The EMMED-HF Study

Evaluating Metabolic Mechanisms of Ertugliflozin in Diabetes & Heart Failure

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University Hospitals Cleveland Medical Center

Clinical Research Protocol for The EMMED-HF Study

Evaluating Metabolic Mechanisms of Ertugliflozin in Diabetes & Heart Failure

IRB Protocol # 2019-00-16

Harrington Heart & Vascular Institute University Hospitals Cleveland Medical Center

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Supported by:

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University Hospitals Cleveland Medical Center

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PARTICIPATING STUDY SITE

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1. STUDY OBJECTIVES

Primary Objective

This clinical trial will determine if subjects with heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes mellitus (DM2) receiving sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy (ertugliflozin) alters cardiac metabolism compared to placebo in a single blinded (to subject), randomized, parallel group, active controlled, single center experimental design.

Specific Aims

Aim 1: Determine if 12 weeks of SGLTi therapy improves peak exercise oxygen uptake compared to placebo. We will perform cardiac MRI exercise testing (CPETExMR) [N=52 (26 intervention / 26 control)] pre- & post 12 weeks of therapy to measure cardiopulmonary fitness by metabolic cart gas exchange and left ventricular myocardial mass. The primary endpoint of the study will be peak oxygen uptake (VO2 peak, ml/kg/min) as a measure of cardiopulmonary fitness with change in LV mass (gm/m2) as a pre-specified secondary endpoint. The impact of SGLT2i on VO2 kinetics in HFpEF remains unreported.

Aim 2: Evaluate the short term (12 weeks effect of SGLTi on metabolic flexibility in HFpEF compared to baseline function and control group. We will measure glucose and lipid metabolism response to SGLT2 inhibition. Serum samples of glucose and ketone bodies (β-hydroxybutyrate) will be assessed pre- and post-12 weeks of therapy. Fasting serum ketone bodies will be a pre-specified endpoint. Serial serum samples will allow us to generate metabolomics profiles before and after treatment. This experimental design will provide insight into ketone body production, peripheral glucose flux, and circulating lipoparticles in response to SGLTi therapy.

2. BACKGROUND AND RATIONALE

Background/ Rationale/ Significance

Heart failure (HF) is an epidemic in patients with type 2 diabetes mellitus (DM2) with prevalence between 10-23%. This association extends to both HF with reduced ejection fraction and with preserved ejection fraction (HFpEF). Of critical importance, there are no current FDA indicated therapies for HFpEF patients. The etiology of HFpEF is heterogenous with phenotypes expressing both central cardiopulmonary and peripheral exrtramyocardial functional limitations. Multiple pathways of metabolic derangement in DM2 individuals have been proposed as mediators of diastolic dysfunction leading to clinical heart failure including: reactive oxygen species generation, advanced glycosylation end product deposition, enhanced collagen cross linking, and ectopic myocellular lipid accumulation. Several comorbidities contribute to the HFpEF phenotype including: hypertension, left ventricular hypertrophy, coronary artery disease, atrial arrhythmias, obstructive sleep apnea, dyslipidemia, and anemia. These metabolic derangements lead to impaired myocardial substrate utilization and mitochondrial dysfunction. Additionally, individuals with HFpEF and DM2 have peripheral organ (liver, adipose, skeletal

muscle) insulin resistance that impairs total body energy homeostasis which may contribute to extracardiac manifestations of clinical heart failure.

The results of recent sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy clinical trials demonstrate clinically significant reductions in cardiovascular endpoints (myocardial infarction, cardiac death, heart failure hospitalization). SGLT2 inhibition appears to exert cardiovascular protection through pleiotrophic effects involving both the myocardium and peripheral organs but the primary pathway of risk reduction of heart failure incidents has not been elucidated. SGLT2 inhibitors induce a loss of 50-100 grams of glucose through urinary excretion daily. There is a compensatory increase in ketone body production in the liver after initiation of SGLT inhibition. Ketone bodies are the most energy efficient myocardial fuel source and reduce myocardial oxidative stress when consumed as the primary energy substrate. Inducing a shift to ketone body metabolism to improves cardiac diastolic performance suggests a unifying paradigm of direct myocardial effect and peripheral metabolic flexibility through which SGLT2 inhibition mediates myocardial protection in HFpEF. We have been funded by the Merck **Sharp & Dohme Corp. Research Foundation** via an investigator-initiated study (IIS) to determine if the SGLT2 inhibitor, ertugliflozin, alters cardiac metabolism compared to placebo.

3. STUDY DESIGN

The EMMED-HF trial will be a single blinded (to patient), randomized, parallel group, active controlled, single center experimental design. 52 subjects with HFpEF and DM2 will comorbidities will be recruited to participate (N = 26 ertugliflozin group, N = 26 placebo group) with a 12 week study intervention period.

Enrollment/Randomization procedure

Subjects will be screened by qualified practitioners for eligibility to participate in the EMMED-HF clinical study. Once the subject has been determined to be eligible, an enrollment visit will be scheduled. Those subjects that meet the inclusion criteria and do not possess any exclusion criteria will be deemed eligible for enrollment by key study personnel and then undergo randomization to treatment arm. Randomization into treatment group will occur at baseline at a 1:1 ratio.

Primary endpoint

The primary endpoint is to assess the degree of change in peak exercise oxygen uptake (peak VO2, ml/kg/min) as measured by metabolic gas exchange during a MRIcardiopulmonary exercise test (CPET-ExMR) protocol.

