Effects of dapagliflozin on biomarkers, symptoms and functional status in patients with PRESERVED ejection fraction Heart Failure (PRESERVED-HF trial)

Statistical Analysis Plan (SAP)

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Abbreviation or special term	Explanation
AE	Adverse Event
AFib	Atrial fibrillation
BMI	Body mass index
BNP	B-type natriuretic peptide
CRF	Case Report Form (electronic/paper)
DBP	Diastolic Blood Pressure
DM	Diabetes mellitus
EPS	Enrolled Patients Set
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
HDL	High-Density Lipoprotein
HF	Heart failure
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
ITTS	Intention to treat set
IP	Investigational Product
IPDs	Important Protocol Deviations
MCAR	Missing completely at random
MDRD	Modification of Diet in Renal Disease
NSVT	Nonsustained ventricular tachycardia
NTproBNP	N-terminal (NT)-pro hormone BNP
NYHA	New York Heart Association
PPS	Per protocol set
PAC	Premature atrial contractions
PTDV	Premature treatment discontinuation visit
PVC	Premature ventricular contractions
SAE	Severe Adverse Event
SAFS	Safety Analysis Set
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure

Abbreviation or special term	Explanation
SD	Standard deviation
SE	Standard error
SGLT-2	Sodium-glucose cotransporter 2
T2DM	Type 2 Diabetes Mellitus
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Contents

1 INTRODUCTION

1.1 Study Objectives

Primary Study Objective	To evaluate the effects of dapagliflozin vs. placebo on heart failure related health status using the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score at 12 weeks.
Secondary Study Objectives	1. To evaluate the effect of dapagliflozin vs. placebo on heart failure related health status using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 12 weeks 2. To evaluate the effect of dapagliflozin vs. placebo on NTproBNP at 6 and 12 weeks 3. To evaluate the effect of dapagliflozin vs. placebo on BNP at 6 and 12 weeks 4. To evaluate the effect of dapagliflozin vs. placebo on 6-minute walk test at 12 weeks 5. To evaluate the effect of dapagliflozin vs. placebo on HbA1c over the treatment period (evaluated separately in patients with and without type 2 diabetes) 6. To evaluate the effect of dapagliflozin vs. placebo on proportion of patients with a ≥ 5pts increase in KCCQ clinical summary score and KCCQ overall summary score at 12 weeks 7. To evaluate the effect of dapagliflozin vs. placebo on proportion of patients with a ≥ 20% decrease in NTproBNP at 6 and 12 weeks 8. To evaluate the effect of dapagliflozin vs. placebo on proportion of patients with a ≥ 5pts increase in KCCQ and a ≥ 20% decrease in NTproBNP at 6 and 12 weeks 9. To evaluate the effect of dapagliflozin vs. placebo on weight at 6 and 12 weeks 10. To evaluate the effect of dapagliflozin vs. placebo on systolic blood pressure at 6 and 12 weeks
Exploratory objectives	1. To evaluate the effect of dapagliflozin vs. placebo on composite hierarchical-rank clinical score. 2. To evaluate the effect of dapagliflozin vs. placebo on heart failure hospitalizations 3. To evaluate the effect of dapagliflozin vs. placebo on urgent heart failure visits 4. To evaluate the effect of dapagliflozin vs. placebo on heart failure hospitalizations and urgent heart failure visits

	5. To evaluate the effect of dapagliflozin vs. placebo on the proportion of patients that progress to diabetes during the treatment period (within the subgroup of patients without diabetes at baseline only) 6. To evaluate the effect of dapagliflozin vs. placebo on weekly loop diuretic dose (furosemide equivalent) 7. To evaluate the effect of dapagliflozin vs. placebo on NYHA Class at 6 and 12 weeks. 8. To evaluate the effect of dapagliflozin vs. placebo on left atrial volume index and other measures of left ventricular diastolic function (among Echocardiography sub study participants only)

1.2 Study Design

Design Configuration and Subject Population	Randomized, double-blind, placebo-controlled trial. The control group will receive placebo administered orally once daily for 12 weeks plus standard of care. The treatment group will receive dapagliflozin 10 mg administered orally once daily for 12 weeks plus standard of care. A follow-up visit at week 13 will be performed to evaluate markers of renal function.
Treatment Groups	Dapagliflozin 10 mg or matching placebo administered orally once daily for 12 weeks, in addition to standard of care for chronic heart failure with preserved systolic function.
Inclusion criteria	1. Age > 18 and < 120 at the screening visit 2. Symptoms of dyspnea (NYHA class II-IV) without evidence of a non-cardiac or ischemic explanation for dyspnea 3. Ejection fraction (EF) ≥ 45% as determined on imaging study within 24 months of enrolment with no change in clinical status suggesting potential for deterioration in systolic function 4. Elevated NT-proBNP (≥ 225 pg/ml) or BNP (≥ 75 pg/ml) ₸ 5. Stable medical therapy for heart failure for 15 days as defined by: i. No addition or removal of ACE, angiotensin receptor blockers (ARBs), valsartan/sacubitril, beta-blockers, calcium channel blockers (CCBs) or aldosterone antagonists ii. No substantial change in dosage (100% or greater increase or decrease from baseline dose) of ACE, ARBs, beta-blockers, CCBs or aldosterone antagonists 6. On a diuretic ≥15 days prior to screening visit and a stable diuretic therapy for 7 days 7. At least one of the following: i. Hospitalization for decompensated HF in the last 12 months ii. Acute treatment for HF with intravenous loop diuretic or hemofiltration in the last 12 months

	iii. Mean pulmonary capillary wedge pressure ≥15 mmHg or LV end diastolic pressure (LVEDP) ≥15 mmHg documented during catheterization at rest, or pulmonary capillary wedge pressure or LVEDP ≥25 mmHg documented during catheterization with exercise. iv. Structural heart disease evidenced by at least one of the following echo findings (any local measurement made within the 24 months prior to screening visit): 1) left atrial (LA) enlargement defined by at least one of the following: LA width ≥3.8cm or LA length ≥5.0 cm or LA area ≥20 cm2 or LA volume ≥55 mL or LA volume index ≥29 mL/m2 2) OR left ventricular hypertrophy (LVH) defined by septal thickness or posterior wall thickness ≥1.1 cm.
Exclusion criteria	1. Decompensated heart failure (hospitalization for heart failure within 7 days prior to screening) 2. History of type 1 diabetes 3. History of diabetic ketoacidosis 4. Estimated glomerular filtration rate (eGFR) < 20 at the screening visit by modified MDRD equation GFR (mL/min/1.73 m2) = 175 x (Scr) -1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if African American) 5. Admission for an acute coronary syndrome (ST-elevation MI, non-ST-elevation MI, or unstable angina), percutaneous coronary intervention, or cardiac surgery within 30 days prior to the screening visit. 6. Admission for cardiac resynchronization therapy (CRT) within 90 days prior to the screening visit. 7. Planned cardiovascular revascularization (percutaneous intervention or surgical) or major cardiac surgery (coronary artery bypass grafting, valve replacement, ventricular assist device, cardiac transplantation, or any other surgery requiring thoracotomy, or transcatheter aortic valve replacement) or CRT within the 90 days after the screening visit. 8. Participation in any interventional clinical trial (with an investigational drug or device) that is not an observational registry within 15 days of the screening visit. 9. History of hypersensitivity to dapagliflozin 10. For women of child-bearing potential: Current or planned pregnancy or currently lactating. Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Post menopausal is defined as 12 consecutive months

