**Protocol**

**Protocol Title:** EMpagliflozin evaluation By measuRing ImpAct on HemodynamiCs in PatiEnts with Heart Failure (EMBRACE-HF)

**Protocol Number:** 1245.129

**ClinicalTrials.gov registration:** NCT03030222

**Version:** 2

**Version Date:** September 24, 2018

**PROTOCOL SYNOPSIS**

A 12-week randomized, double-blind, placebo-controlled trial to explore the effects of empagliflozin on hemodynamic parameters (pulmonary artery pressures) in patients with heart failure (HF) (reduced or preserved ejection fraction, ischemic or non-ischemic etiology) who already have a CardioMEMs device implanted for non-study related clinical reasons.

**Study Hypothesis**

The trial will test a hypothesis that empagliflozin is superior to placebo in lowering pulmonary artery pressures in patients with HF.

**Study Centers and Number of Patients Proposed**

Up to 15 medical centers in the US will participate in the study, with competitive enrollment planned. Approximately 60 patients will be randomized over a target enrollment period of approximately 24 months.

| **Study Period** | | **Phase of Development** |
|---|---|---|
| Estimated date of first patient enrolled | July 5th, 2017 | IV (post marketing) |
| Estimated date of last patient completed | May 31st, 2019 | IV (post marketing) |

**Primary Objective**

To evaluate the effects of empagliflozin 10 mg daily on hemodynamic parameters (pulmonary artery diastolic pressure) in patients with heart failure (HF) (reduced or preserved ejection fraction, ischemic or non-ischemic etiology).

**Target Population**

Male and female patients with heart failure (HF) (reduced or preserved ejection fraction, ischemic or non-ischemic etiology) who already have a CardioMEMs implanted for non-study related clinical reasons.

**Investigational Product, Dosage, and Mode of Administration**

Empagliflozin 10 mg administered orally once daily for 12 weeks, in addition to standard of care for chronic heart failure.

**Comparator, Dosage and Mode of Administration**

Matching placebo administered orally once daily for 12 weeks, in addition to standard of care for chronic heart failure.

**Study Duration**

Activation of all study sites is expected to take 6 months, followed by approximately 24 months to reach complete study enrollment. After randomization, empagliflozin or placebo will be administered for 12 weeks. At week 13 there will be a final study visit. Total study duration (after enrollment of the first patient) is approximately 33 months.

**Primary Endpoint**

Change in pulmonary artery diastolic pressure from baseline to end of treatment period (defined as average of pulmonary artery diastolic pressure measurements between weeks 8-12)

**Secondary Endpoints**

1. Change from baseline in pulmonary artery diastolic pressure at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
2. Change in pulmonary artery systolic pressure from baseline to end of treatment period
3. Change from baseline in pulmonary artery systolic pressure at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
4. Change in mean pulmonary artery pressure from baseline to end of treatment period
5. Change from baseline in mean pulmonary artery pressure at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
6. Change in heart failure related quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score from baseline to follow-up (defined as average of measurements at 6 and 12 weeks).
7. Proportion of patients with a ≥ 5pt increase from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) at either 6 weeks or 12 weeks of follow-up
8. Change in 6-minute walk test from baseline to follow-up (defined as average of measurements at 6 and 12 weeks)
9. Change in NTproBNP from baseline to follow-up (defined as average of measurements at 6 and 12 weeks)
10. Change in BNP from baseline to follow-up (defined as average of measurements at 6 and 12 weeks)
11. Proportion of patients with a ≥ 20% decrease from baseline in NTproBNP at either 6 weeks or 12 weeks of follow-up.

12. Proportion of patients with a ≥ 20% decrease from baseline in BNP at either 6 weeks or 12 weeks of follow-up.
13. Proportion of patients with both a ≥ 5pt increase from baseline in KCCQ and a ≥ 20% decrease from baseline in NTproBNP at either 6 weeks or 12 weeks of follow-up
14. Number of diuretic medication adjustments during the treatment period (up-titration and down-titration of diuretic doses to be evaluated separately)
15. Change in Hemoglobin A1c from baseline to follow-up (defined as average of measurements at 6 and 12 weeks), evaluated separately in patients with and without type 2 diabetes

**Exploratory Endpoints**

1. Change in pulmonary artery diastolic pressure between week 12 and week 13
2. Change in mean pulmonary artery pressure between week 12 and week 13
3. Change in pulmonary artery systolic pressure between week 12 and week 13
4. Change in mean heart rate from baseline to end of treatment period
5. Effects on average weekly loop diuretic dose (furosemide equivalent).
6. Effects on hospitalizations for heart failure.
7. Effects on urgent outpatient heart failure visits.
8. Effects on hospitalizations for heart failure and urgent outpatient visits for heart failure
9. Change in NYHA Class at 6 weeks from baseline and 12 weeks from baseline.
10. Change in NTproBNP and KCCQ at 6 weeks from baseline and 12 weeks from baseline
11. Number of medication adjustments other than diuretics (nitrates, hydralazine, ACE, ARB, b-blockers, sacubitril/valsartan) during the treatment period
12. Proportion of patients that progress to diabetes during the treatment period (within the subgroup of patients without diabetes at baseline only)

**Safety Variables**

1. All cause death
2. Cardiovascular death
3. Non-fatal myocardial infarction (MI)
4. Stroke
5. Acute kidney injury (defined as doubling of serum creatinine based on the modified RIFLE criteria)
6. Adverse events (AEs) and serious adverse events (SAEs). AEs of special interest will include diabetic ketoacidosis (DKA), volume depletion (defined as hypotension, syncope, orthostatic hypotension or dehydration), non-traumatic lower limb amputations, and severe hypoglycemic events.

**Statistical Methods**

Baseline demographic and clinical data will be described between treatment and placebo study arms as mean ± standard deviation for continuous variables and compared using Student's T-test. Whereas discrete variables will be represented as a number and (%) and compared using the $\chi^2$ or Fisher's exact test, as applicable.

The time course of continuous variables will be presented using standard descriptive summary statistics calculated at each scheduled measuring time point and the last individual measuring time point. Moreover, standard descriptive summary statistics will be calculated for the change (absolute or percent) from baseline to each scheduled measuring time point after baseline and the last individual measuring time point.

The primary endpoint of this study is the change in pulmonary artery diastolic pressure from baseline to end of treatment period (defined as average of pulmonary artery diastolic pressure measurements between weeks 8-12). This will be analyzed using a repeated measures model incorporating a within-patient covariance structure to estimate the effect of treatment, and adjusted for diabetes status.

A sample size of 28 patients for each group will achieve 80% power with $\alpha$=0.05 to detect a 20% difference in pulmonary artery diastolic pressure between the empagliflozin 10 mg and placebo groups averaged over four repeated measures (weeks 8 through 12) assuming the following: 1) between-patient standard deviation = 6; 2) Within patient correlation between adjacent time points: 0.7; 3) PA diastolic pressure in the intervention arm of the trial will achieve a plateau by week 9 for the treatment group. Thus, the proposed sample size is 60 patients (30 per arm with 1:1 randomization ratio).

Of note, participation of patients with and without Type 2 diabetes is allowed, but proportion of patients with diabetes may be capped at no more than 67% (40 patients) of the entire cohort.

Statistical significance will be defined using two-sided tests with $\alpha$=0.05, unless otherwise specified. All statistical analyses will be performed by the Department of Biostatistics using SAS version 9.4 (SAS Institute, Cary, North Carolina).

# Contents

# 1 INTRODUCTION

## 1.1 Background and Significance

The prevalence of both heart failure and type 2 diabetes or prediabetes are reaching epidemic proportions globally and in the United States.[1] In a post hoc analysis of PARAGIDM-HF - a contemporary clinical trial of patients with heart failure and reduced ejection fraction (HFrEF), even among patients who reported no known history of T2DM, 49% had prediabetes, and 21% had unrecognized T2DM based on hemoglobin A1c (HbA1c) criteria.[2] In recent clinical trials, HF has emerged as the most common cardiovascular (CV) complication of T2DM, exceeding the incidence of myocardial infraction or stroke.[3] In addition to being common, incident HF is also arguably the most morbid cardiovascular complication of T2DM, with survival of less than 25% over 5 years among older T2D patients.[4]

The intersection of T2DM, prediabetes and HF is quickly becoming a public health crisis, and despite these alarming statistics, remarkably little is known on the optimal strategies of managing patients with prediabetes, T2DM and HF. To date, no single class of glucose-lowering medications has been specifically tested for safety in heart failure patients. Furthermore, several existing classes of glucose-lowering medications present potential safety issues, specifically in terms of volume overload and hospitalizations for heart failure. Foremost among these classes are thiazolidinediones (TZDs)[5-7] and, possibly, dipeptidyl peptidase (DPP-4), according to results of the SAVOR and EXAMINE clinical trials.[8,9] Other classes of glucose-lowering medications (insulin and sulfonylureas) may lead to weight gain and hypoglycemic events[10], which potentially impact heart failure symptoms. As a result, evidence-based recommendations are currently unavailable for optimal type 2 diabetes or prediabetes management in patients with heart failure.

Sodium glucose cotransporter type 2 inhibitors (SGLT-2i) appear to be the most promising therapy to date for patients with HF. While they produce relatively modest HbA1c reduction, SGLT-2i exhibit a novel, entirely insulin-independent mode of action through increased urinary excretion of glucose.[11] SGLT-2i may represent a transformational treatment for patients with HF and T2DM, as they are the first class of glucose-lowering agents ever to demonstrate a robust benefit for reducing HF hospitalizaions.[11-13] The EMPA-REG OUTCOME trial randomized 7,020 patients with T2DM and established CV disease to 10 or 25 mg of empagliflozin vs. placebo. After a median 3.1 years, significantly fewer patients in the empagliflozin group than in the placebo group experienced the primary outcome of MACE (10.5% vs. 12.1%), CV-related death (3.7% vs. 5.9%), or all-cause death (5.7% vs. 8.3%).[13] There was no difference in outcomes between the10 and 25 mg doses of empagliflozin, with both dosage being statistically significantly superior to placebo for primary and secondary endpoints. [13] Though the trial was predominantly of diabetic patients with coronary artery disease (with only 10% of patients having known history of HF at baseline), the majority of the benefit appeared to be due to the highly significant reduction in hospitalizations for heart failure (a 35% relative risk reduction), and prevention of HF-related and arrhythmia-related deaths. The relative risk reduction in HHF was statistically similar between those with and without a history of HF; however, since overwhelming majority of patients did not have HF at baseline, this appeared to represent primarily a HF prevention effect.[14]

Supporting a class effect for SGLT-2i benefit on hospitalizations for HF, are similar results in the Canagliflozin Cardiovascular Assessment Study (CANVAS Program). The CANVAS Program was a combination of CANVAS, the original canagliflozin cardiovascular safety trial, which was used to gain FDA approval in 2013, and a separate CANVAS-R trial, which was combined with CANVAS for the purpose of demonstrating cardiovascular benefit. The CANVAS program enrolled a total of 10,142 patients with established CVD (65%) or at high risk of CV events (35%), randomized to canagliflozin (100 mg or 300 mg) or placebo.[15] The primary outcome (nonfatal myocardial infarction or stroke, or CV-related death) occurred significantly less frequently with canagliflozin than with placebo (26.9 vs. 31.5 per 1000 patient-years).[12] While the reduction in CV and all-cause death with canagliflozin vs. placebo did not reach statistically significance, patients in the pooled canagliflozin arm experienced a significant 33% relative risk reduction in HHF.[12] Real world data from a large multi-national non-interventional study, which combined data from well-established registries across 6 countries also supports the notion of a class benefit for SGLT-2i and HF outcomes. The CVD-REAL study analyzed over 300,000 T2DM patients and compared the HF outcomes in patients being newly initiated on SGLT-2is versus those being started on other glucose lowering medications. The main analysis (matched 1:1 using propensity score methodology), demonstrated a 39% relative risk reduction in HF hospitalizations associated with SGLT-2i use vs. other glucose-lowering drugs.[16] These reductions were also observed for the outcome of total HF events, and were consistent in patients with and without established HF.[17]

While the excitement surrounding SGLT-2is as potential therapeutic class for the management of HF is warranted, many questions remain unanswered. It is unclear if the reduction in heart failure hospitalizations seen with SGLT-2is to date – which is primarily a signal for HF prevention, will also translate to a clinical benefit in patients with established HF, including patients with heart failure and reduced ejection fraction (HFrEF). Also given that patients without diabetes (including those with prediabetes) would also be expected to have some degree of glucosuria with SGLT-2i treatment, and that the CV benefits of SGLT-2i appear to be unrelated to either baseline HbA1c or change in HbA1c, it is possible that the potentially beneficial effects of SGLT-2i on reducing HHF may translate to those without T2DM.[18]Additionally, the mechanisms of action (MOA) through which SGLT-2 inhibitors may produce a benefit on HF remain unclear, and need further clarification.

