Evaluation of the effects of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial

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Background

The principal biological processes that characterize heart failure with a preserved ejection fraction (HFrEF) are systemic inflammation, epicardial adipose tissue accumulation, coronary microcirculatory rarefaction, myocardial fibrosis and vascular stiffness; the resulting impairment of left ventricular and aortic distensibility (especially when accompanied by impaired glomerular function and sodium retention) causes increases in cardiac filling pressures and exertional dyspnoea despite the relative preservation of left ventricular ejection fraction. Independently of their actions on blood glucose, sodium–glucose co-transporter 2 (SGLT2) inhibitors exert a broad range of biological effects (including actions to inhibit cardiac inflammation and fibrosis, antagonize sodium retention and improve glomerular function) that can ameliorate the pathophysiological derangements in HFrEF. Such SGLT2 inhibitors exert favourable effects in experimental models of HFrEF and have been found in large-scale trials to reduce the risk for serious heart failure events in patients with type 2 diabetes, many of whom were retrospectively identified as having HFrEF.

Study design

The EMPEROR-Preserved Trial is enrolling ≈5750 patients with HFrEF (ejection fraction >40%), with and without type 2 diabetes, who are randomized to receive placebo or empagliflozin 10 mg/day, which is added to all appropriate treatments for HFrEF and co-morbidities.

Study aims

The primary endpoint is the time-to-first-event analysis of the combined risk for cardiovascular death or hospitalization for heart failure. The trial will also evaluate the effects of empagliflozin on renal function, cardiovascular death,
Introduction

The two primary phenotypes of chronic heart failure are heart failure with a reduced ejection fraction (HFrEF) and heart failure with a preserved ejection fraction (HFpEF). The principal biological processes that characterize HFrEF are cardiomyocyte loss and stretch; the resulting enlargement of the left ventricle promotes the activation of neurohormonal systems that cause sodium retention, systemic vasoconstriction and adverse chamber remodelling, leading to further cardiomyocyte loss and systolic dysfunction. In contrast, the principal biological processes that characterize HFpEF are systemic inflammation, epicardial adipose tissue accumulation, coronary microcirculatory rarefaction, myocardial fibrosis and vascular stiffness; the resulting impairment of left ventricular and aortic distensibility (especially when accompanied by impaired glomerular function and sodium retention) causes increases in cardiac filling pressures and exertional dyspnoea despite the relative preservation of left ventricular ejection fraction (LVEF). The systemic inflammation in HFpEF can also cause changes in mitochondrial function and in the mass and composition of skeletal muscle, which can contribute to exercise intolerance in this disorder.

The treatment of HFrEF is primarily directed towards interference with deleterious neurohormonal systems (i.e. sympathetic nervous system, renin–angiotensin system, aldosterone and neprilysin) that are responsible for adverse cardiac remodelling. Pharmacological blockade of these pathways has been shown to reduce morbidity and mortality in large-scale randomized controlled trials. In contrast, therapeutic interventions that can successfully ameliorate the derangement of biological pathways in HFpEF are still being explored. Mineralocorticoid receptor antagonists and neprilysin inhibitors, if the latter classes of drugs prove to be effective in this disorder in ongoing trials (Figure 7).

We are evaluating the effects of empagliflozin in two large-scale clinical trials, one focused on patients with a preserved ejection fraction (EMPEROR-Preserved, NCT03057951) and the other focused on patients with a reduced ejection fraction (EMPEROR-Reduced, NCT03057977). The two trials, taken together, constitute the EMPEROR Program. This paper describes the intent and design of the EMPEROR-Preserved Trial.

Trial structure and oversight

The EMPEROR-Preserved Trial is a Phase III international, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial that is evaluating the effects of empagliflozin on morbidity and mortality in patients with established HFpEF, with or without type 2 diabetes. The trial is being carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The conduct of the study is approved by an institutional review board for each participating centre, and all participants provide written informed consent before study entry. The registration identifier on clinicaltrials.gov is NCT03057951. The sponsors of the trial are Boehringer Ingelheim (Ingelheim, Germany) and Eli Lilly and Company (Indianapolis, IN, USA).
The trial was designed by the study’s Executive Committee, the members of which include academic investigators, as well as representatives of Boehringer Ingelheim. The Executive Committee was responsible for the development of the study protocol and had scientific oversight on the development of the case report forms and statistical plan. In addition, the Executive Committee is overseeing the pace of recruitment, the appropriateness of the patients enrolled, and the quality and thoroughness of follow-up. The decisions and recommendations of the Executive Committee are reached through collaboration and by consensus. National leaders from key countries play major regional roles in encouraging recruitment and maintaining the commitment and dedication of investigators. A further committee, the Endpoint Adjudication Committee, is evaluating all reported and potential clinical events while blinded to the treatment assignment; these events will be judged to have met (or not met) prespecified criteria for a prespecified endpoint or safety event. An independent committee, the Data Monitoring Committee, is responsible for ongoing evaluation of the data that accrue during the course of the trial and is charged with making recommendations about the continuation or termination of the trial. At a planned interim analysis, the Data Monitoring Committee may recommend that the trial is stopped because it indicates overwhelming efficacy, which will be guided by prespecified stopping boundaries. The members of the trial committees are listed in Appendix 1.

