EMPA-TROPISM Trial: Are the "cardiac benefits" of Empagliflozin independent of its hypoglycemic activity?

PI: Juan Badimon, MD

NCT03485222

Document Date: Nov 28, 2017

Mount Sinai

Icahn School of Medicine at Mount Sinai Mount Sinai Beth Israel
Mount Sinai Brooklyn
The Mount Sinai Hospital Mount Sinai Queens
New York Eye and Ear Infirmary of Mount Sinai
Mount Sinai St. Luke's Mount Sinai West

Program for the Protection of Human Subjects
Institutional Review Boards
Mount Sinai Health System
One Gustave L. Levy Place, Box 1081
New York, NY 10029-6574 T 212-824-8200
F 212-876-6789
irb@mssm.edu icahn.mssm.edu/pphs

Table of Contents

1. ***Title***

Protocol Title

EMPA-TROPISM Trial: Are the "cardiac benefits" of Empagliflozin independent of its hypoglycemic activity?

Principal Investigator
Juan Badimon

Primary Department
Medicine - Cardiology

Application Initiated By
Juan Badimon

Lay Summary

Empagliflozin is the first drug that improves glucose control and has cardiovascular benefits. A recent trial has shown significant reductions in adverse events. Cardiovascular mortality and hospitalization were reduced by empagliflozin given on top of standard-of-care therapy in diabetics. Some investigators have suggested that these benefits are independent of its glucose lowering effect and thus, Empagliflozin could be considered a "cardiac" drug.

Our overall hypothesis is that the benefits attained from empagliflozin were at least in part, mediated by a glucose- independent mechanism. Thus, we are proposing to conduct a study to investigate the postulated benefits of empagliflozin vs placebo involving non-diabetic patients with heart failure.

2. ***Background***

Objectives

Our overall hypothesis is that the benefits attained in the EMPA-OUTCOME were at least in part, mediated by a glucose-independent mechanism. Thus, to demonstrate the existence of pleiotropic (non-glucose dependent) effects associated with empagliflozin administration, we are proposing to conduct a pilot randomized, double blind, placebo- control, single-center study to investigate the postulated "cardiovascular" benefits of empagliflozin 10mg/day vs placebo involving non-diabetic HF patients with reduced ejection fraction.

Background

Empagliflozin is the first glucose-lowering agent that not only improves glycemic control but also has cardiovascular benefits. The recent EMPA-OUTCOME trial has shown significant reductions in major adverse cardiac events (MACE), cardiovascular mortality, and hospitalization for Heart Failure (HF) with empagliflozin given on top of standard-of-care therapy for T2DM patients with cardiovascular disease (CVD). Some investigators have suggested that these benefits may be independent of its hypoglycemic activity and thus, Empagliflozin could be considered a "cardiac" drug. This hypothesis has emanated from the data of the EMPA OUTCOME clinical trial.

Empagliflozin treatment did not have any effects on the rate of the traditional atherothrombotic events. The dramatic change driving the superiority of the primary composite outcome (major adverse CV events) was a significantly lower CV death rate (38% relative risk reduction). In addition, there were also an impressive 35% and 38% relative risk reductions in hospitalization for heart failure (HF) and death from any cause. Of the major interest is that these benefits occurred in the absence of any major differences in glycemic, lipid, or blood pressure (BP) control. Management of concomitant HF in T2DM is particularly challenging, as some glucose-lowering agents, such as TZDs, are contraindicated in patients with HF. Until recently, there was an unmet need for an oral agent that improved glycemia as well as provided CV benefits, including decreasing HF in patients with, or at risk of, CVD.

Type 2 diabetes mellitus (T2DM) is one of the most common chronic health conditions in the United States; it affects approximately 10% of adults with up to one-quarter being undiagnosed. T2DM is associated with substantial cardiovascular (CV) morbidity and mortality. Heart failure (HF) is a frequent co-morbid condition associated with poor prognosis in diabetes, particularly among older patients. HF accounts for more than 1 Million hospitalizations annually in USA. In addition, HF hospitalizations are associated with significant high risk of post-discharge mortality and recurrent hospitalizations. Almost one-half of patients will be re-hospitalized within 6 months and one-third will die within 12 months of discharge. Median survival after HF diagnosis is about 5 years, and is similar for HFpEF and HFrEF patients. Diabetes as co-morbidity multiplies risk of hospital admissions in HF patients.

