Evaluation of the Cardiac and Metabolic Effects of Dapagliflozin in Heart Failure with preserved Ejection Fraction (CAMEO-DAPA):

A Phase II, Prospective, Double-Blind Study

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Regulatory Sponsor: **Barry A. Borlaug, MD**
Mayo Clinic
Department of Cardiovascular Medicine
200 First Street SW
Rochester, MN 55905
(507) 255-1051

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DAPA	Dapagliflozin
DEXA	Dual Energy X-ray Absorptiometry
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
NYHA	New York Heart Association
PCWP	Pulmonary Capillary Wedge Pressure
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SF-36	Short Form 36 Questionnaire

Study Summary

Title	Evaluation of the Cardiac and Metabolic Effects of Dapagliflozin in Heart Failure with preserved Ejection Fraction (CAMEO-DAPA): A Phase II, Prospective, Double-Blind Study
Running Title	CAMEO-DAPA
Protocol Number	20-005646
Phase	Phase II
Methodology	Randomized, double blind placebo control
Overall Study Duration	24 months
Subject Participation Duration	Approximately 7 months
Single or Multi-Site	Single
Objectives	To determine whether treatment with DAPA for 6 months will improve pulmonary capillary wedge pressure (PCWP) at rest and during exercise in HFpEF and improve cardiac metabolism.
Number of Subjects	Up to 41 Subjects fully completing trial, up to 46 accrual, to account for dropouts
Diagnosis and Main Inclusion Criteria	HFpEF subjects with obesity defined by clinical symptoms of HF: Dyspnea (NYHA II-IV without cardiac or ischemia explanation), EF ≥ 50%
Study Product, Dose, Route, Regimen	Dapagliflozin (DAPA) 10 mg once daily versus matching placebo
Duration of Administration	6 months
Reference therapy	Placebo
Statistical Methodology	The principal comparisons will be a comparison of pulmonary capillary wedge pressure incorporating values measured at rest and during exercise using mixed effects model analysis of covariance.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Over 70% of individuals above the age of 65 years with heart failure (HF) have preserved ejection fraction (HFpEF).[1] There is currently no proven treatment that improves symptoms or outcome in this population.[1-3] The vast majority (75%) of patients with HFpEF are obese.[4-6] Inflammation and metabolic stress secondary to excess body mass are strongly implicated in the pathophysiology of the obese phenotype of HFpEF, leading to alterations in cardiac function that cause abnormal hemodynamics, which then cause symptoms, morbidity and increased mortality.

Despite these signals from various studies, predominantly in animal models, the mechanisms by which SLGT2 inhibitors improve outcome in HF, or whether they improve clinical status in HFpEF, remain unclear. As such, characterization of the mechanisms by which dapagliflozin affects cardiac function and metabolism remains a critical unmet need. The most likely mechanisms involve improvements in hemodynamics that drive symptoms (through improvements in cardiac function and reduction in plasma volume) and improvements in myocardial metabolism, specifically alterations in the uptake and utilization of free fatty acids (FFA) vs other substrates.

The gold standard to assess each of these components is through invasive hemodynamic assessment, simultaneous echocardiography, and transcardiac blood sampling (arterial and coronary sinus), all performed at rest and during supine exercise (where symptoms develop in HFpEF). This study will test the effects of treatment with dapagliflozin for 6 months on cardiac hemodynamics, structure, function and metabolism using these methods, as compared placebo.

1.2 Investigational Agent

Dapagliflozin 10 mg tablet or matching placebo.

1.3 Clinical Data to Date

SGLT2 inhibitors such as dapagliflozin have been shown to reduce incident HF events.[7-9] SGLT2 inhibitors are known to reduce body weight, ventricular mass, enhance insulin sensitivity, reduce plasma volume expansion and blood pressure, and improve renal outcomes.[10-15] Each of these abnormalities has been shown to play a pivotal role in patients with the obese phenotype of HFpEF.[5, 6, 16]

People with obesity display increased free fatty acid (FFA) uptake, which is associated with reduced myocardial efficiency.[17] Treatment with DAPA may favorably alter myocardial substrate utilization by decreasing reliance on FFA and switch to alternative sources such as glucose oxidation or utilization of ketone bodies.[18, 19]