Secondary endpoints

Change in LV mass index (gm/m2) measured by MRI imaging will be a pre-specified secondary endpoint. An additional pre-specified secondary endpoint will be fasting serum β-hydroxybutyrate (ketone body).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

We will be recruiting study participants at University Hospitals Cleveland Medical Center through cardiology clinics (with particular emphasis on heart failure clinics), endocrinology clinics, and the specialized dyspnea clinic run by Dr. Trevor Jenkins.

Subjects with a diagnosis of Type 2 Diabetes with heart failure who met the inclusion and exclusion criteria will be eligible for participation. Labs drawn within 3 months of the screening visit may be used to determine eligibility.

4.1 Inclusion Criteria:
To be eligible for entry into this study, candidates must meet the following eligibility criteria at the time of enrollment:

1. Age > 18 years old but < 75 years old
2. No HF hospitalization within 6 months
3. Overweight or Obesity defined as BMI > 25 but < 42
4. History of insulin resistance or T2DM or recent HgbA1c (> 5.8% and < 10.5%) and on oral diabetes agents other than SGLT2i
5. EF calculated based on a recent echo/cath/nuclear study at screening (preenrollment) > 50%
6. Stable HFpEF (HF with preserved ejection fraction) medications use of 3-6 months with no plans to changes or add medications for at least 12 weeks (course of the study)

Every effort will be made to ensure that the study population reflects the race/ethnic composition of the target population (subjects with diabetes mellitus type 2 & heart failure with preserved ejection fraction). All patients screened who fulfill inclusion criteria as listed above will be invited, without bias, to participate in the study.

4.2 Exclusion Criteria

Candidates will be excluded from study entry if any of the following criteria exist at the time of enrollment.

1. Acute HFpEF hospitalization within 6 months of enrollment.
2. CKD stage 4 or 5 (eGFR < 30 ml/min by CKD-EPI equation).
3. Other known causes of HF including poorly controlled hypertension (SBP > 160 mm Hg) or ischemic cardiomyopathy (etc).
4. Anemia (Hgb < 11.0 mg/dL for women and < 12.0 mg/dL for men) or severe thrombocytopenia (platelets < 50,000 mm3)
5. Anticipated changing of HF medication during anticipated study period.
6. HFREF (LV EF < 50%).
7. Acute coronary syndrome, transient ischemic attack, CVA or critical limb ischemia during the last 6 months or coronary/peripheral revascularization within the last 3 months. Severe life threatening illness or live expectancy < 6 months.
8. Contraindications to MRI (metallic implants, severe claustrophobia) or treadmill exercise (limb amputation, severe osteoarthritis or equivalent functional mechanical limitation).
9. Pregnant or nursing mothers

4.3 Study Recruitment Procedures
We will identify eligible participants through screening of heart failure clinics, endocrinology clinics, and the Dyspnea Clinic run by Dr. Jenkins.

Modality	Study Variable	Measure	Time Point of Measurements				
			Screening	Baseline: Prior to intervention	Follow up Week 4	Follow up Week 8	12 weeks: end of SGLT2i or placebo
			Visit #1	Visit #2	Phone call	Phone call	Visit #3
Personal Characteristics	Demographics Characteristics	Demographic Survey	X				
	Medical History	Chart Review History & Physical	X		X	X	
Symptom Burden	Dyspnea	MRC Scale	X	X			X
	Fatigue	Lee Fatigue Scale	X	X			X
Quality of Life	Global functional wellness	Kansas City Cardiomyopathy Questionnaire (KCCQ)	X	X			X
		International Physical Activity Questionnaire (IPAQ)	X				X
Medical Characteristics	Vital Signs	Height, Weight, BMI, Blood pressure, Heart rate	X	X			X
	Lipid profile	Total chol, HDL, LDL, TG, NMR lipoprotein particle count	X				X
	Metabolism Chemistries	Fasting glucose, Fasting insulin, glucagon, HOMA-IR, β-HB, hs-CRP, BNP		X			X
	Body Composition	DEXA		X			X
Medical Characteristics	Blood chemistries	Comprehensive metabolic panel, CBC, HgbA1c	X				X
Exercise MRI	Metabolic cart	VO_2 Peak, RER, VE/VCO_2, Anaerobic Threshold		X			X
	Cardiac MRI	SSFP Cine LV EF, velocity encoded PA pressure, LV DGE,T1 mapping ECM %		X			X
Echocardiogram	Transthoracic echo	LVEF, LVMI, diastology, RVSP,		X			X
	Speckle tracking strain rate imaging	Global longitudinal strain rate (GLS)		X			X

Note on Visit Schedule: Screening may occur on same day as 1st baseline testing visit if successfully passed. Labs drawn within 3 months of screening visit will be reviewed to determine subject eligibility. Fasting blood work for Visit #3 may occur 24 hours prior to other testing

Approximately 10ml or 2 teaspoons per visit will be drawn for clinical labs as well as 20ml or 4 teaspoons at visit 2 and 3 for research monocyte studies.

4.4 Description of Procedures and Evaluations

Consent Procedure
An informed consent document will be provided to individuals interested in participation. Sufficient time will be given to individuals to read, understand and comprehend the goals of the research study. Key study personnel will then have subjects voice their understanding of the research protocol and provide back a lay summary of their role as a study participant. Key study personnel will then review the consent document with the individual and fully describe the goals of the study, the inclusion / exclusion criteria, the planned monitoring, and the study drug administration. Subjects will be told that ertugliflozin (Steglatro) is an FDA approved medication for diabetes but that its specific effects on the heart in heart failure patients is unknown.