Management of concomitant HF in T2DM patients is particularly challenging. Some glucose-lowering agents, such as TZDs, are contraindicated in patients with HF. Until recently, there was an unmet need for an oral agent capable of improving glycaemia as well as providing CV benefits, including mitigating HF in patients with or at risk of CVD. There are a couple of characteristics that single out the SGLT2 inhibitors from other hypoglycemic drugs. One is their low hypoglycemic risk since their act on the urinary excretion of glucose without interfering with the physiologic response to hypoglycemia, and the other is their "positive" cardiovascular effects such as lowering blood pressure, arterial stiffness, urinary microalbuminuria and triglycerides while increasing HDL-cholesterol levels. The recent EMPA-OUTCOME trial showed significant reductions in major adverse cardiac events (MACE), CV mortality, and hospitalization for HF with Empagliflozin when given on top of standard-of-care therapy for T2DM and CVD. Therefore, the combination of the above-mentioned observations led to some investigators to suggest that these benefits may be, at least in part, independent of its hypoglycemic activity and thus, Empagliflozin could be considered a "cardiac" drug.

Our overall hypothesis is that the benefits attained in the EMPA-OUTCOME were at least in part, mediated by a glucose-independent mechanism. Thus, to demonstrate the existence of pleiotropic (non-glucose dependent)

effects associated with empagliflozin administration, we are proposing to conduct a pilot randomized, double blind, placebo- control, single-center study to investigate the postulated "cardiovascular" benefits of empagliflozin 10mg/day vs placebo involving non-diabetic HF patients with reduced ejection fraction.

Primary Endpoints

The primary end-point will be to determine whether empagliflozin mitigates changes in LV end systolic volume (ESV) or LV end diastolic volume (EDV) in HF patients without diabetes when compared to placebo. We have chosen LV volume because it is the strongest predictor of adverse cardiovascular outcomes even after adjusting for LVEF and MI size (White HD Circulation. 1987;76:44–51 and Migrino RQ Circulation. 1997;96:116–121).

Secondary End-points

1. To determine changes in LV mass, LV-EF and remodeling index (LV mass/LV-EDV) with empagliflozin compared with placebo.
2. To determine if there is a change in left atrial volume (an accurate indicator of chronic increase in LV filling pressures) with empagliflozin compared with placebo.
3. To determine if there is a change in right ventricular (RV) EDV, RV-ESV and, RV-EF with empagliflozin compared with placebo.
4. To determine if there is a change in cardiac interstitial fibrosis as assessed by T1 mapping with empagliflozin compared with placebo.
5. To determine if there is a change in VO2 Oxygen consumption with empagliflozin compared with placebo.
6. To determine if there is a change in Visceral and epicardial fat as measured by CMRI with empagliflozin compared with placebo.
7. To determine if there is a change in arterial stiffness measured by CMRI with empagliflozin compared with placebo.
8. To determine if there is a change in body composition analysis (BCA anthropromorphic measurements) with empagliflozin compared with placebo.
9. Effect of the treatment on several cardiovascular and inflammatory biomarkers with empagliflozin compared with placebo.
10. To determine if there is a change in exercise tolerance by the 6 min walk test with empagliflozin compared with placebo.
11. To determine if there is a change in the patient-reported quality of life by the Minnesota Living with HF and SF-36 questionnaires.

Safety and Tolerability

Patients will be monitored for signs of hypoglycemia, urinary tract infections, bone fractures, diabetic ketoacidosis and thromboembolic during the follow-up period. We will also assess survival, hospitalizations and HF worsening (more visits, increase in prescription of diuretics, etc).

3. ***Research Personnel***

Name/Department	**Role/Status**
Juan Badimon / Medicine - Cardiology	Principal Investigator
Alvaro Garcia Ropero / Cardiology	Co-Investigator
Johanna Contreras / Medicine - Cardiology	Co-Investigator
Valentin Fuster / Medicine - Cardiology	Co-Investigator
Donna Mancini / Medicine - Cardiology	Co-Investigator
Sean Pinney / Medicine - Cardiology	Co-Investigator
Ronald Tamler / Medicine - Endocrinology	Co-Investigator
Javier Sanz / Medicine - Cardiology	Co-Investigator
Mohammad Zafar / Medicine - Cardiology	Co-Investigator
Carlos Santos- Gallego / Medicine - Cardiology	Co-Investigator
Arianna Patricia Vargas Delgado / Cardiology	Co-Investigator

4. ***Subjects - Enrollment***

Site Name
Icahn School of Medicine at Mount Sinai

Subjects To Be Enrolled
100

Total Number of Subjects Needed To Complete Study
80

5. ***Subjects - Setting and Resources***

Feasibility of Meeting Recruitment Goals

HF patients will be identified from the HF clinic at Mount Sinai and the Mount Sinai Consortium database for patients with chronic heart failure. The MSSM consortium includes the Mount Sinai Medical center of Manhattan, Elmhurst Hospital in Queen, the VA Bronx and the Mount Sinai Saint Luke's Hospital in Harlem and the Mount Sinai-West Hospital (former Roosevelt Hospital).

