Study Title:

Economic Impact of Reducing Hospital Admissions for Patients Presenting to the Emergency Department with Worsening Heart Failure: An Adaptive Clinical Trial of Furoscix Infusor

Statistical Analysis Plan

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scPharmaceuticals

Furoscix Real-World Evaluation for Decreasing Hospital Admissions in Heart Failure: FREEDOM-HF Trial Protocol

Economic Impact of Reducing Hospital Admissions for Patients Presenting to the Emergency Department with Worsening Heart Failure: An Adaptive Clinical Trial of Furoscix Infusor

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Version 2.0
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CONFIDENTIALITY STATEMENT

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ABBREVIATIONS

AE	Adverse Event
CPI	Consumer Price Index
CrCl	Creatinine clearance
ED	Emergency Department
ESRD	End Stage Renal Disease
HCRU	Healthcare Resource Utilization
HF	Heart Failure
IFU	Instructions For Use
KCCQ	Kansas City Cardiomyopathy Questionnaire
NYHA	New York Heart Association
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TAU	Treatment As Usual
USA	United States of America

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1. ADMINISTRATIVE INFORMATION

This SAP will be revised as necessary. The statistical analysis lead will be responsible for any revisions and obtaining appropriate approvals. The trial statistician will be responsible for execution of this SAP and distribution of revisions to the appropriate clinical staff.

1.1. Roles and Responsibilities

Team Member	Roles and Responsibilities
[redacted] Associate Director EPI-Q, Inc.	Statistical analysis lead, document preparation
John Mohr, PharmD Senior Vice President Clinical Development and Medical Affairs scPharmaceuticals, Inc.	Clinical and operational oversight
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1.2. Signatures

I, the undersigned, have read and approve this statistical analysis plan (SAP) and agree on its content. It is confirmed that the information and guidance given in this SAP comply with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

Role	Name/Title	Signature	Date
Document Preparer and Statistician	[redacted] Associate Director EPI-Q, Inc.		
Statistician	[redacted] Principal Statistical Programmer ICON plc		

2. BACKGROUND

Heart failure (HF) affects 6.5 million adults in the United States, a figure that is expected to grow to 8 million by 2030. In the United States, HF is implicated as the cause of at least 1-2 million hospitalizations and 700,000 emergency department (ED) visits annually, and HF admissions generate the highest number of 30-day readmissions among Medicare enrollees. It is also estimated that 90% of patients presenting to the ED with worsening HF are admitted to the hospital and approximately 50% of hospital admissions for HF admitted from the emergency department could potentially be avoided.

Intravenous furosemide is commonly indicated for the management of edema which is commonly present in worsening HF as the absolute bioavailability of oral furosemide is low, highly variable and is exacerbated during an acute event. Recognizing this limitation of oral furosemide, national and international guidelines recommend that patients should be administered intravenous diuretics when significant signs and symptoms of volume overload are present. Thus, hospital admission or utilization of an observational unit is generally required. Admitting patients to the hospital, solely for the administration of intravenous furosemide, is expensive and increases risks of hospital-associated morbidity and mortality. Alternative treatment paradigms that shift HF management outside of the hospital are needed.

Approximately 60% of hospital admissions in patients with HF are due to sodium retention and volume overload. While subcutaneous administration of furosemide would enable diuresis as an outpatient, avoiding a hospital admission, the current commercially available furosemide injectable products have an alkaline pH and poor solubility making them unsuitable for subcutaneous administration. A novel, pH neutral formulation of subcutaneous furosemide (Furoscix, Furosemide Injection 80 mg/10 mL for subcutaneous use) has been developed to minimize burning and discomfort with subcutaneous administration and is delivered via the Furoscix Infusor: a wearable, pre-programmed on-body subcutaneous delivery system.

Furoscix administered 80 mg subcutaneously via the Furoscix Infusor, with 30 mg administered over the first hour followed by 12.5 mg per hour over the subsequent four hours produced similar exposures of furosemide and equivalent diuresis and natriuresis compared to two bolus injections of furosemide 40 mg dosed over 2 minutes, two hours apart.