Dapagliflozin has been shown in a large placebo controlled trial (DAPA-HF) to improve the combined primary endpoint of HF hospitalization or cardiovascular mortality in patients with HF and reduced ejection fraction (HFrEF, defined by EF<40%).[20] Patients randomized to dapagliflozin had a statistically significant 26% reduction in the primary outcome, with a 30% reduction in HF hospitalization, 18% reduction in cardiovascular death, and a 17% reduction in all-cause mortality in patients receiving dapagliflozin. Importantly, the beneficial effects were similar in patients with and without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between patients randomized to dapagliflozin or placebo.[20]

More recently, a second pivotal trial has evaluated a related SGLT2 inhibitor, empagliflozin, in the EMPEROR-Reduced trial.[21] In this study, 3730 patients with HFrEF were treated with empagliflozin (10 mg once daily) or placebo. Consistent with the DAPA-HF trial, treatment with the SGLT2 inhibitor empagliflozin was associated with a 25% reduction in the primary outcome of cardiovascular death or hospitalization for worsening heart failure. Efficacy and safety were similar in patients with and without diabetes mellitus. Total hospitalizations were HF were reduced by 30%, and there was a significant reduction in the annual rate of decline in the estimated glomerular filtration rate.

These data have led to a new indication from the FDA to use dapagliflozin as a treatment for patients with HFrEF. While the data from DAPA-HF in HFrEF are supportive of a potential benefit in HFpEF, it is well-known that treatments that are effective in HFrEF are often not effective in HFpEF due to multiple fundamental pathophysiologic differences between the two HF phenotypes.[22] Furthermore, the potential mechanisms of effect on hemodynamic abnormalities and cardiac metabolism (in any type of HF) remain unclear, forming the basis for the present study.

1.4 Dose Rationale

This study will test the same 10 mg dose of dapagliflozin (once daily) that was shown to be safe and effective in the DAPA-HF trial.[20]

1.5 Risks and Benefits

Dapagliflozin has been well-tolerated in patients with HFrEF in both the DAPA-HF trial[20] and the EMPEROR-Reduced trials.[21] Risks reported across all studies include genital and urinary tract infections, and diabetic ketoacidosis. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between patients randomized to dapagliflozin or placebo.[20, 21] A recent meta-analysis combining results from both DAPA-HF and EMPEROR-Reduced (n=8474) has confirmed an excellent safety profile, with lower rate of serious adverse events among patients randomized to active therapy in both trials, as shown in the Table below from Zannad et al.[23]

The potential benefits from dapagliflozin include an improvement in symptoms of dyspnea and fatigue, increase in exercise capacity, improved quality of life, reduction in the risk of HF hospitalization, and reduction in the risk of death. In the meta-analysis combining the results from both DAPA-HF and EMPEROR-Reduced, there was an

estimated 13% reduction in all-cause death, 14% reduction in cardiovascular death, 26% relative reduction in the combined risk of cardiovascular death or first hospitalization for heart failure, and 25% decrease in the composite of recurrent hospitalizations for heart failure or cardiovascular death.[23] Benefits were consistent across all subgroups based on age, sex, diabetes, treatment with angiotensin-neprilysin antagonists, and at different values of baseline kidney function.

The table below presents the summary safety data for DAPA-HF and EMPEROR-Reduced, taken from Zannad et al. Lancet, 2020.[23]

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)	Placebo (n=2371)
Serious adverse events	772 (41·4%)	896 (48·1%)	846 (35·7%)	951(40·2%)
Any renal adverse event	175 (9·4%)	192 (10·3%)	141 (6·0%)	158 (6·7%)
Volume depletion	197 (10·6%)	184 (9·9%)	170 (7·2%)	153 (6·5%)
Ketoacidosis	0	0	3 (0·1%)	0
Severe hypoglycaemic events	6 (0·3%)	7 (0·4%)	4 (0·2%)	4 (0·2%)
Bone fractures	45 (2·4%)	42 (2·3%)	48 (2·0%)	47 (2·0%)
Lower limb amputation	13 (0·7%)	10 (0·5%)	13 (0·5%)	12 (0·5%)
Fournier's Gangrene	1 (0·1%)	0	0	1 (0·1%)

Given the strong evidence of both safety and efficacy in a related form of heart failure, along with the fact that dapagliflozin is FDA approved for both HFrEF and diabetes, the risk-benefit ratio very much favors benefits in the present study testing DAPA in patients with heart failure and preserved EF.

2 Study Objectives

Primary Objective

To determine whether treatment with DAPA for 6 months will improve pulmonary capillary wedge pressure (PCWP) during exercise in HFpEF.