Study patients

Participants in the EMPEROR-Preserved Trial are men and women, aged ≥18 years, who have had chronic heart failure (functional class II, III or IV) for at least 3 months and in whom LVEF is >40% at its most recent assessment prior to enrolment and in whom no prior measurement of ejection fraction of ≤40% is recorded. Patients are required to have elevated N-terminal pro brain natriuretic peptide (NT-proBNP) levels (i.e. >300 pg/mL in patients without atrial fibrillation and >900 pg/mL in patients with atrial fibrillation) and to show evidence of structural changes in the heart (as evidenced by increases in left atrial size or left ventricular mass) on echocardiography or a documented hospitalization for heart failure within 12 months of screening. The dose of oral diuretics must be stable for 1 week prior to randomization.

Patients are excluded if: (i) they have a cardiovascular disorder or are receiving treatments that increase the unpredictability of or may change their clinical course, independently of heart failure; (ii) they have an untreated or undertreated cardiovascular condition that may influence the course of heart failure or tolerability of the study medications; (iii) they have a significant co-morbid condition that may influence the clinical course, independently of heart failure, or (iv) they have any condition that may jeopardize their safety, limit their participation in the trial or undermine the interpretation of trial data. All exclusion criteria are listed in Table 1.

Study visits and follow-up

Following a screening period lasting 4–28 days, patients who fulfill all eligibility criteria are randomized in a double-blinded manner (in a 1:1 manner) to receive placebo or empagliflozin 10 mg/day, in addition to their usual therapy for heart failure. The dose of empagliflozin for this trial was selected based on the observed reduction in the risk for cardiovascular death produced by a dose of 10 mg/day in a large-scale trial in patients with type 2 diabetes (Figure 1).

Randomization is performed by using a permuted block design with a computer pseudo-random number generator and an interactive response technology system. Randomization is stratified by: (i) geographical region (North America, Latin America, Europe, Asia, other); (ii) status of diabetes at screening; (iii) estimated glomerular filtration rate (eGFR) [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] of <60 or ≥60 mL/min/1.73 m²; and (iv) pre-randomization LVEF of <50% or ≥50%. It is expected that approximately half of the patients will not have diabetes at the time of enrolment. Following randomization, any and all appropriate treatment for heart failure or any other medical condition or co-morbidity may be initiated, adjusted or altered at the clinical discretion of each patient’s physician or health care provider according to each patient’s needs, except that open-label use of SGLT2 inhibitors is prohibited.

Patients will be evaluated periodically at prespecified study visits. These assessments will include a description of the patient’s New York Heart Association functional class, as well as the reporting of adverse events. Quality of life related to heart failure will be evaluated using the Kansas City Cardiomyopathy Questionnaire at randomization, after 3, 8 and 12 months of double-blind treatment, and at the end of double-blind treatment. Various biomarkers and end-organ functional assessments will include (but not be restricted to) the periodic measurement of glycated haemoglobin, NT-proBNP, renal function (including eGFR and urinary albumin-to-creatinine ratio) and liver function tests; blood samples will be banked for future biomarker analyses.

Investigators are expected to meticulously document all relevant clinical events that occur from the time of randomization until trial completion. All randomized patients will be followed for the occurrence of prespecified primary and secondary outcome events for the entire duration of the trial, regardless of whether they are taking their study medications or are fully compliant with study procedures.

Primary and secondary endpoints

The primary endpoint of the EMPEROR-Preserved Trial is the time-to-first-event analysis of the combined risk for adjudicated cardiovascular death and adjudicated hospitalization for heart failure. The primary analysis will be based on the intention-to-treat principle and include all randomized patients (from the day of randomization until the end of the planned treatment period), whether or not they continue to receive the study medications. During the trial close-out period, patients will return for an end-of-treatment visit and will be followed for an additional 30 days off treatment. Primary events occurring during this follow-up period will not be included in the primary analysis of efficacy, but will be included in a separate analysis.