	with no menses without an alternative medical cause. Women of child-bearing potential, who are sexually active, must agree to use a medically-accepted method of birth control for the duration of the study. Acceptable birth control methods include: (1) surgical sterilization (such as a hysterectomy or bilateral tubal ligation), (2) progesterone hormonal contraceptives (birth control pills or implants), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Women of child-bearing potential will have a urine pregnancy test at every clinic visit and it must be negative to continue study participation. 11. Life expectancy <1 year at the screening visit 12. Patients who are volume depleted based upon physical examination at the time of the screening or randomization visit 13. BNP <75 pg/mL and NTproBNP<225 pg/mL at the screening visit £ 14. Patients currently being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, dapagliflozin, ertugliflozin) or having received treatment with any SGLT-2 inhibitor within the 12 weeks prior to the screening visit. 15. Average supine systolic BP <100 mmHg at the screening or randomization visit 16. Current history of bladder cancer 17. Donation of blood or bone marrow 12 weeks prior to the screening visit and no planned donations during the study period 18. Heart failure due to restrictive/infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valve disease, and HOCM (hypertrophic obstructive cardiomyopathy). 19. Heart failure due to severe aortic or mitral regurgitation 20. Severe COPD thought to be a primary contributor to dyspnea 21. Isolated right heart failure due to pulmonary disease 22. Active and significant ischemia thought to be a primary contributor to dyspnea 23. Documentation of previous EF < 45%, under stable conditions, within the past 36 months 24. Complex congenital heart disease 25. Uncontrolled hypertension, defined as systolic blood pressure ≥200 mmHg during the screening visit (average value of three blood pressure measurements obtained in supine position)

	26. Any other condition that in the judgment of the investigator would jeopardize the patient's participation in the study or that may interfere with the interpretation of study data or if the patient is considered unlikely to comply with study procedures, restrictions and requirements 27. Bariatric surgery within the past 6 months or planned bariatric surgery within the study time course. 28. CardioMems device implantation within previous 4 weeks or planned CardioMems implantation during study period 29. For echo substudy only: patients with ventricular paced rhythm or left bundle branch block on the most recent clinically available 12-lead electrocardiogram. 30. For echo substudy only: permanent atrial fibrillation Ŧ For patients with permanent atrial fibrillation inclusion thresholds will be BNP ≥ 100 pg/mL or NTproBNP ≥ 375 pg/mL £For patients with permanent atrial fibrillation exclusion thresholds will be BNP<100 pg/mL and NTproBNP<375pg/mL

1.3 Sample Size and Power

Planned Sample Size	Approximately 160 patients will be enrolled in each arm.
Power Statement	For the primary endpoint a sample size of 145 for each group will achieve 82% power with α=0.05 to detect a 4.7 difference in mean KCCQ CS between dapagliflozin group and placebo group at 12 weeks. The assumptions for this calculation was derived from DEFINE-HF trial where the adjusted mean difference between dapagliflozin group and placebo group is 4.7 and the standard deviation is 13.7. Assuming a 10% loss to follow up, we arrive at a sample size of ~320 patients.

2 GENERAL CONSIDERATIONS FOR DATA ANALYSES

2.1 Analysis Data Sets

Efficacy and safety analyses will be performed on data from the following analysis sets:

- Enrolled patients set (EPS) will consist of all patients who signed the informed consent. This data set will be used to summarize the patient disposition data.

- Modified intention to treat set (modified ITTS) is defined as all patients who have been randomized to study treatment, have received at least one dose of study medication, and have sufficient evaluable data for endpoint ascertainment during follow up. For clarity, patients with no evaluable data for a particular outcome during follow up will be excluded from the analyses of these respective endpoints. Subjects will be analysed according to the randomization group. The modified ITTS data set will be used for the primary, secondary, and selected exploratory (, NYHA class, loop diuretic dose, progress to DM, left atrial volume index and other measures of left ventricular diastolic function) efficacy endpoints. Progress to DM will be assessed among participants in the modified ITTS who had no diabetes at baseline. Left atrial volume index and other measures of left ventricular diastolic function will be assessed among participants who are in the modified ITTS dataset and also in the Echocardiography sub study.

- On-treatment set (OTS) includes all subjects in the modified ITTS. Primary and secondary endpoint measurements will be excluded for the follow-up time point(s) when subjects were temporarily or permanently off the study drug at the time the corresponding measurements were obtained. The OTS data set will be used for a sensitivity analyses for the primary, secondary, and selected exploratory (composite hierarchical rank clinical score, NYHA class, loop diuretic dose) efficacy endpoints.

- The per protocol set (PPS) includes all subjects in the modified ITTS who did not have any major protocol deviations. Major protocol deviations, which are detailed in section 2.2, will be determined prior to unblinding of treatment groups. Subjects will be summarized according to actual treatment received regardless of the allocated treatment. This will be used for a sensitivity analysis for the primary efficacy endpoints only.
- The safety analysis set (SAFS) includes all patients who received at least 1 dose of study medication. Throughout the safety results sections, erroneously treated patients (eg, those randomized to dapagliflozin but actually given placebo) will be accounted for in the actual treatment group. If a patient received study drug from the wrong kit for only a part of the treatment duration and then switched to another, the associated actual treatment group for that patient will be the treatment group the patient had the longest exposure to. The main safety analyses will be restricted to adverse events that occurred between randomization and the 12-week visit. Adverse events that occurred between 12 weeks and 13 weeks (after discontinuation of study treatment) will be collected, and presented in a

separate, supplemental analysis. The safety analysis set will be used to summarize safety data and patient demography and their baseline characteristics, and to analyze selected exploratory endpoints (composite hierarchical-rank clinical score, heart failure hospitalizations, urgent heart failure visits, and a composite of heart failure hospitalizations or urgent heart failure visits). If there is a difference between the SAFS and modified ITTS, baseline and demography data will also be presented for the IITS.

