scPharmaceuticals

STUDY PROTOCOL

Avoiding Treatment in the Hospital with Furoscix for the Management of Congestion in Heart Failure – A Pilot Study

AT HOME-HF Pilot

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

IND Number:	118919
Protocol Number:	scP-01-008
Study Type:	Phase II
Investigational Drug-Device Combination:	Furoscix® On-Body Infusor
Original Protocol Date:	25 June 2020
Amendment 1 Date:	04 November 2020
Amendment 2 Date:	08 December 2020
Amendment 3 Date:	10 February 2021
Amendment 4 Date:	30 April 2021
Amendment 5 Date:	09 December 2021

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SUMMARY OF CHANGES

Amendment 1: The protocol has been updated to clarify scheduling of weekend study visits, add designee to study staff and administrative changes. It also clarifies capturing AEs for both groups, removal of "treatment emergent" adverse events and rewording instruction for Dyspnea Status - 7-Point Likert Scale for both study groups. The details of the changes are summarized in the table below.
Amendment 2: The protocol has been amended to clarify that a centralized lab will be used for NT-proBNP analysis. It also includes administrative changes to Screening (Day 0) to align Time and Events Schedule to assess AEs and record medications taken within 48 hours.
Amendment 3: The protocol has been amended to remove that the device can be applied before leaving the clinic and started at home. The device should be applied and started without delay according to the Instructions for Use. It specifies that the initial dose of the study product may be administered in the clinic or at home on the day of enrollment.
Amendment 4: The protocol has been amended to clarify primary endpoint change in NT-proBNP from baseline at Day 7 and add AEs and add secondary endpoint of % Lung Fluid Measurement via Remote Dielectric Sensing (ReDS). It also includes recording device issues, removes Adverse Reaction and Suspected Adverse Reaction definitions, defines AEs of Special Interest, updates statistical analysis, increases number of subjects from 50 to 51 and minor administrative changes.
Amendment 5: The protocol has been amended to add a NT-proBNP assessment on Day 3 clinic visit, clarify 51 subjects will be included, remove the upper age limit of 80 years from inclusion criteria and align populations for analysis with the statistical analysis plan.

Version	Date	Page	Change	Reason for Change
Original	25 Jun 2020	N/A	Original Version	New Document
Amendment 1	04 Nov 2020	Synopsis, Subject Population p. 9, Section 4.2 Exclusion Criteria p. 24.	Added "IV" bumetanide in exclusion criteria.	Added "IV" to specify bumetanide administration route.
Amendment 1	04 Nov 2020	Synopsis, Study Assessments and Procedures p. 10, Section 1.2.3 Risk Management p. 18.	Added "or designee".	Added "or designee" to include additional site staff can be designated to make phone calls.
Amendment 1	04 Nov 2020	Section 6.2 p. 28, Section 6.2.5 p. 31, Section 11.1 Appendix 1: Time and Events Schedule p. 52.	Added "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."	Added to clarify scheduling of weekend visits.
Amendment 1	04 Nov 2020	Section 6.2.2 p. 30.	Added "study staff will" dispense additional doses of Furoscix and removed "Days 1, 2 and 3.	Updated dose dispensing on Day 0 does not include doses for Days 1, 2, and 3. Subject returns to clinic

				on Day 1 for dose evaluation.
Amendment 1	04 Nov 2020	Section 6.2.3 p.30, Section 6.2.4 p.31, Section 6.2.5 p.31, Section 6.2.6 p.32, Section 6.2.7 p.32, Section 6.2.8 p. 33, Section 6.2.9 p. 34, Section 6.2.10 p. 34, Section 6.2.11 p. 35, Section 7 p. 38, Section 8.6 p. 45, Section 11 p. 52.	Removed “treatment emergent” from treatment emergent adverse events.	Removed to capture all adverse events.
Amendment 1	04 Nov 2020	Section 6.2.23 p.37.	Added “(Furoscix treatment group)”	Added to specify Subject Diary instructions.
Amendment 1	04 Nov 2020	Section 7 p. 38.	Removed “Only treatment-emergent AEs and SAEs (occurring after the first placement of the product and/or dose of study drug through the follow-up period) will be recorded in this study” and “after placement of the product and administration of study drug”.	Removed to capture all adverse events continuously through the study.
Amendment 1	04 Nov 2020	Section 8.6 Safety Analyses p. 45.	Removed “A treatment emergent adverse event is an event that began or worsened in severity after start of study treatment”.	Removed treatment emergent adverse events to capture all adverse events.
Amendment 1	04 Nov 2020	Section 11.6 Appendix 6: Dyspnea Status-7-Point Likert Scale 11.7, p. 59 Appendix 7: Instructions for study staff administering Dyspnea Status Questionnaires (5-Point and 7-Point Likert Scale) p. 60.	Reworded “breathing just before study drug was started” to “breathing just before starting in the study” from Dyspnea Status - 7-Point Likert Scale. Added “indicate” and removed “check”	Reworded instruction for Dyspnea Status - 7-Point Likert Scale to be used for both study groups. Updated to clarify instructions for study staff for Dyspnea Questionnaires.

			and “drug” from instructions.	
Amendment 2	08 Dec 2020	Section 6.2.1 p.29, Section 6.2.7 p.32, Section 6.2.9 p.34, Section 6.2.10 p. 34, Section 6.2.12 p. 35., Appendix 1: Time and Events Schedule p. 52.	Modified “Central” to “Centralized” lab.	Added to clarify using a centralized lab for NT-proBNP analysis.
Amendment 2	08 Dec 2020	Section 6.2.1 p. 29	Added to Screening (Day 0) “Assess for adverse events” and removed “prior to dosing".	Administrative change to align Time and Events Schedule to assess AEs and record medications taken within 48 hours.
Amendment 3	10 Feb 2021	Synopsis, Study Assessments and Procedures, p. 12, Section 3.2, p. 23, Section 5.5, p. 27, Section 6.2, p. 29, Section 6.2.2, p. 30	Removed “Ideally, one dose would be prepared by the study Subject under the supervision of the study staff. The Subject may opt to apply the device before leaving the clinic but press the start button when they arrive home. The infusion must be started within 1 hour of applying the Furoscix Infusor to the skin of the abdomen.” Removed “Some subjects may not require additional parental diuresis until the next day. In that case, the dose would not be prepared in the clinic.” (Section 3.2 and 5.5). Specified that the initial dose of the study product may be administered in the clinic or at home on the day of enrollment.	Removed device can be applied in the clinic and started at home to align with Instructions for Use and specified initial dose may be administered in the clinic or at home on day of enrollment.

