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STATISTICAL ANALYSIS PLAN

SPONSOR	scPharmaceuticals, Inc. 2400 District Avenue, Suite 310 Burlington, MA 01803
PROTOCOL TITLE	A Multicenter, Randomized, Open Label, Controlled Study Evaluating the Effectiveness and Safety of Furoscix® On-Body Infusor vs Continued Medical Therapy for Worsening Heart Failure
PROTOCOL NUMBER	scP-01-008
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SAP Version Date: 7 April 2022

Version Number: 1.0

The undersigned have reviewed this analysis plan and approve of it in its entirety.

Signature	**Date**
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ABBREVIATIONS

Abbreviation, Acronym or Term	Definition
6MWT	Six Minute Walk Test
6MWD	Six Minute Walk Distance
AE	Adverse event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CCS	Composite Congestion Score
COVID-19	Coronavirus Disease 2019
CS	Clinically Significant
CV	Cardiovascular
EtO	Ethylene Oxide
FS	Finkelstein-Schoenfeld
GEE	Generalized Estimating Equations
HF	Heart Failure
IFU	Instructions for Use
IP	Investigational Product
ITT	Intent-to-Treat population
KCCQ	Kansas City Cardiomyopathy Questionnaire
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium

Abbreviation, Acronym or Term	Definition
mg	Milligram
NCS	Not Clinically Significant
NYHA	New York Heart Association
PP	Per-Protocol population
PT	Preferred Term
ReDS	The ReDS™ system is a noninvasive tool that allows providers to rapidly, and accurately, measure lung fluid in Heart Failure patients at home.
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
VAS	Visual Analogue Scale
WHF	Worsening Heart Failure

1. TITLE

A Multicenter, Randomized, Open Label, Controlled Study Evaluating the Effectiveness and Safety of Furoscix On-Body Infusor vs Continued Medical Therapy for Worsening Heart Failure

2. STUDY DESIGN

This is a multicenter, randomized, open label, controlled study evaluating the effectiveness, and safety of the Furoscix Infusor versus continued medical therapy in patients with chronic heart failure and fluid overload requiring augmentation in diuretic therapy outside of an acute care setting. 51 subjects will be randomly assigned (2:1) to receive Furoscix (n=34) versus continued medical therapy (n=17). Within a single 24-hour period, the 80 mg dose can be repeated at the discretion of the investigator $\geq$ 2 hours after the completion of the first dose. Subjects should be transitioned back to their oral *maintenance* diuretic regimen when clinically indicated at the discretion of the investigator. 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 congestion symptoms (e.g., dyspnea, edema, and/or excess weight gain) as determined by the investigator. No more than 7 doses of Furoscix are permitted during the 30-day study period. Additional doses beyond 7 requires approval by the medical monitor. Over the initial 7 days, all subjects will receive daily clinic or phone follow-up by the study staff. Decision of treatment with Furoscix in the intervention arm (Furoscix On-Body Infusor) as well as changes in oral diuretic dosing in the continued medical therapy group will be determined by the treating physician in coordination with the study nurse. Safety labs will be done on Days 1, 3, 7 and 30.

Each Subject will complete Screening, Treatment, and Follow-Up Phases on an outpatient basis. During the Screening Phase, all Subjects who sign the informed consent form and satisfy the inclusion/exclusion criteria will be enrolled into the trial. Drug administration will start on the day of enrollment (same day as screening after all eligibility criteria have been confirmed) after randomization.

The Treatment Phase comprises a pre-programmed bi-phasic 5-hour drug subcutaneous administration of Furoscix (80 mg/10 mL) via the On-body Infusor. Subjects and/or their caregivers will be trained on device preparation, placement, and removal in accordance with product instructions for use (IFU). Subjects will return to the clinic on Days 1, 3 and 7 for assessments including limited physical exam (including NYHA Class), CCS, 5-point Current Dyspnea Score, 7-point Dyspnea Score, vital signs, laboratory analyses, NT-proBNP (Day 3 and 7), adverse events, Visual Analog Scale (VAS), % Lung Fluid Measurement (ReDS), 6MWT (Day 1 and 7) and the KCCQ-12 (Day 7) and review Subject Diary including recorded device issues. On Days 2, 4, 5, 6 and 17 subjects will receive a phone call from the site staff to review Subject's Diary, assess Subject's weight and vital signs that were obtained using the study equipment, 5-point Current Dyspnea Score, 7-point Dyspnea Score, VAS, and report any adverse events and device issues. After Subjects have been transitioned to their oral maintenance diuretic regimen, additional doses of Furoscix for the treatment group or oral diuretics for the treatment as usual continued medical therapy group can be prescribed during the 30-day study period as needed based on the presence of congestion symptoms (e.g., dyspnea, edema, and/or excess weight gain) as determined by the investigator. If diuretic modifications are made after Subjects are transitioned to their oral maintenance diuretic regimen, the Subjects' follow-up assessments and timing of those assessments will be based on the investigator's clinical judgement. Unscheduled clinic and phone visits can be conducted as needed. All follow-up assessments done by phone or in-clinic will be documented.