2.2 Protocol Deviations and Major Eligibility Violations

Important Protocol Deviations (IPDs) are defined as those important deviations from the protocol that are likely to have an impact on the efficacy and/or safety of study treatments, or integrity of study data.

Protocol deviations will be reviewed in a blinded fashion by the study team prior to database lock. All decisions to exclude patients and/or data from the modified ITTS or PPS will be made prior to the unblinding of the study and agreed by the study team.

Error! Reference source not found.10.2 specifies the criteria for IPDs.

2.3 Strata, Covariates, and pre-specified subgroup analyses

All efficacy and safety endpoints will be analyzed in the entire cohort, and then within the subgroups of patients with and without diabetes. Analyses for the primary and secondary endpoints will be adjusted for the corresponding baseline measurements as well as sex, eGFR, diabetes (DM), permanent AFib, and LVEF. Restricted cubic splines will be used for continuous variables to accommodate non-linear effects, as appropriate.

A sensitivity analysis will repeat the primary analysis but will also include site as a random effect to account for potential clustering by enrolling centers. Another sensitivity analysis for the primary endpoint will be performed using the imputed KCCQ values as descripted in section 2.6.

Additionally, the following pre-specified subgroup analyses will be performed for the primary endpoints (stratified by the baseline variables below):

- Baseline NTproBNP (< median, ≥ median)
- Baseline LVEF (≤60%, > 60%)
- Atrial fibrillation type (No AFib, permanent/persistent AFib, paroxysmal AFib)
- Baseline KCCQ overall summary score (<median, ≥median)
- Baseline eGFR (<60, ≥60 mL/min/1.73 m2)
- Age (<70, ≥70)
- Sex (male, female)
- Race (white, non white)
- BMI(<median, ≥median)

- Furosemide equivalent mean daily dose: ≤ 40 mg, >40 mg
- NYHA Class (II , III or IV)

Subgroup analyses will be carried out by augmenting the primary analysis model with terms for subgroup and a subgroup-by-treatment interaction. Adjusted point estimates and 95% confidence intervals will be calculated for the effect of dapagliflozin compared with placebo within each subgroup. An interaction p-value will be provided.

Due to the large number of study sites and the expected low number of patients per site, site effects will not be explored, although study site will be included as a random effect in efficacy sensitivity analyses to account for within-site correlations, as specified above.

2.5 Multiple Testing

The primary endpoint will be tested at the 2-sided 5% significance level. No adjustments for multiplicity will be made for secondary and exploratory endpoints.

2.6 Missing Data

There are three possible sources for missing data:

1. Deaths
2. Administrative error
3. Premature study terminations

Missing data due to deaths is expected to be very low (fewer than 10 patients) because of the short follow-up period. Missing data due to administrative error is believed to be negligible due to the study management procedures and is also believed to be missing completely at random (MCAR). For patients who drop out of the study prematurely, a premature treatment discontinuation visit (PTDV) will be scheduled for them, whenever possible, to get the last assessment. The PTDV assessment will be carried forward to the next follow-up time point. For partially completed KCCQ questionnaires, the scoring algorithm accommodates a limited number of skipped responses. Values that are missing at randomization but available at screening will be imputed using the value at screening. Primary, secondary, and exploratory endpoints will be analyzed among patients for whom all relevant data for the given endpoint can be calculated.

For KCCQ scores, additional sensitivity analysis will be conducted using multiple imputation to account for missing values. IVEware (Raghunathan et al. 2002) will be used to perform the multiple imputation which employs iterative sequential regression to sample missing values from the predictive distribution of each variable, conditional on all other variables included in the imputation model. The following variables will be included in the imputation model: baseline KCCQ scores, sex, baseline eGFR, history of diabetes (DM), history of permanent AFib, baseline LVEF, baseline NYHA class, heart failure hospitalization during the trial duration , urgent heart failure visit during the trial duration, and covariates used as subgroup variables in section 2.3. Additionally, the imputation model will also include all follow up

assessments available for KCCQ scores, eGFR, NTproBNP, BNP, Hgb, loop Diuretic dose, 6-minute walk test.

2.7 Data Handling Conventions and Transformations

Diabetes duration will be calculated as (Consent date – DM diagnosis date) / 365.25. It will be rounded to the whole year.

Body mass index (BMI) will be calculated as weight (kg) / [height (m)]^2. It will be displayed to 1 decimal place in listings, but will not be rounded or truncated prior to summarization

Estimated glomerular filtration rate (eGFR) will be calculated using the MDRD-4 equation: GFR in mL/min per 1.73 m^2 = 175 x $SerumCr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if patient is African American) x 0.742 (if female). Patients with missing data in Creatinine Serum, age, race, or gender will not have eGFR calculated.

If urine microalbumin value is reported as being too high for the laboratory to calculate a UACR, 5000 mg value for UACR will be used.

3 SUBJECT DISPOSITION

3.1 Subject Enrollment

The number and percent of subjects randomized for each site will be summarized overall and by treatment group. The denominator for the percent calculation will be number of subjects screened.

3.2 Disposition of Subjects

A summary of subject disposition will be provided overall and by treatment group, as appropriate. This summary will present the number of subjects screened, randomized, included in the safety analysis set, and the number and percent of subjects meeting the following criteria:

- Had known vital status at the end of the study
- Died
- Completed the study drug treatment (defined as on study drug at week 12 visit)
- Did not complete the study drug treatment (with summary of reasons for not completing the study treatment)
- Completed the study (defined as with visit at week 12)
- Completed the study (defined as with visit at week 12) and completed the study drug (defined as on study drug at week 12 visit)
- Had at least one in-person visit
- Had visit at week 6 and week 12
-
-

The denominator for the percent of subjects in each category will be the number of subjects randomized.

No inferential statistics will be generated. A data listing of reasons for premature study treatment/study discontinuation will be provided.

3.3 Extent of Exposure

3.3.1 Study Drug Compliance

Study drug compliance will be derived using the Study Drug Accountability at 12 weeks. Proportion of study drug compliance is defined as proportion of patients respond 'Currently taking study drug' at 12 weeks.

Summaries will be provided by treatment group for the safety analysis set.

3.3.2 Duration of Exposure to Study Drug

Duration of exposure to study drug will be defined as (last dose date – first dose date of double-blind treatment phase + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (shown to one decimal place, e.g., 4.5 weeks).

Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum).

Summaries will be provided by treatment group for the safety analysis set.

3.3.3 Adherence with Study Drug

- The actual number of tablets ingested will be calculated using the Study Drug Accountability CRF:

  Total number of tablets dispensed - total number of tablets returned.

- The expected number of tablets ingested will be calculated based on the Study Drug Dispensed CRF and Study Drug Accountability CRF:

  Total number of days supposed on study drug ([date of last dose of study drug - start date + 1])

- Adherence rate

  100(total number of tablets ingested) / (expected number of tablets ingested).

Adherence will be capped at 100% for summarization. Patients with unreturned bottles will be excluded from adherence calculations.

Descriptive statistics for adherence (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be provided by treatment group and overall for the safety analysis set.

4 Endpoints variables

4.1 Primary endpoints:

- Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score at 12 weeks

4.2 Secondary endpoints:

- Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 12 weeks
- NTproBNP at 6 and 12 weeks
- BNP at 6 and 12 weeks
- Six-minute walk test at 12 weeks
- HbA1c at 6 and 12 weeks
- Proportion of patients with a ≥ 5pts increase in KCCQ clinical summary score at 12 weeks and proportion of patients with a ≥ 5pts increase in KCCQ overall summary score at 12 weeks
- Proportion of patients with a ≥ 20% decrease in 6 and 12 weeks NTproBNP
- Proportion of patients with a ≥ 5pts increase in KCCQ at 12 weeks and a ≥ 20% decrease in 6 and 12 weeks NTproBNP
- Weight at 6 and 12 weeks
- Systolic blood pressure at 6 and 12 weeks.

  Average of the three measures of supine systolic blood pressure at each time point will be used.

4.3 Exploratory Outcome Variables

- Composite mean hierarchical-rank clinical score.

  All patients will receive a global rank endpoint based on time to death (tier 1), time to HF hospitalization or urgent HF visit (tier 2), or change in KCCQ clinical summary score from baseline to 12 weeks. The variable for ranking the patients will be derived as follows.

  - Patients dying during the study will have a value of 0 + (study days from randomization to death). Patients with missing vital status at the end of trial will be excluded from the analysis. Patient dying during the study but with no mortality date will use the average of the last known alive date and the patient's scheduled 12 weeks follow-up date.

- Patients who did not die but had multiple occurrences of HF hospitalization or urgent HF visit will have a value of 200 – number of occurrences.
- Patients who did not die but have only one HF hospitalization or urgent HF visit will have a value of 200 + (study days from randomization to the occurrence of HF hospitalization or urgent HF visit). Patients known to have an event but event date is unknown will be imputed using the median rank based on the rank of other patients in this category.
- Patients who did not die and did not experience HF hospitalization or urgent HF visit will have a value of 400 + (change in KCCQ clinical summary score from baseline to week 12).

  Patients with missing KCCQ at 12 weeks who didn't die and didn't have HF events will be excluded. A sensitivity analysis will be performed where these patients will be kept in the analysis and the KCCQ values will be imputed using multiple imputation as described in section 2.6.

- Number of heart failure hospitalizations and proportion of patients experienced heart failure hospitalizations
- Number of urgent heart failure visits and proportion of patients with urgent heart failure visits
- Total number of heart failure hospitalizations and urgent heart failure visits and proportion of participants who experienced any heart failure hospitalizations and urgent heart failure visits.

  For the four endpoints above, only events positively adjudicated by the clinical event committee will be included. Events that occurred between screening and randomization, and between 12 weeks and 13 weeks will be excluded from this analysis. Events that occurred between the week 12 and week 13 study visits will be reported in a separate, supplemental analysis.

- Proportion of patients that progress to diabetes during the treatment period (within the subgroup of patients without diabetes at baseline only). Progression to diabetes is defined as a HbA1c of 6.5 or greater at either 6 week or 12 week follow-up.
- Average daily loop diuretic dose (furosemide equivalent)

  The following equations will be used to convert doses to Furosemide equivalent:

  - 40 mg Furosemide = 20 mg Torsemide = 2 mg Bumetanide = 50 mg Ethacrynic Acid
  - When patient is not on a loop diuretic, dose = 0 mg.

- For subjects with dosing schedule reported as “as needed (prn)”, we will assume a twice a week dosing regimen for loop diuretic at the recorded dose.

In addition to comparing daily loop diuretic dose between treatment arms, we will also compare the proportion of patients who had their loop diuretic dose reduced or discontinued at any time during the treatment period.

- Change in NYHA Class at 6 and 12 weeks.

  A 3-level categorical variable: 1) Decrease, 2) No change, 3) Increase. For patients missing NYHA class at 12 weeks, value at 6 weeks will be used.

- Echocardiography sub study endpoints: left atrial volume index and other measures of left ventricular diastolic function

  Primary Endpoint
  Left atrial volume index at 12 weeks

  Exploratory endpoints:
  - BSA
  - LVEDD
  - LVESD
  - IVSd
  - PWd
  - Relative Wall Thickness
  - LV Mass
  - LV Mass Index
  - Left ventricular end diastolic volume
  - Left ventricular end systolic volume
  - Estimated LVEF
  - LVEF Calculated
  - Left atrial dimension
  - Left atrial volume
  - Left atrial volume index
  - E
  - E/A
  - E/E' medial
  - E/E' lateral
  - Tricuspid regurgitant velocity
  - Longitudinal strain

5 Analyses of Baseline Characteristics

Patient demographics, baseline clinical characteristics, medical histories, and baseline labs will be described overall and by treatment group. Continuous measures will be summarized by mean $\pm$ standard deviation and compared using Student's T-tests. Categorical variables will be summarized by frequency and percent and compared using χ^2or Fisher's exact tests, as appropriate.