Amendment 4	30 Apr 2021	Synopsis, Endpoint, p. 9, Statistical Analysis, p. 13, Section 3.2.1, p. 23, Section 3.2.2, p. 24, Section 6.1.1, p. 28, Section 6.1.2, p. 29, Section 8.4.1, p. 45, Section 8.4.2, p. 46	Specified primary endpoint change in NT-proBNP from baseline at Day 7 and added AEs. Added secondary endpoint of % Lung Fluid Measurement via Remote Dielectric Sensing (ReDS).	Added clarity to NT-proBNP primary endpoint and clarified AEs primary endpoint. Added % Lung Fluid Measurement secondary endpoint.
Amendment 4	30 Apr 2021	Synopsis, Study Design & Duration, p. 10, Section 6.2.1, p. 30, Section 6.2.3, p. 31, Section 6.2.5, p. 32, Section 6.2.7, p. 33, Section 6.2.9, p. 35, Section 6.2.10, p. 35 Section 6.2.18, p. 38 Time and Events Schedule, p. 53	Added % Lung Fluid Measurement via Remote Dielectric Sensing (ReDS) assessment and added ReDS device and measurement description.	Added ReDS measurement to clinic visits for secondary endpoint and provided device description.
Amendment 4	30 Apr 2021	Synopsis, Study Design & Duration, p. 10, Study Assessments and Procedures, p. 13, Section 6.2.2 – 6.2.11, p. 31 – 36, Section 6.2.2.4, p. 39, Time and Events Schedule, p. 54	Added to record any observed device issues and updated Subject Diary description with device issue instruction and definition.	Updated to capture observed device issues during clinic and phone visits and clarify a device issue.
Amendment 4	30 Apr 2021	Synopsis, Study Design & Duration, p. 10, Number of Subjects, p. 11, Section 3.1, p. 20	Increased number of subjects from 50 to 51.	Increased subject number to preserve 2:1 ratio for randomization.
Amendment 4	30 Apr 2021	Synopsis, Statistical Analysis, p. 13 Section 8.1 – 8.3, p. 44 – 45, Section 8.4.1, p. 45, Section 8.4.2, p. 46	Updated statistical analysis description.	Updated to provide general description of statistical analysis noting details SAP.
Amendment 4	30 Apr 2021	Abbreviations, p. 17	Added abbreviations for AESI, ITT, MITT, PP, ReDS, SAP.	Updated to include new abbreviations.
Amendment 4	30 Apr 2021	Section 7.2. p. 41, Section 7.3. p. 41	Removed Definition of Adverse Reaction and Suspected Adverse Reaction.	All AEs will be collected and assessed if IP caused the adverse event.

Amendment 4	30 Apr 2021	Section 7.3. p. 41, Section 8.6. p. 46	Added Adverse Events of Special Interest definition and analysis.	Clarified Adverse Events of Special Interest and included in safety analysis.
Amendment 5	09 Dec 2021	Synopsis, Study Design & Duration, p. 11, Study Assessments and Procedures, p. 14, Section 3.1, p. 21, Section 6.2. p. 30, Section 6.2.5, p. 33, Section 6.2.12, p. 37 Time and Events Schedule, p. 54-55	Added to Day 3 clinic visit NT-proBNP assessment and specified when NT-proBNP conducted.	Updated to explore change in NT-proBNP from baseline at Day 3 as well as Day 7 and clarify NT-proBNP assessments.
Amendment 5	09 Dec 2021	Synopsis, Study Design & Duration, p. 11, Number of Subjects, p. 12, Section 3.1, p. 21	Removed “Up to 51” and “evaluable” description for number of study subjects.	Updated to clarify 51 subjects will be included in the study.
Amendment 5	09 Dec 2021	Synopsis, Subject Population, p. 12-13, Section 3.1, p. 21, Section 4.1, p. 25	Removed “80” years from age limit and replaced with “18 years or older”.	Updated to remove the upper age limit.
Amendment 5	09 Dec 2021	Synopsis, Statistical Analysis, p.14-15, Section 8.2, p. 46, Section 8.4.2, p. 47	Identified populations for primary endpoints. Added “who received at least 1 dose of the Investigational Product” to the definition of the Safety population. Removed the MITT (Modified Intent to Treat population). Modified the Per-Protocol population definition to specify received “at least one dose” of the Investigational Product, “completed the Day 30 clinic visit assessments AND have a Day 7 NT-proBNP value available for analysis”.	Updated to align populations for analysis with the statistical analysis plan.

PROTOCOL APPROVAL PAGE

Study 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
Original Protocol Date of Issue:	25 June 2020
Amendment 1 Date:	04 November 2020
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Amendment 5 Date:	09 December 2021
Sponsor Name and Address:	scPharmaceuticals, Inc. 2400 District Avenue, Suite 310 Burlington, MA 01803

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies 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.