The purpose of this study is to evaluate the economic impact of hospital avoidance and safety with management of worsening HF due to congestion with Furoscix administered via the Furoscix Infusor outside the hospital setting in patients initially presenting to the emergency department.

2.1. Schedule of Assessments

	DAY 0		DAY 1 (Phone)	DAY 2 - DAY 4 (Clinic)	DAY 7 (Phone)	DAY 14 - Day 21 (Phone)	Unscheduled (Clinic)	Unscheduled (Phone)[5]	DAY 30 ±3 (Clinic)
Informed Consent	X								
Confirmation of Eligibility	X								
Medical History & Demographics	X								
Interim Medical History				X			X		X
Concomitant Medications	X		X	X	X	X	X	X	X
Cardiopulmonary Exam[1], NYHA	X			X			X		X
Vital Signs[2], Height, Weight	X			X			X		X
Clinical Chemistries[3]	X			X			X		X
Hematology	X			X			X		X
Urine Pregnancy Test	X								
KCCQ-12 Short Form	X								X
Device/Product Training	X								
Device/Product Administration[4]	X		X	X					
Subject Diary			X	X	X	X	X	X	X
Comfort of Wear Questionnaire				X					
Skin Assessment	X			X					X
Adverse Events	X		X	X	X	X	X	X	X
Schedule Next Study Visit	X			X					
Phone Call Visit			X		X	X			
Suggested Telephone Script			X		X	X		X	

[1] Cardiopulmonary Exam includes consists of assessments of the following: jugular venous distension, lungs/chest, heart, abdomen and edema. Includes NYHA classification.
[2] Vital signs include respiratory rate, blood pressure, heart rate, and weight. BP and HR obtained after Subject resting in sitting position for 5 minutes. Height recorded Day 0 only.
[3] Clinical Labs are done locally and include Cr, BUN, Na+, K+, Chl, CO_2, and Mg; BNP or NT-proBNP will be drawn and sent to a local laboratory
[4] If Subject receives IV furosemide in the emergency department, the at-home treatment using Furoscix Infusor may begin one day later (i.e. not on Day 0). Subjects should be transitioned back to their oral maintenance diuretic regimen when clinically indicated at the discretion of the investigator (approximately 4 doses). After Subjects have been transitioned to their oral maintenance diuretic regimen, additional doses of Furoscix can be prescribed during the 30-day study period as needed based on the presence of clinical triggers (dyspnea on exertion, edema, and/or excess weight gain) as determined by the investigator. No more than 7 doses of Furoscix is permitted during the 30-day study period. Additional doses beyond 7 requires approval by the medical monitor. In addition to the scheduled phone and clinic visits, the investigator can utilize unscheduled clinic or phone visits for additional assessments at any time.
[5] If Subject receives unscheduled at-home phone call by an HF nurse, or designee, the nurse, or designee, should perform assessments in Unscheduled (Phone) column.

3. DESCRIPTION OF ANALYSIS

The primary outcome will be assessed with a superiority testing framework on the basis of the following primary endpoint:

a. Overall and heart failure related healthcare costs between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department for worsening heart failure due to fluid overload compared to propensity matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge.

3.1. Statistical Software

Analysis will be conducted in SAS version 9.4 or newer (SAS Institute, Cary, North Carolina, USA).

3.2. Baseline Variables

Baseline demographic and background clinical variables common to both the prospective cohort and the propensity-matched historical control group will be summarized. Additional variables applicable only to the prospective cohort will separately be summarized. Continuous variables will be summarized with means, standard deviations, medians, interquartile ranges, minima, and maxima. Categorical variables will be summarized with frequencies and percentages.

3.3. Important Considerations

3.3.1. Defined Populations applicable to the prospective arm

3.3.1.1. Intent to Treat (ITT) Population – Subjects who meet all of the inclusion criteria and none of the exclusion criteria and whose IRB-approved informed consent form has been signed and dated by all required parties.