While the change in hemodynamic status (reflected by pulmonary artery pressures) is a critically important predictor of HF symptoms, HF hospitalizations and mortality[19,20], no data currently exist in regards to the impact of SGLT2i on these parameters in patients with HF. One of the key reasons for this lack of data is the inability (until now) to reliably and non-invasively monitor pulmonary artery pressure in patients with T2DM and HF. CardioMEMS (Figure 1), a wireless hemodynamic monitoring system, approved in both U.S. and Europe for management of patients with symptomatic HF, is the first means to obtain hemodynamics wirelessly[21]. CardioMEMS is delivered through a catheter-based system and permanently implanted in the pulmonary artery. It is powered externally and has a pressure sensor (uses nanometer deflections) to provide continuous stream of hemodynamic data (Figure 2) through a wireless communication with a home receiver. The hemodynamic data is streamed to the physician through a secure database. Management using CardioMEMS hemodynamic data has been shown, in the CHAMPION trial[22-24], to decrease hospitalizations for NYHA class III heart failure patients compared to management based on clinical information without CardioMEMS. Based on its effectiveness in decreasing hospitalizations in HF

patients and excellent safety profile, many patients have already had the CardioMEMS system implanted for HF management. Based on the existing epidemiologic data, and based on data from the CHAMPION trial, at least half of these HF patients likely have diabetes.

This presents a unique and previously unavailable opportunity to better understand the impact of empagliflozin on the hemodynamic profile of patients (with or without T2DM) and HF, and provide key mechanistic insights into the empagliflozin effects on prevention of HF hospitalization and reduction in CV mortality seen in EMPA-REG Outcomes study[13]. Given the known link between filling pressures and risk of HF hospitalizations, further investigation in this field has substantial mechanistic and clinical importance. Therefore, we propose to perform a pilot randomized clinical trial to evaluate the effects of empagliflozin on filling pressures (pulmonary artery pressures) in patients (with or without type 2 diabetes) that have chronic heart failure.

Figure 1: CardioMEMS device.

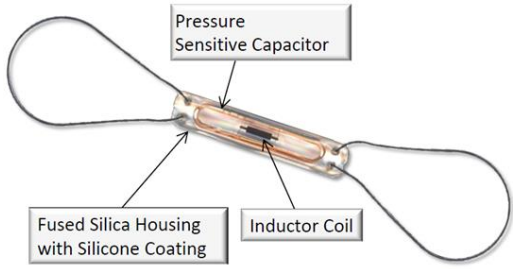
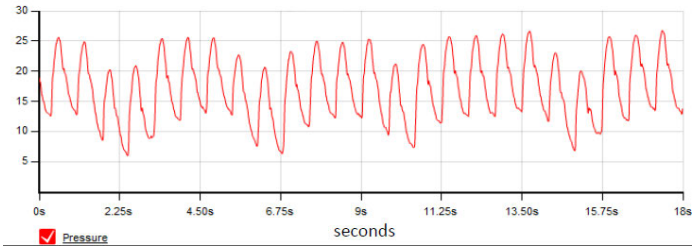



Figure 2: Sample of CardioMEMS PA pressure continuous wave




## 1.2 Research Hypothesis

Treatment with empagliflozin 10 mg daily for 12 weeks will produce greater reductions in pulmonary artery diastolic pressure as compared with placebo in patients with chronic heart failure.

## 1.3 Rationale for conducting this study

This is a Phase IV study that will present a unique and previously unavailable opportunity to better understand the impact of empagliflozin on the hemodynamic profile of patients with HF, and provide key mechanistic insights into the empagliflozin effects on prevention of HF hospitalization and reduction in CV mortality seen in EMPA-REG Outcomes study.

## 1.4 Benefit/risk and ethical assessment

Empagliflozin is approved for the treatment of type 2 diabetes, therefore patients enrolled in the study that have type 2 diabetes will have an established indication for empagliflozin therapy. Although empagliflozin is currently not approved in patients without diabetes, when empagliflozin is used either as monotherapy or in addition to metformin, it does not cause excess hypoglycemia as compared with placebo. No additional safety issues (beyond those observed with empagliflozin in patients with Type 2 diabetes) are anticipated in patients without diabetes treated with empagliflozin. Of note, several large cardiovascular outcome trials are currently evaluating various SGLT-2i as potential therapies for HF, and include patients with and without diabetes.[25-27]

Moreover, we will target patients with previously implanted CardioMEMs pulmonary artery pressure monitor for a clinical indication unrelated to the study, thus avoiding exposure of patients to an invasive procedure for the purposes of the study. Accordingly, we consider the benefit/risk balance to patients enrolled in the study to be similar to that encountered in the usual clinical practice, with no additional ethical concerns.

### 1.4.1 Risk Category

Considering empagliflozin's mechanism of action, the previous clinical experience with empagliflozin, the study's design features (including the inclusion, exclusion, and discontinuation criteria), and the planned safety procedures, participation in this study presents a minimal and thus acceptable risk to the individual patients that will be included.

### 1.4.2 Potential Risks

The potential risks associated with empagliflozin that have been identified based upon the mechanism of action, the preclinical results, and the clinical experience to date, as well as precautions included in the Phase III program to monitor and/or minimize these risks, are included in the empagliflozin prescribing information. [28]

In the overall pooled analysis in the phase III clinical studies, 17.3% of patients discontinued the drug due to adverse events. In clinical Phase III studies, events suggestive of genital fungal infections were reported in higher proportion of empagliflozin-treated patients than the placebo group and this can be explained by increased urinary glucose. Overall there were no imbalances of liver function test parameters between empagliflozin and placebo in Phase III studies.

Due to the diuretic effect of empagliflozin, volume depletion (dehydration, hypovolemia and/or hypotension) is a potential concern. In the clinical program, from which subjects who in the judgment of investigator may be at risk of dehydration or volume depletion were excluded, very few serious events related to volume depletion were reported, and they were equally distributed between empagliflozin and placebo groups. In the EMPA-REG Trial – the largest large empagliflozin study to date - there was no difference in hypovolemia events between empagliflozin and placebo. Of note, all patients in this study will have symptomatic heart failure and elevated pulmonary artery pressures at baseline, which will further minimize the risk of hypovolemic adverse events.

The U.S. Food and Drug Administration (FDA) on Dec 4th 2015 reported a warning for sodium-glucose cotransporter-2 (SGLT2) inhibitors which may lead to ketoacidosis, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization. At the time of this report there were 73 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors, only 4 patients were on empagliflozin.[29] DKA, a subset of ketoacidosis or ketosis in diabetic patients, is a type of acidosis that usually develops when insulin levels are too low or during prolonged fasting. DKA most commonly occurs in patients with type 1 diabetes and is usually accompanied by high blood sugar levels. The FDA reported cases were not

typical for DKA because most of the patients had type 2 diabetes and their blood sugar levels, when reported, were only slightly increased compared to typical cases of DKA. Factors identified in some reports as having potentially triggered the ketoacidosis included major illness, reduced food and fluid intake, and reduced insulin dose. The risk of euglycemic DKA is estimated to be very low in this study (given the small sample size, short duration of treatment, and the fact that patients without diabetes are likely not at risk for DKA) and provided that EMPA-REG study showed no difference in DKA incidence between the Empagliflozin and the placebo arms, and a recent meta analysis of all SGLT-2 inhibitors in patients with type 2 DM, showed no significant increase in the risk of DKA.[29] Nevertheless, out of an abundance of caution all patients will be provided with home urine ketone testing kits and patients will be monitored for symptoms of DKA during in-person visits and study-related phone calls. Patients will be instructed to self-test for urine ketones and directed to the closest emergency department if the urine ketone test is more than mildly positive. The instances of DKA (if any) will be closely monitored as AE of special interest by the study investigators, as well as the Independent Data and Safety Monitoring Committee. In addition, all patients that have T2D in this study will continue taking glucose-lowering medications (other than open-label SGLT-2 inhibitors) as background therapy. These drugs are widely used anti-hyperglycemic treatments and will be prescribed according to the approved label.

Moreover, the FDA also reported a warning for SGLT2 inhibitors that might lead to serious urinary tract infections. However in the Phase III clinical studies, and in the more than 7000 patient EMPA-REG Outcome Trial,[13] there was no difference in urinary tract infections overall - or complicated urinary tract infections specifically - between empagliflozin and placebo, both occurring at low rate.

The US FDA has issued a more recent safety alert in regards to SGLT2-inihibtors and potential risk for acute kidney injury. However, in the large randomized EMPA-REG outcome trial, there was no difference in acute kidney injury between empagliflozin and placebo, and patients treated with empagliflozin experienced significantly better renal outcomes long term. Similarly, data from other SGLT-2 inhibitor trials have confirmed no difference in acute kidney injury, and the long term nephroprotective benefits of SGLT-2 inhibitors in patients with type 2 DM.[30] We plan to monitor renal function carefully in the EMBRACE-HF study, and doubling of serum creatinine is a safety variable that is being carefully ascertained; furthermore, all patients in EMBRACE-HF Trial are volume overloaded at baseline given the requirement for significantly elevated PA diastolic pressure, and therefore should be at low risk for hypovolemic events. Additionally all patients will have invasive hemodynamic monitoring as a part of their routine clinical care, which should decrease a possibility of significant volume depletion and acute kidney injury due to pre-renal etiology. The Independent Safety and Data Monitoring Committee will also be reviewing safety data continuously.

Thus, the benefits and risks associated with the background medication and comparator treatment are well established and presented in their respective approved prescribing information. No study procedure will put patients at a risk beyond those ordinarily encountered during the performance of routine medical examinations or routine tests.

### 1.4.3 Protection against Risks

This study has been designed with appropriate measures in place so as to monitor and minimize any of the potential health risks to participating patients. This includes careful monitoring of patient's vital signs and laboratory values, and the temporary and if necessary permanent discontinuation of investigational product in individual patients in whom a potential health risk or a laboratory abnormality of clinical concern has been identified. Further, in order to ensure the safety of all patients participating in this study, an Independent Data and Safety Monitoring Committee (IDSMC) will be formed that will continuously review safety data, including the incidence of serious adverse events

(SAEs), and conduct assessments to ensure the ongoing safety of study patients. The IDSMC responsibilities, authorities, and procedures will be documented in an IDSMC charter. The personnel involved in the clinical study at will remain blinded to these analyses and will have no knowledge of the results presented to the IDSMC.

### 1.4.4 Benefit to Patients

All patients will continue taking their active background therapy; although a direct benefit from randomized treatment cannot be assured as one half of patients will receive placebo, those with type 2 diabetes randomized to empagliflozin may obtain better glucose control. In this study, the dose of empagliflozin 10 mg once daily was chosen to provide efficacy in improving heart failure symptoms and biomarkers, while mitigating the potential for AEs, based on previous clinical experience. In addition, among patients randomized to active drug, empagliflozin is expected to help maintain better glucose control (among those with type 2 diabetes), decrease body weight (or prevent weight gain) as well as help lower blood pressure especially in patients with elevated baseline blood pressure. All patients are also expected to receive some benefit in the form of increased medical care/attention when participating in study procedures, which includes at least 5 clinic visits with at least 5 physical examinations and at least 4 phone call visits over the 13-week study.

### 1.4.5 Informed Consent and Alternatives to Patients

All prospective participants will be informed of the possible risks and benefits associated with this study, and their consent will be received prior to performing any study-related activity. When a prospective participant elects to not participate in the study or to withdraw from the study, other medications are available to treat their heart failure, and the patient will not be disadvantaged in any way.

### 1.4.6 Conclusion

Considering the pre-clinical and clinical experience with empagliflozin and the precautions included in the study protocol, participation in this study presents a minimal and thus acceptable risk to patients who meet the inclusion/exclusion criteria and consent to take part in the study.

For additional details on benefits and risk, please see the empagliflozin prescribing information.

# 2 STUDY OBJECTIVE

To evaluate the effects of empagliflozin 10 mg daily, as compared with placebo, on hemodynamic parameters (pulmonary artery diastolic pressure) in patients with heart failure (HF) (reduced or preserved ejection fraction, ischemic or non-ischemic etiology).

## 2.1 Primary Objective

To compare the change in pulmonary artery diastolic pressure from baseline to end of treatment period (defined as average of pulmonary artery diastolic pressure measurements between weeks 8-12) between empagliflozin and placebo.