Approval Section		
	Name/Title	**Signature / Date**
Reviewed and Approved by:	John Mohr, Pharm D SVP, Clinical Development and Medical Affairs	Approvals obtained through MasterControl
Reviewed and Approved by:	Barbara Cornelius Associate Director, Clinical Operations	Approvals obtained through MasterControl
Reviewed and Approved by:	Lucy Johnston VP, Program Management and Regulatory Affairs	Approvals obtained through MasterControl
Reviewed and Approved by:	Michelle Whipple VP, Quality	Approvals obtained through MasterControl

INVESTIGATOR PROTOCOL AGREEMENT

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 Amendment 5

By my signature, I

- agree to conduct the study in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of Subjects.
- agree to personally conduct or supervise the described investigation(s).
- agree to inform any patients, or any persons used as controls, that the study product is being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- agree to report to the Sponsor adverse experiences that occur during the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the Investigator's brochure, including the potential risks and side effects of the study product.
- agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without consent from the Sponsor and will not institute those changes in the research protocol until after IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Investigator's Signature Date

Print Name

SYNOPSIS	
SHORT TITLE	AT HOME-HF Pilot
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
SPONSOR	scPharmaceuticals, Inc.
INVESTIGATIONAL PRODUCT	Furosemide Injection, 80 mg per 10 mL for subcutaneous administration via the Infusor (Furoscix On-body Infusor (hereinafter referred to as Furoscix Infusor))
STUDY OBJECTIVES	**Primary Objective:** • Provide pilot data on effectiveness and safety to inform a pivotal trial
	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

ENDPOINTS	**Primary Endpoints:**
	• Improvement in a composite/combined morbidity/mortality endpoint at 30 days using the Finkelstein Schoenfeld method.
	  ○ Cardiovascular (CV) death
	  ○ Heart Failure (HF) hospitalization
	  ○ Urgent Emergency Department (ED)/Clinic visit for worsening heart failure (defined as Intravenous (IV) diuretics, augmentation of or new administration of metolazone)
	  ○ Change in NT-proBNP from baseline at Day 7
	• Incidence of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

	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 (Kansas City Cardiomyopathy Questionnaire (KCCQ-12)) • Renal Function and Electrolytes • Weight • Exercise tolerance (Six Minute Walking Test (6MWT)) • % Lung Fluid Measurement via Remote Dielectric Sensing (ReDS)

STUDY DURATION	9 months
PARTICIPANT DURATION	30 days
STUDY DESIGN & DURATION	Study Design: This is a multicenter, randomized, open label, controlled study evaluating the effectiveness, and safety of the Furoscix Infusor vs continued medical therapy in patients with chronic heart failure and fluid overload requiring augmentation in diuretic therapy outside of acute care setting. Subjects will be randomly assigned (2:1) to receive Furoscix vs continued medical therapy. Within a single 24-hour period, the 80 mg dose can be repeated at the discretion of the investigator ≥ 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 is 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 as well as changes in oral diuretic dosing in the control arm 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. Methodology: 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. NT-proBNP will be sent to centralized laboratory for subjects who qualify to participate. The Treatment Phase comprises a pre-programmed bi-phasic 5-hour drug 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 of 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 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 control 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.
STUDY TREATMENTS	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).
NUMBER OF SUBJECTS	Fifty-one (51) subjects will be included and randomly assigned (2:1) to receive Furoscix or continued medical therapy in the home setting with 30 days of follow-up.
NUMBER OF SITES	This is a Multicenter, Randomized, Open Label, Controlled Study to be conducted at up to 20 sites.
PARTICIPATING COUNTRIES	US
SUBJECT POPULATION	Patients 18 years or older with chronic heart failure, NYHA Class II-IV symptoms, evidence of fluid overload requiring additional diuresis as assessed by the investigator, with either reduced or preserved LVEF, who are on background therapy including oral furosemide equivalent dose

between 40 and 160 mg of loop diuretic daily, inclusive or equivalent (20-80 mg per day of torsemide or 1-4 mg per day of bumetanide).

Subjects may be enrolled in the study only if all the inclusion criteria and none of the exclusion criteria are met.

Inclusion Criteria:
Subjects are eligible for inclusion only if all the following criteria are met:

1. Age 18 years or older.
2. Diagnosis of symptomatic chronic heart failure (NYHA Class II-IV) with background loop diuretic therapy for at least 4 weeks.
3. Need for augmented diuresis outside of the acute care setting as determined by the investigator.
4. On background therapy including daily total furosemide equivalent dose (40-160 mg) of loop diuretic or equivalent.
5. The subject must have signs of volume expansion, defined as two or more of the following six signs:
   a) jugular venous distention
   b) edema (≥ 1+)
   c) ascites
   d) pulmonary congestion on chest x-ray
   e) pulmonary rales
   f) NT-proBNP ≥1000 pg/ml (1400 for patients in atrial fibrillation) or, for patients not on Entresto, BNP ≥200 (400 for patients in atrial fibrillation)
6. Increase over the preceding 30 days in at least one of the following symptoms characteristic of worsening heart failure:
   a) dyspnea
   b) fatigue
   c) exercise intolerance
7. Adequate environment for at home administration of Furoscix by patient or caregiver.

Exclusion Criteria:
A Subject is <u>not</u> eligible for inclusion if <u>any</u> of the following criteria apply:

1. Suspected high risk clinical instability with outpatient treatment.
2. Presence of a complicating condition, other than heart failure likely to require hospitalization in next 30 days.
3. Pregnant women or women of childbearing age who are not willing to use an adequate form of contraception.
4. Known allergy to the active and inactive ingredients of the study medication or device adhesive.
5. On experimental medication or currently participating in another interventional research study.
6. eGFR $\leq$ 20
7. Serum potassium at baseline > 5.4 or < 3.6
8. Concomitant infection
9. Heart rate > 110
10. Received IV furosemide or IV bumetanide within last 24 hours