The Follow-Up Phase will include a visit to the clinic on Day 30 $\pm$ 5 days where effectiveness and safety assessments will be performed including limited physical exam (including NYHA Class), CCS, 5-point Current Dyspnea Score, 7-point Dyspnea Score, vital signs, laboratory analyses, NT-proBNP, KCCQ-12, VAS, 6MWT, % Lung Fluid Measurement (ReDS), adverse events and review Subject Diary including recorded device issues.

With respect to blinding, this is an open label study.

A Time and Events Schedule is provided in Table 1.

TABLE 1: TIME AND EVENTS SCHEDULE

	Screening and Treatment Phase											Follow-Up Phase
	DAY 0 (Clinic)	DAY 1 (Clinic)	DAY 2 (Phone)[5]	DAY 3* (Clinic)	DAY 4 (Phone)	DAY 5 (Phone)	DAY 6 (Phone)	DAY 7 (Clinic)	Day 17± 3 (Phone)	Unscheduled Clinic Visit[7]	Unscheduled Phone Visit[8]	DAY 30 ± 5 (Clinic)
Informed Consent	X											
Confirmation of Eligibility	X											
Randomization	X											
Medical History & Demographics	X											
Limited Physical Exam[1] including NYHA Class	X	X		X				X		X		X
Composite Congestion Score	X	X		X				X		X		X
5-Point Current Dyspnea Score	X	X	X	X	X	X	X	X	X	X	X	X
7-Point Dyspnea Score		X	X	X	X	X	X	X	X	X	X	X
Vital Signs (RR, BP, HR), Weight + Height (Day 0 only)[2]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory[3]	X	X		X				X		X		X
Urine Pregnancy Test[4]	X											
NT-proBNP[3]	X			X				X		X		X
KCCQ-12	X							X				X
Patient Global Assessment VAS	X	X	X	X	X	X	X	X	X			X
Device/Product Training	X											
6MWT	X	X						X				X
ReDS Measurement[6]	X	X		X				X		X		X
Device/Product Administration[7]	X	X	X	X	X	X	X					
Device/Product Accountability	X	X		X				X		X		X
Subject Diary[9]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Schedule Next Study Visit	X	X		X				X	X (If Necessary)	X (If Necessary)	X (If Necessary)	

* If Day 3 falls on a Saturday or Sunday, subjects may be seen in the clinic and have Day 3 assessments completed on either Day 2 (Friday if Day 3 falls on Saturday) or Day 4 (Monday if Day 3 falls on Sunday). On Day 3 the subject will have a phone call visit.

[1]Limited PE includes minimally evaluation of the skin of abdominal area, lungs/chest, heart, abdomen and periphery.

[2]Vital signs include respiratory rate (RR), blood pressure (BP) and heart rate (HR) and will be obtained at clinic visits. BP and HR will be obtained with phone assessments. Weight, BP and HR should be obtained at home each day in the morning after Day 0, even on clinic visit days. Height recorded Day 0 only.

[3]Clinical Labs are done locally and include BUN, Cr, Na+, K+, Cl, $C0_2$, and Mg; Day 0 NT-proBNP will be done locally to determine eligibility and 2nd sample sent to centralized lab for subjects who qualify. NT-proBNP drawn Day 3, Day 7 and Day 30 will be done at centralized lab.

[4]Urine pregnancy test on females of childbearing potential.

[5]Scheduled Phone Calls will have a written script to guide the site staff on what questions to ask the Subject.

[6]Remote Dielectric Sensing (ReDS) System for % lung fluid measurement.

[7]If modifications are made to the diuretic regimen after Subjects are transitioned to their oral maintenance diuretic regimen, including additional doses of Furoscix for the treatment group or oral diuretics for the treatment as usual control group, the Subject will have follow-up assessments and timing of those assessments based on the investigator's clinical judgement and document those under Unscheduled Visit (clinic or phone) column. Unscheduled clinic and phone visits can be conducted as needed.

[8]If Subject receives unscheduled at-home phone call, the staff should perform assessments in the Unscheduled Phone Visit column.

[9]Device issues should be recorded by the subject in the comments/issues section of the Subject Diary. For each device issue recorded by the subject, a Device Issue Intake Form should be completed and submitted to the sponsor by the study staff.