Secondary Objectives

1. To determine whether treatment with DAPA for 6 months can improve myocardial metabolism and substrate utilization, shifting from high uptake of free fatty acids to favor glucose utilization.
2. To determine whether treatment with DAPA for 6 months will improve other hemodynamic markers of HF severity (at rest and with exercise) in HFpEF.
3. To determine whether treatment with DAPA for 6 months can improve ventricular function and functional reserve as assessed by tissue Doppler echocardiography and strain imaging.
4. To determine whether treatment with DAPA for 6 months can reduce plasma volume assessed by labelled albumin indicator dilution technique.

5. To determine whether treatment with DAPA for 6 months can improve exercise capacity and quality of life in HFpEF, and explore how these clinical changes relate to changes in hemodynamics, cardiac function, and cardiac metabolism.

3 Study Design

3.1 General Description

This is a mechanistic phase II placebo-controlled trial designed to determine whether treatment with dapagliflozin for 6 months will improve exercise hemodynamics, cardiac metabolism, and clinically relevant endpoints in patients with HFpEF.

Brief Synopsis of Methods:

1) Enroll subjects with HFpEF. Some patients will have previously been identified and some will have be referred to the catheterization lab for evaluation of dyspnea and suspected HFpEF. The latter patients will only qualify for randomization if they meet hemodynamic entry criteria for HFpEF (PCWP of ≥25 mmHg with exercise).
2) Safety lab sampling (complete blood count, creatinine, blood urea nitrogen, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, total, direct and indirect bilirubin) hs-CRP, HgA1c, NTproBNP will be performed. Values may be used up to a week prior to study if the same bloods have already been drawn.
3) In the preparation area, an IV cannula will be inserted in a forearm vein for initiation of isotope infusion ([U-13C] palmitate), allowing for attainment of steady-state prior to transfer to the catheterization laboratory (~60 min). Isotope infusions will be continued until blood sampling studies have been completed.
4) Assess hemodynamics at rest and during exercise using gold standard invasive techniques in patients with HFpEF. Venous, arterial and coronary sinus blood samples obtained at rest and during exercise. Focused echocardiography examination with measurement of LV and RV tissue Doppler echocardiography and cardiac volumes will be performed. This will conclude the invasive catheterization visit. The patient will be monitored per standard clinical protocols following right heart catheterization and discharged the same day.
5) At a separate visit following cardiac catheterization, but prior to receipt of study drug, participants will have a QOL assessment, dual energy X-ray absorptiometry (DEXA), and measurement of plasma volume using the labelled albumin indicator dilution technique. Study coordinator will review patient preferences regarding contact during the study including video teleconference (preferred) or phone call.
6) Patients will be randomized in a double-blind fashion to dapagliflozin 10 mg once daily or matching placebo. Study drug dispensed by research pharmacy.
7) Telephone visits will be conducted at 2 days, 1 week, 2 weeks, and then every 4 weeks thereafter, for a total of 24 weeks. One week after visit 4, there will be an additional telephone visit for safety after patient is no longer on study drug. All phone visits will have a window of +/- 3 days. Participants will be contacted by phone or through videoconference visits (based upon patient preference) to evaluate for AEs/SAEs, and encourage compliance with the study medication. Adverse events will be determined using a general approach, asking participants if there have been any changes to their overall health since the prior visit, including any unplanned hospital

or clinic visits. At 2 weeks, as part of standard of care, patients will undergo laboratory draw from complete blood count, electrolytes and renal function at their local lab, with results reviewed by the study teamIf needed, a physician on the trial can put in a referral order for the lab work.

8) At the conclusion the 24 week treatment period, participants will return to complete the same invasive hemodynamic assessments and noninvasive assessments as described in steps (1) through (5) above (2 visits). Patient must remain on study drug through Visit 4, and may be on drug up to 7 days after the 24 week mark.
9) A follow up telephone/videoconference visit will be scheduled 1 week after completion of the trial to evaluate for AEs/SAEs following completion. This will have a window of +/- 3 days.

3.2 Number of Subjects

Up to 60 subjects will sign consent and be screened and an anticipated 46 subjects will be randomized and will complete the first part of the study assessments. It is anticipated that 41 subjects will be needed to be randomized to account for drop outs, in order to have 41 subjects complete all study assessments.

3.3 Duration of Participation

Subjects will participate in this study for up to 28 weeks.

3.4 Primary Study Endpoints

The primary endpoint will be the PCWP incorporating values at rest, with feet elevated, and at 20 Watts exercise after treatment with study drug for 6 months relative to the respective PCWP values at each stage in the initial assessment prior to study drug. This will be analyzed using a mixed model with repeated measures (MMRM).