Visit #1: Screening and Randomization

Once the participant has signed the informed consent document, a screening visit will take place to ensure that the individual remains eligible for participation. The participant will undergo the following procedures during the screening visit:

- Demographic Information
- Standard health screen
- Urine Pregnancy Test (if applicable)
- Physical examination
- Review of all current medications with reconciliation placed in study binder
- Review and documentation of all medical history.
- Laboratory assessment (serum CMP, CBC, lipid panel, HgbA1c, insulin, glucagon, HOMA-IR, β-HB).
- Vital Signs
- Symptom surveys (MRC dyspnea scale, Lee fatigue scale, Kansas City Cardiomyopathy Questionnaire)

Demographic information: Prospective volunteers will be required to provide demographic information including their full name, age, gender, race/ethnicity, home/business telephone number(s), date of birth, and emergency contact information. Volunteers will be requested to show a form of photo-identification; these can be any state or federal government issued identification(s), CWRU or UH identity card, and/or club membership card.

Physical Screening/Evaluation: Volunteer physical screening will include overall assessment of appearance, age, height, weight, body temperature, blood pressure, and pulse. Physical examination will include assessment of at least 10 organ systems with documentation in the study binder. All volunteer screenings are conducted in a private exam room at the medical facility with only the volunteer, the historian, and any other required health care professionals. Volunteers not meeting the pre-stated standards will be excluded from the study.

1. The volunteer must appear to be in good health.
2. The volunteer must be > 18 years old.
3. The volunteer's temperature must be ≤ 37.5˚C.

4. The volunteer's resting pulse must be between 50 to 100 beats per minutes and free from any pathologic irregularities. Pulses lower than 50 may be acceptable if the volunteer participates in endurance training; the study physician will be consulted for evaluation.
5. Systolic blood pressure must be in the range of 100-160 mm Hg at screening.
6. The volunteer should have a pre-enrollment hemoglobin of > 11.5 mg/dL for women and > 12.5 mg/dL for men).
7. A positive pregnancy test is grounds for subsequent exclusion from the study.

Medical History: The criteria for participation will also include responses to a series of questions designed to protect the volunteer's health and well-being. The interviewer must allow opportunity and encourage the prospective volunteer to ask questions. Any information impacting volunteer eligibility determination should be meticulously documented on the volunteer history questionnaire in sufficient detail to determine the reason for volunteer eligibility or ineligibility.

The questions include the following:

1. Past Medical History Review (PMHx): The volunteer must be in good health on the day of screening. A thorough past medical history will be taken from study volunteers at the time of screening. Particular attention will be paid to heart failure with preserved ejection fraction and diabetes mellitus history. All major hospitalizations in the prior 6 months will be reviewed carefully and likely lead to study exclusion. (Self-limited medical conditions such as acute appendicitis treated with surgical removal would be an exception and will be adjudicated by Study Physician on case-by-case basis.)
2. Current Medication Review: Current medications and duration of treatment will be documented in the study binder. The volunteer be afebrile and symptom free. If a volunteer is taking a medication that causes uncertainty concerning that volunteer's eligibility, blood collection will be deferred.
3. Social and Family History Review: Volunteers will be screened for social behaviors (tobacco, alcohol or drug abuse) and for familial medical conditions.
4. Allergy Review: Study Physician will review all drug allergies with volunteer and document reactions.
5. Review of systems: A full 14 point review of systems will be asked during initial study visit.

Symptom Surveys: Symptom survey including severity of baseline dyspnea (MRC dyspnea scale), fatigue (Lee fatigue scale), and heart failure quality of life (Kansas City Cardiomyopathy Questionnaire) will be completed by the subject during the visit and reviewed by qualified study personnel.

Group assignment protocol: Randomization into treatment group will occur at baseline at a 1:1 ratio. Each subject will assigned an unique identification number for use for the duration of study. Oversight of the master list of identification numbers will be the responsibility of the PI (Trevor Jenkins) and the study coordinator. Randomization will be conducted by an unblinded study personnel (statistician), through REDCap with a "treatment A" and "treatment B" identification using a random number generator. Our statistician will communicate directly with the investigational pharmacy to indicate treatment plan.

Follow up phone calls during 12 week intervention period

Subjects will be contacted by a research staff member at week 4 and week 8 during the intervention period. Phone calls will measure a patient's medication compliance while giving the patients the

opportunity to update the research coordinator on any medical or medication changes made during the study.

Visit #2: Baseline Testing
Subjects that complete Visit #1 screening criteria will be approved by the study physician to be scheduled for Visit #2 baseline testing. Prior to starting therapeutic intervention 12 week period, subjects will undergo a battery of clinical testing including quantification of exercise capacity (CPET) with concurrent cardiovascular magnetic resonance imaging (CPET-Ex-MRI protocol), transthoracic echocardiogram (TTE), and DEXA scanning for body composition analysis.

Transthoracic Echocardiography: Standard echocardiography windows will be acquired with special focus on left ventricular ejection fraction (LV EF), LV size, LV wall mass, diastology (mitral inflow velocities, tissue Doppler velocities), left ventricular global longitudinal strain imaging via Speckle tracking (Q Lab 9.0 Philips package), left atrial size and right ventricular systolic pressure as measured by tricuspid regurgitant velocity. All 52 subjects will undergo echo imaging at baseline and study completion in the Mather Pavilion 1800 echo lab. Echocardiography protocols will be supervised by the primary investigator, Dr. Trevor Jenkins.

Cardiopulmonary Exercise Cardiac Magnetic Resonance Imaging (CPET-ExMR): The CPET-ExMR exercise protocol, combining metabolic exercise testing assessing exercise oxygen consumption (VO2) performed on an MRI-compatible bicycle ergometer or hydraulic treadmill in combination with a MRI stress test (baseline and peak exercise imaging) will be performed at baseline. All subjects will complete the CPET-ExMR prior to starting study drug. CPET-ExMR testing provides whole body metabolic assessment including peak VO2 oxygen consumption, resting metabolic substrate (measured by resting respiratory exchange ratio [RER]), and ventilatory efficiency (VE/VCO2). Cardiac function will be assessed by MRI sequences to quantitate LV mass, LVEF, diastolic and systolic function, extracellular volume fraction (ECV), and tissue edema using T2 mapping.