STUDY ASSESSMENTS AND PROCEDURES	The following study assessments and procedures will be performed: Patients will be assessed in the clinic or medical practice by the investigator and/or study staff for NYHA Class II-IV heart failure and signs and symptoms associated with volume overload. If it is determined by the investigator that the patient requires augmented diuresis outside of the acute care setting and meets all eligibility criteria, he/she may be consented and enrolled into the study. NT-proBNP will be sent to centralized laboratory. For Subjects within the 2 randomization groups, continued medical therapy or Furoscix therapy will be managed by the investigator. Subjects randomized to Furoscix will be instructed on the use of the Infusor by the investigator and/or study staff in accordance with the Instructions for Use. The initial dose of the study product may be administered in the clinic or at home on the day of enrollment. Additional doses will be provided to the Subject for self-administration or administration by a caregiver in the home setting as directed by the investigator or study staff. All subjects will receive daily follow-up for the initial 7 days. Subjects will receive home telephone calls from heart failure (HF) nurse, or designee, on Days 2, 4, 5, 6 and 17 and clinic visits with laboratory analyses on Days 1, 3, 7 and 30 and NT-proBNP Days 3, 7 and 30. To the extent possible, the same caregiver will be used for all visits. Administration by the Subject and/or caregiver will be assessed by HF nurse, or designee, telephone interviews. Subjects will record the start of each administered dose, presence of congestion symptoms and their assessment of the ease of utilization with the Furoscix Infusor including device issues in a diary. 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 congestion symptoms (e.g. dyspnea, 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. 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 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. The study period will be 30 ± 5 days after enrollment. Survival and unplanned heart failure events will be assessed for 30 ± 5 days after enrollment.
STATISTICAL ANALYSIS	Baseline variables will be assessed by treatment group using descriptive statistics. The primary endpoints will be measured using the Finkelstein-Schoenfeld Method. *Primary Endpoints* The primary analysis is to compare the components of the primary composite endpoint hierarchically using the Finkelstein-Schoenfeld Method. The primary endpoints will be compared between treatment groups

	on the Intent-to-Treat (ITT) population and Per-Protocol populations as described in the SAP. Each patient is compared to all other patients with respect to each of the following endpoints at 30 days: ▪ CV death ▪ HF hospitalization ▪ Urgent ED/Clinic visit for worsening heart failure (defined as IV diuretics, augmentation of or new administration of metolazone) ▪ Change in NT-proBNP from baseline at Day 7 Incidence of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events will be described in each group. *Secondary Endpoints* Statistical comparison of treatment vs. control groups will be conducted for each secondary endpoint at a two-sided 0.05 level of significance. The following secondary endpoints will be compared between treatment groups on the Intent-to-Treat (ITT) population and Per-Protocol populations as described in the SAP: ▪ Days alive and heart failure event-free (hospitalization for heart failure or ED visits for heart failure) over 30 days. ▪ Changes from baseline in patient global assessment via visual analog scale (VAS) across follow-up timepoints. ▪ Changes from baseline in composite congestion score (CCS) across follow-up timepoints. ▪ Changes from baseline in 5-point Current Dyspnea Score across follow-up timepoints. ▪ 7-point Dyspnea Score across follow-up time points. ▪ Changes from baseline in health-related quality of life measured by the KCCQ-12 Short Form Summary Score across follow-up timepoints. ▪ Changes from baseline in serum creatinine across follow-up timepoints. ▪ Change from baseline in ambulatory body weight across follow-up timepoints. ▪ Changes from baseline in the Six-Minute Walk Test (6MWT) across follow-up timepoints. ▪ Changes from baseline in the ReDS Lung Fluid Measurement across follow-up time points.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
βhCG	Beta-human Chorionic Gonadotropin
BMI	Body Mass Index
Bpm	Beats per minute
CFR	Code of Federal Regulations
CRF	Case Report Form
CCS	Composite Congestion Score
CV	Cardiovascular
ED	Emergency Department
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
ICH	International Conference on Harmonization
IFU	Instructions for Use
IND	Investigational New Drug
IP	Investigational Product
IRB/EC	Institutional Review Board/Ethics Committee
ITT	Intent-to-Treat population
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
mmHg	millimeters of mercury
NYHA	New York Heart Association
PP	Per-Protocol population
ReDS	Remote Dielectric Sensing
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
6MWT	Six Minute Walking Test

1. INTRODUCTION

Heart Failure affects 6.5 million adults in the United States, a figure that is expected to grow to 8 million by 2030. Heart Failure is one of the most common causes of hospital admissions in patients over 65 with at least 1-2 million hospitalizations in the United States annually (Benjamin et al. 2018; Agarwal et al. 2016). Increasing signs and symptoms of congestion and fluid overload are the main reasons heart failure patients seek medical care and are hospitalized (Mullens et al., 2019). Symptoms of congestion generally worsen over several days or weeks providing a window of opportunity to intervene to avoid a potential unnecessary hospitalization (Schiff et al. 2003; Greene et al. 2018).

It is known that during periods of worsening congestion in heart failure, the bioavailability of oral furosemide is reduced and becomes highly variable (Vasko et al. 1985; Ellison et al. 2017). To overcome the limitation of oral furosemide in this setting, two strategies are typically employed. First, the oral furosemide dose is typically doubled, or additional oral diuretics (thiazide diuretics) are added to overcome the blunted pharmacological response to these agents. When this fails, clinicians often rely on giving IV diuretics, either in the hospital, an outpatient heart failure clinic or an infusion center, if available (Greene et al. 2018; Mullens et al. 2019). Hospitalization solely for the purpose of administration of intravenous furosemide is not a cost-effective strategy, is inconvenient for patients and their family, and places patients at risk for increased nosocomial infections and iatrogenic complications.

After hospitalization for heart failure, 25-30% of patients are readmitted within 30 days. It has been estimated that up to 50% of patients hospitalized for an episode of acute decompensated heart failure are discharged on oral diuretics with persistent signs and symptoms of congestion (Costanzo et al. 2007; Fonarow et al. 2005; Neuenschwander et al. 2007). The presence of congestion at discharge has been associated with an increased risk of 30-day all-cause mortality and rehospitalization for heart failure (Ambrosy et al. 2013). Patients hospitalized for heart failure should have a post discharge follow up visit within 14 days of hospital discharge (Yancy et al. 2013).