3. TREATMENT

Study Drug: Furoscix, (Furosemide Injection), 80 mg/10 mL is a proprietary furosemide formulation that is buffered to a neutral pH to enable subcutaneous administration and contained in a prefilled Crystal Zenith® (CZ) cartridge.

Study Device: The Infusor is a compact, ethylene oxide (EtO) sterilized, single-use, electro-mechanical (battery powered, micro-processor controlled), on-body subcutaneous delivery system based on the SmartDose® Gen II 10 mL (West Pharmaceutical Services).

The Furoscix Infusor is an investigational drug-device combination product. The Infusor is applied to the abdomen via a medical grade adhesive and delivers a subcutaneous infusion of Furoscix through a pre-programmed, biphasic delivery profile with 30 mg (3.75 mL) administered over the first hour, followed by 12.5 mg (1.56 mL) per hour for the subsequent 4 hours (Total dose is 80 mg (10 mL) over 5 hours).

4. SAMPLE SIZE

Fifty-one (51) subjects will be included and randomly assigned in a 2 to 1 ratio to receive Furoscix (n=34) or continued medical therapy (n=17) in the home setting with 30 days of follow-up. Given the exploratory nature of this study, no formal power analysis of sample size was conducted.

5. CENTERS

This is a Multicenter, Randomized, Open Label, Controlled Study to be conducted at up to 20 sites.

6. OBJECTIVES

6.1 Primary Objective:

Provide pilot data on effectiveness and safety to inform a pivotal trial

6.2 Secondary Objectives:

- Inform population enrichment strategies
- Refine pivotal trial endpoints and analytical methods
- Identify operational challenges of study design
- Assess patient adherence, competence, and experience
- Familiarize staff and patients with device application and use

7. DATA ANALYSIS CONSIDERATION

7.1 General Data Considerations:

The following conventions will be applied to analyses/data presentation:

All dates will be displayed in DDMMMYYYY format.

Repeat assessments will be considered as unscheduled. Unscheduled visit data will be presented in Listings, but not in Tables and Figures.

The statistical analyses will be performed using Statistical Analysis System (SAS) Version 9.3 (or higher). All Tables, Listings and Figures (TLFs) will be produced in landscape format. In general, all data collected during the study will be presented in the data listings. Unless otherwise noted, the data will be sorted first by treatment group, then by subject number, and then by date within each subject number. The number of variables presented in each listing can vary. Please refer to Mock tables, listings, and figures.

Data will be summarized by treatment group where appropriate. The total number of subjects (N) in the treatment group under the stated population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise stated, descriptive statistics will include number of subjects (n), mean, standard deviation (SD), minimum, median**,** and maximum. When n=0**,** except n, all other summary statistics will be kept blank. In case n=1, only n, minimum and maximum will be reported, and all other summary statistics will be kept blank. The statistic "Missing" will also be evaluated by enumerating the number of missing entries/subjects, if any at that visit, and presented as a summary statistic only for the resulting visits.

For categorical variables, data will be summarized using counts and percentages. The number [n] indicates the actual number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects in the respective treatment group [N]**.** The number and percentage of subjects with missing values for a variable/category/event will also be presented for the resulting visits under the "Missing" category. Percentage will be obtained by: % = (n/m) *100, where m is the number of subjects present at that visit. Unless otherwise stated, all percentages will be expressed to one decimal place. The number and percentage of subjects will always be presented in the form XX (XX.X). Counts of zero in any category will be presented as "0" and if the percentage in any category to be presented is 100, it will be presented as "100".

The laboratory assessment values that are LLOQ (lower limit of quantification) will converted to numeric values such as "<1" = 1 or "<5" = 5.

Tables that involve statistical modeling will not be presented if the model fails due to excessive missing data (e.g., GEE model fails to converge).

When analyzing statistical models (e.g. GEE models), if the unstructured covariance structure fails to converge then different covariance structures (e.g., Exchangeable (EXCH/CS), Independence (IND), Autoregressive(1)) will be applied.

7.2 Decimal Precision Convention:

The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median, Confidence Intervals (CI) will be presented to one more decimal place than the original data, whereas the SD and Standard Error (SE) will be presented to two more decimal places than the original data. P-value will be presented with three decimal places. If p-value is closer to 0, then it should be reported as "<0.001" and if it is closer to 1, then it should be reported as ">0.999".

8. HANDLING OF MISSING DATA

No imputation of missing data will be done.

To handle missing or partial AE and concomitant medication dates, the following rules will be applied.

8.1 For Partial Start Dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    i. If the year matches the year of the first dose date, then impute the month of the dose date.
    ii. Otherwise, assign "January."
3. If the day is unknown, then:
    i. If the month and year match the month and year of the first dose date, then impute the day of the dose date.
    ii. Otherwise, assign "01."