The ExMR protocol is performed on a 1.5T scanner (Siemens Avanto) with a 32- channel phased array coil. CMR subjects positioned on the gantry using individualized molds created from deflatable cushions that allow return to the same scanner position post-exercise. Resting cine images consist of 5 short axis and 4 long axis slices performed as non-triggered real-time steady-state free precession acquisitions with temporal generalized auto calibrating partially parallel acquisition (TGRAPPA x4) with the following scan parameters: repetition time (TR) 2.2 ms, echo time (TE) 1.0 ms, flip angle 58°, receiver bandwidth (BW) 1360 Hz/pixel, 40 frames, temporal resolution 51.8 ms, slice thickness 8 mm, average in-plane spatial resolution of 3.9 × 2.6 mm, scan time of 2 s per slice, and an average field of view (FOV) of 281 × 373 mm as previously described by our group.23 After a full exercise protocol is performed, subjects return the MR scanner with identical non-breathholding images acquired along with immediate real-time, through-plane velocity encoding sequence based on gradient-echo echoplanar imaging (GRE-EPI) with Shared Velocity Encoding (SVE) reconstruction. Three orthogonal slices across the pulmonary artery will be prescribed with the highest velocity vector within these slices and the time velocity integral calculated to represent mean PA velocity. T1 mapping will be performed for extracellular volume measurement and delayed gadolinium enhancement (LGE) sequences using Gadolinium DTPA (MagnevistTM, 0.15 mmol/kg) contrast with imaging delay of 5-10 minutes and using inversion time nulling of the myocardium for fibrosis measurement. Cardiopulmonary metabolic cart measurements will be supervised by primary investigator, Dr. Trevor Jenkins and cardiac MRI protocols will be supervised in collaboration with coinvestigator Dr. Sanjay Rajagopalan. This study will take place in the cardiac MRI scanner at UH Cleveland Medical Center.

Dual-energy absorptiometry (DEXA): Dual-energy absorptiometry (DEXA) scanning will be performed in the Dahms Clinical Research Unit to measure body composition to quantify lean body mass, fat mass, and

Serum Chemistries & Metabolomics: We will assess peripheral metabolic alterations via measurement of fasting serum glucose, insulin, and ketone bodies (β-hydroxybutyrate). These serum chemistries (BNP, hs-CRP, β-HB). will be measured at baseline and following 12 weeks of SGLT2i or placebo to provide direct assessment of SGLT2imodulated peripheral metabolic pathways. Fasting serum ketone bodies will be a prespecified endpoint.

Additional blood samples will be collected and stored for future possible metabolic assessment. We will collect serum samples for biobanking prior to CPET-ExMR exercise testing, immediately after (30 minutes with 10 min window) peak exercise, and post exercise (60 minutes post peak exercise with 10 min window). Whole blood samples will be collected into a vacutainer containing the anticoagulant potassium EDTA. Blood will be placed on ice immediately after collection and centrifuged at 4°C @ 3,500 × g for 15 min to recover the plasma fraction. Plasma will be flash-frozen in liquid nitrogen within 30 min of collection. Potassium EDTA is used as an anti-coagulant to minimize metabolic artifacts associated with anti-coagulation. Serum sample preparation will be supervised by Dr. Jeff Deiuliis.

Symptom Surveys: Symptom survey including severity of baseline dyspnea (MMRC dyspnea scale), fatigue (Lee fatigue scale), and heart failure quality of life (Kansas City Cardiomyopathy Questionnaire) will be completed by the subject during the visit and reviewed by qualified study personnel. Note, if Visit #1 and Visit #2 occur on the same calendar day, only one set of symptom surveys will be completed for both Visit #1 & #2.

Study Intervention Period: At the completion of the Visit #2 baseline testing. The subject will be provided with a 12-week supply (84 days) of study drug (ertugliflozin 5 mg a day or 1 placebo tablet a day) to be provided by the study funder (Merck) and distributed by the UH research pharmacy via prescription from the study physician. Study drug will be provided in a single 12-week supply and be labeled as “Study Medication, take as directed one tablet a day”. The subject will be blinded to which treatment arm of the study they were randomized.

Visit #3: Follow up Testing: At the end of the study intervention period, but prior to the completion of the study medication package (during week #12), the subject will undergo a repeat of the same battery of clinical testing as during Visit #2. Each test will be conducted with an identical protocol to allow for intra-subject assessment of change. Testing during Visit #3 will include:

Transthoracic Echocardiography
Cardiopulmonary Exercise Cardiac Magnetic Resonance Imaging (CPET-ExMR)
Dual-energy absorptiometry (DEXA)
Serum Chemistries & Metabolomics
Symptom Surveys

Study Completion: At the end of the 12 week intervention period, after the subject has completed screening (visit #1), baseline (visit #2), and end of study (visit #3) testing, a SUBJECT COMPLETION CRF must be completed. During the course of the study, it is possible that subjects will be withdrawn from the study. Factors leading to Subject early termination may include, but are not limited to the following.

Subject Withdrawal - A Subject may voluntarily withdraw from the study at any time without affecting their future medical treatment or benefits. In addition, the Investigator may withdraw a Subject from the study if the enrolled Subject does not meet the inclusion/exclusion criteria,

refuses further testing or follow-up evaluations, or for any other reason as determined by the Investigator. A SUBJECT TERMINATION CRF must be completed.