3.5 Secondary Study Endpoints

Secondary exploratory endpoints will include:

1. Trans-cardiac uptake of free fatty acids (FFA), glucose, and ketone bodies uptake relative to O_2, as determined using arterial and coronary sinus blood sampling, at rest and with exercise
2. Changes in resting PCWP after study drug as well as rest and exercise changes in right atrial pressure and pulmonary artery pressures, rest and exercise cardiac output, and other derived hemodynamic indices.
3. Rest and exercise tissue Doppler diastolic (e') and systolic function (s'), LV global longitudinal strain at rest and with exercise.
4. Peak oxygen consumption (VO_2) during exercise, along with related cardiopulmonary indices.
5. Plasma volume and blood volume and quality of life (QOL) using SF-36.
6. Body composition including fat mass and fat free mass by DEXA scan

3.6 Primary Safety Endpoints

Safety endpoints of special interest will include symptoms suggestive of volume depletion or genitourinary infections, and laboratory abnormalities including renal function. These adverse events were not more common that placebo in DAPA-HF and will be therefore

ascertained remotely via telephone/video-teleconference for patient convenience and reduce travel burden.

3.7 Identification of Source Data

Study outcome data will be captured on electronic or paper case report forms and entered into REDCap database for subsequent analysis.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

Subjects are eligible to be randomized in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Signed informed consent prior to any study specific procedures
2. Male or female subject
3. Age ≥ 18
4. Symptoms of dyspnea (NYHA II-III) with no non-cardiac or ischemia explanation
5. EF ≥50%
6. Elevated pulmonary capillary wedge pressure (PCWP) during exercise (≥25 mmHg) ascertained at Visit 1. Patients that have consented to study procedures but do not meet this invasive criterion will be considered as screen failures and will not be randomized.

4.2 Exclusion Criteria

1. Type I diabetes
2. Type II diabetes with poor control (HgbA1c≥10%)
3. Recent hospitalization (<30 days) or revascularization (<90 days)
4. Primary cardiomyopathy (such as amyloid)
5. Constrictive pericarditis
6. Dyspnea due to primary lung disease or myocardial ischemia in the opinion of the investigator
7. Severe anemia (hemoglobin <9 gm/dl)
8. Significant left-sided valvular heart disease (>moderate stenosis, >moderate regurgitation)
9. Severe kidney disease (estimated GFR<30) or liver disease
10. Women of child bearing potential not willing to use a medically accepted method of contraception OR who are currently pregnant (confirmed with positive pregnancy test) or breast feeding.
11. History of serious hypersensitivity reaction to dapagliflozin
12. Subjects on dialysis
13. Subjects with severe hepatic impairment (Child-Pugh class C)
14. Currently taking Empagliflozin or Canagliflozin

4.3 Subject Recruitment, Enrollment and Screening

Eligible patients will be identified from screening of the patients listed for exercise right heart catheterization as well as patients with known HFpEF at the Mayo Clinic in Rochester, Minnesota.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Development of any condition that requires study withdrawal related to safety, disease progression, subject decision or failure to adhere to protocol requirements could qualify as reason to withdraw from the study.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects withdrawing from the study will be contacted 2 weeks following study drug administration to collect any adverse events. Participants that withdraw may be replaced to allow for achievement of target enrollment.

5 Study Drug

5.1 Description

Dapagliflozin is a highly potent, selective, and reversible inhibitor of SGLT2 that improves glycemic control in patients with diabetes mellitus and provides cardio-renal benefits in patients with T2DM and without diabetes. Dapagliflozin is orally available and requires once-daily dosing.

Dapagliflozin is currently approved in 100 countries for the treatment of T2DM as an adjunct to diet and exercise and is also indicated for the treatment of HFrEF.

Dapagliflozin film-coated tablets used in clinical studies are available in strengths of 2.5, 5, and 10 mg. The tablets contain dapagliflozin propanediol (BMS-512148) drug substance, microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, magnesium stearate, and coating material (Opadry® II). The tablets are supplied in HDPE bottles. The chemical composition is C21H25ClO6•C3H8O2•H2O, Formula weight 502.98, Molecular weight 408.87 (dapagliflozin), Appearance is white to off-white powder which may contain lumps, pH 6.9 (1.5 mg/mL), pKa: Non-ionizable compound.

Look-alike placebo tablets are supplied in the same container/closure system. The placebo tablets contain lactose monohydrate, microcrystalline cellulose, magnesium stearate, and coating material (Opadry® II).

