Protocol

Protocol Title: Dapagliflozin Effect on Symptoms and Biomarkers in Patients with Heart Failure (DEFINE-HF)

Protocol Number: D1690C00032

ClinicalTrials.gov registration: NCT02653482

Version Date: November 4, 2017

PROTOCOL SYNOPSIS

A 12-week randomized, double-blind, placebo-controlled trial to evaluate the effects of once-daily dapagliflozin 10 mg on heart failure disease-specific biomarkers (BNP and NTproBNP), symptoms, health status, and quality of life in patients with chronic heart failure with reduced systolic function. Substudies will also be conducted for exploratory biomarker analyses and effects on arrhythmia burden.

Study Hypothesis

Treatment with dapagliflozin 10 mg daily for 12 weeks will produce greater reductions in NTproBNP and improve heart failure symptoms, health status and quality of life as compared with placebo in patients with chronic heart failure with reduced systolic function.

Study Centers and Number of Patients Proposed

This study will be performed at up to 30 centers in the United States. Approximately 250 patients will be randomized over a target enrollment period of approximately 30 months.

Primary Objective

To evaluate the impact of dapagliflozin, as compared with placebo, on heart failure disease-specific biomarkers, symptoms, health status, and quality of life in patients with chronic heart failure with reduced systolic function.

Target Population

Male and female patients with chronic heart failure with reduced systolic function.

Investigational Product, Dosage, and Mode of Administration

Dapagliflozin 10 mg administered orally once daily for 12 weeks, in addition to standard of care for chronic heart failure with reduced systolic function.

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 with reduced systolic function.

Study Duration

After activation of the first site, it is expected that enrollment will take approximately 30 months. After randomization, dapagliflozin or placebo will be administered for 12 weeks. Renal function will be evaluated 1 week after discontinuation of dapagliflozin or placebo.

Primary Outcome Variables (two co-primary endpoints will be evaluated)

1. Difference in mean NTproBNP between the treatment and placebo study arms at 6 and 12 weeks.
2. Increase of ≥ 5pts in heart failure disease specific quality of life (assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score) or a ≥ 20% decrease in NTproBNP over 12 weeks.

Secondary Outcome Variables

1. Proportion of patients with a ≥ 5pts increase in KCCQ.
2. Proportion of patients with a ≥ 20% decrease in NTproBNP.
3. Proportion of patients with a ≥ 5pts increase in KCCQ and a ≥ 20% decrease in NTproBNP.
4. Change in KCCQ score over 12 weeks.
5. Change in 6 minute walk score over 12 weeks.
6. Change in BNP over 12 weeks.
7. Change in HbA1c over 12 weeks. (evaluated separately in patients with and without type 2 diabetes)
8. Change in weight over 12 weeks.
9. Change in systolic blood pressure over 12 weeks.

Exploratory Outcome Variables

1. Effects on average weekly loop diuretic dose (furosemide equivalent).
2. Effects on hospitalizations for heart failure.
3. Effects on rate of urgent outpatient heart failure visits.
4. Effects on the rate of hospitalizations for heart failure and urgent outpatient heart failure visits.
5. Change in NYHA Class over 12 weeks.
6. Change in NTproBNP and KCCQ at 6 weeks from baseline and 12 weeks from baseline,

7. Effect on lung fluid volumes measured by remote dielectric sensing ReDS™ (SensiVest) over the treatment period (at selected sites).
8. Change in mean lung fluid volumes measured by remote dielectric sensing ReDS™ (SensiVest) between week 12 and week 13 (at selected sites)

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 DKA, volume depletion (defined as hypotension, syncope, orthostatic hypotension or dehydration) 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 χ^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.

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

The first co-primary endpoint of this study is to compare dapagliflozin versus placebo on mean NTproBNP at 6 and12 weeks. A generalized linear mixed model with a compound symmetry covariance structure will be used to estimate the average effect over 6 and 12 weeks controlling for baseline NTproBNP. Gamma distribution and log link function will be used because of the skewness nature of NTproBNP. Center is included as a random factor to account for clustering of patients within centers.

The second co-primary endpoint, proportion of patients with a ≥ 5 point KCCQ overall summary score increase or a ≥ 20% decrease in NTproBNP at either 6 or 12 weeks, will be analyzed using Mantel-Haenszel test controlling for center.

For the first co-primary endpoint a sample size of 110 for each group will achieve 80% power with α=0.05 to detect a reduction in NTproBNP between the two groups of at least 302 pg/mL from baseline to 12

weeks. The assumptions for this calculation were derived from the BATTLESCARRED trial where the estimated standard deviation for NTproBNP was 1250 pg/mL. We expect the standard deviation in the DEFINE-HF Trial to be somewhat lower (961 pg/ml) given lower NTproBNP threshold. Of note, 302pg/mL reduction in NTproBNP is equivalent to 31.5% of the standard deviation in NTproBNP (based on the above assumption).

The second co-primary endpoint is a combined endpoint of a ≥ 5 point KCCQ overall summary score increase or a ≥ 20% decrease in NTproBNP. The sample size was determined using two independent groups where the anticipated control group percent change is 30%. A sample size of 110 for each group will achieve 80% power with α=0.05 to detect a difference in proportional change between the two groups of 18% from baseline to 12 weeks for the second co-primary endpoint.

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 more questions regarding the mechanism of action (MOA) through which SGLT-2 inhibitors may produce a benefit on HF remains unclear, and need further clarification. To provide insight into potential beneficial effects of SGLT-2i in patients with HFrEF (with or without DM), as well as to explore potential mechanisms behind these effects, we plan to perform a randomized clinical trial to evaluate the effects of dapagliflozin, on disease-specific heart failure biomarkers, symptoms, health status, and quality of life, in patients with chronic heart failure (both with and without DM) with reduced systolic function.

1.2 Research Hypothesis

Treatment with dapagliflozin 10 mg daily for 12 weeks will produce greater reductions in NTproBNP, and improve symptoms, and quality of life as compared with placebo in patients with chronic heart failure with reduced systolic function.

1.3 Rationale for conducting this study

This is a Phase IV study that will determine whether dapagliflozin provides a unique benefit to patients with chronic heart failure with reduced systolic function by reducing NTproBNP and improving patients' heart failure-related symptoms, health status and quality of life.

1.4 Benefit/risk and ethical assessment

Dapagliflozin 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 dapagliflozin therapy. Although dapagliflozin is currently not approved in patients without diabetes, when dapagliflozin 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 dapagliflozin in patients with Type 2 diabetes) are anticipated in patients without diabetes treated with

dapagliflozin. Accordingly, we consider the benefit/risk balance to patients enrolled in the study to be comparable to that encountered in the usual clinical practice, with no additional ethical concerns. Of note, several large cardiovascular outcome trials are currently evaluating various SGLT-2i as potential therapies for HFrEF, and include patients with and without diabetes.[19-21]

1.4.1 Risk Category

Considering dapagliflozin's mechanism of action, the previous clinical experience with dapagliflozin, 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 dapagliflozin 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 dapagliflozin prescribing information.

In clinical Phase III studies, events suggestive of UTI were reported in a slightly higher proportion of dapagliflozin-treated patients than the placebo group. Increased urinary glucose excretion may also lead to an increased risk of developing genital infections. In Phase III studies, the proportions of patients treated with dapagliflozin who reported adverse events that were indicative of genital infection were higher than those seen for placebo.

In a pooled analysis of all phase 2b and 3 studies in the dapagliflozin development program there was an imbalance in the frequency of subjects who had a serious adverse event of breast cancer or bladder cancer. The significance of these findings is not clear at present; however a causal relationship with the use of dapagliflozin seems unlikely.

Overall there were no imbalances of liver function test parameters in Phase III studies. One subject on dapagliflozin 5 mg had a serious adverse event reported as drug-induced acute hepatitis and was later also diagnosed with probable autoimmune hepatitis.

Due to the diuretic effect of dapagliflozin, 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 dapagliflozin and placebo groups. In the limited experience in subjects with type 2 diabetes on concomitant loop diuretics, events related to volume depletion were more common in the dapagliflozin groups compared with the placebo group. Temporary interruption of dapagliflozin should be considered for subjects who develop volume depletion. In the recent analysis of patients with preexisting heart failure using pooled data from previous dapagliflozin studies, the rate of hypovolemic events was similar between dapagliflozin and placebo. Of note, all patients in our study will be required to have elevated BNP at baseline, which will further minimize the risk of hypovolemic adverse events.

The U.S. Food and Drug Administration (FDA) recently 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 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors. 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. Although the risk of euglycemic DKA is estimated to be very low in this study (given the short duration of treatment, and the fact that patients with Type 2 diabetes are at lower risk for DKA than Type 1 diabetes, and patients without diabetes are likely not at risk for DKA) 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 SAE of special interest by the study investigators, as well as the Independent Data and Safety Monitoring Committee. In addition, all patients that have diabetes 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 in patients with known diabetes.

Dapagliflozin prescribing information states that the drug should not be started in patients with eGFR <60. Per the FDA submission documents the main reason dapagliflozin clinical studies were not designed to include patients with eGFR between 30-45 was because "glycemic efficacy was not expected in the absence of adequate renal function."[4] The focus of the DEFINE Trial is not glycemic control, but rather dapagliflozin effects on heart failure endpoints. There are many reasons to believe that SGLT2 inhibitors may have beneficial effects on heart failure and renal endpoints regardless of baseline eGFR, including in patients with eGFR between 30-60. In fact, a recent secondary analysis from the EMPA-REG Outcome large scale clinical trial of empagliflozin showed dramatic reduction in cardiovascular mortality and hospitalizations for heart failure in patients with Type 2 diabetes; patients with eGFR as low as 30 were allowed to be included in that trial.[4,5] Furthermore, in the same trial (EMPA-REG Outcome) marked benefit was observed with empagliflozin vs. placebo for clinically important renal endpoints, including doubling of creatinine and progression to ESRD.[3,6] These effects were observed consistently across the range of baseline eGFR. Meta analyses of completed dapagliflozin trials suggest a similar effect of dapagliflozin on cardiovascular and renal parameters.[7]

The US FDA also issued a more recent safety alert in regards to SGLT2-inihibtors and potential risk for acute kidney injury. The FDA letter mentions 101 cases of acute kidney injury with SGLT-2 inhibitors, of which only 28 involved dapagliflozin. While the exact denominator is unknown to calculate an incidence rate, these 28 open label cases were reported during a time period when over 300,000 prescriptions were filled for dapagliflozin in the US. Further, these spontaneous reports do not prove a cause-and effect link between SGLT2-inhibitors and renal events. The renal safety (and in fact nephroprotective effects) of these agents have been demonstrated in clinical trials as stated above. The safety meta analysis of dapagliflozin trials also showed no evidence for increase in acute kidney injury or acute renal failure events.[22]

We plan to monitor renal function carefully in the DEFINE-HF study, and doubling of serum creatinine is a safety variable that is being carefully ascertained; furthermore, all patients in DEFINE-HF Trial are volume overloaded at baseline given the requirement for significantly elevated

NTproBNP, and therefore should be at low risk for hypovolemic events. 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 significantly 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 are documented in an IDSMC charter. The personnel involved in the clinical study at [redacted] 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 or prediabetes randomized to dapagliflozin may obtain better glucose control. In this study, the dose of dapagliflozin 10 mg once daily was chosen to provide efficacy in improving heart failure symptoms and biomarkers, as well as reducing HbA1c while mitigating the potential for AEs, based on previous clinical experience. In addition, among patients randomized to active drug, dapagliflozin is expected to help maintain better glucose control among those type 2 diabetes or prediabetes, 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 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 dapagliflozin 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 dapagliflozin prescribing information.

