Treatment of Diabetes in Patients with Systolic Heart Failure

A Randomized Active-Control Double-Blinded Study

The CANA-HF trial

Canagliflozin in **H**eart **F**ailure

STUDY PROTOCOL

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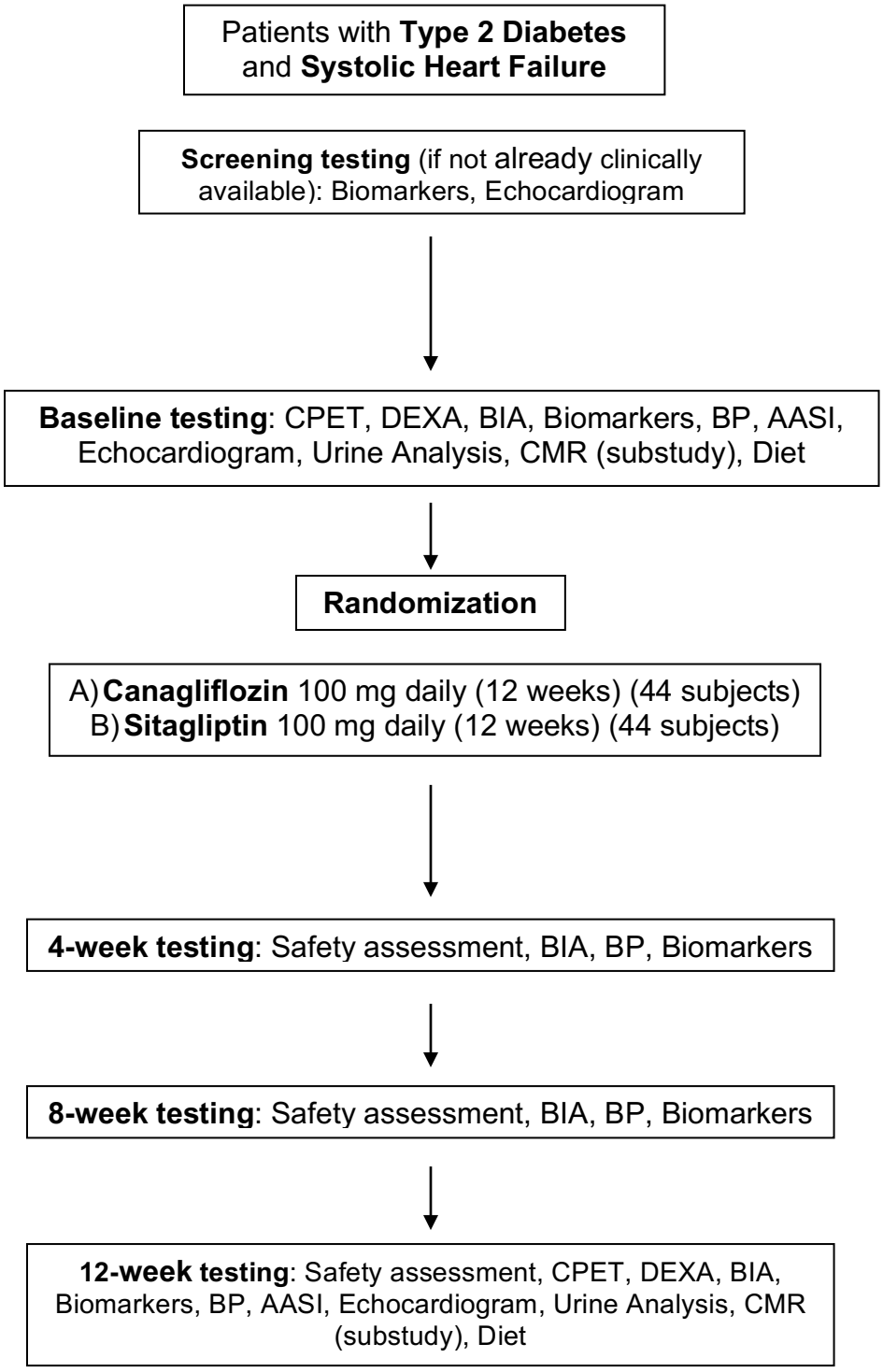
1) PROTOCOL SUMMARY

Title:	**Treatment of Diabetes in patients with Systolic Heart Failure**
Population:	88 Patients aged ≥18 years with type 2 Diabetes Mellitus and systolic Heart Failure
Study Duration:	24 months
Description:	Phase IV clinical trial of Canagliflozin vs Sitagliptin for the treatment of type 2 diabetes mellitus and systolic heart failure.
Objectives:	To determine the safety and efficacy of SGLT2 inhibition in patients with type 2 diabetes and systolic heart failure in terms of aerobic exercise capacity and ventilator efficiency, blood pressure, fluid status, body composition and left ventricular structure and function.
Study Design:	Randomized, double-blinded, active-control clinical trial with allocation to Canagliflozin 100 mg or Sitagliptin 100 mg daily for 12 weeks in a 1:1 ratio. Patients will be assessed at 4, 8 and 12 weeks after treatment initiation.
Estimated Time to Complete Enrollment:	21 months

2) SCHEMATIC OF STUDY DESIGN



3) BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Heart Failure (HF) is defined by the ACCF/AHA as “a complex clinical syndrome that results from any structural or functional impairment of ventricular filling and/or ejection of blood”. It is estimated that about 38 million people worldwide are diagnosed with HF, 5.7 million in the United States (US) alone with 870,000 new HF cases every year. HF patients typically present dyspnea, fatigue, fluid retention and exercise intolerance [1].

The pathophysiologic abnormalities driving to the development and progression of HF are very complex and partly unknown. HF cannot be exclusively considered a cardiac disease, since metabolic abnormalities and disorders, such as insulin-resistance and type II diabetes mellitus (T2DM) are highly prevalent [2-4].

Diabetes mellitus is a “group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion and/or insulin action” [5]. About 347 million people worldwide have diabetes and 86 million have pre-diabetes. In the US alone 21 million people have been diagnosed with diabetes, and about 8 million have undiagnosed diabetes. Moreover, diabetes is the 7th cause of death in the US [6].

Diabetes is associated with many cardiovascular risk factors, which in turn, increase risk for the development of HF [6,7]. Diabetes, however, is an independent risk factor for HF and both diseases simultaneously affect a large population [7]. Moreover diabetes is an independent risk factor for mortality among individuals with diagnosed HF. The survival rate in patients with HF and diabetes is significantly lower compared to subjects with HF or diabetes alone [8,9]. The concurrent presence of HF and diabetes presents a major challenge of improving metabolic control and heart failure symptoms at the same time.

The majority of patients with diabetes mellitus (about 90%) are affected by type 2 Diabetes (T2DM), a result of a chronic insulin-resistant state followed by progressive dysfunction and finally failure of pancreatic β-cells [10]. Overweight and obesity, particularly the excess of body fat, represent the major risk factors for the development of insulin resistance and thus T2DM [6]. Several therapies exist for the treatment of T2DM aimed to improved glucose control [11,12] reflected in the reduction of the HbA1c. Although a reduction in the HbA1c has proven to improve micro-vascular complications related to T2DM [11,12], HbA1c

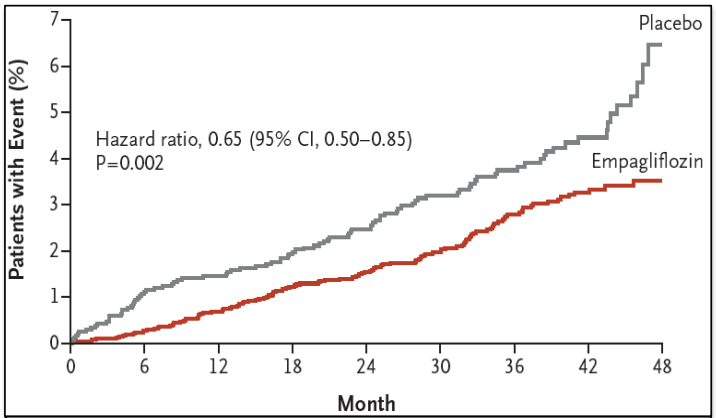


Figure 1. Reduced hospitalization for HF in patients with T2DM treated with empagliflozin, an inhibitor of the SGLT2. From Zinman B et al. N Engl J Med 2015;373(22):2117-28.

control has never been shown to reduce macro-vascular complications and/or overall mortality [14-16], hypothesizing potential alternative mechanisms by which diabetes affects the cardiovascular system. Indeed, only in a recent groundbreaking study [17], the inhibition of the SGLT2 has shown for the first time to reduce cardiovascular mortality and hospitalizations for HF in T2DM patients (**Figure 1**) despite a modest reduction in HbA1c.

In this study we hypothesize that Canagliflozin (Invokana®) will improve cardiorespiratory fitness in patients with systolic heart failure and type 2 diabetes in comparison with Sitagliptin (Januvia®). We also hypothesize that the improved cardiorespiratory fitness is related to an improvement in blood pressure, changes in left ventricular structure and function, and in body composition and fluid status, and not directly to glycemic control.

SGLTs are membrane proteins involved in the transport of glucose, vitamins, amino acids, and ions in the brush border membrane of the gut epithelium, in the proximal renal tubules, and recently found in the heart [18-22]. SGLT1 and SGLT2 are located in proximal kidney tubule, while SGLT1 is also broadly expressed in the gut and the heart [18-22]. SGLT1 is a high-affinity, low capacity transporter while SGLT2 is a low-affinity, high capacity transporter. SGLT2 mediates glucose uptake in the early proximal tubule and is responsible for the majority of glucose reabsorption at the glomerulus level. The remaining glucose (≈10%) is then reabsorbed by the SGLT1 [18-23]. The kidneys reabsorb the majority of glucose before the “glucose renal threshold” (GRT) is reached. When the amount of glucose exceeds the GRT, the exceeding glucose is excreted in the urine proportionally to plasma glucose concentration. The GRT in healthy subjects is ≈180 mg/dL, meaning that when plasma concentration exceeds such a level, glucose begins to be excreted by the kidney into the urine. Importantly, for each molecule of glucose, one sodium molecule is also reabsorbed from the SGLT2, while 2 molecules of sodium for each molecule of glucose are required for the SGLT1 [18-23].

In diabetic patients the glucose renal threshold is significantly increased to roughly 240 mg/dL, increasing the reabsorption of glucose and contributing to hyperglycemia [23]. The mechanisms by which diabetes increases the GRT are still unknown. Researchers have been studying ways to reverse the GRT increase, and to possibly even reduce it below physiologic levels. That allows to further increase glycosuria, finally lowering plasma glucose concentrations.

The SGLTs are overexpressed in diabetic patients. In animal models lacking SGLT2, improvements in glucose control were observed [24]. Inhibitors of the SGLT2 have then been proposed as new strategies to improve glucose control in patients with T2DM. To date, three SGLT2 inhibitors have been approved by the Food and Drug Administration (FDA) in the United States based on their efficacy in improving HbA1c: Empagliflozin,

Canagliflozin and Dapagliflozin. SGLT2 inhibitors are neither insulin sensitizers nor secretagogues acting in an insulin-independent manner [18,23]. They reduce the GRT, thereby increasing the excretion of glucose in the urine by 60-100 g/day, reducing plasma glucose concentrations [23,25,26].

SGLT2 inhibitors also possess non-glucose related effects. They improve blood pressure, arterial compliance, body weight and body composition (fluid status, fat mass, lean mass) [23,25-28] suggesting the existence of alternative mechanisms beyond the mere reduction in kidney reabsorption of glucose (glucose-lowering effect). The definitive proof of extra-glycemic effects was explored in the EMPA-REG OUTCOME trial [17] in which the selective inhibition of the SGLT2 with Empagliflozin, when compared to standard of care, had exciting beneficial effects on total cardiovascular mortality and overall mortality. Moreover, a significant reduction in hospitalization for heart failure was reported [17,29]. Interestingly these results seemed to be independent of the reduction in the HbA1c that was only slightly reduced compared to standard of care. Except for some results seen with metformin on cardiovascular outcomes, the EMPA-REG OUTCOME was the first trial in which an anti-diabetic drug showed benefits on cardiovascular mortality, total mortality and HF hospitalizations, despite minor improvements in glucose control. However, the mechanisms by which SGLT2 inhibition improves cardiovascular outcomes are largely unknown. SGLT2 inhibitors can: 1) Improve blood pressure possibly through the diuretic and natriuretic effects. Diuretics have beneficial effects on mortality in diseases such as hypertension [30], but they have never been broadly investigated in randomized placebo-controlled trials in HF [31]. Diuretics improve symptoms of congestion and quality of life in HF patients [31], but whether these effects translate into improved outcomes remains unknown 2) Improve fluid status possibly related to the above-mentioned natriuretic effects 3) Improve body weight and body composition by reducing body weight, but more importantly reducing fat mass and preserving lean mass, important determinant of cardio-respiratory functionality in patients with and without HF [32,33]. The improvements on body composition parameters seem to be related to the reduced reabsorption of glucose in the kidney, therefore inducing a caloric deficit able to promote weight loss [23,26,27]. These improvements could potentially link SGLT2 inhibitors and proposed improved fitness 4) Improve arterial compliance; arterial stiffness is related to worse cardiovascular outcomes [34]. Selective inhibition of SGLT2 improved arterial stiffness in patients with T2DM [27], suggesting an additional mechanism by which SGLT2 inhibitors affect the vascular tone 5) Reduction in uric acid level. Plasma levels of uric acid predict adverse outcomes in heart disease [35]. Recent data showed that SGLT2 inhibitors could reduce uric acid levels by possibly increasing uric acid excretion [36,37]. Whether these improvements translate in improved outcomes in T2DM and/or HF is unknown. Therefore we cannot exclude that Canagliflozin will be neutral in patients with HF and T2DM. Furthermore, there is a possibility the Canagliflozin may be harmful,

potentially by inducing hypovolemia and hypotension, particularly when administered concomitantly with other antihypertensive drugs. We believe the potential harmful effects, more evident when Canagliflozin was administered at the higher dose (300 mg) in prior studies, will be minimized in this trial since we are planning to use the lower dose (100 mg).