The Consortium's database contains more than 10,000 HF patients. This proposal involves non-diabetic HF patients and given the common co-existence of diabetes affecting to 40-50% of HF patients; the database still offers us a potential 5,000 HF patients that could be candidates for enrollment in our study.

Facilities to be Used for Conducting Research

Consent Form and blood collection: Atran Bldg 6th Room 20 CMRI - Lauder Imaging facilities

O2 consumption and Vo2 consumption: Cardiopulmonary Exercise laboratory on Guggenheim 6.

6. ***Subjects - Populations***

Inclusion Criteria

Patients should meet the following inclusion criteria:

1. Ambulatory patients age more than 18 years
2. Diagnosis of Heart failure (NYHA II to III)
3. LVEF<50% on echocardiography or CMRI
4. Have stable symptoms and therapy for HF more than 1 week.

Exclusion Criteria

1. Pregnant or lactating women.
2. Any history of diabetes by medical history or by any of the established criteria by the American Diabetes Association. It also includes patients with history of diabetes in remission.
3. ACS or cardiac surgery within the last 3 months.
4. Cancer or any other life-threating condition.

5. Glomerular Filtration Rate < 30 ml/Kg/min.
6. Use of continuous parental inotropic agents.
7. Systolic BP < 90 mm Hg.
8. Recreational drugs and /or excessive alcohol.
9. Psychiatric disease incompatible with being in study.
10. Any contraindication to MRI procedures.
11. Any other medical or physical condition precluding the subject's participation.

7. ***Subjects - Participation***

Duration of an Individual Subjects Participation in the Study
6 months

Duration Anticipated to Enroll All Study Subjects
20 months

Estimated Date for the Investigators to Complete This Study
3-5 years

Procedures for Subjects to Request Withdrawal

You may stop taking part in this research study at any time without any penalty. This will not affect your ability to receive medical care at any of the Mount Sinai Health System hospitals or to receive any benefits to which you are otherwise entitled.

If you decide to withdraw your consent, we ask that you contact Dr. Juan J Badimon, and let him know that you are withdrawing from the study. His mailing address is the Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY 10029. If you wish to withdraw your authorization as well you must contact Dr. Badimon in writing at the Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY 10029.

You may also withdraw your permission for the use and disclosure of any of your information for research, but you must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, we may still use the already collected information if it is necessary to complete the study. Your health information may still be used or shared after you withdraw your authorization if you should have an adverse event from participating in the study.

Procedures for Investigator to Withdraw Subjects

The study doctor, the sponsor or the institution may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in your best interest, or for any other reason. If specimens or data have been stored as part of the research study, they too can be destroyed without your consent.

Participants Will Be Recruited
Yes

Recruitment Method(s)
Clinical Practice, Registry/Bank, Records

How Participants Will Be Identified

In all disclosures outside of Mount Sinai, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. Some records and information disclosed may be identified with a unique code number. The Principal Investigator will ensure that the key to the code will be kept in a locked file, or will be securely stored electronically. The code will not be used to link the information back to you without your permission, unless the law requires it, or rarely if the Institutional Review Board allows it after determining that there would be minimal risk to your privacy.

Who Will Initially Approach Potential Participants

Treating Physician, Clinic Personnel

How Research Will Be Introduced to Participants

Research will be introduced by the primary physician or physicians from the Heart Failure Program at ISMMS. They will be informed of the significant cardiac benefits obtained in heart failure and diabetic patients. In addition, we will tell the participants that the objective of the study is to investigate whether the benefits seen in the HF and diabetic population could be extrapolated to HF patients independently of their diabetic status.

How Participants Will Be Screened

All approached participants will have a diagnosis of HF. Upon signing of the informed consent form, a blood sample will be collected and analyzed to assure that participants fulfill ALL the inclusion criteria but NONE of the exclusion criteria. We will ask questions about their medical history and perform a physical exam that includes weight, height, body temperature, blood pressure, pulse rate, and EKG. In addition, we will collect blood and urine to check for routine lab tests, hepatitis B and C, use of recreational drugs and HIV test. The results of the drug testing will NOT be placed in the participant's medical record.