Subject Lost to Follow-Up – If the Investigator has attempted to contact a Subject at least three times and receives no response, the Subject is considered lost to follow-up. The research staff should document at minimum three attempts to contact the Subject, including a certified letter, prior to terminating a Subject from the trial. A SUBJECT COMPLETION CRF must be completed.

Subject Death – The Investigator will notify the UH IRB, the local DSMB, the FDA and the Sponsor within 7 days of knowledge of a subject's death. An ADVERSE EVENT and SUBJECT COMPLETION CRF must be completed, as well as a report from the Investigator explaining the nature of the Subject's death.

5. SAFETY ASSESSMENTS

Subjects will be monitored for safety during the study period in accordance with Steglatro (ertugliflozin) package insert. In accordance with UH IRB regulations, the following documentation will be maintained in the study binder:

5.1 Adverse Events and Serious Adverse Events

The UH IRB has well-established polices (and means) for Prompt Reporting of unanticipated problems involving risk to subjects or others and these policies will be strictly followed. Any non-serious adverse event, either study or not study related, can be reported by the research team at the date of the next continuing review. Any adverse event that is considered serious and is study related must be reported to the UHCMC IRB within 5 business days; however, if the serious adverse event is non-study related, the event can be reported at the next continuing review. In addition, if a serious adverse event occurs, results in the death of a participant, and is study related, the event must be reported to the UHCMC IRB within 5 business days. However, if the event results in a death but is non-study related, the event can be reported to the UHCMC IRB at the next continuing review. The same reporting schedule will be used to communicate information on adverse events to the FDA.

	Study Related	Not Study Related
Death	within 5 business days	at next Continuing Review
Serious	within 5 business days	at next Continuing Review
Non-serious	at next Continuing Review	at next Continuing Review

5.2 Reporting Procedures

Any member of the research team will report any unexpected event or problem and any adverse event, either serious or non-serious, to the principal investigator immediately upon discovery. The principal investigator will then proceed to report the event within the specified timeframes mandated by the UHCMC IRB and the Food and Drug Administration.

5.3 Follow up for Adverse Events

Participant follow up will be one of a case by case basis as directed by the physician.

6. INTERVENTION DISCONTINUATION

Study procedures and interventions will be discontinued immediately if the any of the following occur:

- Volunteer decides that he/she would no longer like to continue with the study
- Side effects of the study drug prevent further safe use
- Study personnel identify a concern with the condition of the subject

7. STATISTICAL CONSIDERATIONS

7.1 Data analysis

Data analysis and statistical evaluation will be the responsibility of the primary investigator (Dr. Jenkins) using statistician resources at UH Cleveland Medical Center Harrington Heart and Vascular Institute (CWRU CTSC Biostatistics Core). Data will be collected in a secure REDCap database that is housed at our institution in accordance with local IRB regulations. Blinding will be maintained by the study team. Medications given to subjects will be labeled "study medication" to maintain subject blinding to treatment status and will be dispensed by the UHCMC Research Pharmacy for each subject after successful enrollment. For the purpose of the final analysis, the official clinical database will not be unblinded until medical/scientific review has been completed, protocol violators have been identified (if appropriate), and data has been declared complete.

7.2 Statistical analysis

The results of experiments will be analyzed by several statistical methods. Continuous variables will be analysis as the group mean and standard deviation. Categorical variables will be analyzed with a $\chi 2$ test between groups. Continuous variables will be analyzed with t test for normally distributed variables and Wilcoxon 2 sample test for skewed distribution continuous variables. ANOVA will be used for evaluation of multiple continuous variables between groups. Curve fitting functions will be used for the detection of associations, using standard software (e.g., Graph pad prism 5.0). In all cases, $p<0.05$ will be considered as statistical significance.

Sample Size and Power Calculations: Our power analysis is based on physiologic outcome measures of primary and secondary endpoints estimated from the reported literature on heart failure with preserved ejection fraction. Power calculations were performed in R software.

For the primary endpoint, peak exercise oxygen uptake (VO2 peak), increased VO2 peak is a marker for reduced mortality and morbidity with associated increase in cardiopulmonary fitness in heart failure with preserved ejection fraction patients.25, 26 The primary endpoint for this trial is increase in VO2 over the duration of the study period. Baseline peak VO2 exercise performance in HFpEF has been reliably reported at 11.7 ml/kg/min in the RELAX trial26 with a within-patient standard deviation for peak VO2 in HFpEF of 2.0 ml/kg/min (used for both INDIE-HFpEF and RELAX trials).25,26 To calculate the primary endpoint power, the ss.1way function with variables: (k=2, alpha=0.05, beta=.2, f=.4, B=100) was used. For a power of 80%, assuming 5% type I error and a standard deviation of 2.0 ml/kg/min, we must enroll 26 subjects to detect a 2.0 ml/kg/min change from baseline in peak VO2 difference between the mean of placebo and ertugliflozin groups based on power calculation.

A secondary endpoint of left ventricular mass by CMRI (measured concurrently to VO2 during Ex-CMR protocol) will be measured. Reduced left ventricular (LV) mass is a marker of response to heart failure therapy. A reduction of LV mass by 10 gm has been reported as a significant marker of clinical response.24 (The same group reported a standard deviation of 9.6 gm for a 10 gm mean change in LV

mass in heart failure patients.30 For a power of 80% assuming 5% type I error, we must enroll 20 subjects to detect a 10 gm change in LV mass assuming a standard deviation of 9.6 gm.