8.2 For Partial End Dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pre-treatment or on/after treatment, the following strategy will be used:

1. If both start date and stop date are missing, then the most conservative approach is taken, and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

2. If the start date is missing but the stop date is not missing and is on or after the day of study dose administration, then the most conservative approach is taken, and the AE (or medication) is considered to be treatment emergent (or concomitant medication).

3. If the start date is missing but the stop date is not missing and is before the day of study dose and after the date of signed informed consent, then the AE (or medication) is considered to be before treatment (or prior medication).

4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken, and medication is considered to be concomitant while the AE is defined by start date.

9. DEFINITIONS

Baseline: Baseline is defined as the last non-missing value prior to the first administration of the study drug, unless otherwise stated.

Change from Baseline: The change from baseline values will be calculated as post-baseline value (p) minus the baseline value (b).

Percent (%) Change from Baseline: The % change from baseline values will be calculated as (p - b)/b x 100.

Adverse Event (AE): Any untoward medical occurrence associated with the use of an Investigational Product (IP) in humans, whether considered related to the IP and does not imply any judgment about causality. The Investigator will assess each AE for seriousness as defined in the protocol and severity and causality based on their best medical judgment, the observed symptoms associated with the event, and the available information on the Investigational Product (IP) as defined in the protocol. The relatedness guidance provided below can be used to assist in determining the relationship of the IP to the AE.

- **Not Related:** Based upon available information regarding subject history, disease process, relationship of adverse event to dosing and drug pharmacology, there is no reasonable relationship between the IP and the adverse event.
- **Possibly Related:** Relationship exists between the adverse event and IP, when the adverse event follows a reasonable sequence from the time of the IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the patient.
- **Probably Related:** Relationship exists between the adverse event and the IP when the adverse event follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the IP is the most likely of all causes.
- **Definitely Related:** Relationship exists between the adverse event and the IP when the adverse event follows a reasonable sequence from the time of the IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.

Treatment-emergent Adverse Events (TEAEs): A treatment-emergent adverse event (TEAE) is any new AE that emerges on or after the start of the first study drug administration having been

absent in pre-treatment (or) worsen in severity relative to the pre-treatment state following administration of study drug.

Composite Congestion Score: A composite congestion score (CCS) will be calculated by summing the individual scores for orthopnoea, JVD, and pedal oedema.

10. ENDPOINTS

10.1 Primary Endpoints

- Improvement in a composite/combined morbidity/mortality endpoint at 30 days using the Finkelstein Schoenfeld method.
    - CV death
    - HF hospitalization
    - Urgent ED/Clinic visit for worsening heart failure (defined as IV diuretics, augmentation of or new administration of metolazone)
    - Percent change in NT-proBNP from baseline at Day 7
- Incidence of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

10.2 Secondary Endpoints (through 30 days)

- Days alive and HF event free days
- Global Visual Analog Scale
- Composite Congestion Score (CCS)
- 5-point Current Dyspnea Score
- 7-point Dyspnea Score
- Health-related quality of life (KCCQ-12)
- Renal Function and Electrolytes
- Weight
- Exercise tolerance (6MWT)
- Percent Lung Fluid Measurement via Remote Dielectric Sensing (ReDS)

10.3 Adverse Events of Special Interest over 30 Days

- Worsening kidney function, defined as increase of $\geq$ 0.5 mg/dl in serum creatinine
- Hyperkalemia, defined as K > 5.5 mEq/L
- Hypokalemia, defined as K < 3.5 mEq/L
- Hypomagnesemia, defined as Mg < 1.5 mg/dL

13. INTERIM ANALYSIS

There will be no formal interim analysis.

14. ANALYSIS POPULATIONS

Intent-to-Treat (ITT): ITT population will include all randomized subjects. The subjects in ITT population will be analyzed according to the treatment group they were originally randomized.

Safety: Safety population will include all randomized subjects who received at least one dose of Investigational Product (IP). The subjects in the Safety population will be analyzed and presented according to the actual treatment received.

Per-Protocol (PP): All randomized subjects who received at least one dose of the IP, completed the 30 Day clinic visit assessments and have a Day 7 NT-proBNP value available for analysis.

All effectiveness analyses, including the primary endpoint and baseline characteristics will be performed on the ITT and Per-Protocol populations. Safety analyses will be performed on the safety population.

15. STATISTICAL ANALYSIS

This is a multicenter, randomized, open label, controlled study evaluating the effectiveness and safety of the Furoscix Infusor versus continued medical therapy in patients with chronic heart failure and fluid overload requiring augmentation in diuretic therapy outside of the acute care setting. The SAP takes precedence over the protocol.