2 STUDY OBJECTIVE

To evaluate the impact of dapagliflozin, as compared with placebo, on heart failure disease-specific symptoms, health status, quality of life and biomarkers in patients with chronic heart failure with reduced systolic function.

2.1 Primary Objective

1. To compare the mean NTproBNP between the treatment and placebo study arms at 6 and 12 weeks.
2. To compare the proportion of patients that achieve a meaningful change from baseline in quality of life (≥ 5pts increase in KCCQ overall summary score) or NTproBNP (≥ 20% decrease) over 12 week treatment period between dapagliflozin 10 mg and placebo.

2.1.1 Secondary Objectives

a) To compare the proportion of patients with a ≥ 5pts increase in the Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline over 12 weeks between dapagliflozin and placebo.
b) To compare the proportion of patients with a ≥ 20% decrease in NTproBNP from baseline over 12 weeks between dapagliflozin and placebo.
c) To compare the proportion of patients with both a ≥ 5pts increase in KCCQ and a ≥ 20% decrease in NTproBNP from baseline over 12 weeks between dapagliflozin and placebo.
d) To compare the change in KCCQ score from baseline over 12 weeks between dapagliflozin and placebo.
e) To compare the change in 6 minute walk test score from baseline over 12 weeks between dapagliflozin and placebo.
f) To compare the mean BNP between dapagliflozin and placebo at 6 and 12 weeks.
g) To compare the change in HbA1c from baseline to week 12 between dapagliflozin and placebo. (evaluated separately in patients with and without type 2 diabetes)
h) To compare the change in weight from baseline over 12 weeks between dapagliflozin and placebo.
i) To compare the change in systolic blood pressure from baseline over 12 weeks between dapagliflozin and placebo.

2.1.2 Exploratory objective

1. To compare the effects on average weekly loop diuretic dose (furosemide equivalent) between dapagliflozin and placebo.
2. To compare the effects on hospitalizations for heart failure between dapagliflozin and placebo.
3. To compare the effects on urgent outpatient heart failure visits between dapagliflozin and placebo.
4. To compare the effects on hospitalizations for heart failure and urgent outpatient heart failure visits between dapagliflozin and placebo.
5. To compare the change in NYHA Class from baseline over 12 weeks between dapagliflozin and placebo.
6. To compare mean NTproBNP and change in KCCQ at 6 weeks from baseline and 12 weeks from baseline between dapagliflozin and placebo.

7. To compare the effect on lung fluid volumes measured by remote dielectric sensing ReDS™ (SensiVest) between dapagliflozin and placebo over the course of 12 weeks (at selected sites).
8. To compare the effect on lung fluid volumes measured by remote dielectric sensing ReDS™ (SensiVest) upon discontinuation of dapagliflozin or placebo (between weeks 12 and 13; at selected sites).

2.1.3 Safety objectives

To evaluate the safety of dapagliflozin by assessment of AEs including mortality, non-fatal MI, stroke, acute kidney injury, volume depletion, severe hypoglycemic events, laboratory values, pulse, blood pressure, ketoacidosis and physical examination findings.

Patients will be encouraged to keep a diary and perform self-monitoring of blood glucose (for patients with established type 2 diabetes only) and weight (as prescribed by their physician and according to the local standard of care), as well as specifically self-monitor for symptoms of hypoglycemia and document severe hypoglycemic events, (defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL or blood glucose <54 mg/dL).).

Patients will be instructed to contact study staff if they should experience any hypoglycemia events including severe hypoglycemic events.

Patients will be instructed to contact study staff if they should have an unexplained weight loss/gain of more than 5 pounds in a day or an unexplained weight loss/gain of more than 10 pounds in a week.

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 dapagliflozin 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 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 (Table 1: Study Plan). At the randomization visit, participants will undergo a physical exam (including vital signs and weight assessment), laboratory testing, including HbA1c, BNP, NTproBNP, and a renal panel, complete the KCCQ, perform a 6 minute walk test and lung fluid volume will be measured with the SensiVest at selected sites. 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, lung fluid volume will be measured with the SensiVest (at selected sites), and AEs/SAEs will be recorded. On days 2 and 10, as well as weeks 4 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 will be evaluated and lung fluid volume will be measured with the SensiVest at a follow-up office visit (at selected sites).

Table 1: Study Plan

			12 –week double-blind treatment period						
	Screening	Randomization							
Visit	**S[J]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week[g)]	**-2**	**0**	**2d**	**10d**	**4**	**6**	**9**	**12** PTDV	**13**
Office Visit	X	X				X		X	X
Phone Visit[f)]			X	X	X		X		
Informed consent	X								
Assess eligibility	X	X							
Physical Exam [a)]	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								
Body Mass Index (BMI)[m)]	X	X				X		X	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[b)]	X [c,k)]				X [c,k)]		X [c,k)]	X [d)]
Urine pregnancy test[e)]	X	X				X		X	X
Urine albumin/ creatinine ratio test[i)]	X	X				X		X	X
Dispense Cardiokey monitor [h)]	X					X			
6 minute walk test		X				X		X	

SensiVest lung fluid measurement at rest[l)]	X				X		X	X
KCCQ	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)] 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).

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

[c)] Randomization, Week 6 and Week 12 laboratory assessment includes HbA1c, Fasting Glucose, BNP, NTproBNP, CBC, renal panel, uric acid, IL-6, HS-CRP, CML, sRAGE, Gal-3, ST-2 and hs-cTnT.

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

[e)] Only for women with childbearing potential.

[f)] Phone visits include recording any AE or SAE, self-monitoring of weight and blood glucose (patients with established type 2 diabetes only), and encouraging compliance with study medication.

[g)] Visit Windows: There may be up to 2 weeks between the screening and randomization visits. For patient that consent for the arrhythmia monitoring substudy, there must be 2 weeks between the screening and randomization visits to allow for the required 2 weeks of wearing the holter monitor. Week 6, 12 and 13 clinic visits have a +/- 2-day visit window. Phone Visits have a +/-1-day visit window.

[h)] For patients that consent for the arrhythmia monitoring substudy, a CARDIOKEY holter monitor will be dispensed at these visits. After wearing for 2 weeks, the patient will return the CARDIOKEY holter monitor by mail.

[i)] The urine specimens collected at 0, 6 and 12 weeks will only be checking urine albumin and urine creatinine. It will not be a standard urinalysis, and any clinical suspicion of urinary tract infection will be left to the local investigator or patient's primary care physician to order a proper screening test to evaluate.

[j] If a patient 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 patient should be treated like a new patient and assigned a new subject number and all screening visit procedures should be completed, including obtaining informed consent.

[k] Subjects should be resting in the supine position for at least 5 minutes prior to collection of blood samples for biomarkers at Visit 1 (Week 0 Randomization), Visit 5 (Week 6) and Visit 7 (Week 12).

[l] The Sensivest test will only be completed on patients at selected sites, and with a BMI of 22-36 and a height of 61 to 77 inches. Testing may not be completed on all eligible patients. Testing completion will depend upon the availability of the SensiVest testing equipment.

[m] Body mass index (BMI Formula: weight (kg) / [height (m)]^2)) will be calculated using the following website[17]: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html

3.3 Definition of Active Treatment

Dapagliflozin 10 mg daily + Standard of Care for heart failure with reduced systolic function.

3.4 Definition of Control Arm

Matching Placebo + Standard of Care for heart failure with reduced systolic function.

3.5 Overall Study Duration

Subjects will participate for a total of 13 weeks. It is estimated that the total study duration will be 30 months.

4 STUDY POPULATION

Voluntary participation will be sought from patients with chronic heart failure with reduced systolic function at outpatient general cardiology and specialized heart failure clinics. 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 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. Any local measurement of LVEF by any modality within the eligibility range made within the past 24 months is acceptable provided there has been no subsequent LVEF measurement above 40%.
3. No change in diuretic management for 1 week prior to screening visit or between the screening and randomization visit
4. NYHA class II or III heart failure symptoms at the screening and randomization visit

5. BNP ≥100 pg/mL and/or NTproBNP ≥ 400 pg/mL[a)Ŧ] at the screening visit
6. 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 30 days prior to screening or NYHA class IV heart failure symptoms at screening)
2. History of type 1 diabetes
3. Estimated glomerular filtration rate (eGFR) < 30 at the screening visit by modified MDRD equation GFR (mL/min/1.73 m2) = 175 x (Scr) $^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if African American)[18]
4. 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.
5. Admission for cardiac resynchronization therapy (CRT) within 90 days prior to the screening visit
6. 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 CRT within the 90 days after the screening visit.
7. Participation in any interventional clinical trial (with an investigational drug or device) that is not an observational registry within the 8 weeks prior to the screening visit.
8. History of hypersensitivity to dapagliflozin
9. For women of child-bearing potential: Current or planned pregnancy or currently lactating.

   Women who are surgically sterile or those who are postmenopausal for at least 1 year are not considered to be of child-bearing potential. 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.

