Sodium-glucose Cotransporter 2 Inhibitors in Transthyretin Amyloid Cardiomyopathy

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STUDY SYNOPSIS

Protocol Title	SGLT2 Inhibitors in Cardiac Amyloidosis
Protocol Number	3
Design	This is a single center, single arm, prospective, 12 week open label pilot trial of the sodium-glucose cotransporter 2 inhibitor (SGLT2i), empagliflozin 10 mg oral daily, in patients with transthyretin amyloid cardiomyopathy (ATTR-CM), an age-related infiltrative cardiomyopathy that causes heart failure and death. The target population for enrollment will be subjects with ATTR-CM and either non-insulin dependent diabetes mellitus (DM) or chronic kidney disease (CKD). The primary aim will be to assess the safety and tolerability of empagliflozin 10 mg oral daily in subjects with heart failure secondary to ATTR, which remain unexplored. In addition, we will evaluate a number of secondary outcomes, including differences in daily diuretic dose, patient important outcomes using the Kansas City Cardiomyopathy Questionnaire (a validated health status measure for heart failure) and the Short Physical Performance Battery (a functional assessment), and potential mechanistic effects by evaluating changes in body composition, echocardiographic features, and cytokine and cardiorenal syndrome biomarker levels. The accrual target is 15 subjects for this single arm pilot study assessing safety and tolerability of the study drug as the primary outcome. Consented eligible patients will be evaluated for safety and tolerability of study drug, empagliflozin 10 mg oral daily, over a period of 3 months. During this time, subjects will undergo a total of 6 study visits: 3 in-person and 3 telephone follow-ups.
Study Sites	This study is to be conducted at 3 locations at Columbia University Irving Medical Center: screening, recruitment, and in-person visits at the Center for Advanced Cardiac Care, Heart Center 4th Floor; in-person visits, laboratory specimen collection, and echocardiography at the Clinical Cardiovascular Research Laboratory for the Elderly (CCRLE) at 21 Audubon Avenue, SB-0180; body composition analysis (including bioimpedance analysis and quantitative magnetic resonance) at the Body Composition Unit of NY Nutrition Obesity Research Center, located at 21 Audubon Avenue, Suite SB-0134.

Time on Study	The duration of patient participation in this study is approximately 4 months.
Primary Objective	To assess safety and tolerability of the SGLT2i empagliflozin in patients with ATTR-CM.
Sample Size	15 subjects
Inclusion and Exclusion Criteria	Every participant must meet all of the following inclusion criteria to be eligible for enrollment in **ALL** parts of this study: 1. Age ≥ 18 years old 2. Diagnosis of TTR cardiac amyloidosis (wild type or variant), confirmed by the presence of amyloid deposits on analysis of biopsy specimens obtained from cardiac and noncardiac sites (e.g. fat aspirate, gastrointestinal sites, salivary glands, or bone marrow), technetium-99m pyrophosphate cardiac scintigraphy, or mass spectrometry 3. Normal serum free light chain ratio and the absence of abnormal monoclonal band on serum and urine immunofixation 4. Subjects will have at least 1 of the FDA-approved indications below for an SGLT2i, and meet package-insert criteria for drug initiation a. Non-insulin dependent diabetes mellitus with hemoglobin A1c ranging from 6.5-9.9 OR b. Chronic kidney disease (defined as an estimated glomerular filtration rate of 20-75 ml/minute/1.73 m^2 of body-surface area) 5. On stable oral diuretics (defined as no more than a 50% increase from baseline diuretic dose established during a sustained 2 week period) within 2 weeks before enrollment 6. Able to understand and sign the informed consent document after the nature of the study has been fully explained The presence of any of the following excludes eligibility for enrollment in this study: 1. Prior liver or heart transplantation 2. Active malignancy or non-amyloid disease with expected survival of less than 1 year 3. Heart failure, in the opinion of the investigator, primarily caused by severe left-sided valve disease. *Note: if valve was repaired, subject may be considered as no longer with severe valve disease* 4. Heart failure, in the opinion of the investigator, primarily caused by ischemic heart disease 5. Current or anticipated ventricular assist device within the next 6 months 6. Pacemaker or implantable cardioverter defibrillator incompatible with magnetic resonance technology***** 7. Absolute contraindication for quantitative magnetic resonance (e.g. aneurysmal clips, metal objects)***** 8. Impairment from stroke, injury or other medical disorder that precludes participation in the study 9. Myocardial infarction, cardiovascular surgery, stroke or transient