### 2.1.1 Secondary Objectives

1. To compare change from baseline in pulmonary artery diastolic pressure between empagliflozin and placebo at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)

2. To compare change in pulmonary artery systolic pressure from baseline to end of treatment period between empagliflozin and placebo
3. To compare change from baseline in pulmonary artery systolic pressure between empagliflozin and placebo at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
4. To compare change in mean pulmonary artery pressure from baseline to end of treatment period between empagliflozin and placebo
5. To compare change from baseline in mean pulmonary artery pressure between empagliflozin and placebo at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
6. To compare change from baseline to follow-up (defined as average of measurements at 6 and 12 weeks) in heart failure related quality of life between empagliflozin and placebo, using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score.
7. To compare proportion of patients with a ≥ 5pts increase from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) at either 6 weeks or 12 weeks of follow-up between empagliflozin and placebo
8. To compare change in 6 minute walk test from baseline to follow-up (defined as average of measurements at 6 and 12 weeks) between empagliflozin and placebo
9. To compare change in NTproBNP from baseline to follow-up (defined as average of measurements at 6 and 12 weeks) between empagliflozin and placebo
10. To compare change in BNP from baseline to follow-up (defined as average of measurements at 6 and 12 weeks) between empagliflozin and placebo
11. To compare proportion of patients with a ≥ 20% decrease from baseline in NTproBNP at either 6 weeks or 12 weeks of follow-up between empagliflozin and placebo.
12. To compare proportion of patients with a ≥ 20% decrease from baseline in BNP at either 6 weeks or 12 weeks of follow-up between empagliflozin and placebo.
13. To compare proportion of patients with both a ≥ 5pts increase from baseline in KCCQ and a ≥ 20% decrease from baseline in NTproBNP at either 6 weeks or 12 weeks of follow-up between empagliflozin and placebo
14. To compare the number of diuretic medication adjustments during the treatment period (up-titration and down-titration of diuretic doses to be evaluated separately) between empagliflozin and placebo
15. To compare change in Hemoglobin A1c from baseline to follow-up (defined as average of measurements at 6 and 12 weeks) between empagliflozin and placebo (evaluated separately in patients with and without type 2 diabetes)

### 2.1.2 Exploratory objectives

1. To compare change in pulmonary artery diastolic pressure between week 12 and week 13 between patients originally randomized to empagliflozin or placebo
2. To compare change in mean pulmonary artery pressure between week 12 and week 13 between patients originally randomized to empagliflozin or placebo
3. To compare change in pulmonary artery systolic pressure between week 12 and week 13 between patients originally randomized to empagliflozin or placebo

4. To compare change in mean heart rate from baseline to end of treatment period between empagliflozin and placebo
5. To compare effects on average weekly loop diuretic dose (furosemide equivalent) between empagliflozin and placebo.
6. To compare effects on hospitalizations for heart failure between empagliflozin and placebo.
7. To compare effects on urgent outpatient heart failure visits between empagliflozin and placebo.
8. To compare effects on hospitalizations for heart failure and urgent outpatient visits for heart failure between empagliflozin and placebo
9. To compare change in NYHA Class at 6 weeks from baseline and 12 weeks from baseline between empagliflozin and placebo.
10. To compare change in NTproBNP and KCCQ at 6 weeks from baseline and 12 weeks from baseline between empagliflozin and placebo
11. To compare the number of medication adjustments other than diuretics (nitrates, hydralazine, ACE, ARB, b-blockers, sacubitril/valsartan) during the treatment period between empagliflozin and placebo
12. Proportion of patients that progress to diabetes during the treatment period (within the subgroup of patients without diabetes at baseline only)

### 2.1.3 Safety topics

Safety of empagliflozin will be monitored by assessment of SAEs, AEs of special interest and other parameters including mortality, non-fatal MI, stroke, acute kidney injury, volume depletion, severe hypoglycemic events, ketoacidosis, laboratory values, pulse, blood pressure, and physical examination findings. Patients with established type 2 diabetes will be encouraged to keep a diary and perform self-monitoring of blood glucose and weight, as well as specifically test for symptoms of hypoglycemia and document severe hypoglycemic events, (a severe hypoglycemic event is defined as symptomatic event requiring external assistance due to severe impairment in consciousness or behavior with resolution of event with administration of glucose, glucagon or other corrective action and a capillary or plasma glucose value <54 mg/dL ).

# 3 STUDY PLAN AND PROCEDURES

## 3.1 Study Design

Randomized, double-blind, placebo-controlled trial. The control group will receive placebo administered orally once daily for 12 weeks plus standard of care. The treatment group will receive empagliflozin 10 mg administered orally once daily for 12 weeks plus standard of care. A follow-up visit at week 13 will be performed to evaluate filling pressures and markers of renal function.

## 3.2 Study Procedures

At the screening visit, participants will undergo a physical exam (including vital signs and weight assessment) a laboratory panel, including HbA1c, BNP, NTproBNP, and a renal panel will be performed to determine study eligibility. CardioMEMs sensor readings will be obtained twice daily (in the morning and in the evening) for the 2 week period between screening and randomization visits to establish a

baseline for systolic, diastolic and mean PA pressure (Table 1). At the randomization visit, participants will be instructed to have a physical exam (including vital signs and weight assessment), laboratory testing, including HbA1c, BNP, NTproBNP, and a renal panel, complete the KCCQ and perform a 6 minute walk test. CardioMEMs sensor readings will be taken by the patient at home twice a day for the 12 weeks, once in the morning (when the patient wakes up) and once at night (before bedtime). Treatment or placebo will be administered for 12 weeks, with follow-up visits at 6 and 12 weeks during which a physical exam (including vital signs and weight assessment), labs, KCCQ, a 6 minute walk test will be performed and AEs/SAEs will be recorded. On days 2 and 7, as well as weeks 3 and 9 participants will be contacted by phone to evaluate for AEs/SAEs, and encourage compliance with the study medication. One week after treatment ends, renal function at a follow-up office visit; CardioMEMs sensor readings will continue to be obtained twice daily between week 12 and week 13.

PA diastolic, systolic and mean pressures will be assessed at weekly time points post-randomization (pulmonary pressures will be measured twice daily and averaged over each week for 12 weeks post-randomization, as well as between week 12 and week 13 post randomization).

**Table 1: Study Plan**

| | | | **12 –week double-blind treatment period** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Screening** | **Randomization** | | | | | | | |
| **Visit** | **S** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| **Week**[h)] | **-2**[i)] | **0** | **2d** | **1** | **3** | **6** | **9** | **12** PTDV | **13** |
| Patient obtains CardioMEMs pressure reading at home [a)] | Twice daily between screening and randomization visits to establish baseline, then twice daily for 12 weeks following randomization visit, then twice daily during week 12 and week 13 (immediately after treatment discontinuation). | | | | | | | | |
| Office Visit | X | X | | | | X | | X | X |
| Phone Visit[g)] | | | X | X | X | | X | | |
| Physical Exam [b)] | X | X | | | | X | | X | X |
| Vital signs (BP, pulse) | X | X | | | | X | | X | X |
| Orthostatic BP, pulse | X | X | | | | X | | X | X |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NYHA Class | X | X | | | | X | | X | X |
| Weight | X | X | | | | X | | X | X |
| Height | X | | | | | | | | |
| Waist circumference | X | X | | | | X | | X | X |
| Medical History | X | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | X | X |
| Laboratory assessments | X[c)] | X [d)] | | | | X [d)] | | X [d)] | X [e)] |
| Urine pregnancy test[f)] | X | X | | | | X | | X | X |
| Urine albumin/ creatinine ratio test | | X | | | | X | | X | X |
| 6 min walk test | | X | | | | X | | X | X |
| KCCQ | | X | | | | X | | X | X |
| AEs | | X | X | X | X | X | X | X | X |
| SAEs | | X | X | X | X | X | X | X | X |
| Hospitalizations | | X | X | X | X | X | X | X | X |
| ER Visits | | X | X | X | X | X | X | X | X |
| Urgent outpatient heart failure visits | | X | X | X | X | X | X | X | X |
| Dispense urine ketone strips | | X | | | | | | | |
| Dispense study medication | | X | | | | | | | |
| Return/redispense study medication | | | | | | X | | X | |
| Study medication accountability | | | | | | X | | X | |

[a)] CardioMEMs sensor reading transmission occurs at home when patients lie down on a special pillow containing an antenna. It is a simple process that takes only a few minutes. In addition to the pillow, patients are usually equipped with an external unit. The external unit transmits the readings to a secure website where the data can be seen by providers.

[b)] Physical Exam includes: complete physical examination consisting of general appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdomen, lymph nodes, extremities, neurological system,

skin, musculoskeletal system, height (screening only), weight, pulse, blood pressure, monitoring for volume depletion, and assessment for ketoacidosis (difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness).

[c)] Screening laboratory assessment includes HbA1c, BNP, NTproBNP and renal panel.

[d)] Randomization, Week 6 and Week 12 laboratory assessment includes HbA1c, Fasting Glucose, BNP, NTproBNP, CBC, renal panel, urine microalbumin/creatinine ration, and uric acid.

[e)] Week 13 laboratory assessment includes only renal panel.

[f)] Only for women with childbearing potential.

[g)] Phone visits include recording any AE or SAE, self-monitoring of weight, self-monitoring of blood glucose (among patients with established T2D), and encouraging compliance with study medication.

[h)] Visit Windows: There may be up to 2 weeks between the screening and randomization visits. Week 6, 12 and 13 clinic visits have a +/- 2-day visit window. Phone Visits have a +/-1-day visit window.

[i)] If a subject is a screen failure at the initial screening visit, they may be rescreened on three additional occasions at the discretion of the investigator. At the rescreening visit, the subject should be treated like a new subject and be assigned a new subject number and all screening visit procedures should be completed, including obtaining informed consent.

### 3.3 Definition of Active Treatment

Empagliflozin 10 mg daily + Standard of Care (for heart failure)

### 3.4 Definition of Control Arm

Matching Placebo + Standard of Care (for heart failure)

### 3.5 Overall Study Duration

Subjects will participate for a total of 13 weeks. It is estimated that one subject will be enrolled per month (or every other month) at each site, with enrollment estimated to be complete within 24 months and an approximate 5 months start-up time for all sites to be activated. Total estimated study duration is 33 months.

## 4 STUDY POPULATION

Voluntary participation will be sought from patients with chronic heart failure at specialized heart failure clinics for patients with previously implanted CardioMEMs for a clinical indication unrelated to the study. Informed consent will be obtained from potentially eligible participants prior to initiating screening visit procedures.

### 4.1 Inclusion criteria

1. Age > 18 and <120 at the screening visit
2. Established diagnosis of heart failure (for at least 16 weeks prior to the screening visit) with either preserved (LVEF>40%) or reduced systolic function (LVEF≤40%), due to either ischemic or non-ischemic etiology, documented by an imaging modality (echocardiography, nuclear imaging, LV angiography, magnetic resonance imaging) within the past 24 months.

3. No major change in diuretic management for 48 hours prior to screening visit or 48 hours prior to randomization visit (major change defined by doubling of diuretic dose or addition of another diuretic medication)
4. NYHA class II, III or IV heart failure symptoms at the screening and randomization visit
5. Presence of previously (≥ 2 weeks prior to screening visit) implanted CardioMEMs pulmonary artery pressure monitor for a clinical indication unrelated to the study.
6. PA diastolic pressure ≥ 12 mmHg at the time of the screening visit (last measurement available prior to the screening visit).
7. Ability to provide informed consent prior to initiating screening visit procedures

**4.2 Exclusion criteria**

1. Decompensated heart failure (hospitalization for heart failure within the 2 weeks prior to screening) or between screening and randomization
2. History of type 1 diabetes
3. Major change in diuretic management during 48 hours prior to screening visit or 48 hours prior to randomization visit. (major change defined by doubling of diuretic dose or addition of another diuretic medications)
4. Significant variability in baseline PA diastolic pressures during screening period. Defined as changes greater than +/- 6 mmHg from average PA diastolic pressure during week 1 of the screening phase and average PA diastolic pressure during week 2 of the screening phase for those patients with an average baseline PA diastolic pressure during week 1 of the screening phase of <30 mmHg. If the average baseline PA diastolic pressure during week 1 of the screening phase is ≥30 mmHg, then ≥20% relative change in average PA diastolic pressure between week 1 and week 2 of the screening phase will be used to define significant variability.
5. Initiation of hydralazine, long-acting nitrates, beta blockers, ACEI/ARBs or Valsartan/sacubitril in the prior 4 weeks prior to screening
6. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 at the screening visit
7. Admission for an acute coronary syndrome (ST-elevation MI, non-ST-elevation MI, or unstable angina), percutaneous coronary intervention, or cardiac surgery within 30 days prior to the screening visit.
8. Implantation of cardiac resynchronization therapy (CRT) device within the previous 90 days.
9. Implantation of the CardioMEMs device within the past 2 weeks.
10. Planned cardiovascular revascularization (percutaneous intervention or surgical) or major cardiac surgery (coronary artery bypass grafting, valve replacement, ventricular assist device, cardiac transplantation, or any other surgery requiring thoracotomy), or planned implantation of CRT device within the 90 days after the screening visit.
11. Participation in any interventional clinical trial (with an investigational drug or device) that is not an observational registry within the 4 weeks prior to the screening visit.
12. History of hypersensitivity to empagliflozin

13. For women of child-bearing potential: Current or planned pregnancy or currently lactating

    Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Post menopausal is defined as 12 consecutive months with no menses without an alternative medical cause. Women of child-bearing potential, who are sexually active, must agree to use a medically-accepted method of birth control for the duration of the study. Acceptable birth control methods include: (1) surgical sterilization (such as a hysterectomy or bilateral tubal ligation), (2) progesterone hormonal contraceptives (birth control pills or implants), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Women of child-bearing potential will have a urine pregnancy test at every clinic visit and it must be negative to continue study participation.