Unless otherwise specified, all baseline data, including demographic data and other clinical characteristics will be compared using descriptive statistics grouped by treatment group (Furoscix On-Body Infusor vs Continued Medical Therapy for Worsening Heart Failure). Change from baseline is the absolute change, unless stated otherwise; which then will be percentage change from baseline. Tables will include footnotes indicating definition implemented. Continuous data will be summarized by reporting the number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical data will be described using frequency tables showing the number and percentage of subjects falling within a particular category. Shift tables will be given where appropriate to show change at follow-up compared to baseline values.

Between-group analyses of baseline characteristics will employ descriptive statistics. Mortality and morbidity events will be assessed using appropriate statistical tests. The primary endpoint will be compared between treatments using the Finkelstein-Schoenfeld Method, comparing components of the composite endpoint between patients hierarchically. Given the nature of the study, there will be no imputation of missing data on endpoints.

The primary endpoints including CV death at 30 days, HF hospitalization at 30 days, Urgent ED/Clinic visit at 30 days for WHF (defined as IV diuretics, augmentation of or new administration of metolazone), and change in NT-proBNP from baseline at 7 days will also be summarized and analyzed separately.

In general, secondary efficacy with follow-up timepoints will be analyzed using Generalized Estimating Equations (GEE) models.

Statistical tests will be performed at a two-sided alpha level of 0.05, unless otherwise specified. Given the nature of the study, there will be no adjustment for multiple comparisons.

15.1 Analysis of Baseline Characteristics

- **Subject Disposition**. The number and percentage of subjects consented but screen failed, enrolled, randomized, lost-to-follow-up, withdrawn (and reasons) and completed will be presented.
  A listing of subject disposition will also be presented.
- **Analysis Populations.** The number and percentage of subjects in each of the analysis populations will be presented for all randomized subjects.
  A listing of analysis populations will be presented for ITT population.
- **Demographic and Baseline Characteristics.** Demographics (Age, Gender, Race, Ethnicity, NYHA Class, BMI) will be summarized by treatment group, and overall for ITT and PP populations. Categorical variables (Gender, Race, Ethnicity, and NYHA Class) will be summarized using frequency count and percentage while continuous variables (Age, and BMI) will be summarized using descriptive statistics.
  Demographic and baseline data will be listed using ITT Population.
- **Vital Signs.** Descriptive statistics by treatment group of systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, weight will be presented for ITT population.
  Vital signs data will also be listed using ITT population.
- **NYHA Class.** A shift table comparing the change in the NYHA Class from baseline to post-baseline visits will be presented by treatment group for ITT population.
  NYHA class data will also be listed using ITT population.
- **Medical History and CV History.** Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 and summarized using the number and percentage of subjects within each System Organ Class (SOC), and Preferred Term (PT) by treatment group for Safety population. Listing of medical history will also be presented.
  The CV history will be summarized using the number and percentage of subjects within each category by treatment group for ITT population. Listing of CV history for subjects in the ITT Population will be provided.
- **Cardiopulmonary Examination.** The number and percentage of subjects within each parameter of each category by treatment group will be presented for ITT population. Listing of cardiopulmonary examination will also be presented for same population.
- **Ejection Fraction.** The number and percentage of subjects within a category of Imaging Modality and descriptive statistics of LVEF (%) will be presented by treatment group for ITT population. Listing of ejection fraction will also be presented.

Continuous data will be compared between treatment groups using a Two-Independent-Sample T-Test. In case when the data is non-normal (based on the Shapiro-Wilk normality

test with a p-value <0.15), the nonparametric Wilcoxon Rank Sum test will be applied. The categorical data will be compared between treatment groups using Chi-Square test for Two-Way tables. In case when frequencies below five are met for more than 20% of the cells, a Fisher's exact test will be applied.

15.2 Analysis of Efficacy

For all analyses, baseline will be considered as information collected on Day 0 prior to device start. For investigational drug-device use, the device start date and time will be used as the reference datapoint.