Alternative treatment paradigms that shift the management of congestion in patients with heart failure to outside of the acute care setting and improve congestion management post hospital discharge are urgently needed. If such options were available, another potential benefit would be early effective treatment in the outpatient setting to avoid early decompensation worsening into the full-blown syndrome of acute decompensated heart failure and potentially reduce 30-day readmission rates.

Furoscix is a novel formulation of furosemide buffered to a neutral pH to enable subcutaneous administration. It is intended to be administered subcutaneously via an On-Body Infusor, a compact, wearable, pre-programmed subcutaneous drug delivery system. The pharmacokinetics of Furoscix 80 mg administered subcutaneously over 5 hours in a biphasic regimen (30 mg in the first hour, followed by 12.5 mg/hour for the subsequent 4 hours) demonstrated comparable drug exposures to 2 doses of furosemide 40mg administered intravenously over 2 minutes 2 hours apart. In addition, the average 8- and 24-hour urine output and natriuresis was comparable between IV furosemide and Furoscix (Sica et al. 2018).

1.1. Rationale for the Current Study

The purpose of this study is to evaluate the effectiveness and safety of the Furoscix Infusor vs continued medical therapy in patients with chronic heart failure and fluid overload requiring augmentation in diuretic therapy outside of acute care setting.

The study is being executed under IND 118919 following all regulations required for Investigational Drug products.

1.2. Risk: Benefit Evaluation

1.2.1. Potential Benefits of Participating in the Study

There are no potential benefits to the participants beyond their contribution to the development and testing of this product.

1.2.2. Potential Risks of Participating in the Study

Furosemide has been widely studied and used clinically for over 50 years. It is generally considered a safe and effective pharmaceutical product. Patients may experience marked diuresis following the placement and activation of this drug-device combination product. Access to bathroom facilities is of critical importance and patients should be instructed to have instant access to suitable facilities. Marked diuresis may be accompanied by a drop-in blood pressure including orthostatic hypotension and associated signs and symptoms.

1.2.3. Risk Management

Subjects will be trained by the study staff on appropriate use of the Furoscix Infusor and will receive specific instructions and study materials created for the study (based on the Furoscix Infusor Instructions for Use) that include information regarding what to do in case of certain events during the drug delivery period.

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 may be prescribed during the 30-day study period as needed based on the presence of symptoms of congestion (dyspnea, 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. If modifications are made 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 Subjects' follow-up assessments and timing of those assessments will be based on the investigator's clinical judgement.

Subjects will receive scheduled at-home telephone calls from a HF nurse, or designee, on Days 2, 4, 5, 6 and 17. Four planned in-clinic visits will be conducted: the first occurring on Day 1, the second on Day 3, the third occurring on Day 7 and the fourth occurring on Day 30 ± 5 days. Unscheduled calls and clinic visits can be conducted as needed. The primary purpose of the calls will be to evaluate the clinical response to diuretic therapy and the need to adjust diuretic therapy. Clinic visits will include assessment of creatinine and electrolytes.

2. STUDY OBJECTIVES

The objectives of this study are:

Primary Objective:

- To provide pilot data on the effectiveness and safety to inform a pivotal trial

Secondary Objectives:

- To inform population enrichment strategies
- To refine pivotal trial endpoints and analytical methods
- To identify operational challenges of study design
- To assess patient adherence, competence, and experience
- To familiarize staff and patients with device application and use

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study is a multicenter, randomized, open label, controlled study evaluating the effectiveness, and safety of the Furoscix Infusor vs continued medical therapy in patients with chronic heart failure and fluid overload requiring augmentation in diuretic therapy outside of acute care setting. The study will enroll 51 subjects 18 years or older with chronic heart failure, NYHA Class II-IV symptoms, evidence of fluid overload requiring additional diuresis as assessed by the investigator, with either reduced or preserved LVEF, who are on background therapy including oral furosemide equivalent dose between 40 and 160 mg of loop diuretic daily, inclusive or equivalent (20-80 mg per day of torsemide or 1-4 mg per day of bumetanide). The subjects will be randomly assigned (2:1) to receive Furoscix Infusor vs continued medical therapy.

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 satisfied) and subject has been randomized. NT-proBNP will be sent to centralized laboratory for subjects who qualify to participate.

The Treatment Phase will start once screening procedures have been completed and eligibility is confirmed. Subjects and/or their caregivers will be trained on device preparation, placement and removal in accordance with product instructions of use (IFU). Furoscix will be administered daily via the Furoscix Infusor whereby 80 mg is administered subcutaneously over 5 hours in a biphasic regimen (30 mg in the first hour, followed 12.5 mg per hour for the subsequent 4 hours). 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. The dosing frequency and duration of therapy will be determined by the investigator based on an estimated volume of diuresis desired to transition Subject back to their oral *maintenance* diuretic therapy. The decision of when to discontinue Furoscix and switch to oral diuretics will be based on clinical judgement.

Subjects will be followed up at an in-clinic visit on Days 1, 3 and 7 and through a phone call from site staff on Days 2, 4, 5, 6 and 17 to assess for signs and/or symptoms of congestion.

After the Day 7 clinic visit, subjects will continue to utilize the provided equipment and weigh themselves and record their blood pressure and heart rate approximately the same time each morning. Additional doses of Furoscix can be prescribed as needed due to congestion symptoms (e.g. dyspnea, edema, and/or excess weight gain) as determined by the investigator. In addition to the scheduled phone and clinic visits, the investigator can utilize unscheduled clinic or phone visits for additional assessments at any time. 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. If diuretic modifications are made after Subjects' are transitioned to their oral maintenance diuretic regimen, including additional doses of Furoscix in the treatment group or oral diuretics for the treatment as usual control group, 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.