5.1 Demographics and Baseline Characteristics

- Age
- Sex
- Race/Ethnicity

5.2 Medical History

5.2.1 Diabetes History

- Diabetes duration
- History of diabetic peripheral neuropathy
- History of diabetic autonomic neuropathy
- History of diabetic retinopathy
- History of diabetic ketoacidosis (DKA) event
- History of hyperosmolar hyperglycemic syndrome (HHS) event
- History of severe hypoglycemic event(s)
- History of amputation

5.2.2 Other Medical History

- History of heart failure
- NYHA Class
- Most Recent LVEF Assessment
- History of PAD
- History of hypertension
- History of coronary artery disease
- History of dyslipidemia
- History of angina
- History of atrial fibrillation
- History of atrial flutter
- History of MI
- History of PCI
- History of CABG
- History of ventricular tachycardia
- ICD implanted

- Permanent pacemaker implanted
- History of valve disease

5.3 Physical examination

- Body Mass Index
- Sitting Pulse and Blood Pressure
- Supine Pulse and Blood Pressure
- Standing Pulse and Blood Pressure

5.4 Lab results

- HbA1c
- BNP
- NT pro-BNP
- Glucose (mg/dL)
- BUN - urea nitrogen (mg/dL)
- Creatinine (mg/dL)
- Estimated Glomerular Filtration Rate (eGFR)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Chloride (mmol/L)
- Carbon Dioxide (mmol/L)
- Calcium (mg/dL)
- Phosphate - as phosphorus (mg/dL)
- Albumin (g/dL)
- Random Urine Creatinine (mg/dL)
- Random Urine Microalbumin < 0.2 mg/dL
- Random Urine Microalbumin (mg/dL)
- Enter Urine Albumin result, if measurable.
- Random Urine Albumin/Creatinine Ratio (mcg/mg creat)

6 EFFICACY ANALYSES

6.1 Analysis of the Primary Efficacy Endpoint

Analysis of the primary efficacy endpoints will be performed on the modified ITT data set, first on the entire cohort, then within the subgroups of patients with and without diabetes, and then within other subgroups as specified in section 2.3. Sensitivity analyses will be performed as outlined in section 2.3; in addition, supportive analyses will be repeated using the same models on the on-treatment set (OTS) and per-protocol set (PPS), as applicable.

Mean, standard deviation, median, and interquartile range (IQR) will be reported for KCCQ clinical summary score and for its change at 12-week follow-up, for the entire cohort and by treatment group.

An ACCOVA model will be used to estimate the effect of dapagliflozin on the 12-week KCCQ clinical summary score, adjusting for baseline KCCQ clinical summary score, sex, eGFR, Diabetes status, permanent atrial fibrillation status, and LVEF. Patient participation in the Echocardiography sub-study will not be controlled for because we don't hypothesize that participation in the Echocardiography sub-study is associated with the primary outcome (KCCQ CS).

A sensitivity analysis will repeat the primary analysis but will also include site as a random effect to account for potential clustering by enrolling center. Another sensitivity analysis will be performed using the imputed KCCQ values as described in section 2.6.

6.2 Secondary outcome variables

The following secondary outcomes will be analyzed on the intention to treat (modified ITT) data set, first on entire patient cohort and then within subgroups of patient with or without diabetes.

6.2.1 Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 12 weeks

KCCQ overall summary score at 12 weeks will be analyzed in a manner analogous to that of the primary endpoint.

6.2.2 NTproBNP at 6 and 12 weeks

Mean, standard deviation, median, and interquartile range (IQR) will be reported for NT pro-BNP and for its change from baseline at 6- and 12-week follow-up, for the entire cohort and by treatment group.

A generalized linear mixed model will be used to estimate the treatment effect on 6- and 12-week NT pro-BNP values, adjusting for log baseline NT pro-BNP, sex, eGFR, diabetes (DM), permanent AFib, and LVEF. Patient will be included as a random effect. A gamma distribution and log link function will be used to account for the skewed nature of NT pro-BNP. The model is as follows:

$$\mathrm{E}(y_{ijk}) = \mu_{ijk}, \qquad \mathrm{Var}(y_{ijk}) = \mu_{ijk}^2 \phi,$$

$$\log(\mu_{ijk}) = \beta_0 + \beta_1 \mathrm{Trt}_{ij} + \beta_2 t_k + \beta_3 \mathrm{Trt}_{ij} * t_k + \mathbf{\beta x} + \gamma_{ij},$$

$$\gamma_{ij} \sim \mathrm{N}(0, \sigma^2),$$

where, μ_{ijk} denotes the expected NT pro-BNP level for patient j from site i at time k, Trt_{ij} is a 0/1 variable denoting treatment group (dapagliflozin vs. placebo), t_k indicates the follow-up assessment time (6 week: t_$k = 1$; 12week: $t_k = 0$), and $\mathbf{x}$ is the design matrix for log baseline NT pro-BNP, age, DM, and baseline eGFR. γ_{ij} are patient random effects with variance σ^2. ϕ is a scale factor. With this parameterization, the quantities $\exp(\beta_1)$ and $\exp(\beta_1 + \beta_3)$ represent the corresponding relative effects at 6 and 12 weeks, respectively.

A few sensitivity analyses will be performed:

- Repeat the model above but also include site as a random effect to account for potential clustering by enrolling center.

- Repeat the model above on the on-treatment set (OTS).

6.2.3 BNP at 6 and 12 weeks

BNP at 6 and 12 weeks will be analyzed in a manner analogous to that of NT pro-BNP.

6.2.4 Six-minute walk test at 12 weeks

Six-minute walk test at 12 weeks will be analyzed in a manner analogous to that of the primary endpoint.

6.2.5 HbA1c at 6 and 12 weeks

HbA1c at 6 and 12 weeks will be analyzed in a manner analogous to that of NT pro-BNP, although appropriate distributions and link functions will be chosen for the given outcomes. Models will also provide separate effect estimates for the 6- and 12-week time points

6.2.6 Proportion of patients with a ≥ 5pts increase in KCCQ clinical summary score and KCCQ overall summary score at 12 weeks

Proportion of patients achieving a ≥ 5pts increase in KCCQ clinical summary score at 12 weeks

Unadjusted proportion of patients achieving a ≥ 5pts increase in KCCQ clinical summary score at 12 weeks, will be reported for the treatment group and placebo group. A logistic regression model will be used to assess the treatment effect. Model will be adjusted for baseline measurement, sex, eGFR, diabetes (DM), permanent AFib, and LVEF.Several sensitivity analyses will be performed:

- Repeat the model above but also include site as a random effect to account for potential clustering by enrolling center.
- Repeat the model above on the on-treatment set (OTS).
- Repeat the model above excluding patients with baseline KCCQ clinical summary score of over 90 (as these patients will have a limited opportunity for improvement in KCCQ)
- Repeat the analysis using the imputed KCCQ values as described in section 2.6.

Proportion of patients achieving a ≥ 5pts increase in KCCQ overall summary score at 12 weeks

Proportion of patients achieving a ≥ 5pts increase in KCCQ overall summary score at 12 weeks will be analyzed in a manner analogous to that of proportion of patients achieving a ≥ 5pts increase in KCCQ clinical summary score at 12 weeks.

6.2.7 Proportions of patients with a ≥ 20% decrease at 6 and 12 weeks NTproBNP

This end point will be analyzed in a manner analogous to 6.2.6.