5.2 Treatment Regimen

Participants will receive dapagliflozin 10 mg by mouth once daily or matching placebo for 24 weeks.

5.3 Method for Assigning Subjects to Treatment Groups

Patients will be randomized 1:1 in a blinded **fashion** to dapagliflozin or placebo with blinding and randomization performed by the Mayo Clinic Research Pharmacy.

5.4 Preparation and Administration of Study Drug

The IMP will be provided in bulk from AstraZeneca, to be labeled by the sponsor with a study specific label. Separate instructions for preparation and handling of the IMP will be provided by AstraZeneca in a Handling instruction.

5.5 Subject Compliance Monitoring

Compliance will be monitored and encouraged through frequent telephone calls/videoconference visits throughout the course of the study.

5.6 Prior and Concomitant Therapy

Participants' chronic medications will not be changed for the purposes of this study. They will continue taking their home medications as prescribed, including on procedure dates unless contraindicated as clinical standards. Data for baseline medication usage will be obtained.

5.7 Packaging

The oral dapagliflozin tablets (10 mg) or matching placebo will be provided in bulk by AstraZeneca, and then shipped to the Research pharmacy at the Mayo Clinic. Appearance of active drug and placebo will be identical.

5.8 Masking/Blinding of Study

Only research pharmacy staff will be aware of randomization scheme and all study personnel and subjects will remain blinded to the identity of study drug. Placebo and dapagliflozin tablets have an identical appearance assuring maintenance of the blind.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The oral dapagliflozin tablets (10 mg) or matching placebo will be provided in bulk by AstraZeneca, and then shipped to the Research pharmacy at the Mayo Clinic. Appearance of active drug and placebo will be identical. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment (active drug or placebo) will be documented in the study files. The sponsor-investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

5.9.2 Storage

The study drug will be securely stored as recommended according to the instructions on the label.

5.9.3 Dispensing of Study Drug

Study drug (12 week supply plus 10 days additional for unavoidable events) will be provided by research pharmacy following randomization. A second 12-week supply of study drug will be may be mailed to participants prior to the 12 week point in the trial schedule.

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

Participants are instructed to return all used, partly used and unused trial product at the final on-site study visit. Returned trial product(s) (used, partly used or unused including empty packaging material) must be stored separately from the non-allocated trial

product(s) until drug accountability has been reconciled. The investigators will keep track of all received, used, partly used and unused trial products.

6 Study Procedures

6.1 Visit 1

At Visit 1, subjects will provide written informed consent. Medications will be documented and history and physical exam performed. Routine blood tests including complete blood count, creatinine, blood urea nitrogen, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, total, direct and indirect bilirubin, hsCRP, NTproBNP, and HgbA1c will be performed up to 7 days before catheterization, if the same labs are drawn for other clinical appointments, study may use those values to save the patient an extra blood draw in addition to pregnancy test for women of child bearing potential.

In the preparation area, an IV cannula will be inserted in a forearm vein for initiation of isotope infusion ([U-^{13}C] palmitate) to quantify free fatty acid (FFA) uptake during the procedure, allowing for attainment of steady-state prior to transfer to the catheterization laboratory (~60 min). Isotope infusions will be continued until blood sampling studies have been completed.

In the laboratory, right heart catheterization with simultaneous limited echocardiography and expired gas analysis will then be performed at rest and during supine cycle ergometer exercise as per standard practice. Pressures are measured in the right atrium, right ventricle, pulmonary artery, pulmonary artery wedge position, and radial artery are measured at end expiration at rest and throughout each stage of exercise. Cardiac output is measured using the direct Fick method.

After resting hemodynamic assessments have been performed, a 6 Fr MPA catheter will be advanced from the right internal jugular vein to the coronary sinus (CS) under fluoroscopic guidance, with CS location confirmed by oximetry (O_2 saturation<45%). Blood samples from the radial artery and CS will be drawn in triplicate (3 ml each) and averaged to measure blood gases (trans-myocardial O_2 uptake and CO_2 release based upon the difference between artery and CS tensions) along with glucose, lactate, triglyceride, pyruvate, ketone, and FFA uptake (total FFA and [U-^{13}C]palmitate – enrichment in arterial and CS blood)). Additional mandatory research blood samples will be drawn frozen and stored for future discovery analysis. Samples will come from the CS, vein and artery once at the beginning of the procedure for future research. Samples will be transferred in iced tubes, centrifuged at 4˚C and stored at -80˚C for analysis.