8. ***Subjects - Risk and Benefits***

Risks to Subjects

Empagliflozin is approved by the FDA for the treatment of high levels of glucose in diabetic subjects. This drug has been studied in tens of thousands of patients and, despite its well-established benefits, the adverse effects observed and that could very rarely affect you are:

- Low sugar levels manifested as blurry vision, accelerated cardiac pulse, irritability, nervousness, headaches, shivers, sweating, tireless, tingles and/or appetite loss.
- Blood pressure lowering manifested as headache, dizziness, confusion, irritability, sweat and irregular cardiac pulse.
- Dehydration manifested as headache, dizziness, confusion, weakness specially when standing up.
- Ketoacidosis manifested as headache, fatigue, nausea/vomiting, stomach ache, breathing difficulties, abdominal pain, urinating urges, appetite loss.
- Urinary infections (penis in men and vagina in women) manifested as frequent urination urges, irritation while urinating, blood and/or bad smell of the urine, pain in the stomach and/or pelvis.
- Allergies manifested as cutaneous rushes, inflammation and/or itching in the face, tongue and throat as well as dizziness and breathing difficulties.
- In case you experience any of these symptoms, stop taking the study drug and immediately contact the investigators at the phone number provided below in this document.

- There are no reports of any psychological or social risks associated with the treatment.
- The risks of a blood draw include pain, bruising, and the slight possibility of infection at the place where the needle goes in. Some people feel dizzy or may faint during or after a blood draw.

Description of Procedures Taken to Lessen the Probability or Magnitude of Risks

Upon randomization, all participants will be invited to come to the MSMC at 1- and 3-months post-therapy initiation to assure the safety of the assigned treatment.

They will be instructed on the symptoms typical of the potential risks associated with the treatment. In case of any doubt, they should stop taking the drug and call the investigators. In conditions of significant discomfort or pain, they should go to the closest Emergency Room and notify the investigators.

Provisions for Research Related Harm / Injury

If you believe that you have suffered an injury related to this research as a participant in this study, you should contact the Principal Investigator, Dr. Juan J Badimon or Dr. Carlos Santos-Gallego, at 212-241-8484. If you are injured or made sick from taking part in this research study, medical care will be provided. Generally, this care will be billed to you or your insurance in the ordinary manner and you will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance. This does not prevent you from seeking payment for injury related to malpractice or negligence. Contact the investigator for more information.

Expected Direct Benefit to Subjects

It is important to know that you may not get any benefit from taking part in this research. However, possible benefits may be a reduction in the frequency of hospitalization and an improvement of the symptoms associated with heart failure in the group receiving the study treatment.

Benefit to Society

It is hoped the knowledge gained from this study will be of benefit to others in the future.

Provisions to Protect the Privacy Interests of Subjects

As part of this research project, it will be necessary for the research team and others to use and share some of the private protected health information. Consistent with the federal Health Insurance Portability and Accountability Act (HIPAA), we are asking your permission to receive, use and share that information.

The research team and other authorized members of The Mount Sinai Hospital and Mount Sinai School of Medicine (together, "Mount Sinai") workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements. For example, the School's Program for the Protection of Human Subjects is responsible for overseeing research on human subjects, and may need to see your information. If you receive any payments for taking part in this study, the Mount Sinai Medical Center Finance Department may need your name, address, social security number, payment amount, and related information for tax reporting purposes. If the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities.

Outside of Mt Sinai, the following agencies may receive some of your protected information:

- The sponsoring government agency and/or their representative who need to confirm the accuracy of the results submitted to the government or the use of government funds.
- National Institutes of Allergies and Infectious Disease National Institutes of Health Department of Health and Human Services (NAID/NIH/DHHS).
- A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety.

- The United States Food and Drug Administration.
- The United States Department of Health and Human Services and the Office of Human Research Protection.

In all disclosures outside of Mount Sinai, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law.

Economic Impact on Subjects

You will not be charged for the clinic visits or laboratory tests that are required by this study.

If you agree to comply with all the visits, you will be given up to $400 for your time and inconvenience. The payment will be pro-rated between all the visits as follow:

V1 - $20; V2 - $150; V3 - $40; V4 - $40; V5 - $150.

Payment will be provided in the form of a check generated by the Mount Sinai Finance depart. Checks require some time to be prepared and will be given to you as available.

Tax laws may require the Mount Sinai Finance Department to report the amount of payment you receive from Mount Sinai to the Internal Revenue Service (IRS) or other agencies as applicable. Generally, this reporting would take place if receiving payments that equal $600 or more from Mount Sinai in a calendar year. You would be responsible for the payment of any tax that may be due.

9. ***Procedures - Narrative***

Description of the Study Design

If you agree to participate in this research study, the following information describes what may be involved. All the research activities will take place at the MSMC.

The first step will be that the study nurse or doctor will explain you the basis for the study and all the research activities involved in your participation. Thereafter, you will be asked to sign this consent form. Before signing it, ask your study nurse or doctor anything that you do not fully understand. After you have signed this form, you will be asked some questions and will undergo some tests at the screening visit to see if you qualify and if it is safe for you to join the study.

All the procedures done during the study are solely for research purposes. The total volume blood collected during the 6-months of the study duration will be 75 mls. (5 table spoons). This amount is much less than one blood donation and, therefore, should not affect your health.