3.3.1.2. Safety Population (SP) – Subset of the ITT received a dose of FUROSCIX (whether they completed or did not complete all study phases through 30-day follow up).

3.3.1.3. Evaluable Population (EP) – Subset of the SP who completed all the study phases as per the protocol.

3.3.2. Handling Missing Data

For the prospective cohort, unless specified otherwise in each objective, there will be no imputation of missing data. Subjects from the prospective arm with missing data will not be included in the analysis. The number of subjects included in each analysis will be reported so that the potential impact of missing data can be assessed. Note that the issue of partial dates has been preemptively accounted for such that the minimum requirement for dates in each variable category has been specified.

It is not expected that there will be a need for imputation for missing data in the historical control arm due to the large pool of historical control candidates. However, the extent of missing data in the candidate pool will be evaluated and addressed if necessary with multiple imputation procedures. Depending on whether the nature of the missing data is monotone or random, either the monotone or Markov chain Monte-Carlo (MCMC) multiple imputation methods will be employed.

3.3.3. P-Values

The statistical test for the primary objective will be performed at two-sided α=0.05. All reported p-values ≥0.0001 will be rounded to four decimal places. P-values <0.0001 will be displayed as "<0.0001".

3.3.4. Analysis Data Sets

The primary analysis will be evaluated for the evaluable population (EP), which will consist of all enrolled subjects who receive study drug and complete all study phases as per protocol. The data from the subjects in the prospective arm who were enrolled but who did not receive study drug (ITT) will be summarized separately, and the relevant details thereof – particularly the rationale for not receiving study drug despite being enrolled – analyzed and reported descriptively.

The propensity score matching procedure will combine data collected from the prospective arm (Furoscix Infusor) and data collected from the claims-based historical control arm. The data set for the latter will be derived from a preliminary analysis of claims for patients with HF who were seen in the emergency department for HF-related causes at any time between the years 2012 to 2017 (later updated to most recent data until 2019). This data set will constitute the candidate pool from which propensity-matched controls will be drawn, and the data elements will include all background demographic and baseline clinical data elements collected for the prospective arm except for lab values.

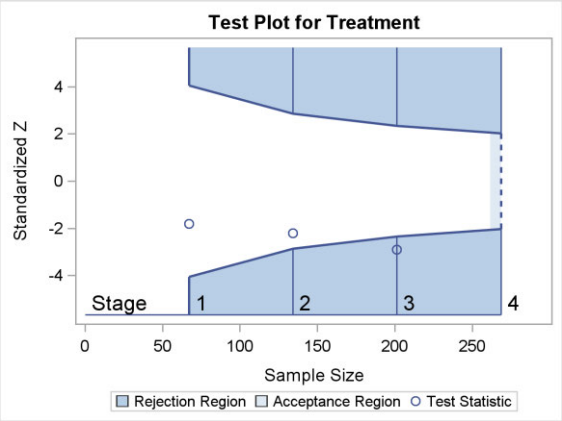
3.3.5. Trial Design

A group sequential design is being employed to allow for stopping due to futility or efficacy. This design includes the following general steps (cite SAS manual for group sequential designs):

1. Specify the statistical details of the design, including the null and alternative hypotheses (null hypothesis being that there is no difference in 30-day HF-related direct medical costs between the Furoscix Infusor and historical control arms), a test statistic for the hypothesis test, the Type I and II error probabilities, a stopping criterion, the total number of stages, and the relative information level at each stage.
2. Compute the boundary values for the trial based on the specifications in Step 1 and compute the sample size required at each stage for the specified hypothesis test.
3. At each stage, collect additional data with the required sample sizes. This includes the data collected at the current stage in addition to the data collected at previous stages.
4. At each stage, analyze the available data and compute the test statistic.
5. At each stage, compare the test statistic with the corresponding boundary values. The trial will stop to reject or accept the hypothesis, or it will continue to the next stage.
6. Once the trial stops, parameter estimates, confidence limits for the parameter, and a p-value for the hypothesis test are computed.