6.2.8 Proportions of patients with a ≥ 5pts increase in KCCQ and a ≥ 20% decrease in 6 and 12 weeks NTproBNP

This end point will be analyzed in a manner analogous to 6.2.6. Proportion will be calculated for patients with a ≥ 5 pts increase in KCCQ and a ≥ 20% decrease in NTproBNP at 6 weeks, and separately for patients with a ≥ 5 pts increase in KCCQ and a ≥ 20% decrease in NTproBNP at 12 weeks.

6.2.9 Weight at 6 and 12 weeks

Weight at 6 and 12 weeks will be analyzed in a manner analogous to that of NT pro-BNP, although appropriate distributions and link functions will be chosen for the given outcomes. Models will also provide separate effect estimates for the 6- and 12-week time points

6.2.10 Systolic blood pressure at 6 and 12 weeks

Systolic blood pressure at 6 and 12 weeks will be analyzed in a manner analogous to that of NT pro-BNP, although appropriate distributions and link functions will be chosen for the given outcomes. Models will also provide separate effect estimates for the 6- and 12-week time points

6.3 Exploratory outcome variables

6.3.1 Composite mean hierarchical-rank clinical score.

The composite hierarchical-rank clinical score will be analyzed on the safety dataset. Patients with missing KCCQ values at 12 weeks will be excluded unless they died or had HF hospitalizations or urgent HF visits. Win ratio will be used to compare the rank score of each patient in the dapagliflozon arm with each patient in the placebo group. Each comparison will result in a "win", "loss" or "tie" for the patient in the dapagliflozin group if the analysis value of the patient in the dapagliflozin group is higher, lower or equal to the analysis value of the patient in the placebo group, respectively. Within the dapagliflozin group, total number of wins will be divided by the total number of losses (ties are split evenly between wins and losses) to form the Win Ratio statistic of the dapagliflozin group against the placebo group (Pocock et al 2012). The confidence interval of the win ratio statistic will be calculated as described in Gasparyan et al 2020 (see APPENDIX).

6.3.2 Heart failure hospitalizations

Number of heart failure hospitalizations and proportion of patients with any heart failure hospitalizations during the length of follow-up will be summarized descriptively for the treatment and placebo group on the safety dataset. This will be completed first on the entire cohort and then within subgroups of patients with or without diabetes. Both endpoints will be summarized by frequency and percent and compared using χ^2or Fisher's exact tests, as appropriate.

In addition, a Cox proportional hazard model will be used to assess the effect of treatment vs. placebo on the time to the first occurrence of heart failure hospitalization, adjusting for sex, eGFR, diabetes (DM), permanent AFib, and LVEF. A second sensitivity analysis will be performed using stratified Cox proportional model conditional on site to account for clustering.

6.3.3 Urgent heart failure visits

Will be analyzed in a manner analogous to that described in 6.3.2.

6.3.4 Heart failure hospitalizations and urgent heart failure visits

Will be analyzed in a manner analogous to that described in 6.3.2.

6.3.5 Proportion of patients that progress to diabetes during the treatment period (within the subgroup of patients without diabetes at baseline only)

Will be analyzed in a manner analogous to that described in 6.3.2.

6.3.6 Change from baseline in average weekly loop diuretic dose (furosemide equivalent)

Change in daily loop diuretic dose will be summarized descriptively for the treatment and placebo group on the intention to treat dataset. This will be completed first on the entire cohort and then within subgroups of patients with or without diabetes. Additionally, among patients who were on loop diuretic at randomization, we will also compare the proportion of patients who had loop diuretic dose reduced or discontinued (using the average of 6- and 12-week doses, and also separately at 6 and 12 weeks).

Furthermore, daily loop diuretic dose will be also analyzed using generalized mixed models as the model used for NTproBNP, although appropriate distributions and link functions will be chosen for the given outcomes.

6.3.7 Change in NYHA Class at 6 and 12 weeks.

Proportion of patients with a Decreased, No change, and Increased NYHA at 6 and 12 weeks will be summarized for the treatment and placebo group on the intention to treat dataset and compared using χ^2or Fisher's exact tests, as appropriate. This will be completed first on the entire cohort and then within subgroups of patients with or without diabetes.

Additionally, NYHA change category will be analyzed in a manner analogous to that of NT pro-BNP, although appropriate distributions and link functions will be chosen for the given outcome.

6.3.8 Echocardiography sub study endpoints: left atrial volume index and other measures of left ventricular diastolic function

Echocardiography sub study endpoints will be analyzed among patients enrolled in the Echocardiography sub study and in the modified ITTS dataset.
Continuous variables will be analyzed in a manner analogous to that of the primary endpoint. Categorical variables will be analyzed in a manner analogous to that described in 6.2.6.

7 SAFETY ANALYSES

Safety analyses will be performed on the safety analysis set (SAF). Total number of adverse events as well as number and proportion of patients developing adverse event(s) will be compared by treatment group. For patient level analyses multiple events will be counted once only per subject in each summary. The following safety variables will be included:

1. All cause death
2. Cardiovascular death
3. Non-fatal myocardial infarction (MI)
4. Stroke
5. Acute kidney injury (defined as doubling of serum creatinine based on the modified RIFLE criteria)
6. Adverse events (AEs).

    - Adverse events of special interest
        - Diabetic Ketoacidosis

    - Volume Depletion Event (defined as hypotension, syncope, orthostatic hypotension or dehydration)
    - Severe Hypoglycemic Event
    - Lower Limb Amputations
- Drug Adverse Event
- Serious Adverse event
    - Resulted in death
    - In-patient hospitalization or prolonging of existing in-patient hospitalization
    - Persistent or significant disability
    - Life-threatening
    - Congenital anomaly/birth defect
    - Important medical event

Safety analyses will be restricted to adverse events that occurred between randomization and 12 weeks. Adverse events occurred between 12 weeks and 13 weeks will be presented separately in a supplemental analysis. As a sensitivity analysis, the above analysis will be repeated with events that occur 2 days after patients discontinue study drug being excluded.

8 REFERENCES

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9 SOFTWARE

All analyses will be performed using SAS 9.4 or higher.