10. Life expectancy <1 year at the screening visit
11. Patients who are volume depleted based upon physical examination at the time of the screening or randomization visit
12. BNP <100 pg/mL and NTproBNP<400 pg/mL at the screening visit [£]
13. Patients currently being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin) or having received treatment with any SGLT-2 inhibitor within the 12 weeks prior to the screening visit.
14. Average supine systolic BP <90 mmHg at the screening or randomization visit

15. Past or current history of bladder cancer
16. Active Hematuria
17. Donation of blood or bone marrow 12 weeks prior to the screening visit and no planned donations during the study period
18. Heart failure due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valve disease, and HOCM (hypertrophic obstructive cardiomyopathy).

[Ŧ] For patients with permanent atrial fibrillation inclusion thresholds will be BNP ≥ 125 pg/mL or NTproBNP ≥ 600 pg/mL

[£]For patients with permanent atrial fibrillation exclusion thresholds will be BNP<125 pg/mL and NTproBNP<600 pg/mL

5 STUDY CONDUCT

5.1 Restrictions during the study

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. It is preferred but not required that patients be fasting at 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 or prediabetes 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. For patients with established type 2 diabetes on basal insulin, it is recommended they only take ½ of their basal dose the evening before they are planning to fast for an office visit. 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. Patients shall not be allowed to participate in any other interventional clinical trial (with a drug or device) for the duration of the study.

5.2 Patient enrollment and randomization

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed
2. Determine patient eligibility
3. Assign potential patients a sequential enrollment number in the form of Site ID and enrollment number i.e.: XXX-XXX
4. Assign enrolled patient a unique randomization code using Sharp Clinical Services interactive web response technology system.

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 interactive web response technology system (IRT). Sharp's IRT is an innovative value-based product for Subject enrollment, randomization, capturing clinical data, drug shipments, and managing drug supply.

Sharp's IRT is 21 CFR Part 11 compliant, user-friendly, and provide value to all users with big reductions in study start up times. The IRT 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, Sharp creates a study-specific user manual and Quick Reference Guide for the IRT System. Site and client users are trained at investigator meetings or scheduled web-based training sessions.

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:

1. The investigator should inform the [redacted] study team physician immediately. Ensuring patient safety must always be the number one priority.
2. 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.
3. 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. Dapagliflozin (10 mg) tablets and matching dapagliflozin 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 [redacted], the EC, 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 [redacted].

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 SAEs, 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 [redacted] 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 [redacted] physician ([redacted] or delegate) should be consulted whenever possible prior to the investigator breaking the blind. The investigator documents and reports the action [redacted], without revealing the treatment given to the patient to the [redacted] 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.

[redacted] 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
Dapagliflozin	Biconvex, diamond shape, green tablet 10 mg (Size: 11 mm)	[redacted]
Matching placebo for dapagliflozin 10 mg	Biconvex, diamond shape, green tablet (Size: 11 mm)	[redacted]

5.6.2 Doses and treatment regimens

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

- Dapagliflozin 10 mg, administered orally once daily for the 12 weeks.
- Matching placebo for dapagliflozin 10 mg, administered orally once daily for the 12 weeks.

The investigational product dapagliflozin 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, patients with established type 2 diabetes or prediabetes should be instructed not to take any glucose-lowering medication in the morning and to 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, one (1) bottle of dapagliflozin 10 mg or matching placebo will be dispensed, with the bottle containing 105 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 dapagliflozin 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 requirements for labeling. The label will include at least the following information:

- Name of sponsor: [redacted]
- 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”

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 dapagliflozin prescribing information specify appropriate storage.

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 and heart failure medications in particular.

5.8 Treatment Compliance

The administration of study medication should be recorded. All stops 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 dapagliflozin 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.

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. [redacted] 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.

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 [redacted].
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 events requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL or blood glucose <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.
- 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 whenever 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 withdraws 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, and at every study visit, 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 Executive Committee (EC)

The EC will be responsible for the overall design, including the development of the protocol and any protocol amendments, supervision, interpretation and reporting (presentations at international congresses and publications in peer reviewed journals) of the study. The EC will make recommendations to [redacted] with regard to early stopping or modifications of the study based on the information received from the IDSMC. The EC will be comprised of the overall study PI (EC Chair) and designated academic leaders with expertise in the fields of heart failure and cardiometabolic disease. The precise responsibilities and procedures applicable for the EC will be detailed in a separate EC charter.

5.11.2 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.

5.11.3 Clinical Endpoint Adjudication Committee (CEC)

An independent CEC will be appointed and will adjudicate all heart failure hospitalizations, urgent heart failure visits and major cardiovascular events (cardiovascular death, myocardial infarction, stroke). 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.

5.11.4 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 [redacted] 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 overall study PI (EC Chair).

The IDSMC may elect to request an Interim efficacy and/or futility analysis at its discretion in consultation with the overall study PI (EC Chair). If this option is elected, the IDSMC charter will be amended accordingly.

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 [redacted] 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***	**10d***	**4**	**6**	**9**	**12**	**13**
HbA1c	X	X				X		X	
Glucose (included in the renal panel)		X				X		X	
BNP	X	X				X		X	
NTproBNP	X	X				X		X	
Urine albumin creatinine Ratio	X	X				X		X	X
Urine Pregnancy Test	X	X				X		X	X
CBC		X				X		X	
Renal Panel**	X	X				X		X	X
Biomarkers***		X				X		X	

*days after randomization

** 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

*** uric acid, IL-6, HS-CRP, CML, sRAGE, Gal-3, sST2 and hs-cTnT

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
- Calculate BMI using the height from the screening visit and the weight at the current visit
- Urine pregnancy test (only applicable for women of childbearing potential)
- Urine albumin/creatinine ratio
- Medical history

- Concomitant medications
- Dispense CARDIOKEY monitor (if participating in the arrhythmia substudy)
- Contact Sharp IRT for screening
- Assess eligibility criteria

6.2.2 Randomization Visit (Visit 1)

Patients that fulfill the eligibility criteria will undergo randomization procedures.

- Assess eligibility criteria
- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Calculate BMI using the height from the screening visit and the weight at the current visit
- 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
- SensiVest measurement of lung fluid volume at rest (at selected sites). The Sensivest test will only be completed on patients with a BMI of 22-36 and a height of 61 inches to 77 inches.
- 6 minute walk test
- KCCQ questionnaire
- Adverse events
- Serious adverse events
- Hospitalizations, ER visits, urgent outpatient visits for heart failure
- Contact Sharp IRT for randomization
- Dispense study medication

6.2.3 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 (for patients with established type 2 diabetes)
- Volume depletion monitoring
- Ketoacidosis monitoring
- Encourage compliance with study medication

6.2.4 Visit 5 and 7 (office visits)

- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Calculate BMI using the height from the screening visit and the weight at the current visit

- Fasting blood sampling for laboratory assessments and biomarkers
- Urine pregnancy test (only for women of childbearing potential)
- Urine albumin/creatinine ratio
- Concomitant medications
- SensiVest measurement of lung fluid volume at rest (at selected sites). The Sensivest test will only be completed on patients with a BMI of 22-36 and a height of 61 inches to 77 inches.
- 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
- Dispense CARDIOKEY monitor (only at Visit 5 (Week 6)) if participating in the arrhythmia substudy)
- Study medication return (redispense only at Visit 5 (Week 6)) and accountability
- Contact Sharp IRT at Visit 7 for treatment completion

6.2.5 Visit 8 (Study Closure Visit)

- Physical exam
- Vital Signs (seated pulse and BP and orthostatic pulse and BP)
- Weight
- Calculate BMI using the height from the screening visit and the weight at the current visit
- 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
- SensiVest measurement of lung fluid volume at rest (at selected sites). The Sensivest test will only be completed on patients with a BMI of 22-36 and a height of 61 inches to 77 inches.
- Adverse events
- Serious adverse events
- Hospitalizations, ER visits, urgent outpatient visits for heart failure
- Volume depletion monitoring
- Ketoacidosis monitoring

6.2.6 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
- Calculate BMI using the height from the screening visit and the weight at the current visit
- Fasting blood sampling for laboratory assessments
- Urine pregnancy test (only applicable for women of childbearing potential)
- Urine albumin/creatinine ratio
- Concomitant medications

- SensiVest measurement of lung fluid volume at rest (at selected sites). The Sensivest test will only be completed on patients with a BMI of 22-36 and a height of 61 inches to 77 inches.
- 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 and accountability
- Contact Sharp IRT for treatment discontinuation

6.3 Patient Monitoring During Study Visits

6.3.1 Patient Monitoring

- For patients with established type 2 diabetes with a screening HbA1c of ≤ 7.0% and receiving insulin at baseline, it is recommended to reduce total daily insulin dose by 20% at randomization. For patients with established type 2 diabetes with a screening HbA1c of ≤ 7.0% and receiving sulfonylurea at baseline, it is recommended to reduce total daily sulfonylurea dose by 50% at randomization, or discontinue sulfonylureas in patients receiving the minimal dose of sulfonylurea at baseline.
- It is recommended that self-monitoring of blood glucose (SMBG) values is performed by the patients with established type 2 diabetes and reviewed during the study visits.
- Review of glucose lowering medications should be performed at all study visits. Investigators are strongly encouraged to not titrate glucose-lowering medications during the study, unless necessary for patient safety reasons.
- It is recommended that self-monitoring of weight is performed by the patients and reviewed during the study visits, with adjustments in loop diuretic dose, if appropriate for optimization of volume status.

6.3.2 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 6.4. 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.

- 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.

6.3.3 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 blood glucose (in patients with established type 2 diabetes).

Upon review of self-monitoring of weight and self-monitoring glucose (in patients with established type 2 diabetes) consider adjustments in loop diuretics and glucose-lowering medications for optimization of glucose control (in patients with established type 2 diabetes) and volume status if considered necessary from patient safety standpoint.

6.4 Vital signs

6.4.1 Blood pressure and pulse

Blood pressure and pulse measurement will be taken after the patient has been sitting and resting for at least 5 minutes and before blood samples are taken. Blood pressure (BP) and pulse should be measured three times with at least 1 minute between each measurement. 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. The average of the three BP readings will be used for study analyses. 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 average seated BP readings will be the one used for all subsequent readings. If there is a contraindication for measuring blood pressure in an arm, then no measurements should be taken in that arm.

Ideally, all blood pressure and pulse measurements should be taken with the same automated or manual blood pressure device, at the same time of day, and by the same personnel at each visit. Patients with persistent atrial fibrillation should have all of their blood pressure and pulse measured with a manual cuff.