Below is a depiction of a hypothetical 4-stage design with two-sided testing.

Figure 1. Boundaries for Two-Sided Group Sequential Test



The four stages of the hypothetical trial presented in the preceding figure are indicated by vertical lines labeled 1, 2, 3, and 4. With early stopping to reject the null hypothesis, the lower rejection boundary is constructed by connecting the lower critical values for the stages. Similarly, the upper rejection boundary is constructed by connecting the upper critical values for the stages. The horizontal axis indicates the sample size for the group sequential trial, and the vertical axis indicates the values of the test statistic on the standardized Z scale. At each interim stage, if the test statistic falls into a rejection region the trial stops and the null hypothesis is rejected. Otherwise, the trial continues to the next stage. At the final stage the null hypothesis is rejected if Z falls into the rejection region. Otherwise, the null hypothesis is not rejected. In the figure, the test statistic falls into the rejection region in stage 3 and the null hypothesis is rejected.

An important concern with group sequential designs is correcting for multiplicity caused by conducting multiple, sequential correlated statistical tests thereby increasing the probability of Type 1 error. To correct for this issue one must preemptively define local significance levels for each statistical test and define the stopping boundaries. Herein, we will employ the O'Brien and Fleming error spending function to distribute the overall Type 1 error rate across the interim and final analyses. Because the O'Brien and Fleming approach includes an increase in the local significance level with each subsequent analysis (i.e., with each stage) it is considered among the more conservative approaches.

3.4. Safety Objective

The safety analysis includes assessment of adverse events (AEs) and device performance. The safety of Furoscix will be monitored during the trial, and identified safety issues (including AEs, SAEs, and adverse reactions) will be summarized descriptively in the safety population for the Furoscix cohort.

The incidence (number and percentage of subjects) of adverse events will be presented overall and by MedDRA System Organ Class and Preferred Term for the Furoscix cohort. Reactions at the infusion site and frequency of these reactions will be reported. This analysis will be repeated for serious adverse events, for treatment-related adverse events, and for adverse events leading to premature study withdrawal.

3.5. Effectiveness Objective

3.5.1. Endpoints

The primary endpoint is as follows:

1. Overall and heart failure related healthcare costs of care between subjects treated with the Furoscix Infusor 30 days post discharge from the emergency department compared to propensity score versus matched controls treated in the hospital for ≤ 72 hours through 30 days post discharge

The primary analysis is to compare the Furoscix Infusor (prospective arm) versus treatment as usual (historical control arm) with respect to overall cost of care and total HF-related costs. Comparison of these data between the matched (paired) cohorts will be conducted via a t-test or a Wilcoxon signed-rank test depending on the distribution of the data.

Secondary endpoints are as follows:

1. Number of hospital admissions and duration with-in 30 days post discharge from the emergency department
2. Number of HF-related hospital admissions and duration with-in 30 days post discharge from the emergency department
3. Number of HF-related emergency department visits with-in 30 days post discharge from the emergency department
4. Number of HF-related clinic visits with-in 30 days post discharge from the emergency department
5. Description of health-related quality of life using the twelve-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12, for Furoscix Infusor cohort only), administered on Day 0 and Day 30.
6. Change in NT-proBNP (for Furoscix Infusor cohort only)
7. Subject and/or caregiver satisfaction with Furoscix Infusor (for Furoscix Infusor cohort only)

3.5.2. Step 1: Determining the Initial Target Sample Size

Although this is an adaptive clinical trial with sequential cohort design whereby the final sample size will ultimately be determined by the prespecified interim analyses, it was necessary for trial planning purposes to generate an estimated final sample size based purely on a priori assumptions.