Canagliflozin will be compared to Sitagliptin, a dypeptidil peptidase (DPP)-IV inhibitor. DPPIV hydrolyzes glucagon-like peptide 1 (GLP1), a gut hormone produced in response to glucose ingestion and responsible for about 70% of insulin secretion [38,39]. DPPIV activity is increased in diabetic patients, thus reducing the level of active GLP1. Therefore by inhibiting DPPIV, there is a significant increase in GLP1 levels to physiologic values. That induces an increase in insulin secretion with improvements in glucose control, measured by reduction in HbA1c [38,40].

As shown in the Diabetes Control and Complication Trial (DCCT) in patients with Type 1 Diabetes [41], and in the United Kingdom Prospective Diabetes Study (UKPDS) in patients with T2DM [42], improvements in glucose control measured by reduction in HbA1c result in prevention or reduction in micro-vascular complications [43]. Therefore Sitagliptin may improve diabetes micro-vascular complications. Moreover Sitagliptin has been tested in several clinical trials and based on its effectiveness and safety has become one of the most prescribed anti-diabetic medications in the US [44].

We are planning to compare doses of Canagliflozin and Sitagliptin that in prior studies provided a comparable reduction in HbA1c compared to placebo at 26 weeks (0.79% for Canagliflozin 100 mg; 0.82% for Sitagliptin 100 mg) and at 52 weeks (0.73% for Canagliflozin 100 mg; 0.73% for Sitagliptin 100 mg)[45].

As already described, the mechanisms of action of Canagliflozin are, however, very different compared to Sitagliptin. Canagliflozin acts in an insulin-independent manner inhibiting the SGLT1 and SGLT2 [18,23], while Sitagliptin increases the production of insulin by increasing the levels of GLP1 [38].

We believe the different mechanisms of action of Canagliflozin may explain the non-glucose lowering effects seen in patients treated with SGLT2 inhibitors, and not in the ones treated with DPPIV inhibitors, like Sitagliptin.

HF is characterized by impaired aerobic exercise capacity and ventilatory inefficiency [46,47]. Similarly to what has been seen in HF, cardio-respiratory fitness (CRF) may predict all-cause mortality in diabetics [48,49]. Therefore when HF and T2DM coexist, the need for improving CRF and thus prognosis is imperative. Peak aerobic exercise capacity is measured using ventilator expired gas analysis and measuring oxygen consumption. Higher peak VO2 reflects better cardiorespiratory fitness in HF, and is an independent predictor of mortality in HF [50-54]. Peak VO2 is not biased by

overexertion, shows minimal familiarization effects over time, exhibits high intra-class correlation coefficients (ICC>0.90) and is insensitive to placebo-effect [46,47,50-54]. Ventilatory efficiency is measured using ventilator expired gas analysis and measuring peak ventilation (VE) and CO2 elimination (VCO2), a high VE/VCO2 reflects an inefficient system requiring larger ventilation for the same degree of CO2 elimination. As for peak VO2, also VE/VCO2 slope is an independent prognostic factor in HF, it is not biased by overexertion, shows minimal familiarization effects over time, exhibits high intra-class correlation coefficients (ICC>0.90) and is insensitive to placebo-effect [46,47,50-54].

4) OBJECTIVES

4.1 Study Objectives

We propose to study the effects of SGLT2 inhibition with Canagliflozin 100 mg vs Sitagliptin 100 mg on parameters of aerobic exercise capacity (peak VO_2) and ventilator efficiency (VE/VCO_2) at CPET after 12 weeks of active treatment (co-primary endpoints). Blood pressure and body water content will be measured at baseline, 4 weeks, 8 weeks and 12 weeks (secondary endpoints). Body composition, cardiac function, left ventricular mass and diet will be measured at baseline and after 12 weeks of treatment (secondary endpoints).

Biomarkers will be collected at baseline and at 12 weeks. Kidney function will be additionally measured at 4 weeks and at 8 weeks.

4.2 Study Outcome Measures

Cardiopulmonary Exercise Test (CPET): We will treat patients with T2DM and HF with Canagliflozin (n=44) or Sitagliptin (n=44) for 12 weeks, in a double-blinded fashion. We will measure CRF with a validated CPET at baseline and after 12 weeks of treatment, to determine whether Canagliflozin improves cardiorespiratory fitness assessed by changes in peak VO2 and VE/VCO2 slope, in comparison with Sitagliptin, for which we do not expect to see changes in cardiopulmonary capacity.

Blood pressure and Bioelectrical Impedance Analysis (BIA): We will measure resting blood pressure and fluid status every 4 weeks. Fluid status will be determined using the BIA, to measure changes in total, extracellular and intracellular body water. We expect to see improvement in blood pressure and fluid status in patients treated with Canagliflozin, while we do not expect significant changes in the Sitagliptin-treated group.

Dual-energy X-ray absorptiometry (DEXA): At baseline (Visit 1) and at 12 weeks (Visit 4) we will accurately quantify body lean mass (LM) and appendicular LM (ALM) in

particular, which correlates best with body strength and functionality [55-61], and we will measure also fat mass (FM). We expect to see improvements in body composition in the Canagliflozin-treated group (reduction in FM and preservation or increase of ALM) and not in the Sitagliptin group.

Echocardiography: structural and functional echocardiographic parameters include left and right ventricular dimensions, mass, systolic and diastolic function, and longitudinal strain analysis. These will provide mechanistic insight as to whether the hypothesized changes in aerobic exercise performance are dependent upon changes in cardiac dimension/function. The data will be collected and electronically stored for further analysis at the conclusion of the study.

FibroScan®: A FibroScan® exam will be performed at baseline (Visit 1) and at 12 weeks (Visit 4) to determine liver fibrosis and fat content.

Biomarkers: Blood will be collected at each time-point throughout the study (0, 4, 8, and 12 weeks). At baseline and at 12 weeks a complete panel of biomarkers (i.e., inflammatory, metabolic, cardiac, neurohormonal, renal functions, etc…) will be measured. At 4 and 8 weeks safety biomarkers will be measured (i.e., renal function).

Urine analysis: Urine will be collected at baseline and at 12-week to measure electrolytes, glucose, volume excretion and renal function.

Dietary assessment: We will estimate the nutritional components of the diet with a standardized 24-hour recall system at baseline and after 12 weeks to measure potential changes in dietary intake.

Ambulatory arterial stiffness index: Patients will undergo an indirect assessment of arterial stiffness by the measurement of the ambulatory arterial stiffness index (AASI) at baseline and 12 weeks.

Cardiac Magnetic Resonance (CMR): A pre-specified subgroup of subjects who have left ventricular hypertrophy (LVH)(N=32 – Stratus A1) will undergo a CMR imaging with intravenous gadolinium infusion using a 3 T magnet in order to quantify left and right ventricular mass and volumes, and extracellular volume content at baseline and at 12 weeks (Visit 4). In order to be included in the sub-study, subjects will need to meet all inclusion criteria for the study and also have a determination of LVH by echocardiography during the screening process, defined as a left ventricular mass index >116 g/m2 in men and >96 g/m2 in women [43]. To reduce the risk of nephrogenic systemic fibrosis or dermopathy, only subjects with glomerular filtration rate >60 $ml \cdot min^{-1}/1.73m^2$ will be considered for the sub-study.

Questionnaires: The Minnesota Living with Heart Failure questionnaire (MLHFQ), the Duke Activity Status Index (DASI) and the International Physical Activity questionnaire (IPAQ) will be used to measure potential impairments in quality of life and physical activity level at Visit 1 (baseline) and at Visit 4 (12 weeks).

5) STUDY DESIGN

5.1 Treatment arms

We designed an active-controlled, double-blinded randomized study of Canagliflozin versus Sitagliptin in patients with heart failure with reduced ejection fraction or systolic heart failure. The study is composed of 2 treatment arms exploring:

a) Canagliflozin 100 mg once daily for 12 weeks;
b) Sitagliptin 100 mg once daily for 12 weeks.

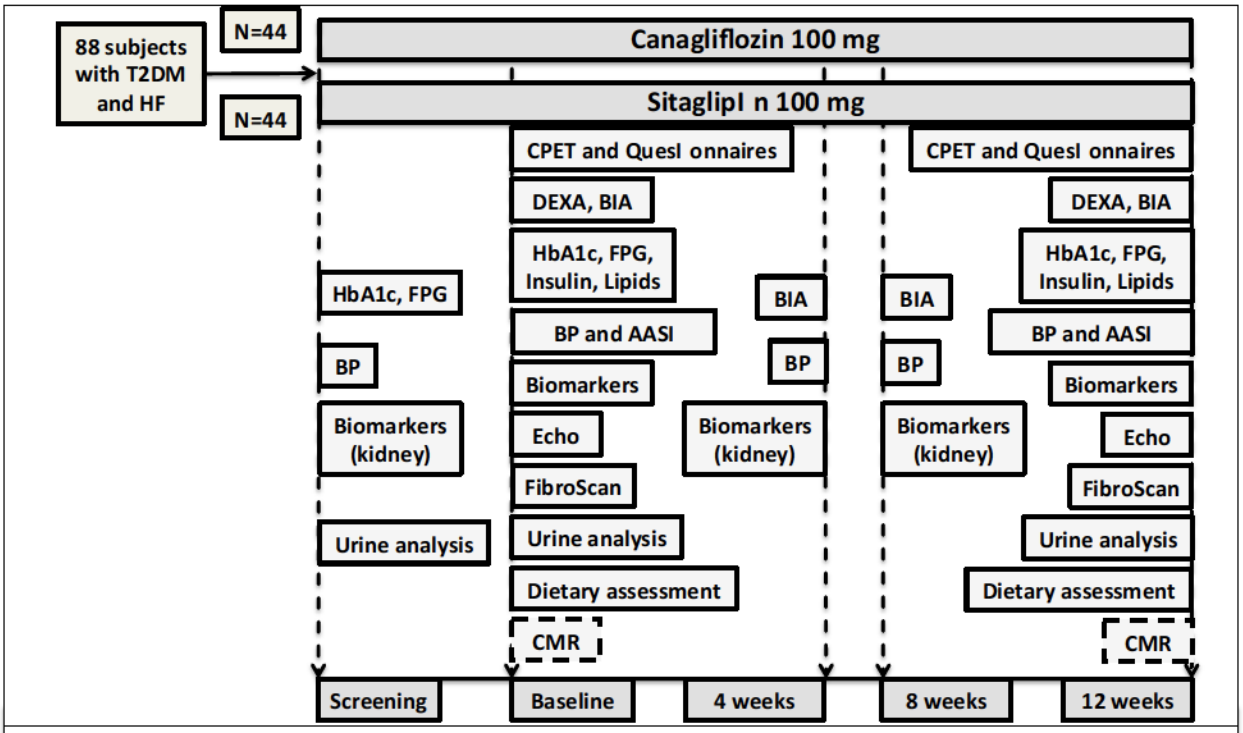


Figure 2 - Study design. Randomized double-blind active-controlled trial, daily treatment with Canagliflozin ti00 mg or Sitagliptin ti00 mg. CPET = cardio-pulmonary exercise test (peak VO_2 and VE/VCO_2); Questionnaires = quality of life (DASI and MLHFQ); DEXA = Dual-energy X-ray absorptiometry (appendicular lean mass, fat mass - body composition); BIA = Bioelectrical Impedance Analysis (fluid status); $HbA_{1}c$ = glycated hemoglobin, FPG = fasting plasma glucose (glucose control); BP = blood pressure; AASI = ambulatory arterial stiffness index; Biomarkers = safety (cardiac, kidney) and inflammation; Biomarkers (kidney) = creatinine, eGFR; Urine analysis; Fibroscan = liver fibrosis and fat content; Dietary assessment = 24-hour dietary recall CMR = cardiac magnetic resonance in 32 patients with left ventricular hypertrophy and eGFR ≥ 60 $ml \bullet kg^{-ti} \bullet min^{-ti}$.

Patients will undergo baseline clinical assessment, CPET, blood pressure and fluid status (BIA), body composition (DEXA), dietary assessment, echocardiogram, FibroScan, AASI (24-hour ABPM), biomarkers and urine analysis, and CMR (substudy in patients with LVH). After 4 weeks and 8 weeks of treatment, blood pressure, fluid

status and kidney biomarkers will be repeated. At 12 weeks (Visit 4), changes in peak VO2 and VE/VCO2 slope in Canagliflozin treated patients versus Sitagliptin will be determined. At 12 weeks, all the baseline tests will be repeated (DEXA, BIA, dietary assessment, blood pressure, echocardiogram, FibroScan, AASI, biomarkers and urine analysis, and CMR (substudy)(**Figure 2**).

At study end, the patients will be transitioned to standard-of-care anti-diabetic treatment according to the patient and physician preference.