14. Life expectancy <1 year at the screening visit
15. Patients who are volume depleted based upon physical examination at the time of the screening or randomization visit
16. PA diastolic pressure < 12 mmHg at the time of the screening visit (average of last four measurements available prior to the screening visit).
17. Patients currently being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or having received treatment with any SGLT-2 inhibitor within the 8 weeks prior to the screening visit
18. Average supine systolic BP <90 mmHg at the screening or randomization visit
19. Current documented history of bladder cancer
20. Active Gross Hematuria
21. Heart failure due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valve disease, and HOCM (hypertrophic obstructive cardiomyopathy).
22. History of heart transplant.
23. Patients on heart transplant list as 1a and 1b status

# 5 STUDY CONDUCT

## 5.1 Restrictions during the study

**For patients:**

Patients should be fasting from all food and beverages (except water) at least 6 hours before blood samples are taken for laboratory analysis at a clinic visit with the exception of the screening visit. Patients should not use alcohol for 24 hrs or use tobacco for 12 hrs prior to testing at a clinic visit. Patients with established type 2 diabetes should not take any glucose-lowering medication when they are fasting. On the day of a clinic visit, investigational product and other concomitant medications will be taken in the morning, after completion of certain required study procedures. Patients shall not be allowed to use any prescribed SGLT-2 inhibitors (dapagliflozin, canagliflozin, empagliflozin), other than the investigational product, at any time during the study. Patients shall not be allowed to donate blood or bone marrow at any time during the study.

**For physicians:**

Since the primary endpoint of the study is the change in pulmonary artery diastolic pressure, physicians will be encouraged to limit medication changes for the study patients. Changes of heart failure medications (and specifically diuretics) should directed by the medical needs of the patients, and patients safety is priority, however, we will encourage using clinical judgment and avoiding frequent medications changes during this 3-month study. The recommended algorithm for medication adjustments is outlined in Section 5.6.7

## 5.2 Patient enrollment and randomization

The Principal Investigator or delegate will:

- Obtain signed informed consent from the potential participants before any study specific procedures are performed
- Determine patient eligibility
- Assign potential patients a sequential enrollment number in the form of Site ID and enrollment number i.e.: XXX-XX
- Assign enrolled patient a unique randomization code using Sharp Clinical Interactive Voice and Web Response Systems (IVR/IWR).

If a patient withdraws from participation in the study, then their enrollment number cannot be reused. Patients can only be randomized into the study once.

## 5.3 Procedures for randomization

Sharp Clinical Services will provide a state-of-the-art Clinical Interactive Voice and Web Response Systems (IVR/IWR). Sharp Clinical IVR/IWR is an innovative value-based product for Subject enrollment, randomization, capturing clinical data, drug shipments, and managing drug supply.

Sharp Clinical IVR/IWR Solutions are 21 CFR Part 11 compliant, user-friendly, and provide value to all users with big reductions in study start up times. The IVR/IWR System ensures data integrity, accelerates clinical site initiations, and can provide real-time metrics for subjects, sites and study inventory for approved users.

Solutions and Services include:

- 24/7 Operation
- Site Administration and Tracking
- Study Drug Distribution and Resupply Management

Training and User-Materials:

During system development, the Sharp PM creates a study-specific user manual and Quick Reference Guide for the IVR/IWR System. Site and client users are trained at investigator meetings or scheduled web-based training sessions conducted by the Sharp PM.

## 5.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomized. There can be no exceptions to this rule.

The following steps should be taken in the event that a patient, who does not meet inclusion/exclusion criteria, is found to have been inadvertently randomized in the study:

- The investigator should inform the study team physician immediately. Ensuring patient safety must always be the number one priority.
- Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. After a discussion between the study team physician and investigator, a decision may be reached that the patient should discontinue study medication. The rationale for discontinuing study medication must be clearly documented. The patient should remain in the study for follow-up in accordance with defined study procedures including follow-up on endpoints through the end of the study consistent with the FAS principle.
- In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. The patient should continue follow-up in accordance with defined study procedures.

## 5.5 Blinding and procedures for unblinding the study

### 5.5.1 Methods for ensuring blinding

The treatment allocation in this study will be double blind. Empagliflozin (10 mg) tablets and matching empagliflozin placebo tablets will be provided, identical in appearance and with the same number**,** size, and packaging of tablets. Each bottle will be labeled with a unique bottle ID number that will be used to assign the treatment to the patient but will not indicate treatment allocation to the investigator.

No member of the extended study team at , the CEC, or personnel at investigational centers will have access to the randomization scheme during the conduct of the study, with the exception of the Sharp Clinical Services, and the Biostatistics department at .

The IDSMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. The IDSMC will review safety data on a periodic basis, including the incidence of AEs, and conduct safety assessments to ensure the ongoing safety of study patients. The IDSMC responsibilities, authorities, and procedures will be documented in a IDSMC charter. The personnel involved in the clinical study at will remain blinded to these analyses and will have no knowledge of the results presented to the IDSMC.

### 5.5.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment allocation for each randomized patient, will be available to the investigator(s) or pharmacists from the Sharp Clinical IVR/IWR system. Routines for this will be described in the Sharp Clinical IVR/IWR system user manual that will be provided to each study site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment. The physician or delegate) should be consulted whenever possible prior to the investigator breaking the blind. The investigator documents and reports the action to , without revealing the treatment given to the patient to the staff. The number of individuals at the study site who become aware of the

treatment status should be kept to an absolute minimum including keeping the patient blinded if possible. Treatment with study medication should be continued if considered appropriate.

retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study drug and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 5.6 Treatments

### 5.6.1 Identity of study medication

**Table 2 Identity of study medication**

| Study Medication | Dosage form and strength | Manufacturer |
|---|---|---|
| Empagliflozin 10 mg | Biconvex, bevel-edged film-coated, round shape, yellow tablet 10 mg (Size: 9.1 mm) | |
| Matching placebo for empagliflozin 10 mg | Biconvex, bevel-edged film-coated, round shape, yellow tablet 10 mg (Size: 9.1 mm) | |

### 5.6.2 Doses and treatment regimens

At the randomization visit eligible patients will be randomly assigned to 1 of 2 treatments:

- Empagliflozin 10 mg, administered orally once daily for the 12 weeks.
- Matching placebo for empagliflozin 10 mg, administered orally once daily for the 12 weeks.

The investigational product empagliflozin and matching placebo will be taken orally. The investigational product should be taken once daily in the morning and at approximately the same time of the day during the study period. Nevertheless prior to each office visit (except for the screening visit), patients with established type 2 diabetes should be instructed not to take any glucose-lowering medication in the morning and all patients should abstain from all food and beverages for 6 hours; however, drinking water is allowed. On the day of an office visit, investigational product and other concomitant medications will be taken in the morning, after completion of certain required study procedures.

### 5.6.3 Drug Dispensing Scheme

At randomization, three (3) bottles of empagliflozin 10 mg or matching placebo will be dispensed, with each bottle containing 30 tablets.

### 5.6.4 Duration of treatment

The control group will receive placebo administered orally once daily for 12 weeks plus standard of care. The treatment group will receive empagliflozin 10 mg administered orally once daily for 12 weeks plus standard of care. Subjects will participate for a total of 13 weeks.

### 5.6.5 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 and US FDA requirements for labeling. The label will include at least the following information:

- Name of sponsor:
- Study drug(s) dosage form, route of administration, and quantity of dosage units
- Study code
- Enrollment code (will be added by the investigator when investigational product is dispensed)
- Kit ID
- Directions for use (For oral use)
- Storage conditions
- "for clinical trial use only"
- "keep out of reach of children"
- US caution statement

### 5.6.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and in the original container. The study medication label and empagliflozin prescribing information, which will be provided to sites by the study Sponsor as part of the study start-up package, specify appropriate storage, which is additionally outlined in Appendix C.

### 5.6.7 Medication Adjustment Protocol

Since the medications used to treat heart failure (including diuretics, afterload reduction medication, etc.) can affect pulmonary artery pressures (the study's primary endpoint), we encourage the investigators to only make changes in medical treatment when absolutely necessary for patient safety. To demonstrate the true effect of empagliflozin on pulmonary artery pressures, investigators are encouraged to adhere to the clinical pulmonary artery pressure monitoring protocol and medication adjustment protocol (detailed below) to avoid extreme variations in treatments across patients/investigators and sites. This protocol is adapted from the CHAMPION trial protocol[20] and clinical experience:

Pulmonary artery clinical monitoring protocol: Patients randomized in the EMBRACE-HF Trial will have pulmonary artery measured twice daily for 2 weeks between screening and randomization visits (to establish a pre-randomization baseline), twice daily during the 12 week treatment period, and twice daily during week 12 and week 13 (immediately after treatment discontinuation). Investigators are directed to clinically evaluate pulmonary artery pressures no more frequently than twice a week following randomization; and use pulmonary artery diastolic pressure averaged over the previous 7 calendar days (~14 previous measurements) to guide management; the only exception will be the first evaluation after randomization, which will use averaged pulmonary artery diastolic pressure over the previous 3-4 days. These averaged pulmonary artery diastolic pressure measurements will be compared with the patient's pre-randomization baseline (itself an averaged measurement over the 2 weeks between screening and randomization), and the difference between these measurements will be used to guide clinical decision making as follows:

**Hemodynamic-Guided Care Strategy**

**Optivolemic patient**

Patients with minimal HF congestive symptoms, minimal evidence of poor perfusion, and no significant change in pulmonary artery diastolic pressure from pre-randomization baseline (defined as no increase or decrease in pulmonary artery diastolic pressure of >6 mmHg for those with pre-randomization average PA diastolic pressure of <30 mmHg; for those with pre-randomization average PA diastolic pressure of ≥30 mmHg, no significant change in pulmonary artery diastolic pressure will be defined as no increase or decrease of ≥20%).

For patients who meet the above guidelines, investigators are directed to make no changes in medical therapy.

**Hypervolemic**

Patients were considered to be hypervolemic if the pulmonary artery diastolic pressure increases by >6 mmHg compared with pre-randomization baseline values (for those with pre-randomization baseline of <30 mmHg) or by ≥20% (for those with pre-randomization baseline of ≥30 mmHg) and/or if congestive symptoms are present.

**Hypervolemic Treatment Recommendations**

Investigators are instructed to add or increase diuretic (and appropriate electrolyte replacement) by an increase or addition of a loop diuretic, change to another loop diuretic, add a thiazide diuretic (with caution), or institute IV doses of loop diuretic in the office setting. Serum electrolyte evaluation with change in baseline medication is required for safety and reassessment of pulmonary artery pressure by using the HF pressure measurement system at least every 2-3 days until optivolemic status is restored. If diuretic strategies are not successful in restoring pressures to baseline, investigators are asked to add or increase nitrate therapy along with attempting to reeducate patients in salt intake and fluid restriction.

If patients developed signs and symptoms of poor perfusion in addition to being hypervolemic the investigators are instructed to consider hospitalization if clinical evidence suggested need for IV diuretics, telemetry monitoring, or other IV therapeutic agents, such as inotropes. Investigators have the option to consider invasive hemodynamic monitoring for determination of cardiac output if indicated.

**Hypovolemic**

Patients are considered hypovolemic if pulmonary artery diastolic pressure decreases by > 6 mmHg compared with pre-randomization baseline values (for those with pre-randomization baseline of <30 mmHg) or by ≥20% (for those with pre-randomization baseline of ≥30 mmHg) and/or those with evidence for poor perfusion in the absence of signs and symptoms of congestion.

**Hypovolemic Treatment Recommendations**

Patients with hypovolemia are treated by lowering or discontinuing diuretics or, if on a thiazide diuretic with loop diuretic, by lowering or discontinuing the dose of thiazide with adjustment of electrolyte

replacements. The investigator should also consider liberalization of oral fluid restriction and salt restriction. If the patient has postural hypotension, vasodilator dosage is to be held or lowered, especially if hypotensive when sitting or supine. If the patient has worsening renal function, the ACE/ARB dose should be held or lowered, especially if hypotensive while supine.