For the Follow-Up Phase, Subjects will return to the clinic on Day 30 $\pm$ 5 days (30-days post randomization) for a final follow-up visit where effectiveness and safety assessments will be performed.

3.2. Furoscix Infusor

The Furoscix Infusor is a drug-device combination product consisting of Furoscix (Furosemide injection, 80 mg per 10 mL), a novel, pH neutral furosemide formulation optimized for subcutaneous administration and contained in a prefilled, Crystal Zenith (CZ) cartridge, and a proprietary wearable, pre-programmed on-body delivery system, the Infusor, based on the SmartDose Gen II 10 mL (West Pharmaceutical Services).

The Infusor is a compact, ethylene oxide (EtO) sterilized, single-use, electro-mechanical (battery powered, micro-processor controlled), on-body delivery system that administers a fixed dose of drug product from a prefilled cartridge assembly into subcutaneous tissue of the abdomen. It is intended for use by patients, caregivers, or a health care professional (HCP) at home or in a clinic setting.

The Furoscix Infusor is 117 mm x 62 mm x 30 mm (length x width x height) and weighs approximately 80 grams without the drug cartridge and 90 grams, with a filled drug cartridge inserted into the drug compartment. It has an integrated, adhesive patch which attaches the Infusor to the skin for dose administration. The device with adhesive is removed from the skin following completion of the dose and discarded.

The system delivery parameters will be pre-programmed as part of the manufacturing process to deliver 80 mg (10 mL) furosemide over 5 hours using a biphasic delivery profile of 30 mg furosemide (3.75 mL) over the first hour and 12.5 mg furosemide (1.56 mL) per hour over the subsequent 4 hours. The device elements are shown in Figure 1.

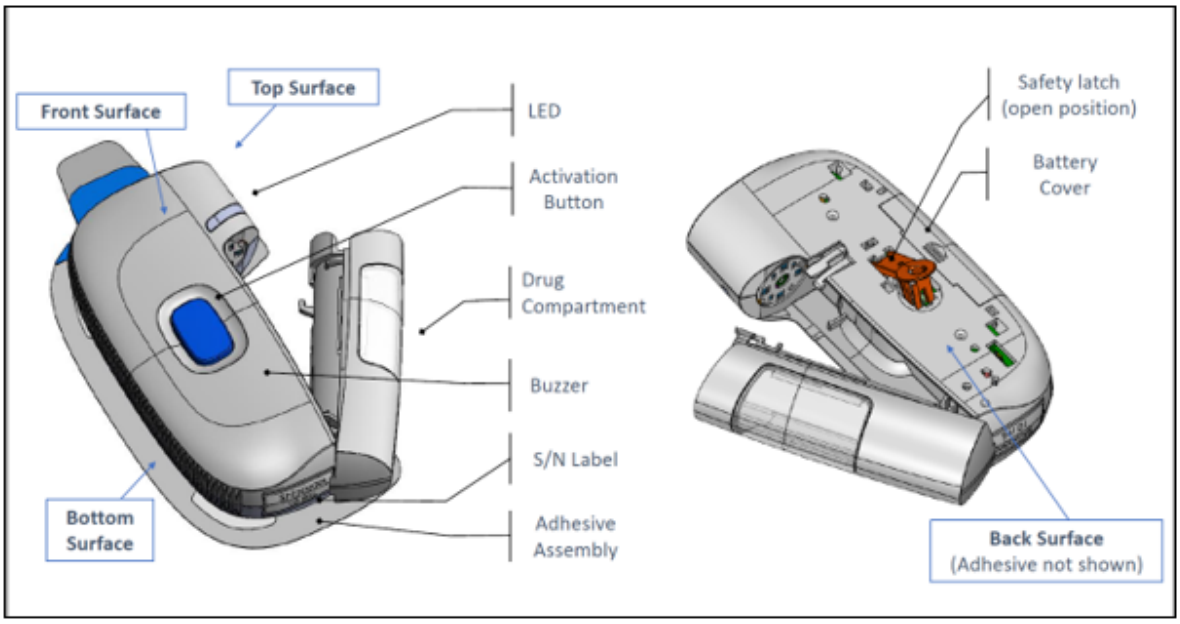


Figure 1: Main components of Furoscix On-Body Infusor

The Furoscix Infusor utilizes a primary container, which consists of the CZ cartridge (CZ barrel and elastomeric septum) and elastomeric piston. The primary container assembly is prefilled with the Furoscix as part of the fill-finish process.

Following removal of the Furoscix Infusor from the packaging, the drug compartment of the device is opened by the user, which turns the device on, and a built-in self-test is performed to verify the needle/button position, correct software parameters, the device was not operated prior to the current activation and the motor and batteries are functional.

The user inserts the prefilled Cartridge into the drug compartment, closes the compartment, removes the adhesive liner and attaches the loaded Furoscix Infusor to the skin of the abdomen. Pressing the activation button automatically inserts the small, 27-guage, 6 mm needle into the subcutaneous tissue and drug administration is initiated. The needle is protected within the device and can only be deployed when the prefilled Cartridge is in place, the cartridge compartment is closed, the device is adhered to the patient, the safety latch is closed, and the activation button has been pressed. Dose administration stops automatically upon completion of drug delivery or opening of the safety latch upon the removal of the device from the abdomen.

The Furoscix Infusor is designed to administer the entire dose without user intervention. The dose volume and dose administration time cannot be changed by the user. Both visual and auditory notifications provide feedback on the progress of drug administration. In the event of a drug delivery error, visual and auditory notification will alert the user. Once drug administration is complete, accompanied by visual and auditory notifications, the user removes the system with the administration needle by carefully peeling the adhesive from the skin which automatically opens the safety latch to conceal and protect the administration needle. The empty Cartridge cannot be removed from the system after administration of the

drug product and the integrated Cartridge/Infusor are disposed of together. The device is battery-powered and enables removal of the battery by the user prior to disposal.