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 (6MWT)

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.[12]

6.6 SensiVest Measurement of Lung Fluid Volume

SensiVest utilizes remote dielectric sensing ReDS™ technology, to estimate lung fluid volumes. The technology has been adapted from the military (which used it to see inside buildings and to find survivors among rubble). Sensible Medical has adapted the same principles and created a vest that when worn sends low-power electromagnetic energy through the lungs, which decipher air content from fluid. At selected DEFINE-HF study sites, patients' lung fluid volume will be measured at rest (prior to 6 minute walk test) during randomization (0 weeks), 6, 12 and 13 weeks. These results will be uploaded to a secure web portal and all data entry will be handled in a de-identified and blinded fashion by the National Coordinating Center. The local site study staff will be blinded to the SensiVest results at all times. A subset of sites may offer NYHA class III patients the option to use SensiVest at home and readings may be taken by these patients twice a day for the 13 weeks, once in the morning (when a patient wakes up) and once at night (when a patient lies down to sleep).

6.7 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. For the KCCQ overall summary score, a small but clinically meaningful change is

considered to be ≥ 5 points.[13] The patients will fill in PRO (KCCQ) paper form under the supervision of the site staff.

6.8 Laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, urinalysis and biomarker 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.

It is recommended that patients do not have their baseline diuretics changed based upon naturietic peptide levels, and that the patient's primary cardiologist be blinded to the BNP and NTproBNP data collected throughout the trial. There have been varying results with trials of NTproBNP guided clinical management of heart failure. Two randomized clinical trials have shown no clear benefit.[23-24] Given the uncertainty of benefit, neither serial collection nor treatment based upon NTproBNP levels are currently endorsed by ACC/AHA guidelines.[25] For these reasons, it is recommended that heart failure medication changes not be made based on naturietic peptide levels. If a patient is clinically symptomatic or endorses signs or symptoms of volume overload, clinical judgment should be used and diuretic adjustments made as warranted.

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
Biomarkers (IL-6, HS-CRP, CML, sRAGE, Gal-3, ST-2 and hs-cTnT)	40 mL whole blood	3	120 mL
Total			190 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. The residual biomarker samples will be stored as described in appendix C.

8 SAFETY

8.1 Definition of adverse events (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

8.2 Definitions of serious adverse event (SAE)

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Any event of cancer, drug dependency/abuse, laboratory abnormalities fulfilling the Hy's law definition or overdose (defined as the accidental or intentional ingestion of any dose of the investigational product that is considered both excessive and medically important) should be reported as an SAE using the most relevant SAE criteria, as judged by the Investigator.

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, 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[14] 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.

8.2.8 Urgent outpatient visits for heart failure

In the event that a patient requires one or more urgent outpatient visits for heart failure over the course of the study, source documents will be obtained to adjudicate events. See appendix A for detailed information

8.2.9 Acute Kidney Injury

Acute kidney injury is defined as a doubling of creatinine, consistent with the modified RIFLE criteria for stage 2 acute kidney injury.

8.2.10 Ketoacidosis (DKA)

Be aware that post marketing cases show a possible 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 (for patients with established type 2 diabetes) during the study among patients receiving insulin at baseline (above and beyond reductions in insulin dose specified in the study protocol). 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.

8.2.11 Volume Depletion

Dapagliflozin 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 Recording of adverse events

8.3.1 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 and AEs of Special Interest will be captured in the e-CRF. Non-serious AEs will not be captured in the e-CRF.

SAEs are defined in section 8.2.

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

AEs of Special Interest will include DKA, volume depletion (defined as hypotension, syncope, orthostatic hypotension or dehydration) and severe hypoglycemic events.

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

8.3.2 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. [redacted] 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 SAEs after database lock will be reported to [redacted], who will notify the appropriate regulatory authorities of [redacted] and study drug manufacturer.

8.3.3 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)
- Description of AE

Maximum intensity will be graded according to the following rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal 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.

8.3.4 Causality collection

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?'

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'.

8.3.5 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 of 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.

8.3.6 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.

8.3.7 Hypoglycemic events

Information about all hypoglycemic events should be collected. Only severe hypoglycemic episodes should be captured in the eCRF. A severe hypoglycemic event is defined as a symptomatic event requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL.

8.4 Reporting of serious adverse events

All SAEs have to be reported to [redacted], 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] representative will work with the Investigator to compile all the necessary information and ensure that all the necessary information is provided to [redacted] 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.

8.4.1 Reporting of serious adverse events to FDA and [redacted]

The Sponsor [redacted] 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 [redacted]. A copy of the MedWatch/AdEERs report must be faxed to [redacted] at the time the event is reported to the FDA. It is the responsibility of the investigator 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 [redacted] at the same time.

When reporting to [redacted] a cover page should accompany the MedWatch/AdEERs form indicating the following:

[redacted]

The investigator IND number assigned by the FDA

The investigator's name and address

The trial name/title [redacted]

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of fax [redacted] designated fax line: [redacted]

Serious adverse events that do not require expedited reporting to the FDA need to be reported to [redacted] preferably using the MedDRA coding language for serious adverse events.

In the case of blinded trials, [redacted] may request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs will be reported to [redacted], whether or not considered causally related to the investigational product. All SAEs will be documented.

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 [redacted] 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 [redacted] before enrolment of any patient into the study.

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

[redacted] 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.

[redacted] will provide Regulatory Authorities (as applicable), 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 their 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

Study procedures will not be changed without the mutual agreement of the EC and [redacted]

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).

[redacted] 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 site's Informed Consent Form, [redacted] and the site's IRB are to approve the revised Informed Consent Form before the revised form is used.

Any administrative change(s) and protocol amendment(s) will be prepared and approved by the study sponsor ([redacted]) and subsequently communicated to the EC.

9.6 Audits and inspections

Authorized representatives of [redacted], 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 [redacted] 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 [redacted]

10.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of [redacted] 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 [redacted] or its representatives. This will be documented in a Clinical Study Agreement between [redacted] and the investigator.

10.2 Training of study site personnel

Before the first patient is entered into the study, a [redacted] 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 [redacted] 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:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- 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
- 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 [redacted] 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 [redacted] 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

[redacted] Planned treatment duration in the study is 13 weeks. [redacted] 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. [redacted] may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with dapagliflozin.

11 DATA MANAGEMENT BY [redacted]

Data management will be performed by [redacted] 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 and completed at least one follow-up where the KCCQ and NTproBNP are collected. 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 dapagliflozin 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 dapagliflozin 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

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 χ^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 α=0.05, unless otherwise specified. All statistical analyses will be performed by the [redacted] Department of Biostatistics using SAS version 9.4 (SAS Institute, Cary, North Carolina).

12.2.1 Primary variable

There are two co-primary efficacy endpoints:

1. Difference in mean NTproBNP between the treatment and placebo study arms at 6 and 12 weeks.
2. Proportion of patients that achieve a meaningful change from baseline in quality of life (≥ 5pts increase in KCCQ overall summary score) or NTproBNP (≥ 20% decrease) over 12 week treatment period between dapagliflozin 10 mg and placebo.

The first co-primary endpoint of this study is to compare dapagliflozin versus placebo on mean NTproBNP at 6 and12 weeks. A generalized linear mixed model with a compound symmetry covariance structure to estimate the average effect over 6 and 12 weeks controlling for baseline NTproBNP. Gamma distribution and log link function will be used because of the skewness nature of NTproBNP. Center is included as a random factor to account for clustering of patients within centers.

The second co-primary endpoint, proportion of patients with a ≥ 5 point KCCQ overall summary score increase or a ≥ 20% decrease in NTproBNP at 6 or 12 weeks will be analyzed using Mantel-Haenszel test controlling for center.

Both co-primary 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).

Statistical significance will be determined using an ordered testing procedure; the alpha will be 0.05 for hypothesis 1. If hypothesis 1 is rejected then hypothesis 2 will be tested at α=0.05 level. However, if hypothesis 1 is not rejected hypothesis 2 will not be tested.

12.2.2 Secondary variables

The following secondary efficacy variables have been identified:

3. Proportion of patients with a ≥ 5pts increase in KCCQ over 12 weeks
4. Proportion of patients with a ≥ 20% decrease in NTproBNP over 12 weeks
5. Proportion of patients with a ≥ 5pts increase in KCCQ and a ≥ 20% decrease in NTproBNP over 12 weeks
6. Change in KCCQ score over 12 weeks.
7. Change in 6 minute walk score over 12 weeks.
8. Difference in mean BNP at 6 and 12 weeks.
9. Change in HbA1c over 12 weeks. (evaluated separately in patients with and without type 2 diabetes)
10. Change in weight over 12 weeks
11. Change in systolic blood pressure over 12 weeks

For secondary analyses proportional comparisons will be analyzed using the same testing method as the primary analyses. For continuous variable comparisons an analysis of covariance (ANCOVA) model including terms for treatment group and baseline covariate. The ANCOVA model will be used to derive the treatment difference with 95% confidence interval and corresponding two-sided p-value. Additionally, the mean change within each treatment group will be calculated with corresponding 95% confidence intervals.

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 variables

The following exploratory variables have been identified:

1. Effects on average weekly loop diuretic dose (furosemide equivalent).
2. Effects on the rate of hospitalizations for heart failure.
3. Effects on rate of urgent outpatient heart failure visits.
4. Effects on the rate of hospitalizations for heart failure and urgent outpatient heart failure visits.
5. Change in NYHA Class over 12 weeks.
6. Change in NTproBNP and KCCQ at 6 weeks from baseline and 12 weeks from baseline.
7. Effect on lung fluid volumes measured by remote dielectric sensing ReDS™ (SensiVest) over the treatment period.
8. Change in mean lung fluid volumes measured by remote dielectric sensing ReDS™ (SensiVest) between week 12 and week 13.

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 of special interest 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. Volume Depletion
7. Severe hypoglycemic events
8. Ketoacidosis

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.

12.3 Determination of sample size

For the first co-primary endpoint a sample size of 110 for each group will achieve 80% power with α=0.05 to detect a reduction in NTproBNP between the two groups of at least 302 pg/mL from baseline to 12 weeks. The assumptions for this calculation were derived from the BATTLESCARRED trial where the estimated standard deviation for NTproBNP was 1250 pg/mL. We expect the standard deviation in the DEFINE-HF Trial to be somewhat lower (961 pg/ml) given lower NTproBNP threshold. Of note, 302pg/mL reduction in NTproBNP is equivalent to 31.5% of the standard deviation in NTproBNP (based on the above assumption).