The procedures included in each one of the visits are described below:

Visit 1 Screening: This visit with last approx. 1 hour and it will take place at the 6th Floor of the Atran Building at the MSMC. We will ask you some questions about your medical history (about your health) and perform a physical exam that includes your weight, height, body temperature, blood pressure, pulse rate, and one EKG (checks the electrical activity of the heart). In addition, we will collect one sample of blood (1 table spoon) and urine to check for routine lab tests, hepatitis B and C, use of recreational drugs use (amphetamines, barbiturates, cocaine, opiates, cannabinoids, etc.) and HIV test. The results of the drug testing will NOT be placed in your medical record.

If you qualify and are willing to participate in the study, we will ask you to return for the 2nd visit within the next 30 days. In case you do not qualify, your participation will end in this visit.

Visit 2 Randomization: This visit will be approx. 4 hours long. You will be asked to report to the 6th Floor, Room 20 of the Atran Building at the MSMC in fasting state. This visit will serve to perform all the baseline (pre-treatment) procedures. The procedures to be performed during this visit will be:

- Magnetic Resonance Imaging to study cardiac parameters of your cardiac function. You will be introduced inside of a magnet where you should stay as quiet as possible for about 45-60 minutes. As routinely done in clinical you will receive Gadolinium that is a contrast that facilitate the visualization of your heart. This procedure does not involve the exposure to any ionizing radiation and thus, does not present any important risk to your health.
- Oxygen consumption. You will be asked to walk on a treadmill while being EKG-monitored. Your blood pressure will be monitored before and after the procedure. You will also wear a mask that will allow to measure the Oxygen consumption. This procedure will take approx. 20-30 minutes
- 6-minute walking test. - We will ask you to walk for a total of 6-minutes and then walked distance will be recorded. If necessary you will be allowed to stop and rest during the 6-minutes period. This walk will be repeated at the end of the 6-months of the study duration and the difference between the distance walked in the two procedures will tell us about the effects of the treatment.
- Heart Failure Questionnaire. - we will ask you some questions about the quality of life. The questioner will be repeated at the end of the 6-months of study.
- We will collect one blood sample (15ml 1 stable spoon) to study some blood parameters

Following baseline testing procedures, you will be randomized to one of two possible treatment groups (Empagliflozin or Placebo). Randomization is a process used in clinical studies to make sure that the observed effects of study treatment are real. The study treatment you get will be chosen by chance, like flipping a coin.

Neither you nor the study doctor will choose what study treatment you get. You will have an equal chance of being assigned to either study treatment group. One group will receive a pill of empagliflozin (10mg/day) while the other (placebo-control) group will receive a sugar pill without active medicine. The study pills will be taken orally and preferable at the same time every day. The study pill will be taken in addition to all the drugs prescribed by your physician. You will be provided detailed instructions on how to take your study pills in person during this visit.

The treatments in this study will be 'blinded', meaning neither you nor the study investigators will know which study treatment you are getting. This information could be obtained in an emergency however, you will not be told which study treatment you are getting, but your study doctor will know.

At the end of this visit, we will provide you with a supply of the assigned pills and you will be allowed to go home. We will schedule your next visit within 1-2 weeks of visit 2.

Visit 3 Safety: This visit will last approx. 1 hour. You will be asked to report to the 6th Floor of the Atran Building at the MSMC in a fasting state. During this visit, we will perform the same procedures at per the visit1. The most important reason for this visit is to monitor the safety and efficacy of the medicine that you are taking. During this visit, we will record your vital signs (weight, height, body temperature, blood pressure, pulse) and collect one blood sample (15mls or 1 table spoon) for routine lab test (lipids, glucose, liver enzymes, etc.). We will ask you questions about your health since your last visit. Thereafter, we will provide you with a supply of the assigned pills and your visit will end.

Visit 4 Maintenance: This visit will last approx.1 hour. Within 12-14 weeks of the previous visit, you will be asked to report to the 6th Floor of the MSMC in a fasting state. The reason for this visit is to continue monitoring the safety and efficacy of the medicine that you are taking. We will repeat the procedures done during your previous visit (i.e. record your vital signs and collect one blood sample for routine lab test) and ask you questions about your health status since your last visit. Thereafter, we will provide you with a supply of the assigned pills and your visit will end.

Visit 5 Final: This will be the last visit and will have an approx. duration of approx. 4 hours. You will be asked to report to the 6th Floor of the Atran Building at the MSMC in a fasting state. During this visit, we will repeat the procedures performed during visit 2. The procedures will be: Magnetic resonance imaging, Oxygen consumption, 6-minute walking test, the Minnesota questioner and collect one blood sample (15 mls or 1 table spoon). We will record your vital signs (body weight, height, body temperature, blood pressure, pulse) and EKG to check your health status. The comparison of the results obtained during visit 2 and visit 5 will allow us to delineate the effects of the study drug. At the end of this visit, your participation in the study will end.