The clinical study will include training the Subject and/or caregiver in the preparation, placement, activation and removal of the Furoscix Infusor based on the Furoscix Infusor Instructions for Use (IFU).

Training for study staff on the device operation and placement following the IFU and subject specific instructions will be conducted during an Investigator Meeting(s) and/or at the Site Initiation(s).

Subjects will be instructed on the use of the Furoscix Infusor by the investigator and/or study staff in accordance with the IFU and subject specific instructions. The initial dose of the study product may be administered in the clinic or at home on the day of enrollment. Additional doses will be provided to the subject for self-administration or administration by a caregiver in the home setting as directed by the investigator or study staff.

Study Subjects will be provided with instructions based on the IFU of the product. These include to not shower, bathe, swim or do activities that may cause sweat while wearing the Furoscix Infusor because it contains parts that should not get wet. Participants will be informed that marked diuresis may ensue after activation and that they should have access to bathroom facilities for up to 8 hours after starting the infusion.

If the Subject experiences leakage or pain during the infusion period, they are instructed to call the study team at the clinical site as designated on the informed consent form and subject specific instructions. If the infusion is interrupted for any reason (i.e. see visual and hear audio notifications) or the device becomes detached during the infusion period, subjects are instructed to call the study team at the clinical site. Following dosing and device removal, subjects should place the used Furoscix Infusor in the box and bring back to the clinic at their next scheduled study visit. Subjects will return all Furoscix Infusors by the Day 30 in-clinic visit.

3.2.1. 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)
    - Change in NT-proBNP from baseline at Day 7
- Incidence of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

3.2.2. Secondary Endpoints (through 30 days)

- Days alive and HF event free days
- Global Visual Analog Scale

- Composite Congestion Score
- 5-point Current Dyspnea Score
- 7-point Dyspnea Score
- Health-related quality of life (KCCQ-12)
- Renal Function and Electrolytes
- Weight
- Exercise tolerance (6MWT)
- % Lung Fluid Measurement via Remote Dielectric Sensing (ReDS)

3.2.3. Adverse Events of Special Interest over 30 Days

- Worsening kidney function, defined as increase of ≥ 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

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Female and male Subjects are eligible for inclusion only if all the following criteria are met:

1. Age 18 years or older.
2. Diagnosis of symptomatic chronic heart failure (NYHA Class II-IV) with background loop diuretic therapy for at least 4 weeks.
3. Need for augmented diuresis outside of the acute care setting as determined by the investigator.
4. On background therapy including daily total furosemide equivalent dose (40-160 mg) of loop diuretic or equivalent.
5. The subject must have signs of volume expansion, defined as two or more of the following six signs:
   a) jugular venous distention
   b) edema (≥1+)
   c) ascites
   d) pulmonary congestion on chest x-ray
   e) pulmonary rales
   f) NT-proBNP ≥1000 pg/ml (1400 for patients in atrial fibrillation) or, for patients not on Entresto, BNP ≥200 (400 for patients in atrial fibrillation)
6. Increase over the preceding 30 days in at least one of the following symptoms characteristic of worsening heart failure:
   a) dyspnea
   b) fatigue
   c) exercise intolerance
7. Adequate environment for at home administration of Furoscix by patient or caregiver.

4.2. Exclusion Criteria

A Subject is not eligible for inclusion if any of the following criteria apply:

1. Suspected high risk clinical instability with outpatient treatment.
2. Presence of a complicating condition, other than heart failure likely to require

hospitalization in next 30 days.
3. Pregnant women or women of childbearing age who are not willing to use an adequate form of contraception.
4. Known allergy to the active and inactive ingredients of the study medication or device adhesive.
5. On experimental medication or currently participating in another interventional research study.
6. eGFR $\leq$ 20
7. Serum potassium at baseline > 5.4 or < 3.6
8. Concomitant infection
9. Heart rate > 110
10. Received IV furosemide or IV bumetanide within last 24 hours

4.3. Removal of Subjects from Therapy/Premature Discontinuation

Subjects may voluntarily withdraw at any time, but once treatment has occurred, every attempt will be made to continue assessments to ensure the safety of the subject. A Subject will be discontinued from the study for the following medical or administrative reasons:

- Subject wishes to withdraw consent
- Safety reasons, e.g. AEs
- Subject non-compliance with study procedures required by the protocol
- Principal Investigator discretion

The Investigator may discontinue individual Subjects from the study if anatomical or skin conditions prevent proper placement of the device.

Subjects who withdraw or are withdrawn prior to study completion may be replaced. As far as possible, subjects who withdraw from the study after treatment, and before completion should be seen by the PI or delegate and undergo the assessments and procedures scheduled for the follow-up visit.

5. TREATMENTS

5.1. Treatments Administered

Study drug will be administered by the Subject or the Subject's caregiver only in accordance with the procedures described in this protocol and in the Instructions for Use.

5.2. Identity of Investigational Product(s)

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.

Furoscix (Furosemide Injection), 10 mL buffered furosemide solution (8 mg/mL), is manufactured by Swissfilllon AG, Rottenstrasse 7, CH-3930 Visp, Switzerland under good manufacturing practice conditions. Contains Tris Hydrochloride and may contain Sodium Chloride Hydrochloric Acid for pH adjustment: pH 7.4 (range 7.0 to 7.8).

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).

5.2.1. Labeling

Study drug (Furosemide Injection (Furoscix)) and study device (On-Body Infusor) will bear labels that meet applicable laws for an investigational drug-device combination, which may include, but is not limited to, the following information:

- Federal law statement
- Batch number
- Storage information

Study specific instructions for the use and operation of the product will be available to the PI, study staff and subjects. These materials will be based on the Furoscix Infusor Instructions for Use of the study product as it exists at the time of the study.

5.2.2. Storage and Handling

Store study drug at 15° - 30°C, (59° - 86°F). Protect from Light.