The second co-primary endpoint is a combined endpoint of a ≥ 5 point KCCQ overall summary score increase or a ≥ 20% decrease in NTproBNP. The sample size was determined using two independent groups where the anticipated control group percent change is 30%. A sample size of 110 for each group will achieve 80% power with α=0.05 to detect a difference in proportional change between the two groups of 18% from baseline to 12 weeks for the second co-primary endpoint.

There is an anticipated loss to follow-up of approximately 13% so the final sample size per group will be 125.

13 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and [redacted] 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 [redacted]

Name	Role in the study	Address & telephone number
[redacted]	Lead Study Team Physician responsible for the protocol	[redacted]

[redacted]	Study Manager	[redacted]

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. Dapagliflozin has been well tolerated at doses of up to 500 mg/day in single dose testing in healthy volunteers and up to 100 mg/day in repeat dose testing for 14 days in healthy volunteers and patients with type 2 diabetes. 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 [redacted] representatives immediately but no later than the end of the next business day of when he or she becomes aware of it.

14 BIOMARKER SUBSTUDY

A biomarker substudy will be conducted. Specimens will be collected for exploratory biomarker testing from all patients at the Randomization, Week 6 and Week 12 visits to assess the impact of dapagliflozin versus placebo on known markers of myocardial fibrosis/necrosis, inflammation, and oxidative stress. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual. Information regarding the biomarker substudy is included in appendix C.

15 FUTURE RESEARCH

The residual sample from the biomarker substudy will be stored indefinitely to allow for possible future research. Information regarding the storage and possible use of banked biospecimens is included in appendix C.

16 ARRYTHMIA SUBSTUDY

An arrhythmia substudy will be conducted. Patient participation will be optional. At the screening visit, those likely to be enrolled will be given the option to participate in the arrhythmia substudy. If they elect to enroll they will wear a holter monitor for 14 days to establish a baseline. The 14-day holter will be

repeated at the 6-week visit to compare change in arrhythmia burden. Information regarding the arrhythmia substudy is included in appendix D.

17 SensiVest Lung Fluid Volume Measurements

SensiVest utilizes remote dielectric sensing ReDS™ technology, to estimate lung fluid volumes. The technology has been adapted from the military who used it to see inside buildings and to find survivors among rubble. Sensible Medical has adapted the same principles and created a vest that when worn sends low-power electromagnetic energy through the lungs, which decipher air content from fluid[19]. Two sensors are attached to the body: one anteriorly on the chest and the other on the back of the patient. Each sensor both transmits and receives the energy either reflected from or transferred through the pulmonary tissue. The signal received reflects the dielectric properties of the section of the lung between the sensors. Water has a very high dielectric coefficient while air in contrast has the lowest dielectric coefficient. These physical properties make pulmonary tissue ideal to sensitively quantify the ratio of fluid to air (or in the case of heart failure estimate volume status and pulmonary edema).[2] The device has received both FDA 510k clearance and European CE markings for non-invasive lung fluid monitoring. The waves emitted are low frequency, which do not interfere with any other implantable devices[17]. The accuracy of ReDS was first established using CT as a gold standard and correlating changes in ReDS values among porcine models of heart failure undergoing both fluid challenge and then diuresis. As a part of the study, patients at selected sites will have blinded lung/fluid volume measurements at rest during the randomization (week 0), 6, 12 and 13 week visits. Site personnel will remain blinded to the Sensivest measurement results; de-identified and blinded Sensivest measurements will be accessible to the National Coordinating Center staff. (See appendix E for further details).

18 REFERENCES

1. Go, A. S. *et al.* Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* **129**, e28-e292, doi:01.cir.0000441139.02102.80 [pii] 10.1161/01.cir.0000441139.02102.80 (2014).
2 McMurray, J. J. *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* **371**, 993-1004, doi:10.1056/NEJMoa1409077 (2014).
3 Parving, H.-H. *et al.* Cardiorenal End Points in a Trial of Aliskiren for Type 2 Diabetes. *New England Journal of Medicine* **367**, 2204-2213, doi:10.1056/NEJMoa1208799 (2012).
4 Bertoni, A. G. *et al.* Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* **27**, 699-703 (2004).
5 Erdmann, E. *et al.* Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care* **30**, 2773-2778, doi:dc07-0717 [pii] 10.2337/dc07-0717 (2007).
6 Komajda, M. *et al.* Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J* **31**, 824-831, doi:ehp604 [pii] 10.1093/eurheartj/ehp604 (2010).
7 Ryden, L., Thrainsdottir, I. & Swedberg, K. Adjudication of serious heart failure in patients from PROactive. *Lancet* **369**, 189-190, doi:S0140-6736(07)60106-8 [pii] 10.1016/S0140-6736(07)60106-8 (2007).
8 Scirica, B. M. *et al.* Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* **369**, 1317-1326, doi:10.1056/NEJMoa1307684 (2013).

9 White, W. B. *et al.* Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* **369**, 1327-1335, doi:10.1056/NEJMoa1305889 (2013).
10 Gerstein, H. C. *et al.* Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* **364**, 818-828, doi:10.1056/NEJMoa1006524 (2011).
11 Inzucchi, S. E. *et al.* SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res* **12**, 90-100, doi:10.1177/1479164114559852 (2015).
12 Neal, B. *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine* **0**, null, doi:10.1056/NEJMoa1611925.
13 Zinman, B. *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*, doi:10.1056/NEJMoa1504720 (2015).
14 Fitchett, D. *et al.* <div xmlns="http://www.w3.org/1999/xhtml failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial . *European Heart Journal*, doi:10.1093/eurheartj/ehv728 (2016).
15 Neal, B. *et al.* Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)—a randomized placebo-controlled trial. *Am Heart J* **166**, doi:10.1016/j.ahj.2013.05.007 (2013).
16 Kosiborod, M. *et al.* Lower Risk of Heart Failure and Death in Patients Initiated on SGLT-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study. *Circulation*, CIRCULATIONAHA. 117.029190 (2017).
17 Scheerer, M. *et al.* Gesamtereignisraten für die Hospitalisierung bei Herzinsuffizienz (HHI) bei Neueinstellung auf SGLT-2-Hemmer im Vergleich zu anderen Antidiabetika–Daten aus dem klinischen Alltag aus Deutschland, Schweden und Norwegen mit mehr als 45.000 Typ 2 Diabetes Patienten (CVD-Real). *Diabetologie und Stoffwechsel* **12**, LB12* (2017).
18 Inzucchi, S. E. *et al.* SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res* **12**, doi:10.1177/1479164114559852 (2015).
19 EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced). ClinicalTrials.gov 2017; https://clinicaltrials.gov/ct2/show/NCT03057977?term=03057977&rank=1
20 EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). ClinicalTrials.gov 2017; https://clinicaltrials.gov/ct2/show/NCT03057951?term=03057951&rank=1
21 Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (Dapa-HF). ClinicalTrials.gov 2017; https://clinicaltrials.gov/ct2/show/NCT03036124?term=03036124&rank=1
22 Kosiborod, M., Gause-Nilsson, I., Sonesson, C. & Johnsson, E. in *DIABETOLOGIA.* S368-S368 (SPRINGER 233 SPRING ST, NEW YORK, NY 10013 USA).
23 Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, Hamid AK, Nicholls MG and Richards AM. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol*. 2009;55:53-60.
24 Pfisterer M, Buser P, Rickli H, Gutmann M, Erne P, Rickenbacher P, Vuillomenet A, Jeker U, Dubach P, Beer H, Yoon SI, Suter T, Osterhues HH, Schieber MM, Hilti P, Schindler R, Brunner-La Rocca HP and Investigators T-C. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA*. 2009;301:383-92

25 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F and American Heart Association Task Force on Practice G. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62:e147-239

19 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.

20 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.

1. **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
☐	☐	☐	☐	☐	☐	☐

1. 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 past 2 weeks, 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 past 2 weeks, 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 past 2 weeks, 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

21 APPENDIX C: BIOMARKER SUBSTUDY

Type 2 diabetes (DM) and prediabetes exacerbate the complications of all forms of cardiovascular disease, and particularly heart failure.[1, 2] DM can directly affect the myocardium, leading to increased left ventricular (LV) hypertrophy, altered LV remodeling, and reduced systolic and diastolic function.[3] In the presence of hypertension or ischemia/infarction, DM worsens adverse LV remodeling and dysfunction, which results in worse heart failure (HF) symptoms and increased mortality.[4-6]

The recently released EMPA-REG OUTCOME trial noted a 38% relative risk reduction of cardiovascular death with empagliflozin, a SGLT-2 inhibitor, versus placebo in patients with diabetes and established CVD.[7] Though the trial was predominantly of diabetic patients with coronary artery disease, the majority of the benefit appeared to be due to the reduction in hospitalizations for heart failure (a 35% relative risk reduction), and prevention of heart failure related and arrhythmia-related deaths. The mechanism of action for such a dramatic benefit in prevention of HF and cardiovascular mortality is not well understood, but does not appear to be due to the glucose lowering effects of empagliflozin.

It is therefore likely that mechanisms beyond glucose lowering and diuresis are behind the reduction in HF events and CV mortality with SGLT-2 inhibitors.[8] We hypothesize that the majority of the benefit of SGLT-2 inhibitors in HF is due to a reduction in oxidative stress, (thus improving both systolic and diastolic function), improvement in endothelial function (thus decreasing vessel stiffness) and possible neurohormonal and anti-inflammatory effects. Supporting this hypothesis are rat models where SGLT-2 inhibition was shown to normalize endothelial function, reduce oxidative stress in aortic vessels, reverse a pro-inflammatory phenotype, and improve AGE/RAGE signaling all pathways of potential importance to a reduction in arterial stiffness.[9]

The biomarker substudy will address the following Specific Aims:

1. Specific Aim #1: To assess the impact of dapagliflozin vs. placebo on known markers of myocardial fibrosis/necrosis, inflammation, and oxidative stress in patients with chronic HF with reduced systolic function (with and without diabetes)

   We will measure systemic biomarkers of oxidative stress: Uric Acid, Fibrosis: galectin-3 (Gal3), ST-2, myocyte necrosis: High sensitivity cardiac troponin T (hs-cTnT), and inflammation: high-sensitivity C reactive protein (hsCRP), interleukin-6 (Il-6). (See Appendix C Biomarker Summary Table). The change in biomarkers between 0, 6 and 12 weeks will be compared between dapagliflozin and placebo.