If patients have signs and symptoms of poor perfusion in addition to being hypovolemic, the investigator should consider admission if clinical evidence suggests need for IV fluid repletion, telemetry monitoring, or the use of IV therapeutic agents. The investigator also has the option for invasive hemodynamic monitoring for determination of cardiac output if indicated.

The detailed recommendations for hemodynamic-guided care strategy are outlined in the Figure below.

## Medication Algorithm Protocol for NP

| Pressure Range | Low | Optimal | High | Very High |
|---|---|---|---|---|
| PADP* | Decrease of ≥6mmHg | No Change | Increase of ≥6mmHg | Increase of ≥ 10mmHg |
| Furosemide | Cut dose and or frequency in half | Continue dosing without change | Double freq and/or dose | Consider adding thiazide-like diuretic |
| Torsemide | Cut dose and or frequency in half | Continue dosing without change | Double freq and/or dose | Consider adding thiazide-like diuretic |
| Hydralazine /Isosorbide | Do not add | Continue or do not add | Reinforce TID dosing | Increase either one by 10mg per dose |
| Thiazide-like diuretic | Do not add or hold | Continue or do not add | Optimize Loop Diuretics, then add single dose | Add standing dose until optimized |

*If PADP is > 30 mmHg at baseline use a 20% change to signify low and high, and 30% change to signify very high.

**Glucose-lowering medications adjustment protocol (only for patients with established T2D):**
For patients with established T2D and HbA1c if ≤ 7.0% and receiving insulin at baseline, it is recommended to reduce total daily insulin dose by 20%. For patients with established T2D and HbA1c if ≤ 7.0% and receiving sulfonylurea at baseline, it is recommended to reduce total daily sulfonylurea dose by 50%, or discontinue sulfonylurea in patients receiving the minimal dose of sulfonylurea at baseline.

### 5.7 Concomitant and post-study treatments

#### 5.7.1 Recording of concomitant medication

Detailed recording of all concomitant medications will be made at screening, randomization, and all subsequent visits. It will include all medication changes, but glucose lowering (in patients with established T2D) and heart failure medications (including every change in diuretic regimen) in particular.

## 5.8 Treatment Compliance

The administration of study medication should be recorded. All stops re-starts of study medication prescribed by the investigator should be recorded. In addition, any non-prescribed temporary stops (>1 week) of study medication should be recorded.

Missed doses of empagliflozin or placebo blinded study medication should not be taken. If a dose is missed the next regularly scheduled dose should be taken and should not be doubled.

Patients are instructed to transmit CardioMEMs sensor readings twice a day per protocol. All missed opportunities to transmit data should be recorded and reviewed each phone and office visit.

### 5.8.1 Accountability

The study medication provided for this study will be used only as directed in the study protocol. The study personnel will account for all study medication dispensed to and returned from the patient. Patients will be asked to bring all unused study medication and empty packages to the site at each office visit. The investigator or delegate will record the number of returned tablets and make an assessment regarding patient treatment compliance. Any patient found to be noncompliant would be counseled on the importance of taking their study medication as prescribed.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

The investigator will retain the returned medication until the termination of the Clinical Study. Then the investigator will return any unused medication to Sharp Clinical Services for destruction of all unused study medication. is responsible for confirming the investigator or delegate has recorded the quantities of returned and unused tablets at a patient level before medication is returned to Sharp Clinical Services.

Patients who are transmitting CardioMEMs sensor readings as instructed will be counseled on the importance of transmitting this information.

## 5.9 Discontinuations of study medication

Patients should be discontinued from study medication in the following situations:

### 5.9.1 General discontinuation criteria

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
2. Adverse Events, i.e., any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
3. Severe non-compliance to protocol as judged by the investigator and/or
   .
4. Risk to patients as judged by the investigator.
5. Incorrectly enrolled patients.
6. Patient lost to follow-up.

### 5.9.2 Study-specific discontinuation criteria

- Doubling of serum creatinine above the baseline value confirmed by a repeated measurement within one week.
- Recurrent severe hypoglycemic events, defined as ≥2 severe events (a severe hypoglycemic event is defined as symptomatic event requiring external assistance due to severe impairment in consciousness or behavior with resolution of event with administration of glucose,

glucagon or other corrective action and a capillary or plasma glucose value <54 mg/dL ). This definition should be applied after possible contributing factors (eg, excessive physical activity, dietary and medication factors) have been excluded or addressed by the investigator.
- Occurrence of diabetic ketoacidosis (DKA)
- Pregnancy confirmed by a positive pregnancy test or otherwise verified.

### 5.9.3 Procedures for permanent discontinuation of a patient from study medication

Patients permanently discontinuing study medication should be given conventional therapy, if applicable, and should continue routine care visits with their primary physician.

A patient that decides to discontinue study medication will always be asked about the reason(s) for their desire to discontinue study medication and the presence of AEs (if any). These data will be ascertained and documented by the investigator. AEs will be followed up and the patient should return all study medications.

It is essential to collect as much data as possible for all patients throughout the study and especially all potential endpoint events. Discontinuation from study medication is not the same as complete withdrawal from the study (withdrawal of consent), which has a direct impact on the potential validity of all study data, and should be avoided wherever possible.

### 5.9.4 Patient agrees to undergo the Premature Treatment Discontinuation Visit and then continue in-person study visits

The patient agrees to undergo the Premature Treatment Discontinuation Visit (PTDV) and then continue in-person study visits according to plan. This is the preferred option and patients who discontinue study medication will always be asked if they agree to this approach. If agreed, as above, the patient will undergo their PTDV at the next scheduled office visit after the study medication is stopped. The patient will continue attending subsequent study visits according to schedule (Table 1).

### 5.9.5 Patient refuses to continue in-person study visits but agrees to undergo modified follow-up

If the patient refuses to continue in-person study visits, but agrees to undergo modified follow-up, the in-person PTDV visit should be performed as soon as possible after the study medication is stopped. All subsequent visits until the end of study date will be done as modified follow-ups (eg, regular telephone contacts, a contact at study closure, or other means) in order to ascertain whether any endpoints or safety events had occurred. Such a patient has not withdrawn his/her consent or withdrawn from the study.

### 5.9.6 Patient refuses any form of follow-up

If the patient refuses any form of follow-up, he/she officially withdraws from the study and may also decide to withdraw consent. This decision must be documented. At the end of the study, vital status on all such patients will be collected from publicly available sources, in accordance with local regulations.

### 5.9.7 Restart of study medication

Whenever possible, restart of randomized study medication should be encouraged, even if a PTDV was previously completed.

### 5.9.8 Study Closure Visit

All randomized patients should return for their study closure visit (visit 8) as soon as possible, but no later than 1 week after the previously scheduled visit 7.

If a patient is unable to attend the study closure visit in person, telephone contact should be made to ascertain endpoint and AE information. At the study closure visit, physicians caring for the patient will decide which medication the patient should receive as part of his/her ongoing clinical care.

## 5.10 Withdrawal from study

Patients are at any time free to withdraw from the study (i.e., discontinue study medication permanently and withdraw from visit assessments), without prejudice to further treatment (withdrawal of consent). Withdrawal of consent from the study must be ascertained and documented by the investigator. Such patients will always be asked about the reason(s) and the presence of any AEs. The reason for permanent discontinuation of treatment with the study medication and the date of the last intake of the study medication must be documented.

5.10.1 Patients permanently discontinuing from study medication should be given conventional therapy, if applicable, and should always be asked to continue to attend protocol visits
If the patient denies any additional protocol follow-up and officially withdraws consent from the study one of the alternatives a) to c) should be followed:

- At the time of discontinuation of treatment and withdrawal of consent from continued assessment the patient should, if possible, undergo the PTDV. The patient should return all study medication
- If the patient does not agree to this option (which must be documented), a modified PTDV (eg, a telephone contact) should be arranged. The approach taken should be documented. The patient should return all study medication
- If the patient does not agree to a) or b) this must be documented in the patient's medical record. The patient should return all study medication.

To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at the SCV. The investigator or delegate will therefore attempt to collect information on all patients' vital status from publicly available sources at the SCV, in accordance with local regulations, even if informed consent has been withdrawn completely.

## 5.11 Study committees

### 5.11.1 Steering Committee

A steering committee will be formed and composed of PIs from each participating site. A publication plan will be developed with input from this committee.

### 5.11.2 Clinical Endpoint Adjudication Committee (CEC)

An independent CEC will be appointed and will adjudicate all heart failure hospitalizations. The committee members will not have access to individual treatment codes for any patient or clinical efficacy and safety event. The precise responsibilities and procedures applicable for the CEC will be detailed in a separate CEC charter.

### 5.11.3 Independent Data and Safety Monitoring Committee (IDSMC)

An independent DSMC will be appointed.

The IDSMC will be responsible for safeguarding the interests of the patients in the study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the clinical study. The IDSMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing.

The EC and will not be made aware of the treatment codes until after clean file and database lock are declared. Similarly, all summary output reviewed at each IDSMC meeting will be held in confidence by the IDSMC members until the end of the study when clean file and database lock are declared.

The IDSMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Study PI.

# 6 COLLECTION OF STUDY VARIABLES

## 6.1 Recording of data

The REDCap Web Based Data Capture (WBDC) system will be used for data collection and query handling. The site Principal Investigator will ensure that data are recorded in the electronic Case Report Forms (eCRF) and will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA).

Data will be entered in the eCRF using the REDCap Web Based Data Capture (WBDC) system by trained personnel at the study site. When data have been entered, reviewed, edited, and source data verification has been performed, as appropriate, by an representative, the data will be frozen to prevent further editing. The site Principal Investigator will be notified to sign the eCRF electronically. A copy of the eCRF data will be archived at the study site.

## 6.2 Data Collection at enrollment and follow-up

**TABLE 3 Laboratory variables**

| **Visit** | **S** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
|---|---|---|---|---|---|---|---|---|---|
| **Week** | **-2** | **0** | **2d*** | **1** | **3** | **6** | **9** | **12** | **13** |
| HbA1c | X | X | | | | X | | X | |
| Glucose** | | X | | | | X | | X | |
| BNP | X | X | | | | X | | X | |
| NTproBNP | X | X | | | | X | | X | |
| Urine albumin creatinine Ratio | | X | | | | X | | X | |
| Urine Pregnancy Test | X | X | | | | X | | X | |
| CBC | | X | | | | X | | X | |
| Renal Panel*** | X | X | | | | X | | X | X |

*days after randomization

** included in the renal panel

*** the renal panel includes albumin, BUN/Creatinine Ratio (calculated), calcium, carbon dioxide, chloride, creatinine, estimated glomerular filtration rate (calculated), glucose, phosphate (as phosphorus), potassium, sodium, urea nitrogen

### 6.2.1 Screening Visit Procedures (Visit S)

- Informed consent
- Blood sampling for laboratory assessments
- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Height
- Urine pregnancy test (only applicable for women of childbearing potential)
- Medical history
- Concomitant medications
- Eligibility criteria
- CardioMEMs pressure readings transmission (to be done twice daily at home between screening and randomization visits)

### 6.2.2 Randomization Visit (Visit 1)

Patients that fulfill the eligibility criteria will undergo randomization procedures.

- Eligibility criteria
- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Fasting blood sampling for laboratory assessments and biomarkers
- Urine pregnancy test (only for women of childbearing potential)
- Urine albumin/creatinine ratio
- Dispensed study medication
- Dispense Urine Ketone Strips
- Concomitant medications
- 6 minute walk test
- KCCQ questionnaire
- CardioMEMs pressure readings transmission (to be done twice daily at home between screening and randomization visit)
- Adverse events
- Serious adverse events
- Hospitalizations, ER visits, urgent outpatient visits for heart failure
- Contact IVR/IWR for randomization
- Dispense study medication (three 30 count bottles of empagliflozin 10 mg. or matching placebo)

### 6.2.3 Daily after randomization for 12 weeks

- CardioMEMs pressure readings transmission twice a day for 12 weeks (once at awakening in the morning and once at night)

### 6.2.4 Visit 2, 3, 4 and 6 (phone visits)

- Concomitant medications
- Adverse events
- Serious adverse events
- Hospitalizations, ER visits, urgent outpatient visits for heart failure

- Self-monitored weight
- Self-monitored Blood Glucose (in patients with established T2D only)
- Volume depletion monitoring
- Ketoacidosis monitoring
- Encourage compliance with study medication

### 6.2.5 Visit 5 and 7 (office visits)

- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Fasting blood sampling for laboratory assessments and biomarkers
- Urine pregnancy test (only for women of childbearing potential)
- Urine albumin/creatinine ratio
- Concomitant medications
- 6 minute walk test
- KCCQ questionnaire
- Concomitant medications
- Adverse events
- Serious adverse events
- Hospitalizations, ER visits, urgent outpatient visits for heart failure
- Volume depletion monitoring
- Ketoacidosis monitoring
- Study medication return (redispense at Visit 5) and accountability
- Contact IVR/IWR at Visit 7 for treatment completion

### 6.2.6 Visit 8 (Study Closure Visit)

- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Fasting blood sampling for laboratory assessments (only for renal panel).
- Urine pregnancy test (only for women of childbearing potential)
- Urine albumin/creatinine ratio
- Concomitant medications
- Adverse events
- Serious adverse events
- Hospitalizations, ER visits, urgent outpatient visits for heart failure
- Volume depletion monitoring
- Ketoacidosis monitoring

### 6.2.7 Premature Treatment Discontinuation Visit (PTDV)

- Performed at next on-site visit or as soon as possible (see section 5.9)
- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Fasting blood sampling for laboratory assessments
- Urine pregnancy test (only applicable for women of childbearing potential)

- Urine albumin/creatinine ratio
- Concomitant medications
- 6 minute walk test
- KCCQ questionnaire
- Concomitant medications Adverse events
- Serious adverse events
- Hospitalizations, ER visits, urgent outpatient visits for heart failure
- Volume status monitoring
- Ketoacidosis monitoring
- Study medication return and accountability
- Contact IVR/IWR for treatment discontinuation

## 6.3 Patient Monitoring During Study Visits

### 6.3.1 Physical examination

A physical examination should be done according to schedule shown in Study Plan (Table 1).