5.2 Randomization

The Investigational Pharmacist not involved in patient care, data gathering, or data analysis, will be in charge of randomization. Patients will be randomized 1:1 to Canagliflozin 100 mg or Sitagliptin 100 mg. Due to the need of stratification for patients with LVH, the Investigational Pharmacist will be notified about presence/absence of LVH to stratify 44 patients to stratum A (presence of LVH) and 44 to stratum B (absence of LVH). Patients in stratum A will be further stratified in stratum A1 (N=32) who will need to have also an estimated glomerular filtration rate >60 $ml \bullet min^{-1}/1.73m^2$ and no contraindications to undergo Cardiac Magnetic Resonance (CMR) with intravenous gadolinium infusion (see Exclusion criteria), and in stratum A2 (N=12) who will meet inclusion in the CANA-HF trial but have contraindications to CMR (i.e., estimated glomerular filtration rate <60 $ml \bullet min^{-1}/1.73m^2$, claustrophobia, body weight over CMR permitted limit).

5.3 Treatment with canagliflozin and sitagliptin

After completion of all baseline testing patients will be given a 12-week supply of Canagliflozin 100 mg or Sitagliptin 100 mg. Intermediate visits, 4-week and 8-week will be scheduled within respectively 28±7 and 56±7 days after baseline visit. Patients will receive instruction from the investigators regarding daily administration of Canagliflozin or Sitagliptin. The 12-week visit will be scheduled within 84±10 days after baseline visit.

Canagliflozin or Sitagliptin are dispensed in non-identifiable capsules over-encapsulated by the investigational pharmacist to create the blinded study capsules. The Canagliflozin 100 mg or Sitagliptin 100 mg capsules will be indistinguishable. Investigational pharmacist will mark capsules containers in a way that neither the patient nor the physician will be able to distinguish between the two drugs.

The investigational Pharmacist at VCU will prepare the randomization. Access to randomization log will be restricted and allowed only on an emergency basis, or at the end of the study, including all data collection. In case of an emergency, a physician treating any patient enrolled in the study may request unblinding of that individual

patient if the physician determines that unblinding is necessary to make a treatment decision. The PI will contact the VCU Investigational Pharmacy to provide the treatment allocation to the PI, who will then relay the information to the treating physician. Upon completion of the study (including completion of all data collection and event adjudication), the PI will request the complete randomization log from the VCU Investigational Pharmacy.

Patients in the study will receive HF and T2DM guidelines-based medical treatments as clinically indicated. Canagliflozin or Sitagliptin will be added in adjunct to standard of care. However, the treatment is blinded to patients and investigators involved in patients care. To avoid providers prescribing additional SGLT2 inhibitors or DPPIV inhibitors, after a subject is enrolled, we will write a note in the clinical chart informing providers about the enrollment in the study and the recommendation to not prescribe SGLT2 inhibitors or DPPIV inhibitors in such patient. That allows avoiding a patient to be treated with two drugs belonging to the same class.

5.4 Study assessments

Upon completion of screening/enrollment, all subjects will be scheduled for Baseline visit (Visit 1) at the cardiopulmonary exercise suite. A **supervised maximal aerobic exercise test** will be administered using a metabolic cart that is interfaced with a treadmill. A conservative ramping treadmill protocol will be used. Prior to each test, the oxygen and carbon dioxide sensors will be calibrated using gases of known oxygen, nitrogen, and carbon dioxide concentrations and the flow sensor will also be calibrated using a 3-liter syringe. Subjects will then be briefed regarding the protocol and will be requested to exercise to fatigue. 12-lead ECG monitoring will be conducted at baseline, throughout the test and into recovery. Blood pressure will be measured every two minutes using an automated exercise-compatible device (Tango, SunTech Medical). In this technique, expired gases are sampled using a mouthpiece-mounted sensor, and analyzed to continuously measure oxygen (O2) uptake; the highest 10-second average value for O2 uptake defines peak oxygen consumption (VO2 peak in $mL \cdot kg^{-1} \cdot min^{-1}$). The ventilatory equivalents method will be used to determine VO2 at ventilatory threshold. Ten second averaged VE and VCO2 data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO2 slope via least squares linear regression ($y = mx + b$, m=slope). Peak Respiratory Exchange Ratio (VCO2/VO2) will be used for determining maximal to near maximal effort. A peak RER >/=1.10 is well accepted as a criterion for maximal effort and a peak RER >/= 1.0 is considered a minimal acceptable threshold. American Heart Association guidelines for exercise testing contraindications and termination criteria will be followed.

Upon completion of exercise testing, the results of the cardiopulmonary exercise test will be reviewed and discussed with the patients. Patients with angina, abnormal blood pressure or heart rate response, or ECG changes suggestive of coronary ischemia will be excluded from the study.

Subjects will return to the cardiopulmonary exercise suite for the additional visits upon completion of 12 weeks (visit 4, 84±10 days) of treatment with Canagliflozin or Sitagliptin. At Visit 1 and Visit 4, subjects will undergo a brief physical exam and repeat exercise testing. Raw data from the cardiopulmonary test will be analyzed at the end of the study, free of patient identifiers.

Resting blood pressure will be measured at baseline, 4, 8 and 12 weeks. The mean of three blood pressure measurements after being seated for 5 minutes will be taken.

Fluid status will also be analyzed. We will measure total body water (TBW) and its distribution in the intra- (ICW) and extra-cellular (ECW) compartments by a **Bioelectrical Impedance Analysis (BIA)**(RJL System). BIA introduces (non-invasively) into subjects' body a current at a given single-frequency (50 kHz) passing through a source electrode and a detector electrode, located in the homolateral hand and ankle. As a result BIA allows the analysis of Resistance (R) and Reactance or Capacitance (Xc) and their vector relationship Impedance (Z) [23-26]. R derives from extra- and intra-cellular fluid while Xc from cell membranes. Based on predictive equation obtained by regression analysis BIA estimates TBW, ICW and ECW. BIA is an indirect measure of body fluids, which has been validated against several direct measurements such as deuterium oxide for the measurement of TBW, bromide dilution for the measurement of ECW and total-body potassium for the assessment of ICW [23-26].

Body composition, particularly LM and FM, are considered better determinants of cardio-respiratory fitness (CRF) than body weight and Body Mass Index (BMI)[40-42]. Body composition will be measured with the **Dual-energy X-ray absorptiometry (DEXA)** at baseline (visit 1) and after 12 weeks (Visit 4). DEXA allows to estimate appendicular LM that describes the amount of LM in the legs and the arms, which are considered the major determinants of strength and functionality. The DEXA uses a small amount of X-rays of two different photon energy levels that pass through the body and are identified by a photon detector. The photon detector measures the attenuation (amount of energy absorbed) at each pixel by the bone and the soft tissue, which is further divided into fat and lean mass[86,87,94]. Radiation exposure amount is very low (0.02-1-5 mrem) compared to other assessments such as conventional X rays technique (25-270 mrem)[61]. Tests will be completed in the dedicated DEXA suite of the

VCU Division of Endocrinology. Subject with body weight exceeding DEXA permitted limit will not undergo DEXA.

Dietary intake data gathered by interview is governed by a 5-pass interview approach in which items are listed, reviewed, then described in details (including preparation), quantified, probed for frequently forgotten foods, and eventually reviewed again [62-65]. Data will be collected using Nutrition Data System for Research (NDSR), a computer-based software application developed at the University of Minnesota Nutrition Coordinating Center (NCC). The NCC Food and Nutrient Database serves as the source of food composition information in the NDSR. This database includes over 18,000 foods. Values for 165 nutrient, including carbohydrates, protein, fat and electrolytes like sodium and potassium, nutrient ratios and other food components are generated [62-65]. The USDA Nutrient Data Laboratory is the primary source of nutrient values and nutrient composition.

Prior to initiation of treatment, all subjects will undergo a **transthoracic echocardiogram** to measure left ventricular diastolic and systolic volumes, transmitral flow Doppler spectra, mitral and tricuspidal valve annulus tissue Doppler spectra, and tricuspidal annulus plane systolic excursion, according to the recommendations of the American Society of Echocardiography [66]. The echocardiogram will be repeated at 12-week visit (Visit 4). All images and loops will be acquired in an electronic format and transferred to the VCU Pauley Heart Center for blinded centralized measurements at the end of the study.

Biomarkers and urine analysis will be measured by LabCorp (Burlington, NC). Blood samples collected from peripheral vein and urine analysis will be performed at baseline (Visit 1), and 12 weeks (Visit 4), and used for analysis of complete cell count with differential, biomarkers (inflammatory, metabolic, cardiac, kidney, neurohormonal). At 4-week (Visit 2) and at 8-week (Visit 3), renal function will be monitored. The tubes will be collected by trained personnel, and immediately inverted 8-10 times after being drawn. Samples are then processed, refrigerated and shipped within 24 hours to LabCorp. Some of the cardiac biomarkers (i.e., high-sensitivity Troponin) will be measured in a single batch at end of study. After collection, samples will be stored in a freezer located our lab. The results from LabCorp will be sent to the PIs and designated investigators by email and/or fax.

Ambulatory arterial stiffness index (AASI) will be measure at baseline and 12 weeks. AASI will be defined as 1 minus the regression slope of diastolic blood pressure and systolic blood pressure measured with a 24-hour ambulatory blood pressure monitor

(ABPM)[67]. The patients will be instructed on the use the ABPM. A date, time and location will be also scheduled to return the ABPM to the study personnel.

Prior to each cardiopulmonary exercise test, subjects will complete the **Minnesota Living with Heart Failure and the Duke Activity Status Index (DASI) questionnaires, and the International Physical Activity questionnaire (IPAQ)**. The Minnesota Living with Heart Failure questionnaire (MLHFQ) is a 21-question graded questionnaire that has been extensively used to measure impairment in quality of life in patients with HF [68]. The questions are designed to measure a wide range of physical, emotional, social, and mental factors that contribute to overall quality of life. The DASI is a twelve-item "yes/no" questionnaire that allows for the calculation of perceived functional capacity. Each question describes a different physical activity and asks the subjects if they feel they can perform the task. The questions are weighted according to their degree of physical exertion. The weighted values from "yes" responses are summed to produce a score in metabolic equivalents. The IPAQ-short is a 7-question questionnaire that allows the estimation of daily physical activity by asking the subjects about duration and intensity of daily physical activity.

Subjects with evidence of LVH will undergo **a cardiac magnetic resonance study (CMR)** including intravenous infusion of gadolinium. CMR studies will be obtained at the VCU Collaborative Advanced Research Imaging (CARI) or at the VCU Medical Center. The rationale for restricting this analysis to patients with LVH is that a reduction in left ventricular mass is associated with more favorable outcomes in patients with LVH, whereas it is not expected to occur nor to portend a favorable prognosis in those without LVH. The subjects will also be evaluated for additional exclusion criteria preventing the completion of the cardiac magnetic resonance (i.e. pacemaker/defibrillator, claustrophobia, prior metal implants not compatible with magnetic resonance imaging, estimated glomerular filtration rate <60 $ml \cdot min^{-1}/1.73m^2$, body weight over CMR permitted limit). We will measure cardiac dimensions (volumes and mass) and systolic and diastolic function. Regional wall motion abnormalities will be assessed at cine-CMR using the 17-segment model [69-71]. Dedicated T1 and T2-weighted acquisition (T2 mapping) to measure the presence of myocardial fibrosis and edema, and the extracellular content. Paired analysis will be performed to determine changes in cardiac dimensions, function or extracellular volume content that can be attributed to study treatment.

5.5 Study Schedule

	Visit 1 (Baseline)	Visit 2 (28±7 days)	Visit 3 (56±7 days)	Visit 4 (84±10 days)
Screening	X			
Consent	X			
Clinical assessment	X	X	X	X
Medication list	X	X	X	X
CPET	X			X
Questionnaires	X			X
Blood pressure	X	X	X	X
DEXA	X			X
BIA	X	X (only in CRSU)	X (only in CRSU)	X
Echocardiogram	X			X
FibroScan ®	X			X
CMR (substudy)	X			X
Biomarkers (complete)	X			X
Biomarkers (kidney)		X	X	
Urine analysis	X			X
AASI	X			X
Dietary assessment	X			X

6) ENROLLMENT IN THE STUDY

Patients seen in clinic will be screened for inclusion and exclusion criteria. Part of the data needed for screening may not be available in the clinical chart, in such cases, after the patient has signed the informed consent form, the necessary laboratory and imaging studies will be ordered and charged to the research study account.

6.1 Screening

All eligible patients will be screened among the patients seen in clinic. Patients meeting inclusion criteria will be approached to obtain informed consent. Patients agreeing to participate in the study will sign the informed consent form and will be given a copy of the consent form signed by the investigator performing the informed consent process.

6.2 Inclusion Criteria

All 5 criteria need to be met for enrollment of the patient in the study

1) Symptomatic stable HF (NYHA class II-III) with reduced left ventricular ejection fraction (LVEF≤40%, measured within 6 months of enrollment – no changes in cardiac including anti-hypertensive medications within past 3 months);
2) Peak exercise limited by shortness of breath and associated with a respiratory exchange ratio (RER) >1.00 (reflecting maximal aerobic effort);
3) Reduced peak aerobic exercise capacity (peak VO_2) to less than 80% of predicted value by age/gender;
4) Poorly controlled T2DM (HbA1c levels between 7.0% and 10.0% if on a treatment regimen including insulin, or between 6.5% and 10.0% if not on an insulin regimen);
5) The patient is willing and able to comply with the protocol (i.e, exercise protocol, body composition)
6) Eighteen years of age or older.

6.3 Exclusion Criteria

Subjects will not be eligible if they meet any of the following 13 exclusion criteria.