Description of Procedures Being Performed

Cardiac Magnetic Resonance Imaging (CMR): CMR studies will be performed at the Cardiac Imaging Facilities of the Mount Sinai Heart under the direction of Dr. Javier Sanz (Investigator of the proposal). Images will be acquired with a 3.0 Tesla magnet (Achieva, Philips Medical Systems, Netherlands). Steady-state free precession short axis images (TR 3.6 ms, TE 1.6 ms, flip angle 45º, field of view 250 x 250 mm, SENSE factor 3, voxel size 1 x 1 x 5 mm, no gap, number of averages 3, bandwidth 1286 Hz, 12 lines per segment) from the LV base through LV apex will be used for the quantification of LV volumes, ejection fraction and mass. Late gadolinium enhancement (LGE) will be performed 15 minutes after the administration of gadolinium (Magnevist, 0.2 mmol/kg) using an inversion- recovery fast gradient echo sequence (TR 9 ms, TE 5.4 ms, TI optimized to null normal myocardium, gating factor 3, field-of-view 250 x 250 mm, pixel size 1 x 1 x 5 mm, SENSE factor 3, number of averages 3, bandwidth 232 Hz, TFE factor 16). A Look-Locker sequence will be performed before and 10 minutes after gadolinium administration to evaluate interstitial myocardial fibrosis using the T1 mapping technique. All CMR images will be blindly analyzed using commercially available software (Extended MR Workspace, Philips Medical Systems, Netherlands). Epicardial and endocardial

contours will be traced in each SSFP cine image to obtain LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV ejection fraction (LVEF) and LV mass; by convention, papillary muscles will be included in the LV cavity. LV scar size will be measured by LGE and expressed as a percentage of the LV mass; the absolute MI size also was quantified in grams (calculated as volume multiplied by myocardial density [1.05 g/cm3]). Infarct was defined as myocardium with signal intensity was higher than 3 standard deviations of that in remote, normal. Longitudinal relaxation times for T1 mapping quantification will be measured using cvi42 software (already present in our clinical facility).

Peak Oxygen Consumption: Cardiopulmonary exercise testing will be done prior to randomization and at 6 months of therapy. Patients will report in the fasting state to the Mount Sinai Research Cardiopulmonary Exercise laboratory on Guggenheim 6. This facility is under the direction of Dr. Donna Mancini (investigator of this proposal). Patients will perform a treadmill exercise using the modified Naughton protocol with continuous EKG monitoring. Blood pressure will be measured prior to exercise, at the end of each exercise stage and at peak exercise. The patient will be connected using a mouthpiece to a metabolic cart (Medical Graphics Ultima Cardio 2, St Paul, Minn) for continuous measurement of oxygen consumption, carbon dioxide production and minute ventilation. Symptom limited exercise will be performed. Perceived levels of dyspnea and fatigue will be measured using the Borg scale. Peak VO2, VE/ VCO2 ratio and the aerobic threshold will be recorded.

6 minute walk test: Patients will perform a 6 min walk test prior to and 6 months post randomization. In a quiet 100 ft hall the patients will be instructed to walk as fast and perform as many laps as possible between the distance markers over a period of 6 minutes. The walk test will be supervised but unencouraged. Blood pressure and heart rate are measured at the start and end of the 6 min. Patients will be allowed to stop and rest if needed. The total distance walk will be recorded.

Heart Failure Questionnaire: We will ask you some questions about the quality of life. The questionnaire will be repeated at the end of the 6-months of study.

Inflammatory and cardiovascular biomarkers: will be assessed two times throughout the study: at the time of randomization and at the end of the study using the Human Cytokine/Chemokine Panel I kit (Luminex; Cat # HCYTMAG-60K-PX41) that allows to measure 41 inflammatory cytokines and chemokines with well-established predictive value for CV risk and mortality. The effect of the treatment will be assessed by changes in the value of the selected biomarkers between the randomization and the end of study time–points.

Description of the Source Records that Will Be Used to Collect Data About Subjects
All the data will be recorded in a specifically prepared Case Report Form (CRF) that includes all the parameters mentioned in the next section

Description of Data that Will Be Collected Including Long-Term Follow-Up
The major end-points are the effect of the treatment on cardiac function assessed by CMRI. Vital signs and routine blood parameters will be assessed at each visit. In addition at the screening and at the end of the 6-months of follow-up we will monitor the effect of the treatments on systemic cytokines and chemokines with well-established predictive value for CV risk and mortality by using the Human Cytokine/Chemokine Panel I kit (Luminex; Cat # HCYTMAG-60K-PX41).