Following resting metabolic assessments, participants will exercise at 20W workload on a supine ergometer for 3 minutes with the CS catheter in place, after which time arterial and CS sampling will be repeated during exercise in the same manner as at rest. The MPA catheter is then removed from the CS and exercise hemodynamic measurements are obtained. After obtaining exercise hemodynamic data at the 20W workload, workload is

increased in 20 W stages (3 minutes each) to volitional exhaustion. Hemodynamics and arterial and mixed venous blood samples are obtained at each stage.

Following exercise, catheters are removed and the patient is observed in the recovery area as per standard clinical practice prior to discharge.

6.2 Visit 2

At a second visit, typically the following day from the invasive catheterization can occur the day before visit 1 to allow flexibility, but no later than one week later, the patient will undergo plasma volume and blood volume assessment using the radiolabeled iodinated albumin (^{131}I, 5–25 μCu) indicator dilution technique (BVA-100 Blood Volume Analyzer, Daxor Corp, NY) as is used clinically at Mayo Clinic and as we have described.[16] Patients will also undergo a DEXA scan in the Mayo CRTU.

At this visit QOL will be assessed using the SF-36 Questionnaire. Participants will receive the first 12 week supply of study drug as allocated in the randomization, and review study procedures and preferences for remote visits throughout the study period.

6.3 Remote Telephone/Video Visits

Multiple visits will occur through videoconference (preferred) or telephone to assess for adverse events and ensure compliance with medication adherence. These visits will occur at the following timepoints: 2 day post procedure and 1, 2, 6, 10, 14, 18, & 22 weeks post procedure.

A final remote telephone/video visit will occur 1 week following the final on-site study visit to assess if there is any clinical change following discontinuation of study treatment.

6.4 Visits 3 & 4

These visits will be identical to visits 1 and 2, with the exception that study drug will be returned at the final on-site study visit.

Test Schedule

Study Activity	Visit 1		Visit 2	Visit 3	Visit 4
	Screen	Procedure	1-7 days following Visit 1 or 1 day prior to Visit 1	Week 24 (+/- 2 weeks)	1-7 days following Visit 3, or 1 day prior to Visit 3
Informed consent[1]	X		X		
History	X				
Concurrent meds	X		X	X	X
Physical exam (Ht, Wt, BSA, VS)	X			X	
Adverse event evaluation		X	X	X	X
NYHA Classification	X			X	
Blood Draw	X[2]	X[3]		X[1]	
Serum pregnancy[4]	X		X	X	
RHC		X		X	
Exercise study with hemodynamics		X		X	
Blood gasses		X		X	
Limited Echo		X		X	
Blood volume test			X		X
SF-36 Questionnaire			X		X
DEXA			X		X

[1] Consent can occur on Visit 1 or Visit 2 and must occur before any research activities take place.
[2] Pre-procedure: CBC, creatinine, BUN, sodium, potassium, aspartate aminotransferase, alanine aminotransferase, total, direct and indirect bilirubin, hsCRP, NTproBNP, and HgbA1c as part of clinical care
[3] Research blood will be drawn, processed, stored and tested in Dr. Michael Jensen's lab.
[4] For women of childbearing potential, required to be done once before any research assessments, either Visit 1 or Visit 2.

DAPA/Placebo		X[5]	X[5]	X[6]	X[6]

[5] 12 week supply dispensed once Visit 1 and Visit 2 are complete and 12 week supply mailed to patient at 12 weeks after remote visit
[6] Study drug returned at either Visit 3 or 4, whichever is later

7 Statistical Plan

7.1 Introduction to the Statistical Design

This study will use a 1:1 randomization to active therapy or control. The control group is scientifically necessary because it is expected that there will be longitudinal changes in cardiac function and hemodynamics in the absence of intervention that need to be accounted for in the analysis. The primary endpoint is left ventricular filling pressure, specifically pulmonary capillary wedge pressure (PCWP) measured invasively in the cardiac catheterization lab. Within each endpoint assessment period (described in section 6), a baseline (resting) and exercise assessment of PCWP will be gathered. The analysis plan described below will detail how the longitudinal measurements will be used to objectively test for differences both within group over time and between groups over time.

7.2 Randomization and Blinding

Scientific rigor is enhanced by randomization and blinding. Mayo Research Pharmacy will be provided a block randomization sequence that will be used by pharmacy to randomize enrolled subjects 1:1. Medical staff and patients will be both blinded about the randomization to achieve the most unbiased results.