1) Type I diabetes;
2) Type II diabetes that is difficult to control (episodes of severe hypoglycemia <50 mg/dl by history, hypoglycemia unawareness by history, frequent changes in anti-diabetic regimen class in the past 3 months) or with prior episode of diabetic ketoacidosis (any time);
3) Open label treatment with SGLT2 inhibitors (within the past 3 months);
4) Current treatment with thiazolidinedione which may induce volume and sodium retention (within the past 3 months);
5) Recent participation in a structured exercise or weight loss program (within the past 6 months);
6) Chronic Renal Disease defined as GFR <50 $ml \cdot min^{-1}/1.73m^2$ according to local laboratory (since Canagliflozin 100 mg is not indicated for GFR <45 $ml \cdot min^{-1}/1.73m^2$, and Sitagliptin 100 mg is not indicated for GFR <50 $ml \cdot min^{-1}/1.73m^2$);
7) Uncontrolled thyroid dysfunction (TSH<0.4>4.5 mcIU/ml);
8) Pregnancy or of child-bearing potential or lactating;
9) Active or recent (within 2 weeks) of genital/urinary infection;
10) Concomitant conditions or treatment which would affect completion or interpretation of the study including physical inability to walk or run on a treadmill such as decompensated HF (edema, NYHA class IV), significant ischemic heart disease, angina, arterial hypotension (BP systolic <100 mmHg), orthostatic arterial hypotension, arterial hypertension (resting BP systolic >160 mmHg), atrial fibrillation

with rapid ventricular response, severe valvular disease, severe chronic obstructive or restrictive pulmonary disease, moderate-severe anemia (Hgb<10 g/dl), diabetic neuropathy or myopathy;

11) Abnormal blood pressure or heart rate response, angina or ECG changes (ischemia or arrhythmias) occurring during baseline cardiopulmonary exercise testing (CPX);
12) Current or recent (within 2 weeks) use of oral corticosteroids;
13) Inability to give informed consent.

Exclusion criteria specific to the CMR substudy.

14) Estimated GFR <60 ml•min^{-1}/1.73m^2;
15) Implantable cardioverter defibrillator, pacemaker or other implantable metal device not compatible with CMR scanning;
16) Severe claustrophobia, inability to lay flat for up to 60 minutes, or other contraindication to CMR scanning, including body weight over CMR permitted weight limit.

7) POTENTIAL BENEFITS AND RISKS

7.1 Canagliflozin

Canagliflozin is a SGLT2 inhibitor (and SGLT1 inhibitor in a smaller extent); it improves glucose control, reduces blood pressure, and additionally improves body composition in T2DM [13-20].

Canagliflozin is orally administered and its safety and efficacy have been broadly investigated in healthy subjects and in patients with T2DM in either monotherapy or combination with other anti-diabetic drugs. Canagliflozin 100 mg once daily was approved by the FDA in 2013 for the treatment of diabetes. Canagliflozin 100 mg is associated with a significant reduction in hemoglobin A1c, blood pressure and body weight. Considering the increased incidence of hypovolemia observed in patients on Canagliflozin, especially if using loop diuretics [72], there will be no uptitration of dose to 300 mg of Canagliflozin during the study. There is no loading dose and no dose-adjustments needed with age or weight. Drug-to-drug interactions are very low and are not expected to be clinically relevant. Co-administration of Canagliflozin with rifampin (UGT enzyme inducer) has shown a reduction of Canagliflozin by 51%, possibly decreasing efficacy. Due do its mechanism of action, monitoring glucose control with urine glucose test is not recommended in patients taking SGLT2 inhibitors, due to false positive results. In subjects taking SGLT2 inhibitors the monitoring of glycemic control with 1,5-AG assay is not recommended since considered unreliable.

Side effects have been reported with Canagliflozin. The most likely side effects associated with the use of Canagliflozin include:

- In men and women:
  - Dizziness or lightheadedness upon standing (up to 1 in 20 people), particularly in subjects already treated with diuretics, older patients and with subjects with reduced kidney function;
  - Hypoglycemia (approximately 4 in 100), particularly if associated with other anti-diabetic drugs such as sulfonylurea or insulin in which case is more common (5 in 10 people) and can be serious (up to 2 in 100 people);
  - Increased urination and thirst (approximately 1 in 20 people);
  - Urinary tract infections (approximately 1 in 20 people);
  - Allergic reaction including rash or hives (approximately 1 in 20 people), generally shortly after starting Canagliflozin and not associated with serious symptoms;
  - Constipation (less than 1 in 25 people);
  - Nausea (less than 1 in 25 people);
  - Diabetic ketoacidosis (approximately 1 in 1000 people);
  - Bone fractures (approximately in 50 people).
  - Amputation of the toes (and to a lesser extent the foot or leg) (up to 1 in 150 people)
  - Laboratory changes observed in prior clinical trials with Canagliflozin but not associated with clinically significant illnesses:
    - Increase of approximately 4.5% in low-density lipoprotein cholesterol;
    - Increase in serum potassium, phosphate and/or hemoglobin of approximately 3.6%, 3.5% and 5% respectively;
    - Decrease of approximately 10% in serum urate.
  - Vaginal yeast infections and vaginal itching (<2 in 10 people)(*in women*);
  - Yeast infection at the head of the penis (up to 1 in 20 people), requiring circumcision in 0.3% in men who are not circumcised (*in men*).

In subjects not enrolled in clinical studies, but who have been prescribed Canagliflozin, the following side effects have been reported. It is however unknown if these side effects are directly linked to the use of Canagliflozin since not reported in the completed clinical trials (serious allergic reactions; severe decrease in kidney function [mostly in dehydrated patients]; urosepsis and pyelonephritis).

7.2 Sitagliptin

Sitagliptin is orally administered and its safety and efficacy have been broadly investigated in healthy subjects and in patients with T2DM in either monotherapy or combination with other anti-diabetic drugs. The FDA has approved Sitagliptin 100 mg for the treatment of diabetes. Sitagliptin 100 mg provides similar glucose-lowering

effects of Canagliflozin 100 mg. There is no loading dose and no dose-adjustments needed with age or weight in subjects with normal or mildly reduced kidney function. Drug-to-drug interactions are very low. Increases in AUC and peak drug concentration of digoxin have been reported when administered with Sitagliptin 100 mg for ten days [73].

Side effects have been reported with Sitagliptin. The most likely side effects associated with the use of Sitagliptin include:

- Hypoglycemia, particularly if associated with other anti-diabetic drugs such as sulfonylurea or insulin (2 in 10 people), which can be severe (less than 1 in 100);
- Upper respiratory infection (up to 3 in 50 people);
- Headache (3 in 50 people);
- Nausea, stomach upset and diarrhea (approximately 3 in 100 people)

In subjects not enrolled in clinical studies, but who have been prescribed Sitagliptin, the following side effects have been reported. The real incidence is unknown. It is however unknown if these side effects are directly linked to the use of Sitagliptin since not reported in the completed clinical trials (swelling of the hands or legs, if used with another anti-diabetic drug ([rosiglitazone]; hypersensitivity reactions including anaphylaxis; rash; urticarial; cutaneous vasculitis; exfoliative skin condition (i.e., Steven-Johnson syndrome); hepatic enzyme elevations; acute pancreatitis; worsening renal function (including acute renal failure); constipation; vomiting).

7.3 Social and psychological risks

There is a social/psychological risk in this study of breaching confidentiality and having a patient's diagnosis discovered. The likelihood of this occurring is very low, and will be further lowered by creating a database that does not link patients' identity with their clinical data. Loss of confidentiality is a potential risk. However, except when required by law, patients will not be identified by name, social security number, address, or any other personal identifier.

7.4 Testing risks

The following risks pertain to the different tests that are being used for monitoring the treatment responses:

- Blood draw: minor bleeding (rare) and infection (extremely rare) at puncture site.
- Urine collection: There are no known risks related to the urine collection.
- Cardio pulmonary exercise test (CPET): very low risk of rhythm disturbance of the heart and syncope. With adequate medical supervision extremely low risk of serious

complication. A physician will be present during the CPET. Minor arm or discomfort/pressure may occur during blood pressure measurement.

- Echocardiogram: no greater than minimal risk. The patient may feel minor discomfort or minor soreness over the area where the ultrasound probe contacts the chest wall, and during the application and removal of the electrodes.
- FibroScan®: there are no known direct risks from the FibroScan® medical device, which uses ultrasound waves. The patient may feel minor discomfort or minor soreness over the area where the ultrasound probe contacts the abdomen.
- Dual-energy X-ray Absorptiometry (DEXA): The radiation exposure amount is very low (0.02-1-5 mrem) if compared with other assessments such as conventional X rays technique (25-270 mrem). The exposure of radiation with DEXA is equivalent to the radiation exposure received during a transcontinental plane trip or to a few days of natural background. A Radiation Safety Committee approval letter will be obtained before study initiation. The duration of the test will be between 10 and 20 minutes, the analysis is noninvasive and painless for the participant.
- Bioelectrical Impedance Analysis (BIA): There are no known risks related to the BIA. In patients with defibrillator or pacemaker, however, cardiac activity will be monitored for potential interferences of BIA with the devices.
- 24-hour blood pressure monitor: Risks are related to minor sleep disturbance due to the inflation/deflation of the device.
- Dietary recall: There are no known risks related to the dietary recall.
- Questionnaires: There are no known risks related to the questionnaires.
- Cardiac magnetic resonance (CMR) – *substudy only*: There are no known risks related to the CMR. Contraindications include implantable pacemakers and defibrillators, neuroaxial stimulators and other conditions in which a metallic implant is present, which may be affected by the magnetic fields. The use of gadolinium contrast requires the placement of intravenous cannula. The risks of placing this cannula are similar to those associated with blood draws (see above). Adverse reactions, including allergic reactions, to the gadolinium contrast agent used are rare. However, mild side effects may occur and include headache, nausea, dizziness, and changes in taste, which are generally self-limited. We will exclude patients with moderate to severe impairment (estimated glomerular filtration rate <60 $ml \bullet min^{-1}/1.73m^2$) because of increased risk of nephrogenic systemic sclerosis.

7.5 Direct benefits to study participants

The hypothesis being tested is that SGLT2 inhibition with Canagliflozin will improve exercise capacity, blood pressure, fluid status, body composition and left ventricular hypertrophy in patients with systolic heart failure and diabetes. In contrast we hypothesize that the active control Sitagliptin will be neutral.

As for all clinical trials, there is no guarantee that there is a benefit with Canagliflozin. We cannot exclude the possibility that Canagliflozin and or Sitagliptin provide harm in the investigated population.

8) ASSESSMENT OF SAFETY

8.1 Specification of safety parameters

Safety parameters will include data deriving from history and physical examination performed at each visit, laboratory data and results of functional and imaging tests. The patient will be encouraged to contact the research team at any time with any concern or change.

Disease-related data will be assessed including change in symptoms (or new symptoms), change in functional capacity, vital signs as well as significant changes in medications.

Data specific to the treatment will also be assessed. The patient will be asked about symptoms. Changes to treatment for side-effects or unanticipated problems will be performed without breaking the randomization code, unless deemed necessary for the treatment of the individual patient by the physician caring for him/her, in which case the physician will be made aware while the remainder of the team, especially the investigators performing and interpreting the tests, will be maintained blinded.

The risks of the tests performed have been described above. In order to reduce risk, the procedures will be performed by skilled practitioners in the standard clinical fashion.

8.2 Methods of timing for assessing, recording, and analyzing safety parameters

8.2.1 Adverse Events

All Adverse Events (AEs) (regardless of causality) will be recorded on an AE form.

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient for medical care, or upon review by an

investigator and/or study coordinator. An event that is considered by the investigator(s) to be expected and related to the natural history of the disease is NOT considered an AE.

All events considered AEs including local and systemic reactions should be recorded on the appropriate AE form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis, which would include a physician) and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

Severity of Event. All AEs will be assessed by the clinician as:

- Mild: events require minimal or no treatment and do not interfere with the daily activities.
- Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and may require local or systemic drug therapy.
- Severe: events interrupt a patient's usual daily activity and will likely require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (it does not include a reaction that had it occurred in a more severe form, might have caused death).

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to the intervention. All suspected AEs must have their relationship to study intervention assessed using the terms: associated or not associated. In a clinical trial, the study intervention must always be a suspect. To help assess, the following guidelines are used to assess causality:

- Definitely related: The event is temporally related to the administration of the study intervention and, in the opinion of the investigator, no other etiology explains the event.
- Probably related: The event is temporally related to the administration of the study intervention and represents, in the opinion of the investigator, the most plausible explanation of the event.
- Possibly related: The event is temporally related to the administration of the study intervention but, in the opinion of the investigator, it does not represent the most likely explanation of the event.
- Definitely Unrelated: The event is temporally independent of study intervention and/or the event appears, in the opinion of the investigator, to be explained by another etiology.

All unexpected and severe AE that are possibly, probably or definitely related to research will be promptly reported to the IRB, the Janssen Scientific Affairs, and the FDA (as applicable).

The AE form will contain the following criteria to meet regulatory reporting requirements:

- An identifiable subject (not disclosing the subject's name and address)
- An identifiable reporter (investigational site)
- A potential Janssen medicinal product (Canagliflozin) or active control (Sitagliptin)
- An adverse event, outcome, or certain special situation

The minimum information required is:

- Suspected Janssen product (doses, indication)
- Date of therapy (start and end date, if available)
- Batch or lot number, if available
- Subject details (subject ID and country)
- Gender
- Age at AE onset
- Reporter ID
- Adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

8.2.2 Product quality complaint (PQC)

A product quality compliant is related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution

of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit.

8.2.3 Serious adverse events

A SAE is any adverse event/experience occurring between baseline assessments and the patients final study visit that results in any of the following outcomes and is considered by the investigator(s) to be unexpected or not consistent with the natural history of the disease:

- Death
- Life threatening (subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Death for any reason should be reported as a serious adverse event.