10. ***Procedures - Details***

Surveys or Interviews
Yes

Names of Standardized Instruments
To determine if there is a change in the patient-reported quality of life by the Minnesota Living with HF and SF-36 questionnaires. We will also ask for any adverse event at each of the visits.

11. ***Consent - Obtaining Consent***

Consent Process
Adult Consent

Where and When Consent Will Be Obtained
Informed consent form will be obtained at the Heart Failure Unit and/or Atran 6th Floor Room 20

Waiting Period for Obtaining Consent
A maximum 4 weeks

SOP HRP-090 Informed Consent Process for Research Is Being Used
Yes

Process to Document Consent in Writing
Will Use Standard Template

Non-English Speaking Participants Will Be Enrolled
Yes

What Languages Other Than English Will Be Used
Spanish speaking participants will be also approached. They will be offered a consent form in Spanish.

What Process Will Be Used
Long Form

12. ***Data – Collection, HIPAA and Storage***

Description of Health Information That Will Be Viewed, Recorded, or Generated

- Clinical History
- Vital signs
- Routine clinical lab tests
- Cardiac function assessed by CMRI
- Oxygen consumption
- Systemic biomarkers

HIV / AIDS Related Information Will Be Viewed or Recorded
No

Obtaining HIPAA Authorization
Yes

How PHI Will Be Protected from Improper Use or Disclosure
Participants will be identified by a study code. Only the PI will have access to the subject identification. The code will be under lock at the PI's office.

PHI Will Be Destroyed at the Earliest Opportunity Consistent with the Research
No

Justification for Retaining PHI Indefinitely
It will be retained for a maximum of 3 years

PHI Will Be Shared
No

Location Where Data Will Be Stored
At the PI's office (Atran Building 6th Floor Room20) in a locked cabinet

How will the data be stored?
Coded and de-identified.

Duration Data Will Be Stored
3 years after the end of the study

Steps That Will Be Taken to Secure the Data During Storage, Use, and Transmission
Only the PI will have access to the identifying code

Power Analysis/Data Analysis Plan (Including Any Statistical Procedures)
At the end of the study, the data analysis will performed. All data will be presented as mean±SD. For statistical comparison, data will be initially tested for Normality by using the Kolmogorov-Smirnov's test. In case the data follow a normal distribution, they will be compared between groups using a Student-t test. If the data do not follow a normal distribution, data will be presented as median ± interquartilic range. Medians will be compared between groups with the nonparametric Mann-Whitney's U (as 2 groups will be compared); when variances look different (ratio >2), the Welch t test will be used instead. Two-way repeated-measures ANOVA will be used to compare values between 2 groups at different time-points. All statistical calculations will be performed with SPSS 18.0. Differences will be considered statistically significant at values of $P<0.05$.

13. ***Data - Safety Monitoring***

More Than the Minimum Data Safety Monitoring Will Be Done
Yes

Principal Monitor Donna Mancini

Additional Monitors

Name Ronald Tamler
Department Medicine - Endocrinology

Name Sean Pinney
Department Medicine - Cardiology

Name Usman Baber
Department Medicine - Cardiology

Name Samantha Sartori
Department Cardiovascular Institute

Specific Items That Will Be Monitored for Safety
Effect of the treatment on routine lab test. Safety and tolerability of the treatments is the major reason for visits 3 and 4. Major items to be monitored are: hypoglycemia, urinary tract infections, bone fractures, diabetic ketoacidosis and thromboembolic events will be monitored during the follow-up period.

We will also assess survival, re-hospitalizations and heart failure worsening (as more visits, increase in prescription of diuretics, etc)

Frequency of Data Review
Each 6-months or more frequently as needed during the study development.

Rules for Alteration of Study Design
Patients showing any adverse effect (as mentioned before) to the treatments will be advised to stop taking the drug and removed from the trial.

Selection Procedures to Minimize Toxicity
Potential candidates will be screened for eligibility prior randomization. Upon treatment initiation, they will be monitored at 1- and 3- months for presence of adverse effects.

We will also performe a test for safety at study termination.

Grading System to Evaluate Adverse Events
The intensity of clinical AEs will be graded on a 3-point scale (mild, moderate, severe) and will be reported on specific AE pages of the CRF. The three categories of intensity are defined as follows:

- Mild. - The event may be noticeable to the subject. It does not usually influence daily activities, and normally does not require intervention.
- Moderate. - The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.
- Severe. - The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious. These terms are used to describe the intensity of a

specific event. Medical judgment should be used on a case-by-case basis. Seriousness, rather than intensity assessment, determines the regulatory reporting obligations.

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by the investigator.