15.2.1 Primary Efficacy Analysis

The primary efficacy endpoint is the improvement in a composite/combined morbidity/mortality endpoint at 30 days using the Finkelstein Schoenfeld method. The analysis of the primary efficacy endpoint will be conducted for the ITT and PP populations. Each component of the primary endpoint will be compared in pairwise fashion hierarchically. Each patient is compared to all other patients with respect to each of the following endpoints hierarchically. The algorithm is as follows when doing a pairwise comparison of Patient B to Patient A:

- CV death at 30 days:
  - if Patient A survives to 30 days and patient B dies before 30 days, then score = -1 for Patient B
  - if Patient B survives to 30 days and patient A dies before 30 days, then score = +1 for Patient B
  - if both patients survive or if both die , then move to the comparison on the next component.
- HF hospitalization at 30 days:
  - if Patient A is not hospitalized for worsening heart failure (WHF) and patient B is, then score = -1 for Patient B
  - if Patient A is hospitalized for WHF and patient B is not, then score = +1 for Patient B
  - if both patients are not hospitalized or if both are hospitalized, then move to the comparison on the next component.
- Urgent ED/Clinic visit at 30 days for WHF (defined as IV diuretics, augmentation of or new administration of metolazone)
  - if Patient A does not have an Urgent/ED visit for WHF and patient B does have a visit, then score = -1 for Patient B
  - if Patient A does have an Urgent/ED visit for WHF and patient B does not have a visit, then score = +1 for Patient B
  - if both patients have an Urgent/ED visit for WHF, then move to the comparison on the next component.

    - if both patients do not have an Urgent/ED visit for WHF, then move to the comparison on the next component.
- Percent Change in NT-proBNP from baseline at 7 days (without imputation):
    - if Patient A's change from baseline at 7 days in NT-proBNP<Patient B's change from baseline at 7 days in NT-proBNP, then score = -1 for Patient B
    - if Patient A's change from baseline at 7 days in NT-proBNP >Patient B's change from baseline at 7 days in NT-proBNP, then score = +1 for Patient B
    - If tied, score=0 for Patient B.

A -1/0/1 score is created for Patient B vs. every other patient in the study, so if there are *n* total patients in the study, then patient B is assigned *n* -1/0/1 scores (including, for completeness, a score of 0 when patient *B* is compared to themselves). Similarly, every other patient in the study is also assigned *n* -1/0/1 scores.

For each patient *i*, the sum of all -1/0/1 scores assigned to that patient is calculated and is denoted as U_i. If $n1$ and $n2$ are the number of patients in the experimental and control arms, respectively, then the lowest possible value of U_i that a given patient can experience is -($n1$ + $n2$- 1), which is achieved if the given patient scored a -1 versus all other (n1 + n2 - 1) patients in the study; similarly, the largest possible of U_i that a given patient can experience is +($n1$ + $n2$-1).

The numerator of the estimate of *T* (the Finkelstein-Schoenfeld test statistic) is the sum of the U_i across patients assigned to the experimental treatment. i.e.,

$$\sum_{i=1}^{n} D_i U_i$$

where U_i is the sum of the -1/0/1 scores for the i^{th} patient in the sample, D_i is the indicator of the treatment group to which the i^{th} patient was randomized (D_i = 0 for control and D_i = 1 for experimental) and *n* is the total sample size.

The denominator of *T* is:

$$\sqrt{\frac{n1 * n2}{n * (n-1)} \sum_{i=1}^{n} U_i^2}$$

where (a) $n1$ and $n2$ are the number of patients in the experimental and control arms, respectively; (b) *n* is the total sample size (= $n1$ + $n2$); and (c) U_i is the sum of the -1/0/1 scores for the i^{th} patient in the sample. The test statistic follows a standard normal distribution; the two-sided p-value is the area in the upper and lower tails of T on the standard normal curve.

The primary efficacy endpoint will be repeated for the ITT and PP analysis populations using the Day 3 NT-proBNP value (instead of the Day 7 NT-proBNP value). The Day 3 NT-proBNP value will be used for calculating the percent change from baseline as follows:

- Percent Change in NT-proBNP from baseline at 3 days:
  - if Patient A's change from baseline at 3 days in NT-proBNP<Patient B's change from baseline at 3 days in NT-proBNP, then score = -1 for Patient B
  - if Patient A's change from baseline at 3 days in NT-proBNP >Patient B's change from baseline at 3 days in NT-proBNP, then score = +1 for Patient B
  - If tied, score=0 for Patient B.

A listing of each endpoint for the composite will be presented for the ITT population.

A sensitivity analysis will be conducted where the primary efficacy endpoint analysis will be conducted on the ITT and PP analysis population and will exclude patients with normal NT pro-BNP values (defined as <125 pg/mL) at baseline. Results will be descriptively compared to the primary efficacy endpoint analysis on the ITT and PP population.

15.2.1.1 INDIVIDUAL ANALYSIS OF PRIMARY ENDPOINTS

Each component of the primary efficacy endpoint will be analyzed individually for the ITT and PP populations between treatment groups.

- CV death at 30 days:

  CV death will be summarized by counts and percentages for Furoscix on-body Infusor and Continued medical therapy.