A secondary endpoint of change in fasting serum β-hydroxybutyrate (µmol/L) will be measured. Ferrannini et al. report fasting BHB levels of 246 (standard deviation 288) prior to exposure to empagliflozin21 with an increase to 561 after 4-week exposure to drug. For a power of 80%,assuming 5% type I error, we must enroll 18 subjects to detect a 125% increase in fasting serum β-hydroxybutyrate.

	Parameter	Reference	δ (Change)	SD (σ)	N (90% power)
Primary Endpoint:					
Oxygen uptake	VO_2 (ml/kg//min)	25, 26	2.0	2.0	21
Secondary Endpoints					
Ventricular Mass (measured by CMRI)	MRI measured LV Mass (gm)	24	5	4	14
Serum ketone bodies	Fasting serum β-hydroxybutyrate (µmol/L)	21	125	117	18

8. DATA COLLECTION AND QUALITY ASSURANCE

8.1 Data Collection Forms

The research coordinator will perform primary data collection based on sourcedocumented hospital and clinic chart reviews. For source documentation regulations require that Investigators maintain information in the study Subject's medical records that corroborate data collected on the CRFs. In order to comply with these regulatory requirements, at a minimum, the following information should be maintained:

- Sufficient medical history/physical condition of the study Subject before involvement in the study to verify protocol entry criteria (if not already present);
- Dated and signed notes on the day of entry into the study including clinical site number, assigned Subject number, and a statement that consent was obtained;
- Document consent process and verify original signed consent by monitor;
- Dated and signed notes from each study Subject visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams);
- Notations on abnormal lab results;
- Adverse events reported, results of diagnostic tests ordered, treatment given, clinical outcome, and their resolution;
- Dictated procedure report;
- Dictated summary;
- Notes regarding concomitant medications taken during the study;
- Study Subject's condition upon completion of, or withdrawal from, the study.

8.2 Data Management

Data management will be overseen by the primary investigator, Trevor Jenkins, will assign roles to the research staff for collating and conducting off-line analyses of the recorded clinical parameters. A study

database will be established in the University Hospital REDCap system for secure data storage and will be accessible only to qualified study personnel. Data contained in the REDCap database will be de-identified with use of only the subject number. The primary investigator, Trevor Jenkins and the study coordinator will be the only members of the study team that have access to the master subject list with identifying subject information.

8.3 Quality Assurance

Arrangements for data and procedural reviews by a quality assurance monitor will made in collaboration with the UH Center for Clinical Research and Technology. The study sponsor, Merck Co. will also make arrangements to review the study binders and provide additional quality assurance.

9. PARTICIPANT RIGHTS AND CONFIDENTIALITY

The following language is taken from the subject consent sheet and explains the risks and benefits of the procedures involved in the EMMED-HF study.

9.1 Potential Benefits

Potential benefits to you:

- You may or may not benefit by taking part in this study. There is no guarantee that you will receive direct benefit from your participation in this study.
- As part of this study, you may benefit from treatment of your Diabetes Mellitus, type 2 and chronic diastolic heart failure. In addition, identifying any causes of shortness of breath, fatigue or exercise limitation during the study can lead to appropriate treatment measures by your doctors.

Potential benefits to society and other people with Diabetes Mellitus, type 2 and chronic diastolic heart failure:

- To determine if using the diabetes medication ertugliflozin can help improve exercise capacity.
- To learn how the heart and lungs respond to treatment with ertugliflozin which could also be applied to other medications in the SGLT2 inhibitor category.
- To learn if there are metabolism changes using ertugliflozin that could benefit the heart and lead to new approaches to study patients with Diabetes Mellitus, type 2 and chronic diastolic heart failure.

9.2 Potential Risks

Risks associated with study drug

The side of effects in this section are listed by frequency. Frequencies are defined as:

- Very common (> 1/10): affects 1 to 10 patients in 10
- Common (>1/100 to < 1/10): affects 1 to 9 patients in 100
- Uncommon (>1/1,000 to < 1/100): affects 1 to 9 patients in 1,000
- Rare (>10,000 to < 1,000): affects 1 to 9 patients in 10,000
- Very rare (<1/10,000): affects less than 1 patient in 10,000

The side effects observed with ertugliflozin include (taken from FDA approved package insert):

- Hypotension (low blood pressure) a sign of volume depletion (decrease in volume of water in the body): Uncommon
- Ketoacidosis (a life-threatening condition with increased chemicals called ketones in the blood): Rare

- Low blood sugar (hypoglycemia) when used with a class of blood sugar lowering medication called sulphonylurea or insulin: Very common
- Urinary tract infection (fungal infection): Common
- Genital infection: Common
- Increase in urinary frequency or amount of urine made: Common
- Blood creatinine increase and glomerular filtration decrease (laboratory tests that are used to measure how well your kidneys are working: Common
- Lower limb amputation: Uncommon
- Thirst: Common

Risks associated with other procedures required for this study

Medical History and Survey Collection:
You will be asked about sensitive topics such as your health status and feelings which may create awkwardness or discomfort for you. You are always free to skip a question that makes you feel uncomfortable.

Blood Draws:
The insertion of the needle to draw blood is painful; however, this discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems. However, having your blood drawn may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

DEXA Scan:
The DEXA scan uses a small amount of radiation to make images of your body. The radiation total of a DEXA scan is 1-5 microsieverts (uSv). For context, we are exposed to about 8 uSv of background radiation each day from cosmic rays, the Earth's crust and soils, buildings, food, and medical scans. Therefore, the DEXA scan you will receive will be about the amount of radiation you normally are exposed to in 3-12 hours of day to day living. This cumulative radiation exposure from our study is very small and not likely to adversely affect you or your disease. However, the effects of radiation add up over a lifetime. When deciding to enter this study, think about your past and future contact with radiation.