	ischemic attack within the prior 90 days 10. Disabling dementia or other mental or behavioral disease 11. Enrollment in a clinical trial not approved for co-enrollment 12. Expected use of continuous intravenous inotropic therapy in the next 6 months 13. High risk for non-adherence as determined by screening evaluation 14. Inability or unwillingness to comply with the study requirements 15. Chronic kidney disease with eGFR <15 mL/min/1.73 m^2 or end-stage renal disease 16. Current or prior SGLT2i use 17. Type 1 diabetes mellitus or insulin-dependent diabetes mellitus 18. NT-proBNP < 300 pg/mL or < 900 pg/mL if concomitant diagnosis of atrial fibrillation 19. History of ketoacidosis 20. History of complex urinary tract or genital infections 21. History of pyelonephritis 22. Systolic blood pressure < 90 mmHg and symptomatic hypotension 23. Systolic blood pressure ≥ 180 mmg Hg 24. Severe chronic obstructive pulmonary disease thought to be a primary contributor to dyspnea 25. Major surgery in the 90 days before or after screening 26. Chronic alcohol or drug abuse 27. Nursing home resident 28. Other reason that would make the subject inappropriate for entry into this study ***Subjects with exclusion criteria 6 or 7 may be enrolled in a study subset that entails all study procedures EXCEPT the body composition analysis, which would necessarily be excluded.** ****In addition, all subjects will be offered the opportunity of opting out of the body composition analysis if they meet eligibility criteria (e.g. if a subject has a compatible pacemaker / defibrillator but does not want to undergo device adjustments, a physical limitation or claustrophobia making it difficult to lay in the scanner, they may opt OUT of the body composition analysis scans).**
Aims	The specific aims of this investigation include: 1. To evaluate the safety and tolerability of SGLT2i therapy in patients with ATTR-CM and DM or CKD on oral loop diuretic therapy 2. To evaluate the change in oral loop diuretic daily dose in patients with ATTR-CM and DM or CKD on an SGLT2i.

	3. To evaluate the effect of SGLT2i therapy on body composition in patients with ATTR-CM and DM or CKD. 4. To evaluate the effect of SGLT2i therapy on echocardiographic features of volume status in patients with ATTR-CM and DM or CKD. We will explore the following: 1. The effect of SGLT2i therapy on urinary PAPPA2, a potential urinary biomarker of volume status by measuring differences in urinary PAPPA2 before and after SGLT2i therapy. 2. The effect of SGLT2i therapy on markers of systemic inflammation and uricosuria in patients with ATTR-CM and DM or CKD by measuring differences in cytokine and cardiorenal syndrome biomarker levels before and after SGLT2i therapy utilizing proteomics.
	The safety of study participants will be evaluated by: 1. Assessment of adverse events (AEs), including serious adverse events (SAEs). 2. Clinical laboratory safety tests (serum chemistry). 3. Vital sign measurements (blood pressure, pulse rate, and respiratory rate). 4. 12-Lead electrocardiogram (ECG). 5. Physical examinations 6. Scheduled phone follow-ups to screen for signs and symptoms related to study drug 7. Review of subjects' available medical records, including for urgent care or emergency room visits, hospitalizations, and office visits

SCHEDULE OF ACTIVITIES

The following table summarizes the activities to be performed at each of the designated study visits. Details of the different procedures can be found in subsequent section of this protocol. For every study visit, a checklist will be used to help ensure completion of all the study procedures.