  In addition, comparison of the proportion of death among Furoscix on-body Infusor and Continued medical therapy will be conducted using chi-square test. Proportion of death in each treatment group and also the proportion difference along with its corresponding 95% CI and p-value will be presented at Day 30.

  If any of the cells has expected frequency count less than 5 then the comparisons will be performed through a Fisher exact test. The p-value will also be presented using Chi-square/Fisher exact test to identify statistically significant differences in proportion of deaths for Furoscix on-body Infusor vs Continued medical therapy.

- HF hospitalization at 30 days:

  The analysis of HF hospitalization will be conducted similar to CV death at 30 Days.

- Urgent ED/Clinic visit at 30 days for WHF (defined as IV diuretics, augmentation of or new administration of metolazone):

The analysis of Urgent ED/Clinic visit for worsening heart failure will be conducted similar to CV death at 30 Days.

- Percent Change from baseline in NT-proBNP at Day 3, at Day 7 and at Day 30:

  The percent change in NT-proBNP from baseline across timepoints will be analyzed using a GEE model which includes change in NT-proBNP from baseline as the response variable, treatment, timepoint and treatment by timepoint interaction as fixed effects and baseline value of NT-proBNP as the covariate. An unstructured covariance matrix structure will be used to model the within subject errors. Least square means, corresponding 95% Confidence Interval (CI) and standard error (SE) from the model will be presented for Furoscix on-body Infusor and Continued medical therapy. The LS means estimate, standard error, 95% CI, and p-value for the treatment difference will also be presented.

  Additionally, non-parametric correlation (Spearman's Rank) analysis of percent change from baseline in NT-proBNP at Day 3, 7 and 30 and number of doses (Infusion) will be performed. The significance of correlation coefficient will be tested using a t-test.

  Finally, all outcomes of the primary endpoint will be summarized using descriptive statistics such as n, mean, median, minimum, and maximum for continuous variables and count and percentages will be provided for categorical variables by treatment group and overall.

15.2.2 Secondary Efficacy Analysis

The observed and change from baseline values of secondary endpoints will be summarized using descriptive statistics such as n, mean, median, minimum, and maximum for continuous variables and count and percentages will be provided for categorical variables by treatment group and overall. Individual subject data listings for all secondary endpoints will be presented for ITT population. Secondary endpoints will also be compared between treatment groups on the ITT, and PP population; a two-sided 0.05 level of significance will be used for each endpoint:

- Days alive and heart failure event-free (hospitalization for heart failure or ED visits for heart failure) over 30 days will be compared using the non-parametric Wilcoxon rank sum test.
- Changes from baseline in patient global assessment via visual analog scale (VAS) across follow-up timepoints will be analyzed using a GEE model with treatment arm, timepoint and treatment by timepoint interaction as fixed effects, and the baseline value

of VAS as covariates. An unstructured covariance matrix structure will be used to model the within subject errors.

- Changes from baseline in composite congestion score across follow-up timepoints will be analyzed using a GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect, and the baseline value of congestion score as covariates. An unstructured covariance matrix structure will be used to model the within subject errors.
- Changes from baseline in 5-point Current Dyspnea Score across follow-up timepoints will be analyzed using a GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect, and the baseline value of 5-point Current Dyspnea Score as covariates. An unstructured covariance matrix structure will be used to model the within subject errors.
- A repeated measures analysis of 7-point Dyspnea Score across follow-up timepoints will be analyzed using a GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect. An unstructured covariance matrix structure will be used to model the within subject errors.
- Changes from baseline in health-related quality of life, measured by the KCCQ-12 Short Form Overall Summary Score, across follow-up timepoints will be analyzed using a GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect, and the baseline value of the KCCQ-12 Overall Summary Score as covariates. An unstructured covariance matrix structure will be used to model the within subject errors.
- Changes from baseline in serum creatinine across follow-up timepoints will be analyzed using GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect, and the baseline value of serum creatinine as covariates. An unstructured covariance matrix structure will be used to model the within subject errors.
- Changes from baseline in body weight across follow-up timepoints will be analyzed using a GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect, and the baseline value of body weight as covariates. An unstructured covariance matrix structure will be used to model the within subject errors.
- Changes from baseline in Six-Minute Walk Distance (6MWD) across follow-up timepoints will be analyzed using a GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect, and the baseline value of 6MWD as covariates. An unstructured covariance matrix structure will be used to model the within subject errors.
- Changes from baseline in the ReDS percent lung fluid measurement across follow-up time points will be analyzed using a GEE model with treatment arm, and timepoint and treatment by timepoint interaction as a fixed effect, and baseline value as covariates.

An unstructured covariance matrix structure will be used to model the within subject errors.