- A complete physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular system, lungs, abdomen, lymph nodes, extremities, neurological system, skin, and musculoskeletal system. Collection of pulse and blood pressure should also be collected as described in section 7.5. The patient should always be evaluated for the presence of edema and other signs of volume overload (jugular venous distention, rales, ascites, etc).
- Evaluation of volume depletion, including orthostatic vital signs and other physical exam findings consistent with dehydration
- Evaluation for the presence of ketoacidosis, in patients experiencing signs or symptoms of ketoacidosis, such as tachypnea or hyperventilation, anorexia, abdominal pain, nausea, vomiting, lethargy, or mental status changes; administer appropriate testing for ketoacidosis and direct patients to the emergency department if ketoacidosis is confirmed.
- For patients with established T2D and HbA1c ≤ 7.0% and receiving insulin at baseline, it is recommended to reduce total daily insulin dose by 20%. For patients with established T2D and HbA1c ≤ 7.0% and receiving sulfonylurea at baseline, it is recommended to reduce total daily sulfonylurea dose by 50%, or discontinue sulfonylureas in patients receiving the minimal dose of sulfonylurea at baseline.
- Baseline data are collected at Visit 1 and any new or aggravated findings discovered on subsequent physical examinations should be recorded as AE if clinically relevant.
- It is recommend that self monitoring of blood glucose (SMBG) values is performed by the patients with established T2D, as per standard of care, and reviewed during the study visits. Investigators are strongly encouraged to not titrate glucose-lowering medications in patients with established T2D during the study, except if required for patient safety.
- Review of self-monitoring of weight, with adjustments in diuretic dose if appropriate for optimization of volume status

### 6.3.2 Phone Visits

Phone visits should be done according to the schedule shown in Study Plan (Table 1).
Evaluate possible AE and SAEs, medication usage, self-monitoring of weight, and self-monitoring of blood glucose (in patients with established type 2 diabetes only).
Upon review of self-monitoring of weight, and self-monitoring of blood glucose (in patients with established type 2 diabetes only), consider adjustments in diuretics for optimization of volume status, and adjustments of glucose-lowering medications for optimization of glucose control (in

patients with established type 2 diabetes only) if required for patient safety. Remind patients about importance to transmit CardioMEMs pressures twice a day.

## 6.4 Vital signs

### 6.4.1 Pulse and blood pressure

One pulse measurement will be taken after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken. The pulse measurement will be followed by three blood pressure (BP) measurements separated by at least 1 minute each. All three BP readings should be recorded. At screening, the seated BP will be recorded three times in both the left and the right arms. All three measurements should be made in one arm before transferring the cuff to the other arm. The arm with the highest mean seated BP readings will be the one used for all subsequent readings. The average of the three BP readings will be used for study analyses. BP readings should be taken while the patient is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same personnel at each visit.

### 6.4.2 Orthostatic blood pressure

At visits where orthostatic BP and pulse are collected, supine and standing measurements should be made after the seated BP and pulse measurements have been made, using the same arm that was used for the seated BP measurements. All readings should be recorded. Ideally, blood pressure should be measured with the same machine, at the same time of day, and by the same personnel at each visit.

### 6.4.3 Supine BP and pulse

The supine BP and pulse must be measured prior to the standing BP and pulse. After the patient rests in the supine position for at least 5 minutes, supine BP and pulse will be determined from three replicate measurements obtained at least 1 minute apart. All three readings must be recorded. For study analyses, the average of the three BP and pulse readings will be used.

### 6.4.4 Standing BP and pulse

After the supine BP and pulse measurements are obtained, the patient will stand for 2 to 3 minutes. After this time, the BP will be measured with the arm supported at the level of the heart. Standing BP and pulse will be determined from three replicate measurements obtained at least 1 minute apart. All 3 readings must be recorded. For study analyses, the average of the three BP and pulse readings will be used.

If a new occurrence of previously absent orthostatic hypotension is demonstrated, it should be recorded as AE. The investigator may consider reducing concomitant anti- hypertensive medication to alleviate signs and symptoms of orthostatic hypotension.

## 6.5 Six Minute Walk Test

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in

exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities. [31]

### 6.6 Collection of Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ (see appendix B) is a disease-specific health status instrument composed of 23 items that quantify the domains of physical limitation, symptoms, self-efficacy, social limitation, and quality of life limitation from heart failure. The overall summary score and all domains have been independently demonstrated to be valid, reliable, and responsive to clinical change. Scores range from 0 to 100. The KCCQ overall summary score, a small but clinically meaningful change is considered to be ≥ 5 points.[32] The patients will fill in PRO (KCCQ) paper form under the supervision of the site staff.

### 6.7 Laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis testing will be taken at the times indicated in the Study Plan (see Table 1). Any additional laboratory safety samples taken at the investigator's discretion will be analyzed locally.

## 7 BIOLOGICAL SAMPLING PROCEDURES

### 7.1 Volume of blood

The total volume of blood that will be drawn from each patient for this study is listed in Table 4 below. The collection of additional samples is performed locally at the discretion of the investigator and recorded in the eCRF as appropriate, thus requiring additional sample volumes.

Table 4 Volume of blood to be drawn from each patient

| Assessment | Sample volume (mL) | Number of Samples | Total Volume (mL) |
|---|---|---|---|
| HbA1c | 4 mL whole blood | 4 | 16 mL |
| Glucose | 2 mL whole blood | 3 | 6 mL |
| BNP | 2 mL whole blood | 4 | 8 mL |
| NTproBNP | 2 mL whole blood | 4 | 8 mL |
| CBC | 4 mL whole blood | 3 | 12 mL |
| Renal Panel/Uric Acid | 4 mL whole blood | 5 | 20 mL |
| Total | | | 70 mL |

### 7.2 Handling, storage and destruction of biological samples

Blood and urine samples will be processed by local staff for shipment to the central laboratory (Quest Diagnostics). All samples should be taken by adequately trained study personnel and handled in accordance with instructions in the central laboratory manual. Up to date reference ranges will be provided during the study and laboratory results will be compared to the laboratory standard normal

ranges and flagged if they are outside the normal range. The Investigator should make an assessment of any clinically significant abnormalities in the laboratory reports. The laboratory reports should be signed, dated and retained at the study site as source data for laboratory variables. The clinical chemistry, hematology, and urinalysis samples will be disposed after analyses.

# 8 SAFETY

## 8.1 Definition of adverse events (AE)

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

## 8.2 Definitions of serious adverse event (SAE)

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Patients may be hospitalized for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site,). These and other hospitalizations planned at the beginning of the study do not need to be reported as a SAE in case they have been reported at screening visit in the source data and have been performed as planned.

### 8.2.1 Classification of Death

Deaths will be sub-classified by CV and non-CV primary cause. CV death includes sudden cardiac death, death due to acute MI, death due to heart failure, death due to a cerebrovascular event, death due to other CV causes (e.g., pulmonary embolism, aortic disease, CV intervention), and deaths for which there was no clearly documented non-CV cause (presumed CV death).

Additionally, CV deaths will be sub-classified by coronary heart diseases death (CHD death) and non-CHD death. CHD death includes Sudden Cardiac Death, Death due to Acute MI, and the subset of Death due to other CV Causes that are secondary to a coronary revascularization procedure.

### 8.2.2 Universal classification of Myocardial Infarction (MI)

The Third Universal MI definition[33] will be used as study specific MI criteria.

### 8.2.3 Definition of Stroke

Stroke is defined as an acute episode of neurologic dysfunction attributed to a central nervous system vascular cause. Stroke should be documented by imaging (eg, CT scan or magnetic resonance imaging [MRI] scan). Evidence obtained from autopsy can also confirm the diagnosis. Stroke will be sub classified, when possible, as either:

### 8.2.4 Primary ischemic stroke

Primary ischemic stroke is defined as an acute episode of focal brain, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue and documented by imaging. A primary ischemic stroke may also undergo hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study, but appearance on a subsequent scan).

### 8.2.5 Primary hemorrhagic stroke

Primary hemorrhagic stroke is defined as an acute episode of focal or global brain, spinal, or retinal dysfunction caused by non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage as documented by neuroimaging or autopsy. Microhemorrhages (<10 mm) evident only on MRI are not considered to be a hemorrhagic stroke. Subdural and epidural bleeding will be considered intracranial hemorrhage, but not strokes.

### 8.2.6 Unclassified stroke

Stroke with unknown etiology will be classified as unclassified stroke if the type of stroke could not be determined by imaging or other means.

### 8.2.7 Hospitalizations for heart failure

In the event that a patient is hospitalized for heart failure over the course of the study, source documents will be obtained to adjudicate events. See appendix A for detailed information.

## 8.3 Definitions of adverse events of special interest (AESI)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the Pharmacovigilance Department of within the same timeframe that applies to SAEs.

Patients with AESIs need to be followed up appropriately, regardless of the origin of the laboratory data (e.g. central, local etc.). The Investigator should consider which, if any, concomitant therapies should not be taken during evaluation. Discontinued treatments can be reintroduced per Investigator discretion.

The following are considered as AESIs:

### 8.3.1 Acute kidney injury (Decreased renal function)

Defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN, consistent with the RIFLE criteria for stage 2 acute kidney injury.

For the AESI “acute kidney injury” the Investigator shall collect an unscheduled laboratory sample for creatinine as soon as possible and initiate follow-up laboratory tests of creatinine according to medical judgment.

### 8.3.2 Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)

Postmarketing cases show an association between sodium-glucose cotransporter-2 (SGLT2) inhibitor use and the development of a high anion gap metabolic acidosis accompanied by elevation in urine or serum ketones, frequently in the setting of only mildly elevated glucose levels (euglycemic DKA). Investigators are strongly encouraged to instruct patients and caregivers about the signs and symptoms of ketoacidosis, such as tachypnea or hyperventilation, anorexia, abdominal pain, nausea, vomiting, lethargy, or mental status changes; evaluate for the presence of ketoacidosis in patients experiencing such signs or symptoms – using provided urine ketone testing kits; discontinue study medication and advice patients to go to the nearest emergency department

if ketoacidosis is confirmed; and take appropriate measures to correct the ketoacidosis and to monitor glucose levels. Investigators are also strongly encouraged to avoid concomitant risk factors potentially predisposing to DKA, including carbohydrate-restricted diets and marked reductions in insulin dose during the study among patients with established type 2 diabetes and receiving insulin at baseline (above and beyond reductions in insulin dose specified in the study protocol for patients with established type 2 diabetes)). Advise patients to alert you and seek medical attention immediately if they experience symptoms consistent with DKA such as: nausea, vomiting, abdominal pain, confusion, change in breathing pattern and unusual fatigue or sleepiness.

In case of metabolic acidosis ketoacidosis and DKA, further investigations should be done according to the medical judgement and the clinical course until a diagnosis is made and/or the patient is recovered.

DKA is defined by the diagnostic criteria in the table below, and as defined by the American Diabetes Association (ADA).[34]

Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgment should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in the table below.

Diagnostic criteria for DKA:

| | DKA | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| Plasma glucose (mg/dL) | >250 | >250 | >250 |
| Arterial pH | 7.25-7.30 | 7.00-7.24 | <7.00 |
| Serum bicarbonate (mEq/L) | 15-18 | 10 to <15 | <10 |
| Urine ketones* | Positive | Positive | Positive |
| Serum ketones* | Positive | Positive | Positive |
| Effective serum osmolality (mOsm/kg)** | Variable | Variable | Variable |
| Anion gap*** | >10 | >12 | >12 |
| Alteration in sensoria or mental obtundation | Alert | Alert/drowsy | Stupor/coma |

* Nitroprusside reaction method

** Calculation: 2[measured Na (mEq/L) + glucose (mg/dL)/18

*** Calculation: (Na+) – (Cl- + HCO3-) (mEq/L)

### 8.3.3 Volume Depletion

Empagliflozin has a modest diuretic effect. The risk of volume depletion is enhanced when two diuretics are used in combination and in patients that otherwise are at risk for volume depletion. Therefore, caution should be exercised when administering to patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics. These patients should be carefully monitored for volume status, electrolytes, and renal function, and encouraged to self-monitor weight during the study.