MRI and Contrast Agent:
University Hospitals Cleveland Medical Center standard screening guidelines for MRI safety will be followed as explained below. There have been no bad effects reported from exposure to the magnet or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. The MRI machine uses a strong magnet and radiofrequency magnetic fields to make images of the inside of your body. A known risk is that the MRI scanner uses a very strong magnet that will attract some metals and affect some electronic devices. As metal objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. You may also feel temporary muscle stiffness and minor discomfort due to lying still for long periods.

Contrast agent injection may cause you to experience some discomfort with general sensation of warmth, coolness or a sensation of local pressure or pain at the injection site. Less frequently reported are dizziness, nausea, headache and a metallic taste in the mouth. There is a slight risk (less than 1%) of allergic reaction. Rare reactions are vomiting, prolonged drowsiness, visual disturbances, diarrhea,

anxiety, difficulty breathing, chest pain, increased heart rate, trembling, joint-pain or allergy-like symptoms such as hives, itching or an irritation in the throat. Anaphylactic (severe allergic) reactions are extremely rare, but may occur. Some anaphylactic reactions can be severe and if not treated, death can occur.

A rare but serious condition called Nephrogenic Systemic Fibrosis (NSF) has been linked to MRI and gadolinium contrast dye agents. University Hospitals Cleveland Medical Center and the Food and Drug Administration (FDA) approved screening guidelines for reducing the risk of NSF will be followed. This condition has only occurred in patients with severe kidney disease; for this reason, you will not be included in the study if your kidney tests are significantly abnormal. You will have a kidney blood test upon enrollment and at each time before the MRI scan at no cost to you. Extensive clinical experience with the particular contrast agent used in this study indicates that the risk of reaction is minimal. The agent has been used safely in over 6 million procedures, confirming that it is extremely well tolerated. If you have a reaction to the contrast agent, you will be monitored and treated.

Cardiopulmonary Exercise Test (CPET):
This procedure is commonly performed as part of usual care in people with heart failure. The procedure has a low risk of complications including heart attack, stroke, dizziness, fainting, and nausea, although these are not common. Patients will undergo continuous ECG, oxygen saturation and blood pressure monitoring. The test will be supervised by a qualified healthcare professional who will be knowledgeable about the test, the risk and the criteria for terminating the exercise test. Analysis will be undertaken after full instructions are given and understood by the patient.

If you have an exercise MRI, a qualified nurse or exercise physiologist familiar with normal and abnormal response to exercise will continuously monitor you including your electrocardiogram, blood pressure, and general appearance. There is a low risk of cardiac events (heart attack, stroke, dangerous heart rhythms, hypotension, syncope) and death during any exercise test. The supervising doctor present during your exam will also monitor you during the procedure.

Claustrophobia:
You will be asked to lie on a long narrow table while the MRI machine gathers data. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling. Some participants may experience anxiety inside the MRI scanner if they are uncomfortable with small enclosed spaces. Some portions of the MRI study generate loud noises; you will be given earplugs to prevent discomfort.

Echocardiogram:
There are no established risk from a standard transthoracic echocardiogram performed by passing sound waves across your chest wall from a probe placed against your chest wall. You may experience temporary mild discomfort during the scan from pressure placed against your chest by the probe to form the proper images of your heart. You may request the sonographer reposition the probe if it becomes uncomfortable at any time during the test.

Electrocardiogram (ECG)
ECG side effects may include a mild rash where the electrodes (soft patches) were attached. This rash often goes away without treatment.

Reproductive risks:

Being a part of this study while pregnant may expose your unborn child to serious risks. You cannot be in this study if you are pregnant or at risk of becoming pregnant.

Confidentiality:
Although every effort will be made to keep information collected about you confidential, there is a small risk that this information may be seen by unauthorized persons. Loss of confidentiality will be minimized by storing data in locked cabinets and electronic data will be password protected on the University Hospitals computer network using secure research data collection software.

9.3 Alternatives to Participation
This is a voluntary study. The alternative is to choose to not participate. The decision on the part of the research participant will in no way influence any care they might receive at University Hospital nor will it affect their interactions with any of the study personnel.

9.4 Financial Information
As part of clinical care, if you are diagnosed with pulmonary artery hypertension, you may also have a cardiac catheterization and cardiopulmonary exercise test. These clinically indicated exams, ordered by your doctor, will be billed to you or your insurance company.

- There is no cost to you or your insurance company for having the research tests. The costs of the Echo, DEXA, MRI, ECG, muscle strength test, cardiopulmonary exercise test, and blood and urine testing will be covered under the research study.
- Any additional testing needed according to standard clinical practice is outside the scope of this research study and billed accordingly to either you or your insurance company.

9.5 Payments for Participants
You will be reimbursed $150 for your participation in the planned 3 research study visits and the completion of your participation as compensation for your volunteered time. In addition, participants will be eligible to receive, a parking pass, bus pass, or arranged transportation (Lyft or service car) to ease your transportation to University Hospital Cleveland Medical Center. To receive payment you must agree to complete a W-9 form which requires you to provide an address and social security number to the University Hospitals accounting department. This payment to you may be considered taxable income by the IRS. You will be issued a 1099-Misc form only if payment exceeds $600 from all studies in which you are participating, in a fiscal year.

9.6 Research Related Injury
If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

9.7 Use of specimens
By participating in this study the research participant is authorizing the research team to test your blood for standard clinical tests of body organ function, as well as blood to be stored in a biorepository for future measurements of metabolism. The results of metabolism tests drawn from the biorepository will will not be placed in the University Hospitals patient chart and will not be used to guide clinical care.