For reports of hospitalization, it is the sign, symptom or diagnosis, which led to the hospitalization, that is the serious event for which details must be provided.

Any event requiring in-patient hospital admission (or the prolongation of hospitalization) must be reported as an SAE. Events that do not meet the criteria for SAE reporting are:

- Reasons described in the protocol, e.g. drug administration, protocol-required testing
- Social reasons, e.g. overnight stay because of distance between home and hospital
- Surgery or procedure planned and documented prior to entry into the study

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event].

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

8.2.4 Unlisted (Unexpected) adverse event/reference safety information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via a medicinal
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, they are treated in the same manner as adverse events.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs **within 24 hours of becoming aware of the event.**

8.2.5 Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 hours of their awareness of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment. Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects potentially exposed to a Janssen medicinal product will be reported by the Sponsor Investigator **within 24 hours of their awareness of the event** using the Serious Adverse Event Form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3. Reporting Procedures

8.3.1 Adverse events and pregnancies [and/or pregnancies in partners]

All adverse events, whether serious or non-serious, related or not related, special situations, pregnancy exposures and/or pregnancies in partners following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

All serious adverse events that are unexpected and possibly, probably or definitely related to research and all pregnancy-related events (including exposures and/or pregnancies in partners) will be reported directly by the Sponsor Investigator, **within 24 business hours of becoming aware,** to the IRB to the Janssen Scientific Affairs using the Janssen Scientific Affairs Serious Adverse Event Report Form, and to the FDA (as applicable). Decision to unblind treatment will be made by the investigators on a case-to-case basis, after consultation with the IRB.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Sponsor Investigator, **within 24 business hours becoming aware**, to the IRB, the Janssen Scientific Affairs using the Janssen Scientific Affair's Serious Adverse Event Report Form, and the FDA (as applicable).

8.3.2 Product quality complaints (PQC) for Janssen Medicinal Products

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports of failure of expected pharmacological action (i.e., lack of effect).
All initial PQCs involving a Janssen product under study must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 business hours after being made aware of the event.** If the defect for a Janssen product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor Investigator must report the PQC to Janssen Scientific Affairs according to the serious adverse event reporting timelines, and to the FDA (as applicable). A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs.

8.3.3 Maintenance of safety information

All safety data should be maintained in a clinical database in a retrievable format. The Institution and Sponsor Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affair's request.

8.3.4 Transmission methods:

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
- Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

8.4 Regulatory Reporting

8.4.1 Procedures for reporting adverse events (AE), serious adverse events (SAE), pregnancy, and product quality complaints (PQC) to Janssen Scientific Affairs

The Institution and the Sponsor Investigator will transmit SAEs that are both unexpected and possibly, probably or definitely related to research and Special Situations in a form provided by Janssen Scientific Affairs in accordance with Section VIII Transmission methods, in English **within 24 business hours** of becoming aware of the event(s).

The Institution and/or Sponsor Investigator are responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs using a transmission method in Section 9.4.2 **within 24 business hours of such report or correspondence being sent to applicable health authorities.**

The Institution and the Sponsor Investigator will report any suspected PQC to the Janssen contact **within 24 business hours of becoming aware of the complaint**. The product should be quarantined immediately and if possible, take a picture.

8.5 Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the Institution and/or Sponsor Investigator, a listing of all SAEs reported to Janssen Scientific Affairs. The Sponsor Investigator will review this listing and provide any discrepancies to Janssen Scientific Affairs.

Upon request, Institution and/or Sponsor Investigator shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

9) DISCONTINUATION OF TREATMENT AND WITHDRAWAL

Patients may withdraw from the study at any time. The patient can decide to forgo any study procedures that makes him/her uncomfortable or wish not to complete. The study doctor may however stop the participation of the patient in this study at any time for many reasons including *(but not limited to)* the study doctor thinks it is necessary for patient health or safety, the patient has not followed study instructions, or administrative reasons requiring withdrawal.

Pre-defined reasons for discontinuation of the investigational drug (Canagliflozin or Sitagliptin):

1) Diabetic ketoacidosis;
2) Reduced eGFR (<45 ml•min^{-1}/1.73m^2)*;
3) Clinically significant hypotension*;
4) Hypersensitivity reaction;

* treatment may be restarted after condition resolved

Loss to follow-up can occur due to patients' withdrawal or death. Patients that have withdrawn from treatment will still be offered to complete all the functional assessment to analyze data in an intention-to-treat strategy. If patients are lost to follow up and their clinical condition cannot be established (alive vs dead, hospitalized vs not), they will be excluded from the initial analysis, and then reintroduced for sensitivity analysis considering all potential outcomes. A 10% attrition rate is a reasonable assumption. To account for this attrition a larger number of patients will need to be enrolled, resulting in a total number of 88 study patients.

10) STATISTICAL CONSIDERATIONS

All statistical analyses will be performed with the SPSS 22.0 package. Continuous data will be reported as median and interquartile range for potential deviation for the Gaussian distribution, and discrete variables will be reported as N and %. The Spearman test will be used to test correlations between 2 continuous variables. We expect a baseline peak VO_2 of 14.5 ml•Kg^{-1}•min^{-1} [74]. A sample size of 40 patients per group (total of 80 patients) provides sufficient power to detect a mean difference in the interval change in peak VO_2 of 1.50±1.76 ml•Kg^{-1}•min^{-1} (primary endpoint) expected with Canagliflozin compared to Sitagliptin, which we predict to have no significant effect on peak VO_2 (0±1.76 ml•Kg^{-1}•min^{-1})(power of >90%, □ value 0.025 two-sided). A sample size of 88 patients will allow for a 10% loss to follow up. We also anticipate additional 20 screen failure patients based on biomarkers findings that would preclude participation in the study (i.e., HbA1c <7% or >10%, eGFR<50 ml•min^{-1}/1.73m^2, TSH<0.4>4.5 mcIU/ml, etc…) and additional 10 screen failure patients based on findings at the cardiopulmonary exercise test (i.e. RER<1.00 indicating a sub-maximal aerobic exercise test, peak VO_2 >80% than predicted) and at the echocardiogram (i.e., LVEF>40%). Therefore, approximately 120 subjects will be screened in this study, and of these we expect to enroll 88 subjects and complete 80 cases.

Baseline measurement and demographic characteristics will be summarized for the patients into each of the treatment arms. Descriptive summaries of continuous measurements will consist of means, standard deviations and 95% confidence intervals; if the measurements have markedly non-normal distributions, then medians and interquartile ranges will be provided instead. Descriptive summaries of categorical measurements will consist of frequencies, proportions and 95% confidence intervals on those proportions. The summaries for each measurement will be provided separately for each treatment group.

The CPET data will be collected and data analyzed at the end of the study. All randomized subjects in the study who received at least one dose of study medication will be entered in the database and constitute the full analysis set, to be used to the assessment of safety. The differences in interval changes between the treatments will be compared using a random-effect analysis of variance model for repeated measures to analyze the effects of time and group allocation. Unadjusted p values will be reported throughout, with statistical significance set at the 2-tailed 0.05 level. Only randomized subjects who received at least 1 dose of the study drug and completed the study per protocol-specified criteria with available data sufficient to compute the primary endpoints (peak VO_2 and VE/VCO2 slope at baseline and 12 weeks) will be included in the per protocol analysis set. The cases with missing data in the primary endpoint will be

omitted from all the remaining per-protocol analyses, and analyzed only for safety as part of the full analysis set.

The data will be collected and electronically stored. The analysis will be performed at the conclusion of the study as described above. For statistical analysis, all values will be reported as the median and interquartile range for potential deviation from Gaussian distribution. The differences between treatment groups will be computed using the Wilcoxon signed-rank test for continuous variables or Fisher's exact test for discrete variables. Only cases with available data used to compute the primary endpoint (peak VO_2 at baseline and 2 weeks) will be included in the analyses of the secondary endpoints. Missing data in the data for the analysis of the secondary endpoints will be omitted, and not imputed.

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Appendix B – CASE REPORT FORMS

- Screening and Enrollment Form
- Patient Flow Sheet
- Data Collection Form
- Medication charts
- Echocardiographic data
- 24-hour dietary recall form
- Event or Drug Discontinuation

CANA-HF Screening and enrollment form

Subject number: **CANA-HF** _____ **Initials** _____ **Date**_____

INCLUSION CRITERIA: (*All criteria need to be met)*

- ☐ Symptomatic stable HF (NYHA class II-III) with reduced left ventricular ejection fraction (LVEF≤40%, measured within 6 months of enrollment – no changes in cardiac including anti-hypertensive medications within past 3 months); □ check if not clinically available
- ☐ Peak exercise limited by shortness of breath and associated with a respiratory exchange ratio (RER) >1.00 (reflecting maximal aerobic effort): □ check if not clinically available
- ☐ Reduced peak aerobic exercise capacity (peak VO_2) to less than 80% of predicted value by age/gender; □ check if not clinically available
- ☐ Poorly controlled T2DM (check one below):
  - ☐ HbA1c between 7.0% and 10.0% if on a treatment regimen including insulin;
  - ☐ HbA1c between 6.5% and 10.0% if NOT on an insulin treatment regimen.
- ☐ The patient is **willing and able to comply with the protocol** (i.e, exercise protocol, body composition)
- ☐ The patient is ≥18 years old, and **willing and able to provide informed consent**.

EXCLUSION CRITERIA (check only if applicable → ***patient excluded***):

- ☐ Type I diabetes;
- ☐ Type II diabetes that is difficult to control (episodes of severe hypoglycemia <50 mg/dl by history, hypoglycemia unawareness by history, frequent changes in anti-diabetic regimen class in the past 3 months) or with prior episode of diabetic ketoacidosis (any time);
- ☐ Open label treatment with SGLT2 inhibitors (within the past 3 months);
- ☐ Current treatment with thiazolidinedione (within the past 3 months);
- ☐ Recent participation in a structured exercise or weight loss program (within the past 6 months);
- ☐ Chronic Renal Disease (defined as GFR<50 ml/kg*min);
- ☐ Uncontrolled thyroid dysfunction (TSH<0.4>4.5 mcIU/ml);
- ☐ Pregnancy or of child-bearing potential or lactating;
- ☐ Active or recent (within 2 weeks) of genital/urinary infection;
- ☐ Concomitant conditions or treatment which would affect completion or interpretation of the study including physical inability to walk or run on a treadmill such as decompensated HF (edema, NYHA class IV), significant ischemic heart disease, angina, arterial hypotension (BP systolic <100 mmHg), orthostatic arterial hypotension, arterial hypertension (resting BP systolic >160 mmHg), atrial fibrillation with rapid ventricular response, severe valvular disease, severe chronic obstructive or restrictive pulmonary disease, moderate-severe anemia (Hgb<10 g/dl), diabetic neuropathy or myopathy;
- ☐ Abnormal blood pressure or heart rate response, angina or ECG changes (ischemia or arrhythmias) occurring during baseline cardiopulmonary exercise testing (CPET);
- ☐ Current or recent (within 2 weeks) use of oral corticosteroids;
- ☐ Inability to give informed consent.

Eligibility criteria verified and consenting completed by _____ on _____ (date)

- ☐ Patient given a copy of the informed consent and sufficient time to read and have questions, answered.
- ☐ The original signed copy is stored for research; a signed copy is given to the patient.

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Additional inclusion criteria, if not clinically available:

☐ LVEF≤40%

☐ Peak exercise limited by shortness of breath and associated with a respiratory exchange ratio (RER) >1.00 (reflecting maximal aerobic effort);

☐ Reduced peak aerobic exercise capacity (peak VO_2) to less than 80% of predicted value by age/gender;

☐ LVH (left ventricular mass index >116 g/m2 in men and >96 g/m2 in women)(for substudy only);

☐ Estimated Glomerular Filtration rate ≥60 $ml \cdot kg^{-1} \cdot min^{-1}$ (for substudy only).