10 APPENDICES

10.1 Scoring and Interpreting the KCCQ

There are 10 summary scores within the KCCQ, which are calculated as follows:

A. Physical Limitation

The Physical Limitation score corresponds to questions 1a through 1f. Responses to questions 1a through 1f should be coded numerically as follows:

1 = Extremely Limited
2 = Quite a bit Limited
3 = Moderately Limited
4 = Slightly Limited
5 = Not at all Limited
6 = Limited for other reasons or did not do the activity

If the responses to questions 1a through 1f are not values 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 (Limited for other reasons or did not do the activity) is treated as a missing value. If at least three responses to questions 1a-1f are not missing, then the physical limitation score is computed by calculating the mean response and standardizing the result as follows:

$$\text{Physical Limitation} = 100*(\text{Mean Response} - 1)/4$$

B. Symptom Stability

The Symptom Stability score corresponds to question 2. Responses to question 2 should be coded numerically as follows:

1 = Much Worse
2 = Slightly Worse
3 = Not Changed
4 = Slightly Better
5 = Much Better
6 = I've had no symptoms over the last 2 weeks

If the response is 6 (no symptoms over last 2 weeks) then set the response to 3 (not changed). If question 2 is not missing then the symptom stability score is computed by standardizing the result as follows:

$$\text{Symptom Stability} = 100*(\text{Response} - 1)/4$$

C. Symptom Frequency

The Symptom Frequency score corresponds to questions 3, 5, 7 and 9. The responses should be coded sequentially (1, 2, 3…) in order of increasing health status as follows:

Question 3

1 = Every Morning
2 = 3 or more times per week, but not every day
3 = 1-2 times a week
4 = Less than once a week
5 = Never over the past 2 weeks

Questions 5 and 7

1 = All of the time
2 = Several times per day
3 = At least once a day
4 = 3 or more times per week, but not every day
5 = 1-2 times per week
6 = Less than once a week
7 = Never over the past 2 weeks

Question 9

1 = Every night
2 = 3 or more times a week, but not every day
3 = 1-2 times a week
4 = Less than once a week
5 = Never over the past 2 weeks

If two or more responses are missing then symptom frequency cannot be computed and will be missing. Otherwise, the symptom frequency is computed by calculating the mean of the standardized responses and multiplying by 100 as follows:

$$\text{Symptom Frequency} = 100*\text{Mean}((Q3 - 1)/4, (Q5 - 1)/6, (Q7 - 1)/6, (Q9 - 1)/4)$$

D. Symptom Burden

The Symptom Burden score corresponds to questions 4, 6 and 8. The responses should be coded numerically as follows:

1 = Extremely Bothersome
2 = Quite a bit Bothersome
3 = Moderately Bothersome
4 = Slightly Bothersome

5 = Not at all Bothersome
6 = I've had no swelling (fatigue, shortness of breath)

If a response is 6 (none) then set the response to 5 (not at all). If at least one response is present then symptom burden score is computed by calculating the mean response and standardizing the result as follows:

$$\text{Symptom Burden} = 100*(\text{Mean Response} - 1)/4$$

E. Total Symptom Score

The total symptom score is calculated as the mean of the symptom frequency score and symptom burden score.

F. Self-Efficacy

The Self-Efficacy score corresponds to questions 10 and 11. Responses to questions 10 and 11 should be coded sequentially (1, 2, 3, 4, 5) in order of increasing health status, with 1 denoting the response associated with the lowest health status. If at least one question response is present then the self-efficacy score may be computed by standardizing the mean response as follows:

$$\text{Self-Efficacy} = 100*(\text{Mean Response} - 1)/4$$

G. Quality of Life

The Quality of Life score corresponds to questions 12, 13 and 14. Responses to questions 12, 13 and 14 should be coded sequentially (1, 2, 3, 4, 5) in order of increasing health status, with 1 denoting the response associated with the lowest health status. If at least one question response is present then the quality of life score may be computed by standardizing the mean response as follows:

$$\text{Quality of Life} = 100*(\text{Mean Response} - 1)/4$$

H. Social Limitation

The Social Limitation score corresponds to questions 15a through 15d. These responses should be coded numerically as follows:

1 = Severely Limited
2 = Limited Quite a bit
3 = Moderately Limited
4 = Slightly Limited
5 = Did Not Limit at All
6 = Does not apply or did not do for other reasons

If the responses to questions 15a through 15d are not values 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 is treated as a missing value. If at least two question responses are present then the social limitation score may be computed by standardizing the mean response as follows:

$$\text{Social Limitation} = 100*(\text{Mean Response} - 1)/4$$

I. Clinical Summary Score

The clinical summary score is calculated as the mean of the physical limitation score and total symptom score.

J. Overall Summary Score

The overall summary score is calculated as the mean of the physical limitation score, total symptom score, quality of life score and social limitation score.

10.2 Protocol deviations

Number	Important Protocol Deviations Criteria	Major Impact on Analysis (MIA)/Other	Exclusion level
1. Did not fulfil eligibility criteria – inclusion criteria:			
1.1	Ability to provide informed consent prior to initiating screening visit procedures	MIA	Complete exclusion from PPS and MODIFIED ITTS
1.2	Age > 18 and < 120 at the screening visit	Other	No exclusion
1.3	Ejection fraction (EF) ≥ 45% as determined on imaging study within 24 months of enrolment with no change in clinical status suggesting potential for deterioration in systolic function	Other	To be decided on a case by case basis
1.4	Elevated NT-proBNP (≥ 225 pg/ml) or BNP (≥ 75 pg/ml)	Other	To be decided on a case by case basis
1.5	Stable medical therapy for heart failure for 15 days	Other	To be decided on a case by case basis
1.6	On a diuretic ≥15 days prior to screening visit and a stable diuretic therapy for 7 days	Other	To be decided on a case by case basis
1.7	At least one of the following: 1. Hospitalization for decompensated HF in the last 12 months 2. Acute treatment for HF with intravenous loop diuretic or hemofiltration in the last 12 months 3. Mean pulmonary capillary wedge pressure ≥15 mmHg or LV end diastolic pressure (LVEDP) ≥15 mmHg documented during catheterization at rest, or pulmonary capillary wedge pressure or LVEDP ≥25 mmHg documented during catheterization with exercise. 4. Structural heart disease		To be decided on a case by case basis