In addition, if a participant consents to have their blood stored for future research, specimens mat be used in genetic testing for unrelated research from biobanked samples.

9.8 Confidentiality

Results of blood testing done outside of the University Hospitals clinical laboratory will be treated as confidential information and the results will not be included in the volunteer's medical record. Similarly, medical history obtained in this study will also be treated as confidential with no identifiable information released or shared with individuals outside the study team. If the study results are published your name will not be used. Once all study results are collected any identifiers will be removed and the information assigned a code. The data will be identified by a study number and not by name or identifying information. The code assignment key will be maintained by the Principal Investigator, Trevor Jenkins, on a password-secured computer kept in a locked office. Access to the code key will be limited to the Principal Investigator and study personnel on a need-only basis.

9.9 Privacy of Protected Health Information

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your health information and to whom this information may be shared within and outside of University Hospitals. This Authorization form is specifically for a research study titled "Evaluating Metabolic Mechanisms of Ertugliflozin in Diabetes & Heart Failure (The EMMED-HF Study)" and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your PHI and in what ways they can use the information. In order for the Principal Investigator, Trevor L. Jenkins, M.D., and the research study staff to collect and use your PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If a volunteer chooses do not sign the IRB-approved informed consent, they may not join this study. Their decision to allow the use and disclosure of your PHI is voluntary and will have no impact on their treatment at University Hospitals. By signing this form, they are allowing the researchers for this study to use and disclose PHI in the manner described below. Generally, the Principal Investigator and study staff at University Hospitals and Case Western Reserve University who are working on this research project will know that the volunteer is in the research study and will see and use PHI. The researchers working on this study will collect the following PHI:

- age, sex, height, weight
- any pre-existing medical condition
- blood pressures, heart rate, respiration, temperature
- blood chemistry results; and
- exercise capacity testing
- ultrasound imaging of the heart

This PHI will be used to relate the impact of the diabetes medication, Steglatro (ertugliflozin) on the physical condition of the heart and blood vessels and the impact on peak exercise capacity. Access to PHI may be limited during the study to protect the study results.

PHI will only be shared with the members of the research team and the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law. Permission to use and disclose PHI does not expire. However, the study volunteer has the right to change their mind at any time and revoke their authorization. If permission to use PHI is revoked, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization you may no longer be able to participate in the research study. To revoke your permission, you must do so in writing by sending a letter to:

Trevor L. Jenkins, M.D.
Harrington Heart & Vascular Institute
University Hospital Cleveland Medical Center
Lakeside 3 rd Floor Mailstop 5038
11100 Euclid Ave
Cleveland, OH 44106

If you have a complaint or concerns about the privacy of your health information, you may also write to:

UH Privacy Officer, Management Service Center
3605 Warrensville Center, MSC 9105
Shaker Heights, OH 44122

Or to:

DHHS Regional Manager
Office of Civil Rights
US Department of Health and Human Services Government Center
JF Kennedy Federal Building, Room 1875
Boston, MA 02203.

Complaints should be sent within 180 days of finding out about the problem.

The researchers and staff agree to protect health information by using and disclosing it only as permitted by singed Authorization and as directed by state and Federal law. University Hospitals is committed to protecting your confidentiality. Once PHI has been disclosed to anyone outside of University Hospitals, there is a risk that the volunteers PHI may no longer be protected; however other Federal and State laws may provide continued protection of information.

9.10 Summary of Rights As a Participant in a Research Study

Participation in this research study is voluntary. Refusing to participate will not alter usual health care or involve any penalty or loss of benefits to which the participant is otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Cleveland Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

9.11 Disclosure of Study Records

Efforts will be made to keep the personal information in the research records private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Cleveland Medical Center Institutional Review Board may review your study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records. If your records are reviewed your identity could become known.

9.11 Data Safety Monitoring Board

The DSMB will review all the adverse events and categorize them as either serious, nonserious, device related or procedure related. The time frame for evaluation of events by the Medical Monitor will be 7 - 10 days from the time the event is reported to the Sponsor. Based on the safety data, the DSMB has the authority to request a modification of the study. These modifications are only meant to be a guideline for the DSMB to review the study and make a recommendation to continue, or modify, not necessarily a mandate for terminating the study. The formal DSMB consists of:

Voting member: Darren McGuire, M.D.
Office: University of Texas Southwestern Medical Center,
5323 Harry Hines Blvd, E5.726,
Dallas TX, 75390
e-mail: Darren.McGuire@utsouthwestern.edu
Voting member: Varun Sundaram, M.D.
Office: University Hospitals Cleveland Medical Center,
11100 Euclid Ave,
Cleveland, OH 44106
e-mail: Varun.Sundaram@UHhospitals.org
Voting member: Nadine El Asmar, M.D.
Office: University Hospitals Cleveland Medical Center,
11100 Euclid Ave,
Cleveland, OH 44106
e-mail: Nadine.ElAsmar@UHhospitals.org

The members have no involvement in the planned study but do have the requisite clinical expertise to oversee volunteer safety. The DSMB will meet at least twice per year and will prepare written reports of the results of these meetings. The protocol PI will alert the DSMB (along with the IRB) to any adverse events. The DSMB Charter is appended in the study documents. It was ratified by the DSMB at its 1 st meeting, held on ##/##/20##. At this meeting, Dr. #### was voted-in to serve as the board Chair and Safety Officer.

9.12 Institutional Review Board

It is the Primary Investigator's responsibility to submit the clinical protocol and any Amendments to the IRB/EC, if required, for approval prior to any Subject being enrolled at that Investigational Site and to obtain renewals at periods determined by the IRB/EC for the duration of the study.

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