Verified on ___/___/_____ by _____

Canagliflozin in Patients with Diabetes Mellitus and Heart Failure (CANA-HF)

Participant Study ID:			
- Was the patient re-admitted between baseline and 4-week FU? NO / YES - Was the patient re-admitted between 4-week FU and 8-week FU? NO / YES - Was the patient re-admitted between 8-week FU and 12-week FU? NO / YES - Was the patient re-admitted between 12-week FU and 24-week FU? NO / YES		Drug Dispensed to Participant Date: __/__/____ # of syringes dispensed: _____ Date for 4-week follow-up: __/__/_____ Date for 8-week follow-up: __/__/_____ Date for 12-week follow-up: __/__/_____	
Eligibility Confirmed on __/__/____ Signed/Performed by: _____		If Re-Consented: Date ICF signed: __/__/_____ Withdrew Consent: Date: __/__/_____ Reason?	
Informed Consent: Version __/__/____ WIRB approval __/__/_____; signed on __/__/____		Notes:	
Randomization: __/__/____		Notes:	
Study Time Point	**Study Procedure**	**Completed**	**Notes**
Screening Visit __/__/____	Blood Draw		
	Echocardiogram (if not clinically available)		
	Other:		
	Other:		
	Other:		
Baseline __/__/____	Note in CIS re: Clinical Trial/ICF Process		
	SGLT-2 and DPPIV note		
	Blood Draw		
	Echocardiogram		
	Resting Blood Pressure		
	BIA		
	Dietary Assessment		
	Concomitant Rx		
	Baseline History		
	Questionnaires		
	CPET		
	FibroScan		
	DEXA		
	24-hour ABPM		
	CMR (if LVH) scheduled on___/___/____		
	Invest. Drug Dispensed		
	Other:		
4-week FU __/__/____	Blood Draw		
	BIA		
	Resting Blood Pressure		

	Concomitant Rx		
	AE review/History		
	Other:		
8-week FU __/__/____	Blood Draw		
	BIA		
	Resting Blood Pressure		
	Concomitant Rx		
	AE review/History		
	Other:		
12-week FU __/__/____	Note in CIS re: Clinical Trial ends		
	SGLT-2 and DPPIV note to cancel		
	Blood Draw		
	Echocardiogram		
	Resting Blood Pressure		
	BIA		
	Dietary Assessment		
	Concomitant Rx		
	Questionnaires		
	CPET		
	FibroScan		
	DEXA		
	24-hour ABPM		
	CMR (if LVH) scheduled on___/___/____		
	AE review/History		
	Other:		
Notes:			

CANA-HF Subject #_____ Initials _____

Baseline Visit (Visit 1) – Date ____/____/_____

[ ] Inclusion/exclusion criteria reviewed; [ ] consent obtained

[ ] Heart Failure symptoms – NYHA II [ ] or III [ ]

Current symptoms and signs: (check all that apply)
[ ] shortness of breath; [ ] orthopnea; [ ] paroxysmal nocturnal dyspnea
[ ] chest pain; [ ] tiredness/fatigue; [ ] edema (symptom); [ ] abdominal fullness
On exam: [ ] pitting edema, [ ] S3 gallop, [ ] S4 gallop, [ ] JVD, [ ] rales

Notes _____

Medical History: (check all that apply)
[ ] Ischemic heart disease; [ ] Prior PCI; [ ] Prior CABG; [ ] Prior CVA; [ ] Hypertension
[ ] Diabetes; [ ] Hyperlipidemia; [ ] Current Tobacco user; [ ] Peripheral Vasc Disease
[ ] Chronic Kidney Disease; [ ] Chronic Obstructive Lung Disease; [ ] DVT/PE;
[ ] Obstructive sleep apnea; [ ] Obesity [ ] Morbid obesity[ ] BMI ≥35 [ ] BMI ≥40

Body weight: _____kg/_____lb Height: ____m/____ft BMI: _____kg/m^2
Waist circumference _____cm Blood Pressure: _____/_____ mmHg HR: _____min

Notes _____

Planning: (check all completed)
[ ] Echocardiogram Doppler
[ ] BIA (Rz:_____; Xc_____)
[ ] Dietary assessment
[ ] Heart failure questionnaires
[ ] Baseline cardiopulmonary exercise test
[ ] Urines collected
[ ] Labs collected
[ ] Labs and Urines sent
[ ] Recording of current medications
[ ] DEXA
[ ] 24-hour ABPM
[ ] FibroScan
[ ] CMR → If patient has LVH
[ ] Dispensing of study medication by_____
[ ] Patient education on drug handling, storage, and administration
[ ] Outpatient Hospital Follow up on day 28 (21-35) on _____ at ____:____

Notes _____

CANA-HF Subject #_____ Initials _____

4-week Visit (Visit 2) – Date ____/____/_____

Clinical conditions: (check all that apply)
[ ] heart failure symptoms, _____ NYHA class (I→IV), check [ ] if re-hospitalization
[ ] re-hospitalization for other cause (complete dedicated sheet)
[ ] death, check [ ] if presumed cardiac death, check [ ] if sudden death
[ ] interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)
[ ] shortness of breath; [ ] orthopnea; [ ] paroxysmal nocturnal dyspnea
[ ] chest pain; [ ] tiredness/fatigue; [ ] edema (symptom); [ ] abdominal fullness
On exam: [ ] pitting edema, [ ] S3 gallop, [ ] S4 gallop, [ ] JVD, [ ] rales

Notes _____

Past Medical History: (changes vs prior – new diagnoses)
[ ] _____; [ ] _____; [ ] _____; [ ] _____

Notes _____

Body weight: _____kg/_____lb Height: ____m/____ft BMI: _____kg/m^2
Waist circumference _____cm Blood Pressure: _____/_____ mmHg HR: _____min

Planning: (check all completed)
[ ] BIA (Rz:_____; Xc_____)
[ ] Labs collected
[ ] Labs sent
[ ] Recording of current medications
[ ] Outpatient Hospital Follow up on day 56 (49-63) on _____ at ____:____

CANA-HF Subject #_____ Initials _____

8-week Visit (Visit 3) – Date ____/____/_____

Clinical conditions: (check all that apply)
[ ] heart failure symptoms, _____ NYHA class (I→IV), check [ ] if re-hospitalization
[ ] re-hospitalization for other cause (complete dedicated sheet)
[ ] death, check [ ] if presumed cardiac death, check [ ] if sudden death
[ ] interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)
[ ] shortness of breath; [ ] orthopnea; [ ] paroxysmal nocturnal dyspnea
[ ] chest pain; [ ] tiredness/fatigue; [ ] edema (symptom); [ ] abdominal fullness
On exam: [ ] pitting edema, [ ] S3 gallop, [ ] S4 gallop, [ ] JVD, [ ] rales

Notes _____

Past Medical History: (changes vs prior – new diagnoses)
[ ] _____; [ ] _____; [ ] _____; [ ] _____

Notes _____

Body weight: _____kg/_____lb Height: ____m/____ft BMI: _____kg/m^2
Waist circumference _____cm Blood Pressure: _____/_____ mmHg HR: _____min

Planning: (check all completed)
[ ] BIA (Rz:_____; Xc_____)
[ ] Labs collected
[ ] Labs sent
[ ] Recording of current medications
[ ] Outpatient Hospital Follow up on day 56 (49-63) on _____ at ____:____

CANA-HF Subject #_____ Initials _____

12-week Visit (Visit 4) – Date ____/____/_____

Clinical conditions: (check all that apply)
[ ] heart failure symptoms, _____ NYHA class (I→IV), check [ ] if re-hospitalization
[ ] re-hospitalization for other cause (complete dedicated sheet)
[ ] death, check [ ] if presumed cardiac death, check [ ] if sudden death
[ ] interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)
[ ] shortness of breath; [ ] orthopnea; [ ] paroxysmal nocturnal dyspnea
[ ] chest pain; [ ] tiredness/fatigue; [ ] edema (symptom); [ ] abdominal fullness
On exam: [ ] pitting edema, [ ] S3 gallop, [ ] S4 gallop, [ ] JVD, [ ] rales

Notes _____

Past Medical History: (changes vs prior – new diagnoses)
[ ] _____; [ ] _____; [ ] _____; [ ] _____

Notes _____

Body weight: _____kg/_____lb Height: ____m/____ft BMI: _____kg/m^2
Waist circumference _____cm Blood Pressure: _____/_____ mmHg HR: _____min

Planning: (check all completed)
[ ] Echocardiogram Doppler
[ ] BIA (Rz:_____; Xc_____)
[ ] Dietary assessment
[ ] Heart failure questionnaires
[ ] Cardiopulmonary exercise test
[ ] Urines collected
[ ] Labs collected
[ ] Labs and Urines sent
[ ] Recording of current medications
[ ] DEXA
[ ] 24-hour ABPM
[ ] FibroScan
[ ] CMR → If patient has LVH

Notes _____

CANA-HF Subject #_____ Initials _____

Unscheduled Visit – Date ____/____/_____

Clinical conditions: (check all that apply)
[ ] heart failure symptoms, _____ NYHA class (I→IV), check [ ] if re-hospitalization
[ ] re-hospitalization for other cause (complete dedicated sheet)
[ ] death, check [ ] if presumed cardiac death, check [ ] if sudden death
[ ] interruption of investigational treatment (complete dedicated sheet)

Notes _____

Current symptoms and signs: (check all that apply)
[ ] shortness of breath; [ ] orthopnea; [ ] paroxysmal nocturnal dyspnea
[ ] chest pain; [ ] tiredness/fatigue; [ ] edema (symptom); [ ] abdominal fullness
On exam: [ ] pitting edema, [ ] S3 gallop, [ ] S4 gallop, [ ] JVD, [ ] rales

Notes _____

Past Medical History: (changes vs prior – new diagnoses)
[ ] _____; [ ] _____; [ ] _____; [ ] _____

Notes (**Reason for unscheduled visit**)_____

Body weight: _____kg/_____lb Height: ____m/____ft BMI: _____kg/m^2
Waist circumference _____cm Blood Pressure: _____/_____ mmHg HR: _____min

Planning: (check all completed)
[ ] Labs collected
[ ] Labs sent
[ ] Recording of current medications
[ ] Scheduling next appointment on _____/_____/_____ at ____:____

CANA-HF Study

Subject _____ Initials _____

MEDICATION (specify dose/frequency, note if changes)	BASELINE Date_____	4 WEEKS Date_____	8 WEEKS Date_____	12 WEEKS Date_____

Use additional pages if needed. Add Notes:

CANA-HF EchocardioDoppler Analysis

(Measurements can be made off-line)

Date _____Subject number: CANA-HF _____ Initials _____

Obtain apical 4-chamber view:

- Record 2 dimension imaging to measure LVEDV and LVESV
  - LVEDV _____ / LVESV _____ / LVEF _____
- Record Color-Doppler of Mitral Inflow and Regurgitation
- Record Color-Doppler of Left Ventricular Outflow tract
- Record transmitral Doppler flow spectra
  - E _____/ DT_____/ A_____ HR_____
- Record lateral wall Mitral Annular tissue Doppler spectra
  - E'lat_____ /A'_____/ S'_____
- Record septal Mitral Annular tissue Doppler spectra
-
  - E'sept_____ /A'_____/ S'_____
- Record Tricuspidal Annulus tissue Doppler spectra S'lat _____
- Record TAPSE (M-mode) Excursion _____

Obtain apical 2-chamber view:

- Record 2 dimension imaging to measure LVEDV and LVESV
  - LVEDV _____ / LVESV _____ / LVEF _____

Obtain apical 3-chamber view:

- Record 2 dimension recording of the left ventricle (to be used for strain analysis)

Strain analysis:

Apical 4C _____; 2C _____; 3C_____

24 h Dietary Recall Subject Number: **CANA-HF** _____ Initials_____ Date _____

Date __/__	Food and beverage	Amount (you can use food scale or common kitchen terms as cup, teaspoon, slice, can etc.)
Breakfast		
Time:		
Snack		
Time:		
Lunch		
Time:		
Snack		
Time:		
Dinner		
Time:		
Snack		
Time:		
Note (i.e. physical activity):		

Version Feb 23, 2016

CLINICAL SERIOUS ADVERSE EVENT REPORT
Janssen Scientific Affairs, LLC

COVER PAGE

Protocol Number: 28431754DIA4021 EUDRACT Number: (if applicable)

To: Send secure email to: IISProgram@ompus.jnj.com

Pages: ☐ Initial report ☐ Follow-up report Date of Report: d d M O N y y

SITE INFORMATION

Site ID Number Dummy Initials*: [redacted] Subject ID Number:

Country where SAE occurred:

Date Investigator/Investigational Staff became aware of SAE: d d M O N y y

Principal Investigator's Name: Reported By:

Site Address:

Telephone #: (country code) Fax #: (country code)

**(Dummy) initials to be removed by GTM/LTM for trials where study subjects will be identified by the Subject ID and Date of Birth (DOB).*

REPORTING

Investigator's Statement (Principal or Sub-Investigator)

I have verified the data on this SAE Report and have determined they are accurate and compatible with source documents.

Investigator Name (Please print):

Investigator Signature (required): _____ Date: d d M O N y y

FOR SPONSOR USE ONLY

Date SAE report received: d d M O N y y GMS Reference Number:

Sponsor Rep/Agent who received this report: (*please print name clearly)*

Clinical Contact's Telephone Number, please include country code:

Additional information requested? ☐ No ☐ Yes, specify:

Investigator: File original SAE report in TCF.
Sponsor: File a copy of the SAE report in the Investigator File with a copy of the attachments.

Janssen Scientific Affairs, LLC

CLINICAL SERIOUS ADVERSE EVENT REPORT COVER PAGE

SAE DESCRIPTION

ATTACH SAE CRF PAGES AND COPIES OF OTHER RELEVANT CRF PAGES/DOCUMENTS AND INDICATE IN CHECKBOXES BELOW:

☐ SAE CRF ☐ Concomitant Therapy ☐ Medical History ☐ Exposure/Study Drug Administration ☐ Relevant Labs, X-rays

☐ Other:

Investigator Narrative : For **EACH SAE** describe the course of events, timing and suspected causes

Signs & Symptoms	
Risk Factors	
Investigations and Supporting Diagnostics (eg labs)	
Differential Diagnosis	
Course of Events	
Treatment for SAE/ Response to Treatment	
Suspected Causes	
Other Comments	
Dechallenge	If applicable, describe whether and which event(s) abated on withdrawal of the study agent(s).
Rechallenge	If applicable, describe whether and which event(s) re-occurred on re-initiation of the study agent(s).

Investigator: File original SAE report in TCF.
Sponsor: File a copy of the SAE report in the Investigator File with a copy of the attachments.