Procedure	**Screening (within 30 days of baseline visit)**	**Baseline (day 1)**	**Week 1 (7 ± 2 days)**	**Week 4 (28± 3 days)**	**Week 6 (42± 4 days)**	**Week 8 (56± 5 days)**	**Week 12 (84± 7 days)**
Site	Clinic	Clinic	Phone	Phone	Clinic	Phone	Clinic
Informed Consent	X						
Inclusion and Exclusion Criteria	X						
Baseline History		X					
Vitals Signs, Clinical Exam		X			X		X
Medications		X	X	X	X	X	X
Adverse Events Review		X	X	X	X	X	X
Electrocardiogram		X			X		X
Laboratory Analysis‡		X	X[∫]		X		X
Transthoracic Echocardiogram		X					X
KCCQ		X			X		X
SPPB		X			X		X
*Body Composition Analysis**		X			X		X

‡ Includes: NT-proBNP, troponin-t, basic metabolic panel, hepatic function panel, complete blood count, hemoglobin A1c (at baseline and week 12), uric acid, cystatin C, beta-hydroxybutyrate, erythrocyte sedimentation rate, c-reactive protein; urinalysis, urine albumin, urine uric acid, urine creatinine.

*Body composition analysis includes bioimpedance and quantitative magnetic resonance measurements. ***As described in Inclusions and Exclusion Criteria section, a subset of study subjects may not be eligible for, OR may opt out of body composition analysis.***

∫ Laboratory analysis includes a single test, basic metabolic panel, to be drawn 7-10 days after study drug initiation to assess for significant flucations in renal function and ensure subjects' safety. Lab draw may be performed at CUIMC or locally to reduce subject burden.

Description of Study Procedures

*All study procedures will take place at Center for Advanced Cardiac Care, Heart Center 4th floor, or the Clinical Cardiovascular Research Laboratory for the Elderly (CCRLE) at 21 Audubon Avenue, unless otherwise noted.

I. Analysis of existing data and/or prospective record review

Study personnel will screen charts of patients seen in the Center for Advanced Cardiac Care for study eligibility. Medical records will be screened for assessment of cardiac function, renal function, inclusion and exclusion criteria.

II. Biological specimens (collection or use of)

Study participants will have fasted blood samples obtained via routine phlebotomy during each of 3 in-person clinic visits, each 6 weeks apart. Blood samples obtained will consist of routine bloodwork for clinical care, in addition to specific lab tests for study purposes; 15 cc of blood (plasma and serum) sample will also be collected and stored in the CUIMC biobank for future research, which may include analysis of cytokines, biomarkers of cardiorenal syndrome, and proteomics. Study participants will also be asked to provide a urine specimen during each in-person clinic visit, 10 cc of which will be stored in the CUIMC biobank for future research, including analysis of biomarkers of cardiorenal syndrome. See table for specification of blood and urine laboratory measures to be made at each time interval. Laboratory analysis at the 1 week timepoint (which consists of a single lab test, a basic metabolic panel) may be performed at CUIMC or locally to reduce subject burden.

III. Drugs or Biologics

As part of this trial, study participants will be asked to take 1 tablet of empagliflozin 10 mg oral daily for 3 months. Empagliflozin is a sodium-glucose cotransporter 2 inhibitor (SGLT2i) approved by the U.S. Food and Drug Administration (FDA) for treatment of diabetes mellitus (type 2), chronic kidney disease, and heart failure with reduced ejection fraction. Subjects who are enrolled in this study will have either diabetes mellitus or chronic kidney disease, consistent with FDA approved indications for this drug.

IV. Future use of data and/or specimens

Biobanked blood and urine specimens may be analyzed in the future for cytokine expression profiles, biomarkers of cardiorenal syndrome, and proteomics. Data collected during this pilot trial may be used for design and development of future larger trials of SGLT2i in subjects with ATTR-CM.

V. Transthoracic Echocardiogram

Study participants will have a transthoracic echocardiogram (TTE) performed at trial start and 12 weeks during the in-person clinic visits. TTE will be performed by certified echocardiographer and CCRLE lab manager, Steve Helmke. Estimated time for TTE: 40 minutes.

VI. Survey/interview/questionnaire

Study participants will be administered the Kansas City Cardiomyopathy Questionnaire (KCCQ) at trial start, 6 weeks, and 12 weeks during 3 in-person clinic visits. Questionnaire data will be collected and recorded in a secure manner as previously described. See attached PDF entitled "KCCQ" for questionnaire (English and Spanish versions provided).