7.3 Data Management Plan

The data will be secured in a central registry using REDCap. The principle investigator will be responsible for proper data quality assurance (data matching, source verification, and deidentification). Data will be stored on password protected computers with access only allowed to the investigators. The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigator will retain the specified records and reports during the study and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

7.4 Outcomes

The complete list of primary and secondary outcome measures is provided in the Outcomes section of the application (section 3.4-3.5). The primary outcome measure for this mechanistic trial is the PCWP assessed at baseline and 6 months after treatment under rest and exercise within the same catheterization session.

7.5 Sample Size Estimation

Based on preliminary data from our previous studies (Borlaug et al 2015, 2016), we know the PCWP is positively correlated within individuals between rest and exercise. Furthermore, the standard deviation of PCWP has been consistently ~5 mmHg, with some proportionality to the mean (i.e., more variability in those with pulmonary hypertension). To initially frame the sample size, we first focus on the exercise PCWP. We expect little, if

any, improvement in PCWP in the control group (some improvement possible due to the Hawthorn effect). We assume the average exercise PCWP in obese HFpEF patients is 30 mmHg and expect a 20% (6 mmHg) reduction in exercise PCWP in patients treated with DAPA compared with patients with placebo. The test-retest variability in exercise PCWP is <5 mmHg.

Based on two sample t test, 36 patients (18 receiving DAPA and 18 placebo) would provide 93% power to detect a difference of 6mmHG or greater in PCWP during exercise workloads between the DAPA and placebo groups, with a common standard deviation of 5 mmHg, at 0.05 significance level. By including resting values of PCWP in the mixed model with repeated measures, this is expected to increase the power further.

7.6 Primary Analysis

The primary analysis will be conducted using a mixed model using all available data. There will be main effects and interactions used to classify the PCWP as of randomized treatment DAPA/control, exercise yes/no, and baseline yes/no. A random subject effect will be utilized to block data on individual participant. The model configured this way provided the means to conduct a likelihood ratio test for the importance of DAPA on altering the PCWP profiles as the test for the primary hypothesis. Statistical contrasts will be utilized to compare PCWP under exercise at the end of the treatment period between groups and the differences in the change in PCWP over the study period between groups. These two hypotheses are a priori specified and will not be adjusted for multiple comparisons as they are intrinsically linked to the primary likelihood ratio test. This statistical model does not per se adjust for measured covariates as fixed effects in the model. The model, however, does include the random effect that effectively "adjusts for baseline" using a random variance term. However, it is acknowledged while the design is randomized, the sample size is relatively small to rely on the large sample balancing properties of randomization to account for all confounding in the study. To this end, we will compute standardized differences for all putative confounding variables captured at baseline prior to randomization. Absolute values for the standardized mean differences (SMD) <10% will be considered support for "balance" between the groups. If there are plausible confounding variables with SMD >10%, sensitivity analyses will be conducted using standard covariate adjustment methods including propensity score analysis. The propensity score analysis is to help mitigate the number of estimated parameters in the mixed model to help ensure convergence of the estimation process.

For the more general patient reported outcomes and other clinical assessment that have >2 replications, we will use a more generalized modeling framework that accounts for the actual time from baseline in the repeated measures model. Time varying covariates (e.g., marking the period of bariatric surgery) will also be considered to provide a model framework for the data over time. As with the primary analysis, the treatment group by time interaction terms will serve as the main statistical tests of the treatment effect. As with the primary analysis, additional adjustment for imbalance that was not controlled via randomization will be implemented.

Missing data occur. We will conduct sensitivity analyses using modern machine learning based imputation approaches including chained equations and random forest imputation. Differences in estimates between the imputed and the observed data will be examined through pattern mixture models. Lack of consistency of results may indicate an internal bias, so therefore we will disclose our findings by reporting data analysis under the various data imputation strategies.

Reproducible research principles will be integrated throughout the statistical analysis process. The two primary statistical languages of SAS and R will be utilized. In both cases, version controlled datasets will be utilized for any formal statistical reports. Programming code will be written such that all derivations and assumptions are documented within the source code and accompanying materials (i.e., no human manipulation of raw data values once entered into the master REDCap database). R markdown reports are the preferred study report formats as they allow for each communication of interpretation, raw numeric results and figures/tables.