Janssen Scientific Affairs, LLC
Protocol Number *28431754DIA4021* EUDRACT Number *NA*

CLINICAL SERIOUS ADVERSE EVENT REPORT

☐ Initial Report ☐ Follow-up report | (Dummy) Initials* [redacted] | Subject ID Number:

SUBJECT					
	Sex: ☐ Male ☐ Female ☐ Undifferentiated	**Height:** ☐ cm ☐ in	**Weight:** ☐ kg ☐ lb	**Date of Birth:** d d M O N y y y y	**Age at Onset of SAE** ☐ Days ☐ Months ☐ Years

SAE DIAGNOSIS

If this is a follow-up report, please indicate for each SAE, whether the SAE Diagnosis provided is ***replacing*** *the initial diagnosis, or if the SAE Diagnosis is a new term, reported* ***in addition to*** *the SAE Term(s) reported in the initial report.*
** (Dummy) initials to be removed by GTM/LTM for trials where study subjects will be identified by the Subject ID and Date of Birth (DOB).*

	SAE 1	SAE 2	SAE 3
SAE Diagnosis	**SAE** (if diagnosis unknown, list symptoms)	**SAE** (if diagnosis unknown, list symptoms)	**SAE** (if diagnosis unknown, list symptoms)
Onset	d d M O N y y; 24 hour clock	d d M O N y y; 24 hour clock	d d M O N y y; 24 hour clock
Severity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe

	Causality	Action taken with agent	Causality	Action taken with agent	Causality	Action taken with agent
Agent A	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
Agent B	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely	☐ Drug withdrawn ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable

Related to Trial Procedure?

Is SAE related to any trial procedure **not** including study agent therapy? If yes, please specify the specific trial procedure in narrative

	SAE 1	SAE 2	SAE 3
Related to Trial Procedure?	☐ No ☐ Yes	☐ No ☐ Yes	☐ No ☐ Yes
SAE Outcome	☐ Recovered/resolved ☐ Recovered/resolved with sequelae Recovery date: d d M O N y y ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal[1] ☐ Unknown	☐ Recovered/resolved ☐ Recovered/resolved with sequelae Recovery date: d d M O N y y ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal[1] ☐ Unknown	☐ Recovered/resolved ☐ Recovered/resolved with sequelae Recovery date: d d M O N y y ☐ Recovering/resolving ☐ Not recovered/not resolved ☐ Fatal[1] ☐ Unknown
SAE Seriousness Category	☐ Death[2] ☐ Hospitalization required[3] ☐ Prolonged hospitalization ☐ Life threatening ☐ Persistent or significant disability/incapacity ☐ Congenital anomaly/ birth defect ☐ Other medically important condition	☐ Death[2] ☐ Hospitalization required[3] ☐ Prolonged hospitalization ☐ Life threatening ☐ Persistent or significant disability/incapacity ☐ Congenital anomaly/ birth defect ☐ Other medically important condition	☐ Death[2] ☐ Hospitalization required[3] ☐ Prolonged hospitalization ☐ Life threatening ☐ Persistent or significant disability/incapacity ☐ Congenital anomaly/ birth defect ☐ Other medically important condition

[1] If the SAE outcome is "Fatal", please ensure that the "Death" checkbox in the "SAE Seriousness Category" section is marked.
[2] Record death information on the following page in the "SAE General" section. [3] Record hospital admission date on the following page in the "SAE General" section.

Continue on next page

Janssen Scientific Affairs, LLC
Protocol Number *28431754DIA4021* EUDRACT Number *NA*

CLINICAL SERIOUS ADVERSE EVENT REPORT (continued)

☐ Initial Report ☐ Follow-up report | (Dummy) Initials*: [redacted] | Subject ID Number:

** (Dummy) initials to be removed by GTM/LTM for trials where study subjects will be identified by the Subject ID and Date of Birth (DOB).

Death

Date of death*: d d M O N y y

Was autopsy performed?
☐ No ☐ Yes (If yes, attach copy of report if available)

Hosp

Hospital admission date: d d O N y y

Hospital discharge date: d d M O N y y

Trial Design

☐ Open-label only
☐ Blinded only
☐ Multi-phased: ☐ Open-label phase ☐ Blinded phase

If blinded trial or blinded phase of trial:
Random. No:

Blind broken?
☐ No
☐ Yes**

STUDY AGENT(S) AND DOSING

☐ **Subject has NEVER received any study agent (skip remainder of this section)**

Start Date	Start Time	Stop Date	Stop Time	Indication
d d M O N y y	24 hour clock	d d M O N y y	24 hour clock	

Agent A	Batch/Lot No.	Med. Kit No.

Dose	Unit	Frequency	Route

Start Date	Start Time	Stop Date	Stop Time	Indication
d d M O N y y	24 hour clock	d d M O y y	24 hour clock	

Agent B	Batch/Lot No.	Med. Kit No.

Dose	Unit	Frequency	Route

* Ensure this Date of death is entered on the 'End of Trial' (Death information) or other disposition page in the subject's CRF.
** If blind broken, ensure that 'Date randomization code was broken' is entered on the appropriate CRF page.

Investigator: File original SAE report in TCF.
Sponsor: File a copy of the SAE report in the Investigator File with a copy of the attachments.

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	Treatment of Diabetes in Patients with Systolic Heart Failure: A Randomized Active-Control Double-Blinded Study
PROTOCOL NO.:	VCU Cana-HF WIRB® Protocol #20161437 HM20007043
SPONSOR:	Virginia Commonwealth University
INVESTIGATOR:	Antonio Abbate, MD, PhD 1200 East Broad St., West Hospital, 10th Floor East Wing, Rm. 1041 Richmond, Virginia 23298 United States
STUDY-RELATED PHONE NUMBER(S):	Antonio Abbate, MD, PhD 804-828-0513 804-828-0951 (telepage/24-hours)

If any information contained in this consent form is not clear, please ask the study doctor or the study staff to explain any information that you do not fully understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Diabetes is a medical condition in which the sugar (glucose) level in the blood is high, increasing the risk to develop heart disease. ***Heart failure*** is a disease of the heart muscle in which the heart contractions are weakened, causing tiredness (fatigue) and difficulty breathing (dyspnea).

The purpose of this study it to measure the safety and the effects of two medications used to treat diabetes (Canagliflozin or Sitagliptin) in patients with heart failure. You are being asked to participate in this study because you are affected by both diabetes and heart failure and you may meet the requirements for study participation.

Canagliflozin (Invokana®) is a medication approved by the United States (US) Food and Drug Administration (FDA) in 2013 for the treatment of Type 2 Diabetes Mellitus (T2DM) in subjects in which blood sugar is not well controlled with diet, exercise and/or other anti-diabetic medications. Canagliflozin improves blood sugar by increasing the amount of sugar (glucose) in the urine. ***Sitagliptin (Januvia®)*** is also a medication approved by the US FDA in 2006 in patients in which diabetes is not well controlled with diet, exercise and/or other anti-diabetic medication. Sitagliptin improves blood sugar by increasing the level of a hormone (insulin) in your body leading to a reduction in blood sugar (glucose) levels.

Prior studies comparing these two medications have shown similar effects in improving blood sugar. This study is designed to measure the effects of Canagliflozin or Sitagliptin given for 12 weeks on heart function. The different way by which Canagliflozin and Sitagliptin lower blood sugar level may determine whether one of the two is better tolerated or more efficacious than the other in patients with heart failure.

During participation in this study you will take one pill daily of Canagliflozin (100 mg) or Sitagliptin (100 mg). Your assignment to treatment with one of the medications will be determined by randomization like the "flip of a coin". Approximately 44 patients will receive Canagliflozin and 44 will receive Sitagliptin. You will not know whether you are receiving one or the other medication: the medication will be prepared by the pharmacy in a capsule so that it will not be possible to determine which one is which.

During your initial and follow-up visits, you will undergo an exercise test on a treadmill, an ultrasound of the heart and the liver, a body scan to measure composition (amount of fat and muscle in your body) and fluid status (amount of water in your body). We will ask you questions about your diet. You will also receive a portable blood pressure device for 24 hours that you will return back to us the following day. You may be asked also to undergo cardiac magnetic resonance imaging to measure the thickness of your heart muscle. You will be in the study for approximately 12 weeks. During the course of the research, we will inform you (and, if you wish, also your doctor) of any significant new findings deriving from these tests (or new data derived by other studies published in the meantime) that might affect your willingness to continue participation.

PROCEDURES

If you decide to participate in this research study, you will be asked to sign this consent form after you have had all your questions answered. After you sign this consent form, the investigators will perform a thorough evaluation to determine your eligibility for the study. This evaluation will consist of an interview about your medical history, followed by a brief physical exam, a blood draw (2 tablespoons of blood), and, if indicated, a pregnancy test.

If you meet all the requirements to participate in this study, you will be asked to schedule 4 study visits at the Clinical Research Unit (North Hospital 8th floor) over approximately 12 weeks.

Visit 1

This visit constitutes your baseline assessment (before initiation of treatment). You will be asked to fast for at least 8 hours before the visit. The assessment will occur in the Clinical Research Unit (North Hospital, 8th floor), and it will last approximately 2 hours and 30 min. Upon arrival, we will measure your body weight, height, waist circumference and blood pressure. You will undergo a blood draw (2-3 tablespoons of blood) and urine collection.

You will then undergo an ultrasound of your heart (transthoracic echocardiogram) and of the liver (FibroScan®). To perform this ultrasound, you will lie down in a bed while a technician applies a small amount of gel to your chest and abdomen and uses a probe on your skin to take pictures of your heart. You will be asked to remain still and to hold your breath for approximately 10 seconds. These procedures will last approximately 30 to 60 minutes.

We will measure the amount of fluid (water) in your body using a procedure called bio-electrical impedance analysis (BIA). This procedure involves placing small adhesive patches on your skin that can measure electricity running through the body. You will not be able to sense the electricity being delivered or running through the body. This test will last approximately 10 min, and by examining how the current is distributed it allows us to determine your body's fluid content. Afterwards, the investigators will ask you some questions about your diet, particularly regarding what you ate during the 24 hours prior to the visit. You will be asked to complete three surveys to evaluate your heart failure symptoms and your physical activity. The Duke Activity Status Index (DASI) questionnaire contains 12 questions to which you will answer "yes" or "no". Each question asks you to describe your ability to perform different activities. The Minnesota Living with Heart Failure Questionnaire (MLHFQ) contains 21 questions that ask you to mark how often you experience symptoms of heart failure (i.e. swelling in your legs, shortness of breath). The International Physical Activity Questionnaire-short (IPAQ-short) is a 7-question questionnaire that asks you about amount and intensity of your daily physical activity. These procedures will last approximately 30 minutes.

Upon completion of the questionnaires, a physician-supervised maximal aerobic exercise test will be administered using a treadmill. Monitoring with non-invasive blood pressure, heart rate and 12-lead electrocardiogram (ECG) will be conducted. This procedure will last approximately 60 minutes. If you experience any chest discomfort or pain, abnormal blood pressure and heart rate response, or ECG signs of poor blood flow to the heart ("ischemia") that limit your ability to complete the exercise test, you will not be permitted to continue the study.

On the same day, or within a few days, you will undergo a low-intensity X-ray routinely used to measure the composition of the bones (dual-energy X-ray absorptiometry - DEXA). The DEXA can measure the content of fat and muscle in your body. You will be asked to lie flat on a table and a machine will take pictures of different areas of the body. This test will last 15 minutes.

We will give you a portable blood pressure measurement device for you to wear for 24 hours. After you wear it for 24 hours, you will be asked to return the device to the clinic.

After you complete all evaluations, you will be provided with study medication (90 capsules in a bottle) to take home for daily administration for 12 weeks.

If during the echocardiogram or based on prior medical history we find that your heart is enlarged ("left ventricular hypertrophy"), we will ask you to undergo a scan of the heart using magnetic waves to accurately measure thickness and function of the heart muscle and valves (cardiac magnetic resonance - CMR). You will be asked to lie flat on a table in a large metallic tube and a machine will take pictures of your body. Before completing the test, you will be asked several questions about your health to determine whether you can have a CMR scan done (i.e. individuals with a pacemaker cannot have a CMR because the waves would interfere with the pacemaker function). You will also have a small cannula inserted into a vein in your hand or arm through which a contrast agent, gadolinium, is injected to enhance the quality of the images. This test will be performed at the VCU Medical Center or at VCU Collaborative

Advanced Research Imaging (CARI) site, located at 203 E. Cary Street, Richmond, VA. The test will last about 45 minutes.

Visit 2 and Visit 3

After approximately 4 weeks (Visit 2) and 8 weeks (Visit 3) from when you start the study medication, you will be seen in the Clinical Research Unit (North Hospital, 8th Floor), or by your own doctor, for a shorter visit (30 minutes) for a brief history and medical examination, and a blood draw (1 to 2 tablespoons) to assess for kidney function. If the visit is performed in the Clinical Research Unit, the 'bio-electrical impedance' test will also be repeated.

Visit 4

After approximately 12 weeks, you will undergo a complete assessment, as described in Visit 1, that will last approximately 2 hours.

Upon completion of Visit 4, your active participation in the study will be over. Treatment with the study drug will be terminated. If you agree, the results of the study will be shared with your doctor. You and your doctor will discuss how to continue treatment for diabetes, which may include the use of one of the drugs used in the study or other drugs.

Study schedule

Procedure	Visit 1 (Baseline)	Visit 2 (4 weeks)	Visit 3 (8 weeks)	Visit 4 (12 weeks)
Screening	X			
Consent	X			
Clinical assessment	X	X	X	X
Blood draw	X	X	X	X
Urine analysis	X			X
Fluid status assessment (BIA)	X	X (only at VCU)	X (only at VCU)	X
Echocardiogram and FibroScan®	X			X
Dietary recall and surveys	X			X
Exercise Test	X			X
Questionnaires (DASI and MLHFQ)	X			X
24-hour blood pressure measurement	X			X
Body composition (DEXA)	X			X
Cardiac magnetic resonance (only for a subgroup of subjects)	X			X
Receive study medication	X			

RISKS AND DISCOMFORTS

All drugs can cause unwanted effects, called side effects. It is important that you read the risks and discomforts listed herein, and discuss with the study doctor or your own doctor if you have any questions.