### 8.3.4 Severe Hypoglycemia

All severe hypoglycemic events, (defined as symptomatic event requiring external assistance due to severe impairment in consciousness or behavior with resolution of event with administration of glucose, glucagon or other corrective action and a capillary or plasma glucose value <54 mg/dL), must be documented and reported.

### 8.3.5 Non-Traumatic Lower limb Amputation

There is no evidence to date that use of empagliflozin impacts the risk of non-traumatic lower limb amputations. This AESI is being collected for surveillance of non-traumatic lower limb amputation events across the current clinical trials of empagliflozin.

## 8.4 Recording of adverse events

### 8.4.1 Collection of Adverse Events

AEs and SAEs (including hospitalizations for heart failure) will be recorded from Screening throughout the treatment period and including the follow-up period (Visit 8).

All AEs/SAEs are to be recorded by the site. SAEs, DAEs, AEs of Special Interest and non-serious AEs will be captured in the e-CRF. Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the e-CRF. Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the e-CRF , if they are judged clinically relevant by the investigator.

SAEs and AESI are defined in section 8.

A drug adverse event (DAE) is an adverse event which leads to premature and permanent discontinuation of study medication.

Information about all urgent outpatient heart failure visits will also be recorded by the site and captured in the e-CRF.

### 8.4.2 Follow-up of unresolved Adverse Events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated. retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. The requirement to follow-up is not intended to delay database lock or production of the clinical study report. Both these activities should proceed as planned with ongoing AEs if necessary.

Any follow-up of ongoing AEs/SAEs after database lock will be reported to , who will notify the appropriate regulatory authorities of and study drug manufacturer.

### 8.4.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- Date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)

- Action taken with regard to investigational product
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

The intensity of the AE should be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- Moderate: Enough discomfort to cause interference with usual activity
- Severe: Incapacitating or causing inability to work or perform usual activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

### 8.4.4 Causal Relationship of Adverse Event

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

### 8.4.5 Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 8.4.6 Adverse Events based on examinations and tests

The results from protocol mandated laboratory test and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs will only be reported as AEs if they are clinically significant, fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product, or require the patient to receive specific corrective therapy.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated measurements will be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

## 8.5 Reporting of serious adverse events

All AEs/SAEs have to be reported to , whether or not considered causally related to the investigational product. The site investigator is responsible for informing their local IRB as per local requirements.

Investigators and other center personnel must inform appropriate representatives via the web based data capture (WBDC) system of any SAE that occurs in the course of the study within 1 day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it. Follow-up information on SAEs must also be reported by the Investigator within the same time frame.

An automated email alert will be sent to the designated representative, when the page with SAE information is saved in WBDC system by the Investigators or other site personnel. If the WBDC system is not available, then the Investigator or other study site personnel reports by fax an SAE to the appropriate representative. A paper back- up SAE report is used for this purpose. The same reporting time frames still apply. The investigator is responsible for completing the eCRF as soon as the system becomes available again.

The representative will work with the Investigator to compile all the necessary information and ensure that all the necessary information is provided to within one calendar day of initial receipt for fatal and life threatening events and within five calendar days of initial receipt for all other SAEs.

### 8.5.1 Reporting of serious adverse events to FDA and Boehringer Ingelheim Pharmaceuticals

The Sponsor ( will inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to . It is the responsibility of the Sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to at the same time. The Sponsor shall report (i.e., from signing the informed consent onwards through the trial defined follow-up period) all SAEs and non-serious AEs which are relevant for a reported SAE and Adverse Events of Special Interest (AESI) by fax or other secure method using MedWatch/AdEERs form to the Unique Entry Point in accordance with timeline specified below:

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;
- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

For each adverse event, the investigator will provide the onset date, end date, intensity,treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Investigator Brochure for the Productor Drug Information e.g. Summary of Product Characteristics (SmPC) or Product Information (PI) for the authorised Study Drug provided by

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to the Sponsor if investigator considers it as relevant to the study drug.

# 9 ETHICAL AND REGULATORY REQUIREMENTS

## 9.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice (GCP), applicable regulatory requirements and the policy on Bioethics.

## 9.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

## 9.3 Ethics and regulatory review

An Ethics Committee/Institutional Review Board (IRB) should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patient. The investigator/Head of the study site will ensure the distribution of these documents to the applicable Ethics Committee/IRB, and to the study site staff.

The opinion of the Ethics Committee should be received in writing. The investigator should submit a notification of direction/determination as well as a copy of the IRB written approval to before enrolment of any patient into the study.

The Ethics Committee/IRB should approve all advertising used to recruit patients for the study.

should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

will handle the distribution of any of these documents to the national regulatory authorities.

will provide Regulatory Authorities, Ethics Committees/IRB and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions that occur with the study medication during the study, according to their local Ethics Committee/IRB regulations.

## 9.4 Informed consent

The Principal Investigator or delegate at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any study specific procedure

- Ensure the original, signed Informed Consent Form(s) is/are stored in the
- Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

### 9.5 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). If a protocol amendment requires a change to a center's Informed Consent Form, and the center's IRB are to approve the revised Informed Consent Form before the revised form is used.

### 9.6 Audits and inspections

Authorized representatives of , a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study- related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator will contact immediately if contacted by a regulatory agency about an inspection at the center.

### 9.7 Posting of information on clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrollment of patients begins.

## 10 STUDY MANAGEMENT BY

### 10.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of to evaluate the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of or its representatives. This will be documented in a Clinical Study Agreement between and the investigator.

### 10.2 Training of study site personnel

Before the first patient is entered into the study, a representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

### 10.3 Monitoring of the study

During the study, a representative will conduct regular monitoring visits with the study site. The monitoring visits may be conducted by phone, e-mail or by in-person visits to the study site. The monitoring visits will:

1. Provide information and support to the investigator(s)
2. Confirm that facilities remain acceptable
3. Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRF and that study drug accountability checks are being performed
4. Perform source data verification (a comparison of the data in the eCRF with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients.

The representative will be available between visits if the investigator(s) or other study site personnel need information and advice about the study conduct.

### 10.4 Source data

The Clinical Study Agreement (CSA) will specify the location of source data. Access to source documents and source data is essential to inspection and review of clinical studies by the Food and Drug Administration (FDA).

### 10.5 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

### 10.6 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

### 10.7 Study timetable and end of study

The study is expected to start in December 2016 and to end in June 2018. Planned treatment duration in the study is 12 weeks. will notify investigators when recruitment

is complete. The end of the entire study is defined as 'the last visit of the last patient undergoing the study'.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with empagliflozin.

# 11 DATA MANAGEMENT BY

Data management will be performed by Data Management Center staff. Data will be entered in the WBDC system at the study site. Trained site staff will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be source data verified, reviewed/queried and updated as needed. The Principal Investigator is responsible for electronically signing the eCRF. Data queries will be raised for inconsistent, improbable or missing data. All entries to the study database will be available in an audit trail. The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study has been locked.

# 12 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

## 12.1 Description of analysis sets

### 12.1.1 Efficacy analysis set

Intention to treat (ITT) is defined as all patients who have been randomized to study treatment, received at least one dose of study medication and completed at least one CardioMeMs transmission after randomization. The ITT data set will be used for the primary and secondary efficacy endpoints and exploratory endpoints.

### 12.1.2 Safety analysis set

All patients who received at least 1 dose of randomized empagliflozin or placebo, and for whom post-dose data are available, will be included in the safety analysis set. Throughout the safety results sections, erroneously treated patients (eg, those randomized to empagliflozin but actually given placebo) will be accounted for in the actual treatment group. If a patient received study drug from the wrong kit for only a part of the treatment duration and then switched to another, the associated actual treatment group for that patient will be the treatment group the patient had the longest exposure to.

## 12.2 Methods of statistical analyses

Randomization will be stratified by diabetes status (diabetes vs. no-diabetes). All analyses will be on the ITT unless otherwise specified. Baseline demographic and clinical data will be described between treatment and placebo study arms as mean ± standard deviation for continuous variables and compared using Student's T-test. Whereas discrete variables will be represented as a number and (%) and compared using the $\chi^2$ or Fisher's exact test, as applicable.

The time course of continuous variables will be presented using standard descriptive summary statistics calculated at each scheduled measuring time point and the last individual measuring time point. Moreover, standard descriptive summary statistics will be calculated for the change (absolute or percent) from baseline to each scheduled measuring time point after baseline and the last individual measuring time point.

Due to the large number of study sites and the expected low number of patients per site it will not be appropriate to explore site effects.

Statistical significance will be defined using two-sided tests with $\alpha$=0.05, unless otherwise specified. All statistical analyses will be performed by the Department of Biostatistics using SAS version 9.4 (SAS Institute, Cary, North Carolina).

### 12.2.1 Primary endpoint

The primary endpoint of this study is the change in pulmonary artery diastolic pressure from baseline to end of treatment period (defined as average of pulmonary artery diastolic pressure measurements between weeks 8-12). This will be analyzed using a repeated measures model incorporating a within-patient covariance structure to estimate the effect of treatment.

Primary endpoint will be analyzed in the entire patient cohort, and then within the subgroups of patients with and without diabetes (as pre-specified subgroup analyses).

### 12.2.2 Secondary endpoints

The following secondary endpoints have been identified:

1. Change from baseline in pulmonary artery diastolic pressure at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
2. Change in pulmonary artery systolic pressure from baseline to end of treatment period
3. Change from baseline in pulmonary artery systolic pressure at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
4. Change in mean pulmonary artery pressure from baseline to end of treatment period
5. Change from baseline in mean pulmonary artery pressure at each interim time point (weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
6. Change in heart failure related quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score from baseline to follow-up (defined as average of measurements at 6 and 12 weeks).
7. Proportion of patients with a ≥ 5pts increase from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) at either 6 weeks or 12 weeks of follow-up
8. Change in 6 minute walk test from baseline to follow-up (defined as average of measurements at 6 and 12 weeks)
9. Change in NTproBNP from baseline to follow-up (defined as average of measurements at 6 and 12 weeks)

10. Change in BNP from baseline to follow-up (defined as average of measurements at 6 and 12 weeks)
11. Proportion of patients with a ≥ 20% decrease from baseline in NTproBNP at either 6 weeks or 12 weeks of follow-up.
12. Proportion of patients with a ≥ 20% decrease from baseline in BNP at either 6 weeks or 12 weeks of follow-up.
13. Proportion of patients with both a ≥ 5pts increase from baseline in KCCQ and a ≥ 20% decrease from baseline in NTproBNP at either 6 weeks or 12 weeks of follow-up
14. Number of diuretic medication adjustments during the treatment period (up-titration and down-titration of diuretic doses to be evaluated separately)
15. Change in Hemoglobin A1c from baseline to follow-up (defined as average of measurements at 6 and 12 weeks), evaluated separately in patient with and without type 2 diabetes

Continuous variable comparisons will be analyzed using the same repeated measures method as the primary analyses. Treatment and time interaction will be included to model the effect patterns. The mean change within each treatment group will be calculated with corresponding 95% confidence intervals for each time point. Dichotomous outcomes will be analyzed using logistic regression including a fixed effect for treatment; odds ratios and 95% confidence intervals will be reported.

Secondary endpoints will be analyzed in the entire patient cohort, and then within the subgroups of patients with and without diabetes (as pre-specified subgroup analyses).

### 12.2.3 Exploratory endpoints

The following exploratory endpoints have been identified:

1. Change in pulmonary artery diastolic pressure between week 12 and week 13
2. Change in mean pulmonary artery pressure between week 12 and week 13
3. Change in pulmonary artery systolic pressure between week 12 and week 13
4. Change in mean heart rate from baseline to end of treatment period
5. Effects on average weekly loop diuretic dose (furosemide equivalent).
6. Effects on hospitalizations for heart failure.
7. Effects on urgent outpatient heart failure visits.
8. Effects on hospitalizations for heart failure and urgent outpatient visits for heart failure
9. Change in NYHA Class at 6 weeks from baseline and 12 weeks from baseline.
10. Change in NTproBNP and KCCQ at 6 weeks from baseline and 12 weeks from baseline
11. Number of medication adjustments other than diuretics (nitrates, hydralazine, ACE, ARB, b-blockers, sacubitril/valsartan) during the treatment period
12. Proportion of patients that progress to diabetes during the treatment period (within the subgroup of patients without diabetes at baseline only)

Exploratory data will be summarized descriptively and presented by treatment group.