7.7 Moderators of treatment effect

It is plausible that increased obesity may result is differential responses to the DAPA treatment. We will test this using splined fits of BMI. In addition, age group will be examined a priori. The type III estimates of the treatment effect will be compared to the unadjusted analysis to assess the robustness of the randomization process. Graphical displays such as the customary forest plot will be used to present the means and 95% confidence intervals for the estimated responses in these subgroups. Likewise, additional subgroups based on baseline demographic and medical history will be plotted for completeness.

7.8 Analysis Sets

The primary efficacy and safety analyses will be conducted according to "Intention-to-Treat" (ITT) principles; that is, each subject will be analyzed according to the randomized sequence using all available data collected.

8 Safety and Adverse Events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. Common adverse events of DAPA include genital and urinary tract infections, and diabetic ketoacidosis, and pollakiuria/polyuria.

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly
- an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if there is a clinically significant change compared to the baseline values. This may include measures of renal function such as creatinine or electrolyte levels. The clinical significance of any change will be determined by the principal investigator.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

8.2 Recording of Adverse Events

Adverse Events will be collected from the time of enrollment, throughout the treatment period and including the follow-up phone call/remote visit 1 week after Visit 4). SAEs will be recorded from the time of signing of informed consent form. If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the serious adverse event. At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been

ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event (SAE) Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required. Additionally, AstraZeneca will be informed of the SAE. All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product.

SAEs related to the Investigational Product (IP) must be provided to AstraZeneca in an ongoing basis as individual case reports.

SAEs unrelated to the IP must be provided to AstraZeneca as a quarterly line listing.

At the end of the study a final unblinded summary line listing of all SAEs notified to the regulatory authority and/or AstraZeneca during the study, must be provided to the Company to enable reconciliation of safety information held by Company for its product(s).

Send SAE reports (individual case reports and line listings) and accompanying cover page by way of fax to AstraZeneca's designated fax line: +1 302 886 4114 or Email: AEmailboxclinicaltrialTCS@astrazeneca.com

SAEs that do not require expedited reporting to the Regulatory Authority/IRB still need to be reported to AstraZeneca as a quarterly listing.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to Company at the same time these events are notified to the Regulatory Authority.

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

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Information collected on the adverse event worksheet (*and entered in the research database)*:

- Subject's name:
- Medical record number:

- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

Relationship Index Example

The relationship of an AE to the Investigational Drug is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the CRF and is graded as follows:

1. Not related: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is c1early related to other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.
2. Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.
3. Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.
4. Probable: a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfi1 this definition.
5. Definite: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the

suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

Severity Index Example
The maximum intensity of an AE during a day should be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.
2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

8.4 Pregnancy

All pregnancies must be reported to AstraZeneca. The Pregnancy and breast-feeding exclusion criterion should be used in combination with the discontinuation criterion for pregnancy If a patient becomes pregnant during the course of the study, investigational product should be discontinued immediately and an AZ representative notified. Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented, even if the patient was discontinued from the study.

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca's designated fax line: +1 302 886 4114 or email: AEmailboxclinicaltrialTCS@astrazeneca.com

8.5 Unmasking/Unblinding Procedures

The investigators will be given access to the treatment code for their Participants for emergency un-blinding. Any suspected study drug-related events should be treated as though the Participant received active therapy.

Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of un-blinding.

8.6 Stopping Rules

The study may be terminated prematurely if:

- The PI (sponsor) and AstraZeneca assess that the number and/or severity of AEs justify discontinuation of the study. For instance if there were a case of fatal SAE or 2 cases of other SAEs that were considered related by the Investigator and AstraZeneca.

- AstraZeneca considers the applied doses of the study drug to be no longer relevant.
- The PI (sponsor) decides to discontinue the study.
- Data not known before become available and raise concern about the safety of study drug so that continuation would pose potential risks to the subjects.
- Premature termination of the study must be mutually agreed upon by the PI (sponsor) and AstraZeneca and must be documented. However, study results will be reported according to the requirements outlined in this clinical study protocol as far as applicable.

8.7 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period. Data will be stored on password protected computers with access only allowed to the investigators.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. REDCap is the research data base that will be used to create the CRF's and securely store the data.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717 whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the

study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study is financed through AstraZeneca. Study drug dapagliflozin and placebo will be provided by AstraZeneca.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

12.3 Subject Stipends or Payments

Participants will receive payment for study participation of up to $400 in total, $100 after completion of visit 1, $100 after completion of visit 2, $100 after completion of visit 3 and a final payment of $100 after completion of visit 4.

13 Publication Plan

The primary responsibility for publication of the results lies with the principal investigator. The trial will be registered on ClinicalTrials.gov: *https://register.clinicaltrials.gov/*.

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