Side effects that are more likely to occur with Canagliflozin (Invokana®) include:

- Dizziness or lightheadedness upon standing (approximately 1 in 20 people), particularly in subjects already treated with diuretics (fluid pill, i.e., Lasix/Furosemide), or older patients or patients with impaired kidney function;
- Hypoglycemia (approximately 4 in 100), particularly if associated with other anti-diabetic drugs such as sulfonylurea or insulin in which case it is more frequent (up to 5 in 10 people) and can be serious (up to 2 in 100 can be severe);
- Increased urination and thirst (approximately 1 in 20 people);
- Urinary tract infections (approximately 1 in 20 people);
- Allergic reaction including rash (approximately 1 in 20 people), generally self-limiting;
- Constipation (less than 1 in 25 people);
- Nausea (less than 1 in 25 people);
- Diabetic ketoacidosis (approximately 1 in 1000 people):
    - The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness;
    - Symptoms of diabetic ketoacidosis may include difficulty breathing, nausea, vomiting, excessive thirst, rapid weight loss, abdominal pain, confusion, fruity-smelling breath, a sweet or metallic taste in your mouth, a different odor to your urine or sweat, and unusual fatigue or sleepiness.
- Bone fractures (approximately 1 in 50 people):
- Amputation of the toes (and to a lesser extent the foot or leg) could occur in up to 1 in 150 people per year on canagliflozin.
    - This risk of amputation is greater in those with a prior history of amputation, disease of the circulation involving the legs or in those with nerve damage due to diabetes.
- Laboratory changes not associated with clinical adverse events in clinical trials:
    - Increase of approximately 5% in low-density lipoprotein cholesterol;
    - Increase in serum potassium, phosphate and/or hemoglobin of approximately 4%, 4% and 5% respectively;
    - Decrease of approximately 10% in serum urate.
- Vaginal yeast infections and vaginal itching (up to 2 in 10 women) or yeast infection at the head of the penis (up to 1 in 20 men), requiring circumcision in 0.3% in not circumcised.

In subjects not enrolled in clinical studies, but who have been prescribed Canagliflozin, the following side effects have also been reported. It is however unknown if these side effects are directly linked to the use of Canagliflozin since not reported in the completed clinical trials: serious allergic reactions, severe decrease in kidney function (mostly in dehydrated patients—see below), infections of the urinary tract that can spread to the kidneys or into the bloodstream. Symptoms of urinary tract infections may include high fever, increased heart rate and breathing, low blood pressure, low urine output and lower back pain. Subjects experiencing these symptoms should call their doctor promptly if experiencing these symptoms.

As noted above, cases of acute kidney injury, some requiring hospitalization and dialysis, have been reported in patients receiving canagliflozin, about half of the cases occurring within 1 month of starting the drug. Please seek medical attention immediately if you experience decreased urine or swelling of your legs or feet. Please talk with your study doctor if you are eating or drinking less due to illness or fasting, or are losing fluids due to vomiting, diarrhea, or excessive heat exposure. Your health care professional may determine it is appropriate to temporarily stop taking the study drug.

Side effects have been reported with Sitagliptin (Januvia®). The most likely side effects associated with the use of Sitagliptin include:

- Hypoglycemia, particularly if associated with other anti-diabetic drugs such as sulfonylurea or insulin (approximately 2 in 10 people) which can be serious (in less than 1 in 100 people);
- Upper respiratory infection (stuffy or runny nose and sore throat)(up to 3 in 50 people);
- Headache (approximately 3 in 50 people);
- Nausea, stomach upset and diarrhea (approximately 3 in 100 people).

In subjects not enrolled in clinical studies, but who have been prescribed Sitagliptin, the following side effects have been reported. It is however unknown if these side effects are directly linked to the use of Sitagliptin since not reported in the completed clinical trials: hypersensitivity reactions including anaphylaxis, rash, urticarial, cutaneous vasculitis, skin condition (i.e., Steven-Johnson syndrome), hepatic enzyme elevation, pancreatitis (acute inflammation of the pancreas), worsening renal function (including acute renal failure), constipation, vomiting.

Although animal studies do not suggest that either Canagliflozin or Sitagliptin are associated with birth defects, human studies have not been performed in this field. Women who are pregnant, lactating or intend to become pregnant will not be allowed to be in the study. Women who could possibly become pregnant must have a negative pregnancy test (urine test) prior to starting on the study medication and report immediately to the study personnel if they suspect they are pregnant during the study. If you are able to have children and you are heterosexually active, you must use birth control (contraception) during the study. Birth control methods that can be used while in this study include: avoiding sex, birth control pills, birth control injections or patch, intrauterine device, barrier method (for example, condoms or diaphragm) combined with spermicide (foam, cream, or gel), or your male partner is sterile (e.g. sperm tubes are cut or blocked). The type of birth control you use must be discussed with the study doctor before you begin the study. The study doctor must approve the method you use before you can enter the study. If you become pregnant during the study, you must tell the doctor immediately. You will have to stop taking the study medication. The doctor will advise you about your medical care and will ask you to allow him/her to collect information about your pregnancy and the health of your baby. For male subjects, if your partner becomes pregnant, you must tell the study doctor immediately.

Risks related to procedures:

- Blood draw: the discomfort may derive from minor bruising (occasional), bleeding (rare, less than 1 in 100), and infection (extremely rare, less than 1 in 1,000) at the puncture site. To minimize the potential discomforts, all blood samples will be taken by trained personnel.
- Urine collection: there are no known risks or discomforts related to the urine collection.
- Cardio pulmonary exercise test (CPET): with adequate medical supervision, there is extremely low risk of serious complications such as heart attack or stroke (less than 1 in 1,000). Abnormal cardiovascular response during exercise testing (i.e. markedly elevated blood pressure or heart rate) may occur (approximately 1 in 10). A physician will be present during the CPET. Minor arm or discomfort/pressure may occur during blood pressure measurement.
- Echocardiogram: there are no known risks related to the echocardiogram. Minor discomfort is associated with the applying the probe to the chest wall and the placement and removal of the electrodes on your skin.
- FibroScan®: there are no known direct risks from the FibroScan® medical device, which uses ultrasound waves. However, you may feel minor discomfort or soreness over the area where the ultrasound probe contacts the abdomen.
- Dual-energy X-ray Absorptiometry (DEXA): as a participant in this study, you will receive extra radiation exposure from the scans that are for research purposes only (not for your direct clinical benefit). The radiation dose from these procedures is minimal, less than 1% of the annual permissible occupational exposure level for radiation workers. These limits are defined as the dose of radiation that, in light of present knowledge, is not expected to cause appreciable bodily injury to a person at any time during his/her lifetime. The risk of this amount of occupational exposure to radiation is, thus, considered to be very small and less than that associated with normal everyday activities.
- Bioelectrical Impedance Analysis (BIA): there are no known risks or discomforts related to the BIA. If you have a defibrillator or a pacemaker, the activity of your heart will be monitored because BIA may interfere with defibrillator or pacemaker function. Minor discomfort is associated with the placement and removal of the electrodes on your skin.
- 24-hour blood pressure monitor: the blood pressure measurement may provide minor discomfort to your arm during cuff inflation and affect your sleep since it will automatically inflate every 60 minutes during the night.
- Cardiac magnetic resonance (CMR): there are no known risks related to the CMR, except for the use of gadolinium described below and a potential psychological risk of claustrophobia due to the tight space of the CMR machine. Please alert staff should this be a concern. If you have a pacemaker and/or a defibrillator and/or other conditions in which a metallic implant is present, you will not undergo CMR. The use of gadolinium contrast may cause mild headache, nausea, dizziness, and change in taste – these events are generally mild and self-resolving. Gadolinium can cause an allergic reaction in some patients – this is a rare but potentially dangerous event, the personnel administering the gadolinium will monitor you for side effects, and treat an allergy reaction if it were to occur. A condition known as nephrogenic systemic fibrosis has been related to the use of Gadolinium-enhanced MRI, this is a rare occurrence and has only been observed in individuals with severe kidney disease.

Your kidney function will be assessed prior to this testing, and you will be unable to participate if it is compromised.

- Dietary recall: there are no known risks or discomforts related to the 24-hour dietary recall.
- Questionnaires: there are no known risks or discomforts related to the questionnaires.

There is a social/psychological risk in this study of breaching confidentiality and having your diagnosis discovered, which may be stressful. The likelihood of this occurring is very low.

BENEFITS

There is no guarantee that you will receive any cardiovascular benefit from being in this study. Canagliflozin (Invokana®) and Sitagliptin (Januvia®) improve blood sugar in a similar manner. Due to the differences in the way the 2 drugs reduce blood glucose levels, Canagliflozin and Sitagliptin may be differently tolerated and may be associated with a difference in exercise capacity and heart function.

COSTS

You or your insurance will not be charged for the study visits or any study-related procedures.

PAYMENT FOR PARTICIPATION

To compensate for your time and travel related expenses (transportation, parking fees etc.), you will be paid as follows: $25 for the screening visit, $100 for Visit 1 and 4 each, and $25 for Visit 2 and 3 each, for a maximum amount of $275. You will receive a check at home within a few weeks of visit 4.

ALTERNATIVE TREATMENT

You do not have to participate in this study. You will still receive the standard medical treatments for heart failure and diabetes whether you participate or not. Your physician may decide to prescribe you Invokana® and/or Januvia® outside the study, since both drugs have been approved by the FDA for the treatment of diabetes.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES or CONFIDENTIALITY

Authority to Request Protected Health Information

The following people and/or groups may request my Protected Health Information:

- Virginia Commonwealth University
- Research Collaborators
- Sponsor, Investigators, and Research Staff
- U.S. Food and Drug Administration (FDA)
- The Western Institutional Review Board® (WIRB®)
- Others as required by law
- Janssen Scientific Affairs, LLC (funding company) and their representatives
- Institutional Review Boards
- Government/Health Agencies in US and in other countries
- Department of Health and Human Services (DHHS) agencies

Authority to Release Protected Health Information
The VCU Health System (VCUHS) may release the information identified in this authorization from my medical records and provide this information to:

- Health Care Providers at the VCUHS
- Virginia Commonwealth University
- Research Collaborators
- Sponsor, Investigators and Research Staff
- U.S. Food and Drug Administration (FDA)
- The Western Institutional Review Board® (WIRB®)
- Others as required by law
- Data Safety Monitoring Boards
- Janssen Scientific Affairs, LLC (funding company)
- Institutional Review Boards
- Government/Health Agencies in US and in other countries
- Department of Health and Human Services (DHHS) agencies

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

Type of Information that may be released: complete health record.

Right to Revoke Authorization and Re-disclosure
You may change your mind and revoke (take back) the right to use your protected health information at any time. If you revoke this authorization you may no longer be allowed to participate in the research study. To revoke this authorization, you must write to the Principal Investigator(s).

Expiration of This Authorization: this authorization will expire when the research study is closed, or there is no need to review, analyze and consider the data generated by the research project, whichever is later.

CONFIDENTIALITY
Potentially identifiable information about you will consist of data abstracted from the medical record. Data are being collected only for research purposes. Your data will be identified by ID numbers, (will not include your name) and will be stored separately from medical records in a locked research area. All personal identifying information will be kept in password-protected files. Access to research data will be limited to study personnel.

You should know that research data about you might be reviewed by Virginia Commonwealth University. Although results of this research may be presented at meetings or in publications, identifiable personal information pertaining to participants will not be disclosed. The information from this study will not be stored in your permanent medical record. However, the investigators can provide copies of your study information upon request.

COMPENSATION FOR INJURY

If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study.

To help avoid research-related injury or illness it is very important to follow all study directions.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide to not participate in this study. Your decision not to take part will involve no penalty or loss of benefits to which you are otherwise entitled. If you do participate, you may freely withdraw from the study at any time. Your decision to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled. You can decide to forgo any study procedures that make you uncomfortable or you wish not to complete. The study doctor may however stop your participation in this study at any time for reasons including *(but not limited to)* the study doctor thinks it is necessary for your health or safety, you have not followed study instructions, or administrative reasons require your withdrawal.

SOURCE OF FUNDING FOR THE STUDY AND DISCLOSURES

Janssen Pharmaceuticals is the manufacturer of Canagliflozin (Invokana®), one of the drugs studied in this trial. Dr. Abbate has served as a paid consultant on an Advisory Board for the development of Canagliflozin for heart disease. Please feel free to ask any questions you may have about this matter.

QUESTIONS

If you have any questions, complaints, or concerns about your participation in this research, or if you feel you have experienced a research-related injury, contact:

Antonio Abbate, MD, PhD
Virginia Commonwealth University
West Hospital 5th Floor – Room 525
Richmond, VA, 23298
Phone: (804) 828-0513
804-828-0951 (telepage/24-hours)
Fax: (804) 628-3984

Salvatore Carbone, MS
Virginia Commonwealth University
West Hospital 5th Floor – Room 520
Richmond, VA, 23298
Phone: (804) 628-3980
Fax: (804) 628-3984

The researchers named above are the best persons to call for questions about your participation in this study.

If you have general questions about your rights as a participant in this or any other research, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
P.O. Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number to ask general questions, to obtain information or offer input, and to express concerns or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else.

General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

CONSENT

I have been provided with an opportunity to carefully read this consent form composed of 10 pages. All of the questions that I wish to raise concerning this study have been answered.

By signing this consent form, I have not waived any of the legal rights or benefits to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form once I have agreed to participate.

_____

Participant Name, printed

_____ _____

Participant Signature Date

_____

Name of Person Conducting Informed Consent / Witness
(Printed)

_____ _____

Signature of Person Conducting Informed Consent / Witness Date

_____ _____

Principal Investigator Signature (if different from above) Date