Exploratory endpoints will be analyzed in the entire patient cohort, and then within the subgroups of patients with and without diabetes (as pre-specified subgroup analyses).

### 12.2.4 Safety variables

The safety evaluations will include the analyses of all AEs and SAEs, however the following safety variables have been identified a priori:

1. All cause death
2. Cardiovascular death
3. Non-fatal myocardial infarction (MI)
4. Stroke
5. Acute kidney injury (defined as doubling of serum creatinine based on the RIFLE criteria)
6. Adverse events (AEs) and serious adverse events (SAEs). AEs of special interest will include diabetic ketoacidosis (DKA), volume depletion (defined as hypotension, syncope, orthostatic hypotension or dehydration), severe hypoglycemic events, and non-traumatic lower limb amputations.

Safety data will be summarized descriptively and presented by treatment group.

### 12.2.5 Analysis for safety

Safety analyses will be done periodically during the study and reported to the IDSMC. A formal IDSMC charter will be developed along with the possible stopping rules.

## 12.3 Determination of sample size

A sample size of 28 patients for each group will achieve 80% power with $\alpha$=0.05 to detect a 20% difference in mean pulmonary artery pressure between the empagliflozin 10 mg and placebo groups over the treatment period.

The assumptions for this calculation were: 1) between-patient standard deviation = 6, 2) Within patient correlation between adjacent time points: 0.7, 3) Mean PA pressure in the intervention arm of the trial will achieve a plateau at the 9th time point for treatment group.

# 13 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

## 13.1 Medical emergencies and Contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

In the case of a medical emergency the investigator may contact the Study Team Physician at

.

| Name | Role in the study | Address & telephone number |
|---|---|---|
| | Lead Study Team Physician responsible for the protocol | |
| | Study Manager | |

### 13.2 Overdose

Overdose is defined as the accidental or intentional ingestion of any dose of investigational product that is considered both excessive and medically important. Empagliflozin has been well tolerated at doses of up to 800 mg/day in single dose testing in healthy volunteers[35] and up to 100 mg/day in repeat dose testing for 8 days in healthy volunteers and patients with type 2 diabetes[36]. If an overdose is suspected, monitoring of vital functions as well as treatment, as appropriate, should be performed. If an overdose occurrence meets the criteria for a Serious Adverse Event, then it must be reported as Serious Adverse Event.

### 13.3 Pregnancy

Any pregnancy during the course of this study should be recorded. Pregnancy itself is not regarded as an Adverse Event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication.

If any pregnancy occurs in the course of the study, the patient should be discontinued, the investigational product should be stopped and then investigators or other site personnel must inform appropriate immediately but no later than the end of the next business day of when he or she becomes aware of it.

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# 15 APPENDIX A: HEART FAILURE HOSPITALIZATION/URGENT OUTPATIENT VISIT

A **Heart Failure Event** includes hospitalization for heart failure and may include urgent outpatient visits. Heart failure hospitalizations should remain delineated from urgent visits.

A **Heart Failure Hospitalization** is defined as an event that meets ALL of the following criteria:

- The patient is admitted to the hospital with a primary diagnosis of heart failure
- The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)
- The patient exhibits documented new or worsening symptoms due to heart failure on presentation, including at least ONE of the following:
    - Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
    - Decreased exercise tolerance
    - Fatigue
    - Other symptoms of worsened end-organ perfusion or volume overload
- The patient has objective evidence of new or worsening heart failure, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion), including:
    - Physical examination findings considered to be due to heart failure, including new or worsened:
        - Peripheral edema
        - Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
        - Pulmonary rales/crackles/crepitations
        - Increased jugular venous pressure and/or hepatojugular reflux
        - S3 gallop
        - Clinically significant or rapid weight gain thought to be related to fluid retention
    - Laboratory evidence of new or worsening heart failure, if obtained within 24 hours of presentation, including:
        - Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT- proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
        - Radiological evidence of pulmonary congestion
        - Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration

          OR

- Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) • ≥18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/$m^2$

- The patient receives initiation or intensification of treatment specifically for heart failure, including <u>at least ONE</u> of the following:

    - Augmentation in oral diuretic therapy
    - Intravenous diuretic, inotrope, or vasodilator therapy
    - Mechanical or surgical intervention, including:
        - Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
        - Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis) Using available information, Heart Failure will be categorized based on the following:
            - Left ventricular ejection fraction (LVEF)
            - Type
            - Etiology

- An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

    - The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of heart failure, but not meeting the criteria for a heart failure hospitalization.
    - All signs and symptoms for heart failure hospitalization (i.e., 3) symptoms; 4) physical examination findings/laboratory evidence of new or worsening heart failure, as indicated above) must be met
    - The patient receives initiation or intensification of treatment specifically for heart failure, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

# 16 APPENDIX B: KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

**Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

| Activity | Extremely Limited | Quite a bit Limited | Moderately Limited | Slightly Limited | Not at all Limited | Limited for other reasons or did not do the activity |
|---|---|---|---|---|---|---|
| Dressing yourself | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Showering/Bathing | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Walking 1 block on level ground | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Doing yardwork, housework or carrying groceries | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Climbing a flight of stairs without stopping | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Hurrying or jogging (as if to catch a bus) | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

| Much worse | Slightly worse | Not changed | Slightly better | Much better | I've had no symptoms over the last 2 weeks |
|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

| Every morning | 3 or more times a week, but not every day | 1-2 times a week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

| **Extremely** bothersome | **Quite a bit** bothersome | **Moderately** bothersome | **Slightly** bothersome | **Not at all** bothersome | I've had **no swelling** |
|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

| All of the time | Several times per day | At least once a day | 3 or more times per week but not every day | 1-2 times per week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

| **Extremely** bothersome | **Quite a bit** bothersome | **Moderately** bothersome | **Slightly** bothersome | **Not at all** bothersome | I've had **no fatigue** |
|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

| All of the time | Several times per day | At least once a day | 3 or more times per week but not every day | 1-2 times per week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

8. Over the <u>past 2 weeks,</u> how much has your **shortness of breath** bothered you?

It has been ...

| **Extremely** bothersome | **Quite a bit** bothersome | **Moderately** bothersome | **Slightly** bothersome | **Not at all** bothersome | I've had **no shortness of breath** |
|---|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

9. Over the <u>past 2 weeks,</u> on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

| Every night | 3 or more times a week, but not every day | 1-2 times a week | Less than once a week | Never over the past 2 weeks |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

| **Not at all** sure | **Not very** sure | **Somewhat** sure | **Mostly** sure | **Completely** sure |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

| Do not understand at all | Do not understand very well | Somewhat understand | Mostly understand | Completely understand |
|---|---|---|---|---|

12. Over the <u>past 2 weeks</u>, how much has your **heart failure** limited your enjoyment of life?

| It has **extremely** limited my enjoyment of life | It has limited my enjoyment of life **quite a bit** | It has **moderately** limited my enjoyment of life | It has **slightly** limited my enjoyment of life | It has **not limited** my enjoyment of life at all |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

| Not at all satisfied | Mostly dissatisfied | Somewhat satisfied | Mostly satisfied | Completely satisfied |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

| I felt that way **all of the time** | I felt that way **most of the time** | I **occasionally** felt that way | I **rarely** felt that way | I **never** felt that way |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

| **Activity** | **Severely** limited | Limited **quite a bit** | **Moderately** limited | **Slightly** limited | **Did not** limit at all | Does not apply or did not do for other reasons |
|---|---|---|---|---|---|---|
| Hobbies, recreational activities | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Working or doing household chores | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |
| Visiting family or friends out of your home | | | ☐ | ☐ | ☐ | ☐ |
| Intimate relationships with loved ones | ☐ | ☐ | ☐ | ☐ | ☐ | ☐ |

Place an **X** in one box on each line

# 17 APPENDIX C: STORAGE CONDITIONS FOR THE TRIAL MEDICATION

| **Storage conditions for Trial Medications (STORM)** | |
|---|---|
| Code/Project | (Empagliflozin); |
| Study Number | 1245.(IIS) PP double blinded |
| Replaces document | --- |
| Attachment | --- |

| | | | | |
|---|---|---|---|---|
| Climatic zones | Climatic zones I/II | | Climatic zones III/IV | |
| Regions: | EU | RoW | US | CA |

# (Part A)

## 1. Products included in trial medication:

**Medication kit type *** 1

| Storage conditions labeled by CTSU/Vendor<br>blinded open label | Storage conditions **not** labeled by CTSU/Vendor<br>open label commercial product |
|---|---|
| ☒ ☐ | ☐ |

| Product, Formulation, Dosage strength<br>(for comparators incl. INN, trade name and manufacturer name; EU or US) | | Packaging material |
|---|---|---|
| **Empagliflozin** | **Film-coated tablets 10 mg or placebo** | PP Bottle |

**Medication kit type *** 2

| Storage conditions labeled by CTSU/Vendor<br>blinded open label | Storage conditions **not** labeled by CTSU/Vendor<br>open label commercial product |
|---|---|
| ☒ ☐ | ☐ |

| Product, Formulation, Dosage strength<br>(for comparators incl. INN, trade name and manufacturer name; EU or US) | | Packaging material |
|---|---|---|
| **Empagliflozin** | **Film-coated tablets 25 mg or placebo** | PP Bottle |

*table might be adopted or multiplicated due to study design

# (Part B)

## 2. Storage conditions based on current SPI for included products:

**Medication kit type(s) * 1 + 2** (requiring identical storage statement)

| Product, Formulation, Dosage strength | | SPI no. incl version |
|---|---|---|
| | | *Either released or in preparation* |
| **Empagliflozin** | **Film-coated tablets 10 mg or placebo** | **007-SPI-1264-ABCD-01 ( 11.0 )** |
| **Empagliflozin** | **Film-coated tablets 25 mg or placebo** | **007-SPI-1264-ABCD-01 ( 11.0 )** |

| | | |
|---|---|---|
| **Storage conditions:** (outer carton**) | EU / ROW CZ I/II (except for KR)***: | This medicinal product does not require any special storage conditions. |
| | ROW CZ III/IV and KR | Do not store above 30°C. |
| | US/CA: | Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). |
| **Stability of reconstituted/diluted/ mixed solution / In-Use-Stability:** | EU/ROW: | --- |
| | US/CA: | --- |
| **Shipping conditions:** | No temperature relevance | |

| | |
|---|---|
| **Alert settings for temperature loggers:** | --- |
| **Remarks:** | --- |

* Tables might be adopted or multiplicated due to study design

** Text on immediate containers may be shortened or omitted by CTSU in accordance with applicable regulations

*** Storage conditions might be tightened due to country specific requirements

# (Part C)

## 3. Criteria for assessment of temperature excursions (relevant to ALL countries):

**Medication kit type(s) * 1 + 2** (requiring identical storage statement)

| Product, Formulation, Dosage strength | | SPI no. incl version |
|---|---|---|
| | | *Either released or in preparation* |
| **Empagliflozin** | **Film-coated tablets 10 mg or placebo** | **007-SPI-1264-ABCD-01 ( 11.0 )** |
| **Empagliflozin** | **Film-coated tablets 25 mg or placebo** | **007-SPI-1264-ABCD-01 ( 11.0 )** |

Table A *

| **Assessment criteria in the event of a *LOWER* temperature excursion:** | | |
|---|---|---|
| **Criterion: *< 15°C (< 59°F)*** | | |
| **Documented lowest temperature [°C]** | **Documented lowest temperature [°F]** | **Acceptable excursion period [days]** |
| 14 - (-20)°C | 58 - (-4)°F | any duration |
| < (-20)°C | < (-4)°F | not acceptable |

Table B *

| **Assessment criteria in the event of an *UPPER* temperature excursion:** | | |
|---|---|---|
| **Criterion: > *30°C (> 86°F)*** | | |
| **Documented highest temperature [°C]** | **Documented highest temperature [°F]** | **Acceptable excursion period [days]** |
| 31 - 40°C | 87 - 104°F | up to 180 days |
| 41 - 50°C | 105 - 122°F | up to 42 days |
| 51 - 60°C | 123 - 140°F | up to 14 days |
| > 60°C | > 140°F | not acceptable |

* Tables might be adopted or multiplicated due to study design / climatic zones, if applicable

# 18 APPENDIX D: PRINCIPAL INVESTIGATOR SIGNATURE

## SIGNATURE OF PRINCIPAL INVESTIGATOR

## EMpagliflozin evaluation By measuRing ImpAct on HemodynamiCs in PatiEnts with Heart Failure (EMBRACE-HF)

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations.

**Site Number:** _____

**Signature:**

_____ _____

Signature of Principal Investigator Date

_____

Principal Investigator Name (print or type)