Number	Important Protocol Deviations Criteria	Major Impact on Analysis (MIA)/Other	Exclusion level
2. Did not fulfil eligibility criteria – exclusion criteria:			
2.0	Decompensated heart failure (hospitalization for heart failure within 7 days prior to screening)	Other	To be decided on a case by case basis
2.1	History of type 1 diabetes	Other	To be decided on a case by case basis
2.2	History of diabetic ketoacidosis	Other	To be decided on a case by case basis
2.3	Estimated glomerular filtration rate (eGFR) < 20 at the screening visit by modified MDRD equation GFR (mL/min/1.73 m2) = 175 x (Scr) $^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if African American)	Other	To be decided on a case by case basis
2.4	Admission for an acute coronary syndrome (ST-elevation MI, non-ST-elevation MI, or unstable angina), percutaneous coronary intervention, or cardiac surgery within 30 days prior to the screening visit.	Other	To be decided on a case by case basis
2.5	Admission for cardiac resynchronization therapy (CRT) within 90 days prior to the screening visit.	Other	To be decided on a case by case basis
2.6	Planned cardiovascular revascularization (percutaneous intervention or surgical) or major cardiac surgery (coronary artery bypass grafting, valve replacement, ventricular assist device, cardiac transplantation, or any other surgery requiring thoracotomy, or transcatheter aortic valve replacement) or CRT within the 90 days after the screening visit.	Other	To be decided on a case by case basis
2.7	Participation in any interventional clinical trial (with an investigational drug or device) that is not an observational registry within 15 days of the screening visit.	Other	To be decided on a case by case basis
2.8	History of hypersensitivity to dapagliflozin	Other	To be decided on a case by case basis
2.9	For women of child-bearing potential: Current or planned pregnancy or currently lactating	Other	To be decided on a case by case basis

Number	Important Protocol Deviations Criteria	Major Impact on Analysis (MIA)/Other	Exclusion level
2.10	Life expectancy <1 year at the screening visit	Other	To be decided on a case by case basis
2.11	Patients who are volume depleted based upon physical examination at the time of the screening or randomization visit	Other	To be decided on a case by case basis
2.12	Patients currently being treated with any SGLT-2 inhibitor (dapagliflozin, canagliflozin, empagliflozin, ertugliflozin) or having received treatment with any SGLT-2 inhibitor within the 12 weeks prior to the screening visit.	Other	To be decided on a case by case basis
2.13	Average supine systolic BP <100 mmHg at the screening or randomization visit	Other	To be decided on a case by case basis
2.14	Current history of bladder cancer	Other	To be decided on a case by case basis
2.15	Donation of blood or bone marrow 12 weeks prior to the screening visit and no planned donations during the study period	Other	To be decided on a case by case basis
2.16	Heart failure due to restrictive/infiltrative cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valve disease, and HOCM (hypertrophic obstructive cardiomyopathy).	Other	To be decided on a case by case basis
2.17	Heart failure due to severe aortic or mitral regurgitation	Other	To be decided on a case by case basis
2.18	Severe COPD thought to be a primary contributor to dyspnea	Other	To be decided on a case by case basis
2.19	Isolated right heart failure due to pulmonary disease	Other	To be decided on a case by case basis
2.20	Active and significant ischemia thought to be a primary contributor to dyspnea	Other	To be decided on a case by case basis
2.21	Documentation of previous EF < 45%, under stable conditions, within the past 36 months	Other	To be decided on a case by case basis

Number	Important Protocol Deviations Criteria	Major Impact on Analysis (MIA)/Other	Exclusion level
2.22	Complex congenital heart disease	Other	To be decided on a case by case basis
2.23	Uncontrolled hypertension, defined as systolic blood pressure ≥200 mmHg during the screening visit (average value of three blood pressure measurements obtained in supine position)	Other	To be decided on a case by case basis
2.24	Any other condition that in the judgment of the investigator would jeopardize the patient's participation in the study or that may interfere with the interpretation of study data or if the patient is considered unlikely to comply with study procedures, restrictions and requirements	Other	To be decided on a case by case basis
2.25	Bariatric surgery within the past 6 months or planned bariatric surgery within the study time course.	Other	To be decided on a case by case basis
2.26	CardioMems device implantation within previous 4 weeks or planned CardioMems implantation during study period	Other	To be decided on a case by case basis
2.27	For echo substudy only: patients with ventricular paced rhythm or left bundle branch block on the most recent clinically available 12-lead electrocardiogram	Other	To be decided on a case by case basis
2.30	For echo substudy only: permanent atrial fibrillation	Other	To be decided on a case by case basis

3. Patient developed discontinuation of investigational product criteria but dosing continued			
3.0	Subject experienced an Adverse Event which in the opinion of the Investigator and/or , contraindicated further dosing	Other	To be reviewed on the case by case basis
3.1	Pregnancy confirmed by a positive pregnancy test or other examinations	Other	Complete exclusion from PPS
3.2	Donation of blood or bone marrow during the study period	Other	To be decided on a case by case basis
3.3	Admission for an acute coronary syndrome (ST-elevation MI, non-ST-elevation MI, or unstable angina), percutaneous coronary intervention, or cardiac surgery during the study period.	Other	To be decided on a case by case basis
4. Patient received prohibited concomitant medication but study treatment not discontinued:			
4.4.1	SGLT2 inhibitors	Other	Only the efficacy endpoints before the start of prohibited medication will be included in PPS analysis
5. Patient received incorrect investigational treatment/dose			
5.0	Patient took incorrect treatment or damaged Investigational Drug Kit	MIA	To be decided on a case by case basis
5.1	Major compliance issues <80% or >120% compliance with IP dosing in double blind treatment period	MIA	To be decided on a case by case basis
5.2	Patient randomized but never took IP	MIA	To be decided on a case by case basis

5.3	Overdose	MIA	To be decided on the case by case basis
6. Protocol-required procedure not adhered to:			
6.0	Study data collection has not been stopped when subject decided to withdraw their consent from the study completely	Other	No exclusion from PPS Data collected after consent withdrawal to be excluded from data base
6.1	Patients with absence of NT-proBNP data at randomization visit and having values at Screening visit.	Other	No exclusion from PPS Values from screening visit will be used to impute the values at randomization visit.
6.2	Patients with absence of baseline NT-proBNP data at both screening and randomization visits	Other	Excluded from the NT-proBNP analyses
6.3	Patients with no NT-proBNP values after randomization	Other	Excluded from the NT-proBNP analyses
6.4	Patients with absence of baseline KCCQ clinical summary score at randomization visit	Other	Excluded from the ITTS KCCQ analyses
6.5	Patients with no KCCQ clinical summary score after randomization	Other	Excluded from ITTS KCCQ analyses
6.6	Patients with absence of baseline 6-minute walk assessment at randomization visit	Other	Excluded from the 6-minute walk analyses
6.7	Patients with no 6-minute walk assessment after randomization	Other	Excluded from 6-minute walk analyses
6.8	Patients with missing values in the covariates:, gender, Hx AFib, AFib type, Hx DM, eGFR at randomization, lvef at randomization	Other	No exclusion from PPS Excluded from the first and second primary analysis