Based on an average hospital cost of a patient hospitalized for ≤ 72 hours with a primary diagnosis of HF (Diagnosis Related Group Code 291, 292 and 293) of $8,600 (standard deviation: $3,045), 68 patients (34 evaluable patients in each group) are required to have an 80% chance of detecting a decrease in hospital costs to $6,500 at a significance level of 5%. The target sample size of the Furoscix cohort will initially be N=34 subjects.

Re-assessment of the sample size will be conducted once 34 subjects in the Furoscix cohort complete all study phases as per protocol (matched 1:1 to 4:1 to propensity matched controls to generate comparisons) by using a group sequential design and testing to allow for stopping. It is not expected that the sample size for the Furoscix Infusor arm would exceed N=75, but the maximum value cannot be definitively stated until the analysis at N=34 is completed.

3.5.3. Step 2: Produce Candidate Pool for Historical Cohort

EPI-Q will produce a candidate pool from which historical controls will be drawn via propensity match for comparison against the Furoscix Infusor cohort. This candidate pool will be comprised of HF-patient lives contained in the Marketscan Commercial Claims and Encounters (CCAE) and Medicare Supplemental Database . This pool will contain HF patients who will be characterized by binary indicators consistent with the demographic and background clinical variables (except laboratory tests) that are collected for the Furoscix Infusor arm (Appendix B).

Initially, the historical cohort will be created using the Marketscan Commercial Claims and Encounters (CCAE) and Medicare Supplemental Database for the years 2015-2017. The historical cohort will be later updated post acquisition of latest data up to year 2019.

The following inclusion criteria will be applied to identify patients with worsening HF:

1. Inpatient claims coded with an HF (ICD-9/ICD-10) diagnosis codes in primary position on the claim
2. Worsening HF defined by all admissions coded with a diagnosis-related group (DRG) for HF (291, 292, or 293)
3. Length of Stay 1-3 days
4. Service Category included ED Visit
5. Age 18-80 years
6. Continuous enrollment for 1 year before and 3 months after the index date
7. Background therapy including oral furosemide equivalents daily (Torsemide or Bumetanide)

First qualifying claim, where all the eligibility criteria is met, will be defined as the index date. Patients will be excluded if one of the following exclusion criteria is met:

1. Presence of diagnosis code for a complicating condition, other than HF (e.g. MI, pneumonia) as identified from the prospective arm data before final matching
2. Presence of diagnosis or procedure code for acute renal failure or Dialysis
3. Estimated Creatinine Clearance (CrCl) <30 (indicated by presence of diagnosis code for chronic kidney disease stage 4/5, ESRD or renal failure.

For the patients that meet all the eligibility criteria, the following demographic and baseline characteristics (i.e., candidate variables for propensity score calculation) will be determined and reconciled between the prospective study and historical controls' databases (i.e., only variables that can be consistently defined will be analyzed):

- Integer age
- Sex
- Geographic region (Northeast, North Central, South, West, Unknown)
- Concomitant Medication Use in prior 3 months (90 days) of index or enrolment date (inclusive)
    - Oral Diuretic
    - Digoxin
    - ACE Inhibitors
    - Nitrates and hydralazine
    - Oral anticoagulant
    - Statin
    - Platelet Inhibitor
    - Beta Blockers
- Baseline conditions/co-morbidities in prior year (364 days) of index or enrolment date (inclusive)
    - Myocardial Infarction
    - Hypertension
    - Diabetes
    - Hyperlipidemia
    - Peripheral vascular disease
    - Arrhythmias
    - Malignancy
    - COPD
    - Stroke
    - Valvular heart disease
    - PCI
    - Acute Coronary syndrome
    - Chronic Kidney Disease Stage

- Baseline resource utilization (All-cause and HF-related) in the 6 months prior to index or enrolment date
    - Hospitalizations
    - ED Visits
    - Clinic Visits

Once the data have been reconciled, distributions of the candidate variables will be assessed. Variables will be excluded from the analysis if none of the subjects from the prospective arm have the characteristic or there is little variability. To maximize the number of subjects from the prospective arm, when discrete variables have missing data, an "unknown" category will be created. With respect to missing data for continuous variables, the population mean will be imputed.

