate the impact of SGLT-2 inhibitors (Empagliflozin and Dapagliflozin) on clinical endpoints in patients with acute/decompensated HF regardless of ejection fraction (HFrEF, HFmEF, HFpEF) or diabetes status within 9 months after the event *Secondary objectives:* 1. to investigate and compare the impact of SGLT-2 inhibitors on cardiac function based on echocardiography and biomarkers, including non-coding RNA (ncRNA) and microbiome metabolites in patients acute/decompensated HF 2. to evaluate the utility of specific circulating ncRNAs along with microbiome metabolites, biomarkers related with fibrosis, inflammation and cardiac remodeling processes and classic biomarkers for monitoring therapy with SGLT 2 inhibitors and its potential impact on expression of ncRNAs related to pathogenesis of acute/decompensated HF 3. to propose a risk score prediction tool for the course of acute/decompensated HF and therapy monitoring with SGLT-2 inhibitors based on concomitant usage of both selected ncRNA and biomarkers related to molecular pathways associated with disease progression.
Outcome measures of the trial	***Primary outcomes*** Composite primary endpoint - time to first event of all-cause death or worsening HF (defined as worsening signs or symptoms of HF that require an intensification of diuretic therapy or any other intravenous therapy for HF or mechanical ventilatory, renal or circulatory support) or HF readmission (unplanned ambulatory visit or hospitalization due to symptoms of HF through 3 months). ***Secondary outcomes*** 1. Composite endpoint - time to first event of all-cause death or worsening HF (defined as worsening signs or symptoms of HF that require an intensification of diuretic therapy or any other intravenous therapy for HF or mechanical ventilatory, renal or circulatory support) or HF readmission (unplanned ambulatory visit or hospitalization due to symptoms of HF through 9 months 2. Difference in the number of recurrent hospitalizations due to heart failure between the treatment groups: at 3 and 9 months. 3. Difference in the number of hospitalizations for CV causes between the treatment groups: - time frame: at 3 and 9 months. 4. Difference in the number of hospitalizations for other than CV causes between the treatment groups: - time frame: at 3 and 9 months. 5. Time to adjudicate CV death- time frame: at 3 and 9 months.

	6. Time to adjudicate all causes of death- time frame: at 3 and 9 months. 7. Time to adjudicate myocardial infarction- time frame: at 3 and 9 months. 8. eGFR (Estimated Glomerular Filtration Rate) (CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration Equation)) CR slope of change from baseline: at 3 and 9 months. 9. Difference in the number of hospital readmissions due to heart failure between the treatment groups- time frame: at 3 and 9 months. 10. Difference in the number of hospital readmissions for any cause between the treatment groups- time frame: at 3 and 9 months. 11. Difference in the duration of hospital stay between the treatment groups after initiation of the study treatment- time frame: at 3 and 9 months. 12. Difference in the number of incidences of new onset AF and re-occurrence of AF between treatment groups- time frame: at 3 and 9 months. 13. Difference in the change of ejection fraction in echocardiography between treatment groups from randomization to 3 and 9 months. 14. Difference in the change of left ventricular diastolic function in echocardiography from randomization to 3 and 9 months. 15. Difference in the change of LV strain analysis in echocardiography from randomization to 3 and 9 months. 16. The time-averaged proportional change in NT-proBNP from baseline through 3 and 9 months. 17. Personalized medicine based on biomarker approach- the time-averaged proportional change in selected ncRNA expression linked to hypertrophy, inflammation, fibrosis, apoptosis, electric stability between treatment groups and placebo group from baseline through months 3 and 9. 18. Personalized medicine based on biomarker approach- the time-averaged bproportional change in PCT- procalcitonin, ANP – atrial natriuretic peptide, FGF-23 - fibroblast growth factor-23, GDF-15 – growth differentiation factor-15, IL-2 - interleukin 2, IL-6 - interleukin 6 between treatment groups and placebo group from baseline through months 3 and 9. 19. Personalized medicine based on biomarker approach- association between primary and secondary clinical endpoints and microbiome metabolites at baseline in both treatment groups and placebo in long term follow-up (3 and 9 months). 20. Personalized medicine based on biomarker approach- association between primary and secondary clinical endpoints and metabolome at baseline in both treatment groups and placebo in long term follow-up (3 and 9 months). 21. Cost-effectiveness substudy. 22. Effect of SGLT-2 inhibitors according to clinical characteristics as age, gender. 23. Symptoms, Function, and Quality of Life substudy. 24. Polypharmacy substudy. 25. Effect of SGLT-2 inhibitors on cardiac muscle fibrosis based on magnetic resonance (MR) substudy.
Safety objectives	- All-cause mortality - Number of serious adverse events - Number of hypoglycemic events - Number of genital infections - Number of ketoacidotic events - Changes in liver function parameters (AST, ALT, GGT) - Changes in renal function parameters (creatinine, eGFR)
Number of patients	1364 patients
Time schedule	*With reference to the trial:* EC Submission: JULY/2020 Local Authority Submission (UPRL): JULY/2021 First Patient In (FPFV): SEPT/2022 Last Patient In: AUG/2024

	Last Patient Out (LPLV): FEB/2026 Data Base Lock: APR/2026 First Results available: SEP/2026 Clinical Study Report: DEC/2026 *With reference to patients:* Duration of the treatment: 9 months
Main inclusion criteria	- Patients 18 years of age with the capacity to provide written informed consent - Currently hospitalized for a primary diagnosis of acute/decompensated HF (HFrEF, HFmrEF,HFpEF), including symptoms and signs of fluid overload regardless of ejection fraction or diabetes status - In patients with HFpEF the diagnosis has to be confirmed according to the current HFpEF definition (by non-invasive testing: evidence of structural or functional changes in the heart as evidenced on echocardiography or by invasive testing as LVEDP assessment or right heart catheterisation). - Randomized no earlier than 24 hours and up to 10 days after initial presentation while still hospitalized - Stable as defined by: systolic blood pressure (SBP>100 mmHg for the preceding 6 hours) - No intensification of IV diuretics within the last 6 hours, - No use of IV vasodilators within the last 6 hours, - No use of IV inotropes or levosimendan within the last 24 hours prior to randomization - Elevated NT-proBNP >600 pg/mL during the current hospitalization in patients with HFrEF and >300 pg/mL in patients with HFmrEF or HFpEF (or above 900 pg/ml if atrial fibrillation is present at admission independently from EF). - eGFR >20 ml/min/1,73m2
Main exclusion criteria	- History of ketoacidosis - Type 1 diabetes - SGLT-2 Inhibitor at baseline or known allergy to SGLT-2 Inhibitors - Current active cancer with less than 2 years of life expectancy - Pulmonary embolism, cerebrovascular accident as the primary trigger for the current hospitalization - Cardiomyopathy based on infiltrative diseases (e.g. amyloidosis), accumulation diseases (e.g. haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g. stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known Pericardial constriction - Any severe (obstructive or regurgitant) valvular heart disease, expected to lead to surgery during the trial period - Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant - Blood pH<7.32 - >1 episode of severe hypoglycaemia within the last 6 months under treatment with insulin or sulfonylurea - Acute symptomatic urinary tract infection or genital infection
Study medications	Active substance 1: Empagliflozin Commercial name: Jardiance Manufacturer: Boehringer Ingelheim Active substance 2: Dapagliflozin Commercial name: Forxiga Manufacturer: Astra Zeneca
Treatment plan	Empagliflozin, 10mg once daily orally administered or matched placebo Dapagliflozin, 10mg once daily orally administered or matched placebo