15.3 Analysis of Safety

Descriptive statistics and appropriate tests will be used to summarize and compare the safety parameters between treatment groups. All safety analyses will be performed on the safety population. Treatment group comparisons may assess the significance of the difference between treatment and control groups.

15.3.1 Adverse Events

Adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA™) dictionary, version 23.1 . Adverse events (AE) will be summarized using number and percentage of subjects within each category of each variable overall for any AE, TEAE, serious AE, treatment related AE, AE resulting in death, AE leading to treatment discontinuation, and AE leading to study discontinuation. The incidence rates of AE will also be presented for severity, outcome, causality, and seriousness. For subjects with more than one AE within a given variable (e.g., severity), the event with the highest level of severity, outcome or causality, seriousness, respectively, will be reported. Incidence rates will also be presented for the System Organ Class (SOC) and Preferred Term (PT) of each AE. Data presented will include the number of subjects and percentage of subjects, the SOC and PT for each AE. All AEs will be presented in a listing for the Safety Population.

15.3.2 Serious and Treatment Emergent Adverse Events

SAEs and TEAEs will be listed, sorted by treatment group, subject identification, and onset date. In addition, the incidence (number and percentage of subjects) with SAEs by MedDRA SOC and PT will be displayed by treatment group.

15.3.3 Adverse Events of Special Interest

AESI will be listed, sorted by treatment group, subject identification number, and onset date. The number and percentage of subjects with an adverse event of special interest by MedDRA™ SOC and PT will be displayed by treatment group.

15.3.4 Laboratory Parameters

Descriptive statistics will be presented for observed and change from baseline values of each laboratory parameter (BUN, Cr, Na+, K+, Cl, C02, and Mg) and cardiac biomarker (NT-proBNP). Individual subject data listings of laboratory results will be presented. The clinically significant (defined as greater than twice the upper reference value or less than ½ the lower reference value) laboratory results will also be flagged.

Additionally, Laboratory data will be summarized by displaying shifts from baseline result (Low/Normal/High) to post-baseline visits by treatment group.

15.3.5 Physical Examination

The number and percentage of subjects within each body system will be presented.

Additionally, Physical Examination data will be summarized by displaying shifts from baseline result (Normal/Abnormal NCS/Abnormal CS) to post-baseline visits by treatment group.

15.3.6 Protocol Deviations

Protocol deviations will be listed by treatment group including date, time point, deviation category, COVID related assessment and a description and explanation for the deviation.

15.3.7 COVID-19 Adverse Events

If two or more COVID-19 positive cases are reported during the study, safety analyses will be conducted to compare rates between treatment arms and a comparison of rates to an external similar population diagnosed with COVID-19 if warranted.

15.3.8 Prior and Concomitant Medications (Non-CV, Non-Diuretic CV, Diuretic)

Prior Medications

Prior medications will include any medication taken prior to subject's first dose of study medication i.e., Prior medications have a stop date/time before study treatment starts. Medications stopped on the same day as the start of first study-drug administration will be considered as prior medication only.

Concomitant Medications

Concomitant medications are defined as prescribed medications and therapies, and over the counter (OTC) preparations, including herbal preparations and vitamins, other than Study medication taken during the study i.e., Concomitant medications are medications taken by subject on/after the start of first study-drug administration. If a medication starts before study entry and continues through the study that will be considered both as prior and concomitant.

Prior and concomitant medication will be categorized by preferred Term and ATC level X class per World Health Organization Drug Dictionary (WHODRUG; Version Global C3 2021SEP) and will be summarized by treatment group and overall, for the Safety Population. The count and percentage of patients using each medication will be displayed. Patients who taken the same medication (in terms of PT) more than once will be counted only once for that medication.

All Prior and concomitant medications will be presented in a listing for the Safety Population.

15.3.9 Device and Product Accountability

Device and product accountability will be summarized using descriptive statistics such as n, mean, median, minimum, and maximum for continuous variables and count and percentages will be provided for categorical variables by treatment group and overall for the Safety Population. A listing will be provided for device and product accountability, including details about the kit dispensing for the Safety Population.

15.4 Subgroup Analysis

The primary endpoint will be compared between the following pre-specified subgroups: gender, age split at the median value, race (white, non-white), etiology (ischemic, non-ischemic), prior hospitalization within 1 year (Yes/No), systolic blood pressure split at the median value, NYHA (II vs. III/IV combined), serum creatinine split at the median, serum urea nitrogen split at the median, NT-proBNP split at the median, history of diabetes (Yes/No), and history of atrial fibrillation (Yes/No). The goal of this analysis is to assess consistency of the treatment effect within subgroups using descriptive statistics by treatment group within each subgroup and the treatment-by-subgroup interaction effect on the ITT, and PP populations.