3.5.3.1. Healthcare Resource Utilization (HCRU) and Costs

For each patient in the historical control and prospective arm, 30-day follow-up HF-related and all-cause healthcare resource utilization (HCRU) will be estimated and reported.

For cost inputs, events that are major contributors of the costs will be included in the analysis, including any visits and hospitalizations that are either HF-related or all-cause. Using the dataset created for matching, cost benchmarks for each event (HF-related and all-cause) i.e. mean and standard deviation will be derived. For each patient in the historical and prospective cohorts, 30-day HF-related and overall costs will be estimated by summation of applied cost benchmarks to each resource utilization event observed during the 30-day period starting from the beginning of HF-worsening episode.

Overall cost of care will include cost attribute to all-cause HCRU. Total HF-related medical costs will be comprised of the hospitalization costs and outpatient visits costs attributable to HF-related HCRU (defined by claims with a primary diagnosis of HF). All costs will be inflated to $2019 using Medical Care Consumer Price Index (CPI). All costs included will be gross costs including payer and patient costs.

3.5.4. Step 3: Compute Boundary Values for Primary Outcome

Boundary values for the primary outcome will be derived via the SEQDESIGN (REF SAS SEQDESIGN) procedure in SAS; specifically using a two-sided O'Brien Fleming design which has conservative stopping boundary values at early stages, and boundary values at the final stage that are close to the fixed-sample design. This produces a conservative design because compared to other approaches, the O'Brien-Fleming approach makes it more difficult to reject the null hypothesis in early stages than in later stages (null hypothesis being that there is no difference in 30-day HF-related direct medical costs between the Furoscix Infusor and historical control arms).

Assume that the total 30-day HF-related direct medical costs are normally distributed with means μ_e and μ_c for individuals in the Furoscix Infusor and historical control groups, respectively. The null hypothesis of no effect for the Furoscix Infusor is $H_0 : \theta = 0$, where $\theta = \mu_e - \mu_c$

The specific procedure for determining the boundary values for the primary outcome are specified elsewhere (REF SAS SEQDESIGN). Utilizing this procedure requires that we prespecify the meaningful difference between groups and the standard deviation thereof in order to achieve the specified power. The boundary values will be estimated based on a difference of $2,100 (based an average hospital cost of a patient hospitalized for ≤ 72 hours with a primary diagnosis of HF (Diagnosis Related Group Code 291, 292 and 293) of $8,600 (standard deviation: $3,045), 68 patients (34 in each group) are required to have an 80% chance of detecting a decrease in hospital costs to $6,500 at a significance level of 5%).

3.5.5. Step 4: Interim and Final Analysis with Propensity Match

Interim analyses to determine whether efficacy or futility has been reached will be conducted in a prespecified manner at N=10 and N=34 in the evaluable population. Additional interim analyses may be conducted as needed. Note that the enrollment for the prospective arm will continue as the interim analysis is carried out up to N=34, at which point re-assessment of sample size will be conducted.

For the interim analyses, the comparators will be historical controls drawn from the aforementioned candidate pool using a 1:1 to 4:1 propensity score matched approach. The propensity score matching process will be conducted via a caliper-based mechanism that allows for an iterative matching approach that will maximize the efficiency of the match protocol using methods reported by Millar and Pasta 2010.

The primary final analysis will include a 1:1 to 4:1 propensity match using the identical algorithm produced in the last interim analysis. Additional final analyses will explore the impact of increasing the ratio of cases to controls up to a 1:10 match. Note that the aforementioned matching method will be applied so that no Furoscix subjects will be dropped from the analysis due to the lack of a suitable match or matches.

The propensity scores (1 for each case and control) will be generated with the SAS PROC LOGISTIC function to produce a multivariate logistic regression. The propensity score is the predicted probability of receiving the Furoscix Infusor treatment. Both automatic stepwise and manual variable selection will be evaluated.