Differences between the placebo and empagliflozin groups in the primary endpoint will be assessed for statistical significance using
Table 1 Exclusion criteria for the EMPEROR-Preserved Trial

| Cardiovascular diseases or treatments that increase the unpredictability of or change the patient’s clinical course, independent of heart failure |
| Myocardial infarction [increase in cardiac enzymes in combination with symptoms of ischaemia or new ischaemic electrocardiography (ECG) changes], coronary artery bypass graft surgery, or other major cardiovascular surgery, stroke or transient ischaemic attack in the past 90 days |
| Heart transplant or listing for heart transplant. Currently implanted left ventricular assist device |
| 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 |
| Acute decompensated heart failure requiring intravenous diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomization |
| Implant of a cardioverter defibrillator within 3 months prior to screening |
| Cardiac resynchronization therapy |
| Untreated or undertreated cardiovascular conditions that might influence the course of heart failure or the tolerability of the study medications |
| Atrial fibrillation or atrial flutter with a resting heart rate of >110 bpm documented by ECG at screening |
| Systolic blood pressure of ≥180 mmHg at randomization. If the systolic blood pressure is 151–179 mmHg, the patient should be receiving at least three antihypertensive drugs |
| Symptomatic hypotension and/or systolic blood pressure of <100 mmHg at screening or at randomization |
| Significant co-morbid conditions that might influence the clinical course, independent of heart failure |
| Chronic pulmonary disease requiring home oxygen, oral corticosteroid therapy or hospitalization for exacerbation within 12 months; significant chronic pulmonary disease or primary pulmonary arterial hypertension |
| Acute or chronic liver disease, defined by serum levels of transaminases or alkaline phosphatase more than three times the upper limit of normal at screening |
| Impaired renal function, defined as an estimated glomerular filtration rate of <20 mL/min/1.73 m² (Chronic Kidney Disease Epidemiology Collaboration) or requiring dialysis at the time of screening |
| Haemoglobin of <9 g/dL at screening |
| Major surgery (major according to the investigator’s assessment) performed within 90 days prior to screening, or major scheduled elective surgery (e.g. hip replacement) within 90 days after screening |
| Gastrointestinal surgery or gastrointestinal disorder that might interfere with trial medication absorption |
| Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or low-risk prostate cancer (patients with pre-treatment prostate-specific antigen levels of <10 ng/mL and biopsy Gleason scores of ≤6 and clinical stage T1c or T2a) |
| Presence of any disease other than heart failure that results in a life expectancy of <1 year (in the opinion of the investigator) |
| Any condition that might jeopardize patient safety, limit the patient’s participation in the trial, or undermine the interpretation of trial data |
| Current use or prior use of a sodium–glucose cotransporter 2 (SGLT2) inhibitor or combined inhibitor of SGLT1 and SGLT2 within 12 weeks prior to screening or randomization. Discontinuation of a SGLT2 inhibitor or combined inhibitor of SGLT1 and SGLT2 inhibitor for the purposes of study enrolment is not permitted |
| Known allergy or hypersensitivity to any SGLT2 inhibitors |
| History of ketoacidosis |
| Need or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial |
| Current enrolment in another investigational device or drug study or completion within <30 days of a trial of another investigational device or drug study. Receipt of any investigative treatment other than the study medications for this trial |
| Chronic alcohol or drug abuse or any condition that, in the investigator’s opinion, will make the patient unlikely to fulfil the trial requirements or complete the trial |
| Pregnancy, current breast-feeding or intention to become pregnant while in the trial |
| Any other clinical condition that might jeopardize patient safety during participation in this trial or prevent the subject from adhering to the trial protocol |

A Cox proportional hazards model, with prespecified covariates of age, gender, geographical region, diabetes status at baseline, LVEF and eGFR at baseline. Age, ejection fraction and eGFR will be included in the model as continuous variables. The most important prespecified subgroup analysis will compare the effects of empagliflozin on the risk for major cardiovascular events in patients with and without diabetes at the time of randomization.