   Anticipated results: We hypothesize that multiple biomarkers reflecting diverse biological pathways would be significantly decreased in patients receiving dapagliflozin vs. placebo. Our overarching hypothesis is that patients taking dapagliflozin for 12 weeks will have a significantly greater reduction in biomarkers of oxidative stress (one of the most likely underlying mechanisms of benefit of SGLT-2 inhibitors) than those on placebo.

2. Specific Aim #2: Examine the relationship between biomarkers of myocardial fibrosis/necrosis, inflammation, and oxidative stress and clinical outcomes, including heart failure specific biomarkers (BNP, NTproBNP), as well as patients' symptoms and functional status (KCCQ and 6-minute walk test)

Linear regression will be employed with heart failure specific biomarkers (BNP, NTproBNP). KCCQ and 6 minute walk, as dependent variables (separate models); independent variables will include biomarkers of oxidative stress, fibrosis/necrosis, inflammation and other potential confounders; the biomarkers will be included in separate models and chosen based on the strongest univariable relationships between biomarkers and the clinical outcomes.

Anticipated results: We hypothesize that those patients with the greatest clinical benefit (by BNP, NTproBNP, KCCQ or 6 min walk) will be those with a significant reduction in pro inflammatory, fibrotic, and oxidative stress biomarkers.

3. Specific Aim #3: Preserve residual blood specimens (banked biospecimens) for long-term storage so that evaluations for additional biomarkers or genetic analyses could be performed in the future.

   To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study ID number. Samples will be kept in a secure storage area. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information.

   It is very unlikely that results generated from the banked biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document that their results will not be given to them, to family members or other physicians; nor will they be recorded in the subject's medical record.

   A research proposal would be submitted to the [redacted] IRB for approval of any future analysis that might be conducted on the banked biospecimens.

Appendix C Biomarker Summary Table:

Circulating biomarkers	Background, rationale, and measurement
Inflammatory (IL-6, HS-CRP)	• Several proinflammatory cytokines such as C-reactive protein (CRP), interleukine-6 (IL-6) seem to play a role in the low-grade systemic inflammation observed in diabetics. • HS-CRP is increased in heart failure. Higher levels are associated with features of more severe heart failure and are independently associated with mortality and morbiditys[10]
Advanced glycation end-products (AGEs) (CML, sRAGE)	• AGEs (circulating carboxymethyl-lysine [CML] and soluble receptor for AGEs [sRAGE]) are products of nonenzymatic glycation and oxidation which are known to rapidly accumulate in vessel walls of diabetics.[11] • In Mouse RAGE mediates inflammatory signaling, is involved in diabetic macro and microvascular complications, and is associated with increased muscle, cartilage, and vascular stiffness.[12-14] Given the adverse effects of AGEs in diabetes, AGEs may play a particularly important role in the pathobiology of heart failure in diabetics
Stress/Fibrosis (Gal-3, soluble ST2)	• Galectin 3 is a biomarker that is actively involved in both inflammatory and fibrotic pathways of cardiac remodeling. Elevated levels of galectin-3 have been found to be significantly associated with higher risk of death in both acute decompensated heart failure and chronic heart failure populations.[19] • Soluble ST2 signals the presence and severity of adverse cardiac remodeling and fibrosis. Its levels are elevated in both diabetics and heart failure with reduce ejection fraction, and prognostic of morbidity and mortality.[18]
Oxidative Stress (Uric Acid)	• In Mouse models SGLT-2 have shown to decrease oxidative stress. This is perhaps confirmed as many trials of SGLT-2 have demonstrated a decrease in uric acid.[21] It is unclear whether the decrease in Uric Acid is through renal loss or truly by a decrease in oxidative stress.
Myocardial Necrosis: **(**High sensitivity cardiac troponin T (hs-cTnT)	• High-sensitivity troponin assays represent an important advance with added sensitivity for cardiac myocyte necrosis, therefore allowing risk stratification and prognostic information in stable disease states such as chronic systolic heart failure.[23, 24]

References:

1. Kannel WB and McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA*. 1979;241:2035-8.
2. Mak KH and Topol EJ. Emerging concepts in the management of acute myocardial infarction in patients with diabetes mellitus. *J Am Coll Cardiol*. 2000;35:563-8.
3. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER and Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation*. 2000;101:2271-6.
4. Abbott RD, Donahue RP, Kannel WB and Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women. The Framingham Study. *JAMA*. 1988;260:3456-60.
5. Bella JN, Devereux RB, Roman MJ, Palmieri V, Liu JE, Paranicas M, Welty TK, Lee ET, Fabsitz RR and Howard BV. Separate and joint effects of systemic hypertension and diabetes mellitus on left ventricular structure and function in American Indians (the Strong Heart Study). *Am J Cardiol*. 2001;87:1260-5.
6. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC and Devereux RB. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. *Circulation*. 2001;103:102-7.
7. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE and Investigators E-RO. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine*. 2015.
8. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC and Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diabetes & vascular disease research*. 2015;12:90-100.
9. Oelze M, Kroller-Schon S, Welschof P, Jansen T, Hausding M, Mikhed Y, Stamm P, Mader M, Zinssius E, Agdauletova S, Gottschlich A, Steven S, Schulz E, Bottari SP, Mayoux E, Munzel T and Daiber A. The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity. *PloS one*. 2014;9:e112394.
10. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, Signorini S, Mocarelli P, Hester A, Glazer R, Cohn JN and Val-He FTI. C-reactive protein in heart failure: prognostic value and the effect of valsartan. *Circulation*. 2005;112:1428-34.
11. Yan SF, Ramasamy R, Naka Y and Schmidt AM. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. *Circulation research*. 2003;93:1159-69.
12. Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertens*. 2003;21:3-12.
13. Ulrich P and Cerami A. Protein glycation, diabetes, and aging. *Recent progress in hormone research*. 2001;56:1-21.
14. Yan SF, Ramasamy R and Schmidt AM. Mechanisms of disease: advanced glycation end-products and their receptor in inflammation and diabetes complications. *Nature clinical practice Endocrinology & metabolism*. 2008;4:285-93.
15. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP and Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*. 2003;111:649-58.
16. Izumiya Y, Shiojima I, Sato K, Sawyer DB, Colucci WS and Walsh K. Vascular endothelial growth factor blockade promotes the transition from compensatory cardiac hypertrophy to failure in response to pressure overload. *Hypertension*. 2006;47:887-93.

17. Ky B, French B, Ruparel K, Sweitzer NK, Fang JC, Levy WC, Sawyer DB and Cappola TP. The vascular marker soluble fms-like tyrosine kinase 1 is associated with disease severity and adverse outcomes in chronic heart failure. *J Am Coll Cardiol*. 2011;58:386-94.
18. Bhardwaj A and Januzzi JL, Jr. ST2: a novel biomarker for heart failure. *Expert review of molecular diagnostics*. 2010;10:459-64.
19. van Kimmenade RR, Januzzi JL, Jr., Ellinor PT, Sharma UC, Bakker JA, Low AF, 19. Martinez A, Crijns HJ, MacRae CA, Menheere PP and Pinto YM. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. *Journal of the American College of Cardiology*. 2006;48:1217-24.
20. Anand IS, Kempf T, Rector TS, Tapken H, Allhoff T, Jantzen F, Kuskowski M, Cohn JN, Drexler H and Wollert KC. Serial measurement of growth-differentiation factor-15 in heart failure: relation to disease severity and prognosis in the Valsartan Heart Failure Trial. *Circulation*. 2010;122:1387-95.
21. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, Capuano G, Canovatchel W and Canagliflozin DIASG. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes care*. 2012;35:1232-8.
22. Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CR and Hamer J. Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. *British heart journal*. 1979;42:316-25.
23. Apple FS, Collinson PO and Biomarkers ITFoCAoC. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clinical chemistry*. 2012;58:54-61.
24. Twerenbold R, Jaffe A, Reichlin T, Reiter M and Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? *European heart journal*. 2012;33:579-86.

22 APPENDIX D: ARRHYTHMIA SUBSTUDY

Heart Failure (HF) is associated with significant morbidity and mortality, with overall 60-day mortality among clinical trial patients hospitalized for CHF estimated as high as 10 percent.[1] It has been demonstrated that patients with NYHA class I–III tend to die suddenly whereas the death is usually due to refractory failure in those with Class IV symptomatology.[2] Estimates from the Framingham study show sudden cardiac death which occurs in 30–50% of patients with heart failure.[3]

It has been shown that beta-blockade and spironolactone reduce such arrhythmias thereby reducing sudden death and total mortality.[4, 5] Additionally, both have been shown to decrease premature ventricular complexes (PVCs) and non-sustained ventricular tachycardia (NSVT), which have both been shown to correlate with sudden cardiac death in HF patients.[6]

The recently released EMPA-REG OUTCOME trial noted a 38% relative risk reduction of cardiovascular death with empagliflozin, a SGLT-2 inhibitor, versus placebo in patients with diabetes and established CVD.[7] Though the trial was predominantly of diabetic patients with coronary artery disease (an overall low risk population for arrhythmia and sudden cardiac death compared to HF patients), empagliflozin demonstrated a 31% relative risk reduction of sudden cardiac death compared to placebo.

Atrial arrhythmias are also associated with significant morbidity and mortality amongst patients with HF.[8] Numerous animal models and some small series of humans demonstrated a potential benefit of thiazolidinedione (TZD) in reducing atrial fibrillation amongst diabetic patients.[9, 10] It was theorized that this was through a pleiotropic effect perhaps secondary to anti-inflammatory and antioxidant effects of TZDs.[11] While the mechanism of benefit of SGLT-2 on cardiovascular outcomes is unknown taking into consideration the aforementioned improvement in cardiac death, sudden cardiac death, death due to worsening HF, and HF hospitalization it could be speculated that this is also likely secondary to pleiotropic effects. It is therefore that we hypothesize dapagliflozin might exert beneficial effects on atrial remodeling reducing AF burden among patients with HF (with and without type 2 diabetes).