Procedures to Assure Data Accuracy

The PI will serve as Investigator of Records (IoR). He will appoint a senior member of his clinical research staff to serve as Study Coordinator, who will work closely with the Regulatory Manager of the Mount Sinai Heart, to monitor case report forms (CRFs) on a weekly basis, and the SMC will meet every 6 months, or more frequently is needed, during the study to review CRFs.

The Study Coordinator will verify data collected on case report forms against source documents. Source documents can include any of the following: hospital records, research records, laboratory values, subject diaries, checklists, pharmacy records, data recorded from automated instruments (such as ECG), medical transcriptions, magnetic media images, and x-rays.

The Study Coordinator will work closely with the Mount Sinai Heart Regulatory Manager to compare the procedures defined in the protocol as well as regulatory requirements to ensure data integrity. Internal auditing includes the review of all the regulatory documents; (IRB, regulatory agency correspondence) and clinical records. The IoR and the Study Coordinator will ensure the following regulatory requirements are met:

- Verify investigator qualifications.
- Review PI and sub-investigator CV's and registrations and verify documentation was current at time of study visit.
- Verify current certifications and lab normal ranges protocol-required procedures.
- Verify equipment not covered under CLIA or CAP certifications are adequately maintained and review certifications.
- Verify facilities remain adequate throughout the trial.
- Ensure drug dispensation and storage complies with regulatory requirements.
- Verify documentation in the master file of receipt of disposition/use and return of product.
- Verify the master file contains guidelines for handling product.
- Verify the site maintains records that indicate product has been supplied only to eligible subjects at protocol specified doses.
- The investigator's records for study drug shipping receipts including lot number and quantity (if applicable).
- Shipping receipts to other sites (if applicable).
- Review of dispensing logs including the subject initials, number, dose or quantity and person dispensing.
- Temperature log.
- Return receipts.
- Verify that the protocol or the master file documents provides the necessary instruction s to the patients on how to use, handle, store, and return drug.
- Verify the site is following the approved IRB protocol.
- Ensure protocol deviations and violations are reported.
- Verify Informed Consent process.
- Informed Consent review.
- Review of the signed informed consent documents for the correct version, completeness of the subject's or legally authorized representative signature and date, signature and date of person obtaining the consent, investigator signature and date, and witness name, signature and date when required.
- Documentation of the informed consent process or enrollment note. The staff member should evaluate for documentation of the informed consent discussion, a question and answer period, the subject had adequate time to reflect, make an informed decision, signed the informed consent prior to the initiation of any study procedures and received a copy of the signed informed consent.
- Verify correct version of IRB-approved consent form was used.
- Verify the subject completed a HIPAA form prior to enrollment.
- Verify staff has adequate training and responsibilities have not been delegated to unauthorized individuals.
- Report subject recruiting and enrollment rate.
- Compare the number of subjects who signed informed consent to the limit approved by the IRB.

- Check subject screening log to document subjects who entered screening but did not participate in the trial.
- Verify accuracy of records and completeness of CRF entries and ensure corrections are made when necessary.

Suspension Reported to
Study suspension would be immediately reported to the IRB and the funding agency (Boehringer-Ingelheim) by the PI.

Anticipated Circumstances of Subject Withdrawal
The anticipated circumstances for a subject withdrawal are:
- presence of an adverse event.
- poor adherence to the study.
- any other circumstances based on the opinion of the treating physician.

Primary or Secondary Safety Endpoints
Primary end-point: hypoglycemia, urinary tract infections, diabetic ketoacidosis and thromboembolic events during the follow-up period. Secondary end-points: bone fractures, re-hospitalizations and heart failure worsening (assessed as more visits, increase in prescription of diuretics, etc)

14. ***Drugs / Biologics***

Generic Name
Empagliflozin

Brand Name
Jardiance

Icahn School of Medicine at Mount Sinai (ISMMS) Is the Coordinating Center
Yes

Role of the Investigational Drug Service (IDS)
None

Controlled Substance
No

Drug / Biologic Will Be Supplied By
Sponsor

Using Placebo
Yes

Placebo Will Be Supplied By
Sponsor

Where Drug / Biologic Will Be Administered
Outpatient Faculty Practice Associates (FPA)

Storage Requirements of Drug / Biologic
Controlled Room Temperature (15 - 30°C)

Where Drug / Biologic Will Be Stored
By Research Personnel at a Site Outside of Hospital Areas

ALL of the Following Storage Criteria Are Met
The storage area is well maintained, provides adequate lighting, ventilation, sanitation, space and security. * The temperature in the storage area is controlled and monitored using calibrated monitoring devices. * The temperature monitoring system has sensors for continuous monitoring and alarms set at the points representing the temperature extremes. * Records of temperatures and alarms are maintained and all excursions outside the labeled storage conditions are appropriately investigated and reported to the sponsor.