VII. Non-invasive physical measurements*

a. At each of 3 in-person visits, subjects will first arrive to the Body Composition Unit of NY Nutrition Obesity Research Center, located at 21 Audubon Avenue, basement level in Suite SB-0134, where they will undergo body composition analysis. Subjects will be asked to change into a hospital gown, void, and undergo body weight measurement on a certified scale, and height measurement.

b. Body composition analysis will be performed using 2 techniques: bioimpedance analysis (BIA) and quantitative magnetic resonance (QMR). Subjects with a pacemaker or implantable cardioverter defibrillator device will require an additional 20 minutes for interrogation and adjustment of their device settings before and after BIA and QMR scan to ensure no cardiac device interference and normal device functioning, a procedure which is consistent with standard of care for patients with cardiac electrophysiologic devices. Device adjustment and interrogation will be performed by Dr. Ani Nalbandian, fellow in cardiovascular disease, under the supervision of Dr. Hirad Yarmohammadi, electrophysiology cardiology attending.

c. Bioelectrical impedance analysis (BIA) is a commonly used method to measure body composition, specifically fat, fat-free mass, and water in the whole body in healthy adults. We will assess how well the seca BIA instrument (seca gmbh & co. kg, Hamburg, Germany) measures the amount of water, fat and fat-free mass in the body compared to quantitative magnetic resonance, another established approach. There are several BIA devices on the market approved for use by the Federal Drug Administration. The accuracy of the BIA approach for use in patients with HF, where edema is common, needs to be determined. BIA offers a rapid and practical approach for estimating body composition in patients, however, both cross-sectional and longitudinal validation studies are needed to confirm whether the method is valid and reliable using an established reference method, such as that proposed here with quantitative magnetic resonance technology. This study will collect BIA measurements when standing. The results from this BIA measure will be compared to the corresponding total body water, fat, fat-free mass values from quantitative magnetic resonance, as described below. This study will help physicians, scientists, and health professionals to interpret the accuracy of the results from this BIA device. Bioimpedance analysis measurements will take approximately 15 minutes.

d. Subjects will undergo quantitative magnetic resonance scan (QMR). Subject set-up and QMR scan will require a total of 6 minutes. The QMR system offers the potential of a safe, rapid, practical, accurate, precise and affordable means of quantifying fat, lean tissue mass, and body water.

e. After completion of the body composition analysis, subjects will proceed next door to the CCRLE where the remaining study procedures will be performed. This will include the Short Physical Performance Battery, a functional assessment tool which includes gait speed, chair stand and balance tests.

***As described in Inclusion and Exclusion Criteria: subjects with exclusion criteria 6 or 7, OR who opt out of body composition analysis will not undergo study procedures VIIb, VIIc, VIId.**

Statistical Procedures:

The primary endpoint for this pilot trial will be a serious adverse event rate greater than 30%, which is an acceptable rate, based on prior clinical trial data with sodium-glucose cotransporter 2 inhibitors in subjects with heart failure over a 3 month period. Secondary endpoints will include mean change in daily diuretic dose (mg/kg of furosemide equivalence), mean change in body weight (kg) and total water content (kg), and mean change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score and Short Physical Performance Battery (SPPB) score. In preliminary analyses, we will describe the baseline characteristics of subjects. In particular, we will present summary measures on patient age, sex, diabetes status, renal function, NT-proBNP level, KCCQ score, SPPB score, daily diuretic dose, echocardiographic features, and body composition analysis (including body weight and total water content). Continuous variable distributions will be assessed for normality and skewness, and log transform applied when appropriate. A matched-paired t-test will be used to test for a significant difference in the means of measured secondary endpoints pre- and post-treatment with empagliflozin 10 mg oral daily for 3 months.

Power calculations:

Primary endpoint: A power calculation for our primary endpoint is not applicable in this pilot safety and tolerability trial.

Sample secondary (daily diuretic dose) endpoint power calculation: Based on prior literature, an estimated mean daily diuretic dose of 0.6 mg/kg with an effect size of 0.5 mg/kg, and a sample size of 15 total accrued subjects, will have 75% power to detect a difference in mean daily diuretic dose before and after study drug treatment using a two-sample t-test at the 5% level of significance.