Arrhythmia sub study design:

At screening visit (-2 weeks) those likely to be enrolled will be given the option to participate in the arrhythmia sub study. If they elect to enroll they will wear a CARDIOKEY holter monitor for 14 days to establish a baseline. The 14-day holter will be repeated at the 6-week visit to compare change in arrhythmia burden.

When a patient has completed wearing the monitor for 14 days they will send the monitor in a pre paid package to Cardionet for processing. The coordinating center ([redacted]) will have a portal with data from all study locations underneath it for data processing and interpretation. Each site will be assigned the necessary number of CARDIOKEY devices, and replacement units ship automatically when a unit is enrolled with a patient. These are shipped second-day air via UPS, so we can set it up so there are enough inventories at each site.

Outcomes of sustained VT episodes, non-sustained VT (NSVT) episodes, VF episodes, atrial fibrillation, PVCs and PACs will be compared between dapagliflozin and placebo (see representative table).

Power Calculation for decrease in PVCs/hour.

Ramires et al reported a baseline PVC/hour burden of 65±15, this amongst a cohort of NYHA class III patients. After 16 weeks of spironolactone the PVC/hour burden decreased to 17±9. Given that the patient population of DEFINE-HF population will be less "sick" (NYHA class II and III), we are predicting a baseline PVC burden of 50±15 per hour. Assuming a 14% reduction in PVC per hour after 6 weeks of dapagliflozin; 98 patients would be required in each cohort to achieve 90% power (see Appendix D Table 1).

Appendix D Table 1.

Placebo (PVC/Hr)	Dapagliflozin	N for each arm	Power
50±15	40±15	36	80%
50±15	43±15	73	80%
50±15	45±15	142	80%
50±15	47±15	393	80%

Ventricular arrhythmias

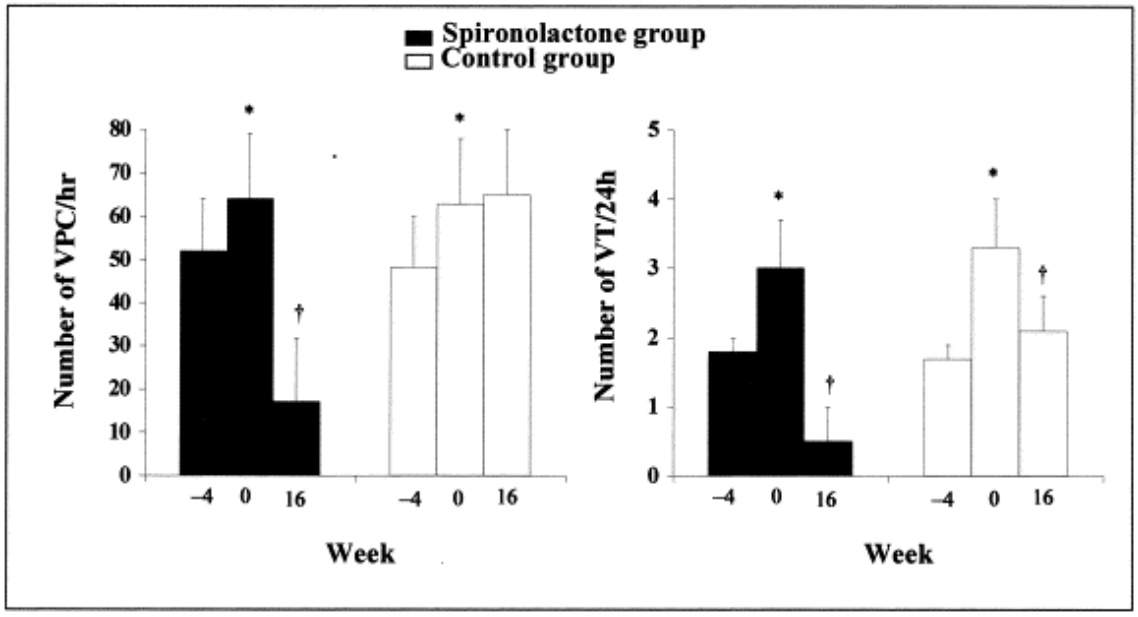
Outcomes	Dapagliflozin	Placebo	P value
VT episodes			
NSVT episodes			
VF episodes			
PVC Burden			

Atrial arrhythmias

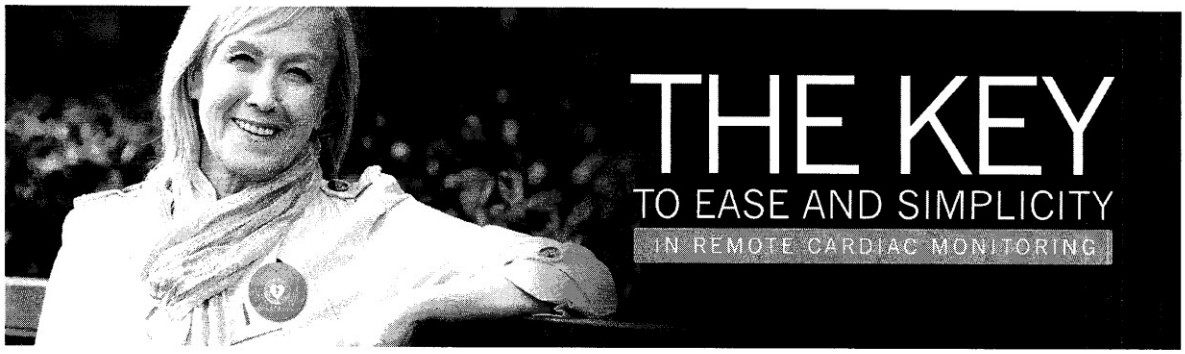
Outcomes	Dapagliflozin	Placebo	P value
A fib burden			
PAC burden			
A fib episodes			

P evaluated with Independent sample t-test.

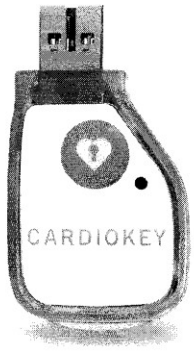
NSVT: non-sustained ventricular tachycardia, VF: ventricular fibrillation, VT: ventricular tachycardia, PVC: premature ventricular contractions, A fib: Atrial fibrillation



Representative figure adapted from (The American Journal of Cardiology, Volume 85, Issue 10, 2000, 1207–1211)



A lightweight, single-channel remote cardiac monitor that continuously records every heartbeat for up to 14 days



SIMPLE

- Small, lightweight cardiac monitor (<1 ounce)
- Simple hook-up process
- No battery changes or charges required

ACCURATE

- One-channel, two-lead cardiac monitor, with high diagnostic arrhythmia yields
- Extended monitoring report provides a concise and accurate summary of findings
- Continuous ECG recording up to 14 days

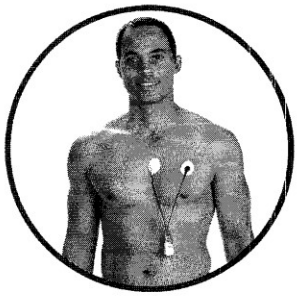
TRUSTED

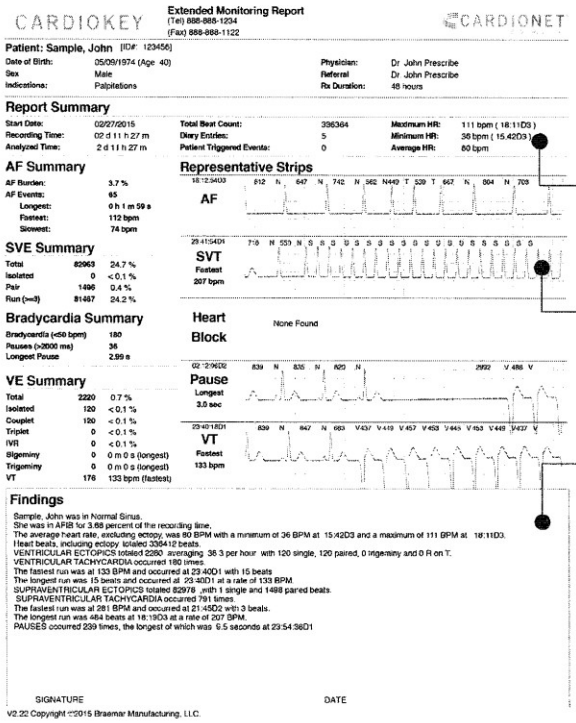
- From CardioNet, the leading remote cardiac monitoring company with a comprehensive portfolio of products and services
- ECG data prospectively analyzed by experienced Certified Rhythm Analysis Technicians (CRAT) or Certified Cardiographic Technicians (CCT)

Accredited by The Joint Commission

CARDIOKEY™

EXTENDED MONITORING REPORT





CARDIOKEY Extended Monitoring Report (Tel) 888-888-1234 (Fax) 888-888-1122 CARDIONET

Patient: Sample, John ID#: 123456

Date of Birth: 05/05/1974 (Age 40) | Physician: Dr John Prescribe
Sex: Male | Referral: Dr John Prescribe
Indications: Palpitations | Rx Duration: 48 hours

Report Summary

Start Date: 02/27/2015 | Total Beat Count: 336364 | Maximum HR: 111 bpm (18:11D3)
Recording Time: 02 d 11 h 27 m | Diary Entries: 5 | Minimum HR: 36 bpm (15:42D3)
Analyzed Time: 2 d 11 h 27 m | Patient Triggered Events: 0 | Average HR: 60 bpm

AF Summary

AF Burden: 3.7 %
AF Events: 65
Longest: 0 h 1 m 59 s
Fastest: 112 bpm
Slowest: 74 bpm

SVE Summary

Total	82963	24.7 %
Isolated	0	< 0.1 %
Pair	1496	0.4 %
Run (>=3)	81467	24.2 %

Bradycardia Summary

Bradycardia (<50 bpm): 180
Pauses (>2000 ms): 36
Longest Pause: 2.99 s

VE Summary

Total	2220	0.7 %
Isolated	120	< 0.1 %
Couplet	120	< 0.1 %
Triplet	0	< 0.1 %
IVR	0	< 0.1 %
Bigeminy	0	0 m 0 s (longest)
Trigeminy	0	0 m 0 s (longest)
VT	176	133 bpm (fastest)