Criteria for propensity score matching are listed below:

- In addition to requiring that the absolute difference between the treatment arm propensity score and the control patient's propensity score be no larger than 0.01, exact sex, the absolute difference in age could be no larger than 5 years, and time between time zero visits could be no more than 730 days (or 1095 days). These key measure requirements reduced the data set substantially to a data set of potential matches.
- A logistic regression model will be developed to estimate a propensity score for each subject. The model will include candidate variables (defined in Section 3.5.2 Step 2: Produce Candidate Pool for Historical Cohort). The dependent variable will be binary and indicate either prospective patient or historical control patient. Backwards stepwise selection will be implemented with alpha level of 0.1 or 0.20 to identify predictor variables of receiving Furoscix (prospective subject vs. historical control). The final model including candidate variables identified from backwards stepwise selection will be used to generate a predicated probability (propensity score of receiving Furoscix) for each subject.
- For treatment arm, the variables will be defined at time zero (enrollment/ED visit); for control patients, the variables will be defined at index as a possible match.
- Once final matches are identified, to assess balance in confounding variables between cases and controls, for each of the candidate variables included in the propensity score modeling, effect sizes (normalized difference between cases and controls) will be calculated based on the differences between the matched pairs. An effect size of <0.20 will be deemed acceptable.
- Control patients' data were weighted based on the number of controls within each matched treatment arm patient set. For instance, if a control patient was part of a set with 1 other control patient, each control patient in that set was weighted 0.50 (1 divided by the set count 2).
- In addition to the effect size evaluation, the baseline characteristics, i.e. all initial candidate variables for propensity model, between the two cohorts will be compared statistically and any variable difference with a p value of <0.1 will be identified.

Analyses, whether they be interim or final, will be conducted sequentially using the SEQTEST procedure in SAS, which has been specified elsewhere (SAS Institute, 2009). Briefly, The SEQTEST procedure performs interim and final

analyses by comparing test statistics with corresponding boundary values obtained with the SEQDESIGN procedure. If the information levels for the test statistics do not match the information levels obtained with the SEQDESIGN procedure, the SEQTEST procedure modifies the original boundary values to adjust for actual (observed) information levels.

3.5.6. Secondary Outcomes

Outcomes for the endpoints related to healthcare utilization (i.e., Secondary Endpoints 1-4) will be evaluated by appropriate statistical test dependent on the distribution of the outcome. Health-related quality of life outcomes will be evaluated for the Furoscix cohort only and will descriptively compare KCCQ-12 questionnaire responses at Day 0 versus Day 30. Change in BNP or NT-proBNP will be evaluated for the Furoscix cohort only and will descriptively compare values obtained at Day 0 versus Day 30. Subject and/or caregiver satisfaction with Furoscix Infusor will be descriptive.

3.6. Additional Analysis

3.6.1. Risk Factors

Risk factors associated with time (in days) to heart failure-related readmission to the emergency department and/or rehospitalization will be evaluated using Cox Proportional Hazards model. Application of the Efron approximation will be explored in order to account for tied observations. A stepwise selection process will be utilized to pare the model down. In this process, the single-term baseline variable with the highest p-value will be removed from the model until all factors have a $p<0.10$. Baseline variables include those described in section 3.5.3 used for propensity score modeling in addition to the following variables: race, ethnicity, potassium supplements, heart failure type, NYHA classification, and baseline vital signs).

4. REFERENCES

Millar SJ and Pasta DJ. 2010. The Last Shall Be First: Matching Patients by Choosing the Least Popular First. Accessed on July 16, 2018. Accessed at: https://www.lexjansen.com/wuss/2010/HOC/2940_2_HOR-Millar.pdf

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5. APPENDICES

Appendix A. Codebook for Claims Analysis

Appendix B. Case Report Form

5.1. Appendix A. Codebook for Claims Analysis

Claims Codebook.pdf

5.2. Appendix B. Case Report Form

FREEDOM HF eCRF