Secondary endpoints will be analysed in a stepwise hierarchical manner in order to preserve the overall type 1 error rate at a study-wide level of 0.05 (two-sided). The first-listed secondary endpoint is the occurrence of adjudicated hospitalization for heart failure (including first and recurrent events), which will be evaluated using a joint frailty model that includes the consideration of cardiovascular death as a potential source of informative censoring. If this endpoint is successfully achieved, the analysis will proceed to an analysis of the second-listed secondary endpoint [i.e. the slope of the change in eGFR (CKD-EPI) from baseline], which will be evaluated by a random coefficient model allowing for
The ongoing EMPEROR-Preserved Trial is designed to specifically evaluate the effect of empagliflozin on the risk for cardiovascular death or hospitalization for heart failure in patients with HFrEF, as well as the drug’s effect on the total number of heart failure hospitalizations. The trial is also examining the ability of empagliflozin to prevent the time-dependent deterioration of glomerular filtration, which characterizes patients with HFrEF. Importantly, because the reported benefits of SGLT2 inhibitors on heart failure do not appear to be related to their effects on glycemic control, the trial is enrolling patients with and without diabetes. Based on current understanding of its enormous range of pleotropic effects, it is not expected that the pre-treatment glycemic status of patients will influence the magnitude or direction of the therapeutic response to treatment.
The likelihood that empagliflozin will be shown to have clinical benefits in the EMPEROR-Preserved Trial is strengthened by the fact that the drug has already been shown to reduce the risk for cardiovascular death or heart failure hospitalization and to improve glomerular function and slow the progression of renal disease in patients with type 2 diabetes, in most of whom heart failure was not identified at the time of randomization.25,50 Although these trials did not fully characterize the phenotype of those who developed heart failure during the course of follow-up, patients with type 2 diabetes are particularly prone to the development of HFrEF.23,24 In post hoc analyses of both the DECLARE-TIMI 58 trial with dapagliflozin and the CANVAS trial with canagliflozin52,53 the use of SGLT2 inhibitors reduced the risk for hospitalization for heart failure in patients who were reported to have HFrEF at the time of enrolment or at the time of a heart failure event that occurred following randomization; however, these data in trials in patients with type 2 diabetes are sparse and incomplete, and thus must be considered to be hypothesis-generating. In contrast, the EMPEROR-Preserved Trial is specifically designed to determine if empagliflozin can treat patients with established HFrEF, whether or not they have diabetes. Importantly, the EMPEROR-Preserved Trial plans to evaluate a diverse array of circulating measures of adiposity and inflammation, as well as biomarkers of cardiac and renal injury. It is therefore well positioned to identify the mechanisms by which empagliflozin is beneficial if it achieves success in its planned endpoints.

Given its projected sample size of \( \approx 5750 \) patients, the EMPEROR-Preserved Trial is likely to be the largest trial ever carried out in patients with HFrEF. It will provide critical insights into the pathogenesis of the disease and the mechanisms that contribute to morbidity and mortality in this disorder. It has been hypothesized that the activation of certain mediators (e.g. the leptin–aldosterone–neprilysin axis) plays an important role in the development of HFrEF in many patients.30 Interestingly, the biological actions of the SGLT2 inhibitors evaluated in the EMPEROR-Preserved Trial can be regarded as opposite to those of leptin,22 whereas other ongoing trials are evaluating the efficacy of inhibitors of aldosterone and neprilisin.22,45 The totality of evidence from these trials may establish a neurohormonal basis for the treatment of HFrEF in a manner that parallels that which exists for patients with HFrEF.14,56,57

Conflict of interest: S.D.A. has recently received fees for steering committee activity, advisory board work and/or speaking from AstraZeneca, Bayer, Boehringer, Brahms, Novartis, Respicardia, Servier and Vifor, and has received grants for the execution of investigator-initiated trials from Abbott Vascular and Vifor. J.B. has received research support from the National Institutes of Health, Patient Centered Outcomes Research and the European Union (EU), and has served as a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Innolite, Janssen, LinaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Pilepsa, Roche, Sanofi, V-Wave and Vifor. G.S.F. has received steering committee fees and/or research grants from Novartis, Bayer, Vifor, Servier, Medtronic, BI and the EU. W.J., A.S., J.S., K.K., C.Z., J.G. and M.B. are employees of Boehringer Ingelheim. F.Z. has received steering committee or advisory board fees from Amgen, AstraZeneca, Bayer, Boehringer, Boston Scientific, Cardior, CVRx, Janssen, Livanova, Merck, Mundipharma, Novartis, NovoNordisk and Vifor Fresenius. M.P. has served as a consultant for Abbott, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance.

Appendix 1

Committees for the EMPEROR-Preserved Trial

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