Representative Strips

AF

SVT — Fastest 207 bpm

Heart Block — None Found

Pause — Longest 3.0 sec

VT — Fastest 133 bpm

Findings

Sample, John was in Normal Sinus.
She was in AFIB for 3.88 percent of the recording time.
The average heart rate, excluding ectopy, was 60 BPM with a minimum of 36 BPM at 15:42D3 and a maximum of 111 BPM at 18:11D3.
Heart beats, including ectopy, totaled 336412 beats.
VENTRICULAR ECTOPICS totaled 2260 averaging 36.3 per hour with 120 single, 120 paired, 0 trigeminy and 0 R on T.
VENTRICULAR TACHYCARDIA occurred 180 times.
The fastest run was at 133 BPM and occurred at 23:40D1 with 15 beats
The longest run was 15 beats and occurred at 23:40D1 at a rate of 133 BPM.
SUPRAVENTRICULAR ECTOPICS totaled 82978 ,with 1 single and 1488 paired beats.
SUPRAVENTRICULAR TACHYCARDIA occurred 791 times.
The fastest run was at 281 BPM and occurred at 21:45D2 with 3 beats.
The longest run was 464 beats at 18:19D3 at a rate of 207 BPM.
PAUSES occurred 239 times, the longest of which was 9.5 seconds at 29:54:36D1

SIGNATURE DATE

V2.22 Copyright ©2015 Braemar Manufacturing, LLC

COMPLETE REPORT OVERVIEW ON ONE PAGE

Report summary overview

Representative ECG recordings of primary arrhythmia areas, including Heart Block, Pause, SVT, VT, and AF

Certified Cardiographic Technicians review data and summarize findings

Report is uploaded and available 24/7/365 through the CardioNet dedicated HIPAA-compliant website

To learn more about CARDIOKEY, contact your local CardioNet Account Executive, or call **1-877-593-6421**

Global – 0295T	Global – 93224
Hookup – 0296T	Hook up – 93225
Technical – 0297T	Technical – 93226
Professional – 0298T	Professional – 93227

1000 Cedar Hollow Road, Suite 102
Malvern, PA 19355

www.cardionet.com

Available on the App Store

References:

1.Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M, Investigators I-H and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *Journal of the American College of Cardiology*. 2004;43:1534-41.
2. Luu M, Stevenson WG, Stevenson LW, Baron K and Walden J. Diverse mechanisms of unexpected cardiac arrest in advanced heart failure. *Circulation*. 1989;80:1675-80.
3. Kannel WB, Plehn JF and Cupples LA. Cardiac failure and sudden death in the Framingham Study. *American heart journal*. 1988;115:869-75.
4. Ramires FJ, Mansur A, Coelho O, Maranhao M, Gruppi CJ, Mady C and Ramires JA. Effect of spironolactone on ventricular arrhythmias in congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. *The American journal of cardiology*. 2000;85:1207-11.
5. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL and Carvedilol Prospective Randomized Cumulative Survival Study G. Effect of carvedilol on survival in severe chronic heart failure. *The New England journal of medicine*. 2001;344:1651-8.
6. Doval HC, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G, Dubner S, Scapin O and Perrone SV. Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA Investigators. *Circulation*. 1996;94:3198-203.
7. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE and Investigators E-RO. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine*. 2015.
8. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C and Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *European heart journal*. 2005;26:1303-8.
9. Korantzopoulos P, Kokkoris S, Kountouris E, Protopsaltis I, Siogas K and Melidonis A. Regression of paroxysmal atrial fibrillation associated with thiazolidinedione therapy. *International journal of cardiology*. 2008;125:e51-3.
10. Anglade MW, Kluger J, White CM, Aberle J and Coleman CI. Thiazolidinedione use and post-operative atrial fibrillation: a US nested case-control study. *Current medical research and opinion*. 2007;23:2849-55.
11. Liu T, Korantzopoulos P, Li G and Li J. The potential role of thiazolidinediones in atrial fibrillation. *International journal of cardiology*. 2008;128:129-30.

23 Appendix E: SensiVest Remote Dielectric Sensing ReDS™ to Assess Lung Fluid Volumes (at selected sites)

SensiVest utilizes remote dielectric sensing ReDS™ technology, to estimate lung fluid volumes. The technology has been adapted from the military who used it to see inside buildings and to find survivors among rubble. Sensible Medical has adapted the same principles and created a vest that when worn sends low-power electromagnetic energy through the lungs, which decipher air content from fluid.[1] Two sensors are attached to the body: one anteriorly on the chest and the other on the back of the patient. Each sensor both transmits and receives the energy either reflected from or transferred through the pulmonary tissue. The signal received reflects the dielectric properties of the section of the lung between the sensors. Water has a very high dielectric coefficient while air in contrast has the lowest dielectric coefficient. These physical properties make pulmonary tissue ideal to sensitively quantify the ratio of fluid to air (or in the case of heart failure estimate volume status and pulmonary edema).[2]

The device has received both FDA 510k clearance and European CE markings for non-invasive lung fluid monitoring. The waves emitted are low frequency, which do not interfere with any other implantable devices.[1]

The accuracy of ReDS was first established using CT as a gold standard and correlating changes in ReDS values among porcine models of heart failure undergoing both fluid challenge and then diuresis. At selected DEFINE-HF study sites patients lung/fluid volume will be measured at randomization (0 weeks), 6, 12 and 13 week visits at rest. The overarching hypothesis is that those on dapagliflozin will have a significantly lower percentage of fluid in their lungs than those on placebo.

Additionally in an attempt to gather more data and correlate lung fluid volumes with heart failure specific quality of life, and biomarkers of fibrosis and remodeling some patients with NYHA class III heart failure at select sites may be able to take a SensiVest home and transmit twice daily lung fluid volumes between randomization and week 13. Patients enrolled prior to SensiVest being available at the trial site will not have any Sensivest measurements preformed. A number of exploratory endpoints will be assessed with this data:

Specific Aim #1: To assess the impact of dapagliflozin vs. placebo on lung fluid volumes in patients with Heart Failure with reduced systolic function.

We will measure sedentary baseline lung fluid volume by percentage at 0, 6, 12 and 13-week office visits and compare values between dapagliflozin and placebo.

Anticipated results: We hypothesize that there will be a significantly lower percentage of lung fluid in patients receiving dapagliflozin vs. placebo. Similarly we hypothesize that on cessation of dapagliflozin or placebo, lung fluid concentration will increase in patients treated with dapagliflozin to a greater extent than in those treated with placebo.

Specific Aim #2: Examine the relationship between lung fluid volume and clinical outcomes, including heart failure specific biomarkers (BNP, NTproBNP), as well as patients' symptoms and functional status (KCCQ and 6-minute walk test), heart failure hospitalization and urgent visits for heart failure.

Anticipated results: We hypothesize that those patients with the greatest reductions in lung fluid volume will be those with the greatest clinical benefit (by BNP, NTproBNP, KCCQ or 6 min walk).

Specific Aim #3: Examine the relationship between lung fluid volume and novel heart failure biomarkers Uric Acid, myeloperoxidase level (MPO), Fibrosis: galectin-3 (Gal3), soluble ST-2, Myocyte necrosis: High sensitivity cardiac troponin T (hs-cTnT), and Inflammation: high-sensitivity C reactive protein (hsCRP), interleukin-6 (Il-6).

Anticipated results: We hypothesize that those patients with the greatest reductions in lung fluid volume will be those with a significant reduction in pro inflammatory, fibrotic, and oxidative stress biomarkers.

References:

1. http://sensible-medical.com/. 1/26/2015
2. Rappaport D. Noninvasive Monitoring of Pulmonary Congestion Using a Remote Dielectric Sensing (ReDS) System: A Prospective Single-Arm Study in Patients Suffering from Heart Failure. Journal of cardiac failure;**18**(8):S61 doi: 10.1016/j.cardfail.2012.06.207[published Online First: Epub Date]|.
3. Amir O, Rappaport D, Zafrir B, et al. A novel approach to monitoring pulmonary congestion in heart failure: initial animal and clinical experiences using remote dielectric sensing technology. Congestive heart failure 2013;**19**(3):149-55 doi: 10.1111/chf.12021[published Online First: Epub Date]|.
4. Abraham WT, Amir O, Weinstein JM, et al. Remote Dielectric Sensing (ReDS™)-Guided Patient Management of Ambulatory Heart Failure Patients Reduces Rehospitalization Rates. Journal of cardiac failure;**21**(8):S77 doi: 10.1016/j.cardfail.2015.06.240[published Online First: Epub Date]|.
5. Sensible Medical Innovations Lung fLuid Status Monitor Allows rEducing Readmission Rate of Heart Failure Patients (SMILE™). Clinicaltrialsgov 2015; https://clinicaltrials.gov/ct2/show/record/NCT02448342?term=sensible&rank=1

Sensor Vest

The right inside of the sensor vest has two sensors, one in the front and one in the back, used for detecting lung fluid content. The measurement information is transferred to the Bedside Console via a cable from the sensor vest.

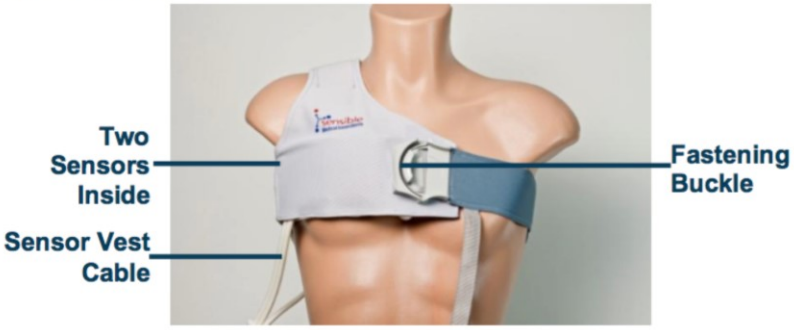


Figure 4: Sensor Vest

Figure 5: Chest and Back Sensors

- **Chest Sensor (Red):** This sensor inflates during measurement for better contact with your upper-right chest through clothing.
- **Back Sensor (White):** This sensor is positioned on the upper-right side of your back.

24 APPENDIX F: PRINCIPAL INVESTIGATOR SIGNATURE

SIGNATURE OF PRINCIPAL INVESTIGATOR

Dapagliflozin EFfect on symptoms and biomarkers iN patiEnts with Heart Failure (DEFINE-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)

This document contains confidential information, which should not be copied, referred to, released or published without written approval. Investigators are cautioned that the information in this protocol may be subject to change and revision.