5.3. Method of Assigning Subjects to Treatment Groups

5.3.1. Treatment Assignment/Randomization

Subjects will be randomly assigned (2:1) to receive the Furoscix Infusor or continued medical therapy.

5.4. Selection of Doses in the Study

The dose of 80 mg is the fixed dose of Furoscix. This was selected based on clinical criteria and physician prescribing and is consistent with the approved labeling of furosemide injection, United States Pharmacopeia. The dosing frequency and duration of the initial therapy will be determined by the investigator based on an estimated volume of diuresis desired to transition Subject back to their oral *maintenance* diuretic therapy. The total duration in days and number of doses will be determined by the treating investigator based on an estimated volume of diuresis desired to transition Subject back to their oral maintenance diuretic therapy.

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 symptoms of congestion (dyspnea, 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.

5.5. Selection and Timing of Dose for Each Subject

Furoscix will be administered daily via the Furoscix Infusor whereby 80 mg is administered subcutaneously over 5 hours in a biphasic regimen (30 mg in the first hour, followed 12.5 mg/hour for the subsequent 4 hours). Within a single 24-hour period, the 80 mg dose can be repeated at the discretion of the investigator ≥ 2 hours after the completion of the first dose. The dosing frequency and duration of the initial therapy will be determined by the investigator based on an estimated volume of diuresis desired to transition Subject back to their oral *maintenance* diuretic therapy.

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 symptoms of congestion (dyspnea, 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. If diuretic modifications are made after Subjects' are transitioned to their oral maintenance diuretic regimen, including additional doses of Furoscix in the treatment group or oral diuretics for the treatment as usual control group, the Subjects' follow-up assessments and timing of those assessments will be based on the investigator's clinical judgement.

Subjects will be instructed on the use of the Furoscix Infusor by the investigator and/or study staff in accordance with the IFU and subject specific instructions. The initial dose of the study product may be administered in the clinic or at home on the day of enrollment. Additional doses will be provided to the subject for self-administration or administration by a caregiver in the home setting as directed by the investigator or study staff.

5.6. Procedures for Blinding

This is an open label study.

5.7. Prior and Concomitant Therapy

Prior and concomitant therapy will include all prescription medications and therapies. All information on prior (within the past 48 hours) and concomitant therapies will be recorded in the Subject's source and on the Subject's CRF. They should include the name of the therapy or drug and duration of the treatment (start and stop dates).

5.8. Prohibited Medications

Concomitant use of any drugs known to interact with furosemide, including aminoglycoside antibiotics, ethacrynic acid, high doses of salicylates, cisplatin, tubocurarine, succinylcholine, chloral hydrate, phenytoin, methotrexate, indomethacin and lithium is not permitted.

5.9. Other Restrictions

Subjects are advised to avoid strenuous physical activity or activities that could expose the device to moisture such as swimming, bathing or showering. Subjects will be informed that marked diuresis may ensue after activation, and that they should avoid travel, operating a vehicle or other situations without immediate access to bathroom facilities.

5.10. Study Stopping Criteria

The study may be stopped if the Investigator, Medical Monitor, Sponsor or IRB determines that subject safety may be compromised by continuing in the study.

5.11. Treatment Compliance

Preparation, fill and placement of the Furoscix Infusor will be done in accordance with the study specific instructions which are based on the Instructions for Use of the study product as it exists at the time of the study. Site staff will perform product accountability (count the number of units used versus the number of days the subject was instructed to administer the study product). Study staff will also inspect the units and cartridge(s) used by the subjects to report/confirm they are empty.

5.12. Study Drug-Device Combination Accountability

The study drug-device combination product will be handled in accordance with the procedures of this protocol. Only subjects enrolled in the study may receive study drug-device combination product, in accordance with applicable regulatory requirements.

Study staff authorized to handle and store the drug-device combination product must keep an accurate accounting of the receipt, disposition and return of the study products received from the sponsor and dispensed to subjects. Drug-device combination product accountability will be assessed by the study monitor during periodic monitoring visits.

6. STUDY PROCEDURES

6.1. Study Measurements and Assessments

6.1.1. Assessment of 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)
    - Change in NT-proBNP from baseline at Day 7
- Incidence of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

6.1.2. Assessment of Secondary Endpoints (through 30 days)

- Days alive and HF event free days
- Global Visual Analog Scale
- Composite Congestion Score
- 5-point Current Dyspnea Score
- 7-point Dyspnea Score
- Health-related quality of life (KCCQ-12)
- Renal Function and Electrolytes
- Weight

- Exercise tolerance (6MWT)
- % Lung Fluid Measurement via Remote Dielectric Sensing (ReDS)

6.1.3. Assessment of Adverse Events of Special Interest

Subjects will have blood drawn at each clinic visit to monitor safety parameters. Subjects will specifically be monitored for the following adverse events:

- Worsening kidney function, defined as increase of ≥ 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

6.2. Study Phases and Procedures

A Time and Events Schedule is provided in Appendix 1.

The Screening Phase will be conducted in the clinic. All Subjects who sign the informed consent form and satisfy the inclusion/exclusion criteria will be enrolled into the trial on the same day as screening. NT-proBNP will be sent to centralized laboratory. Drug administration will start on the day of screening and enrollment after randomization.

The Treatment Phase will begin upon completion of screening through Day 29. Furoscix will be administered via the Furoscix Infusor whereby 80 mg is administered subcutaneously over 5 hours in a biphasic regimen (30 mg in the first hour, followed 12.5 mg/hour for the subsequent 4 hours). Within a single 24-hour period, the 80 mg dose can be repeated at the discretion of the investigator ≥ 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 (dyspnea, 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.

Prior to leaving the clinic on Day 0, the Subject and/or caregiver will be trained by the study staff on how to prepare the study product and apply it to their abdomen and remove it once the infusion is completed. The initial dose of the study product may be administered in the clinic or at home on the day of enrollment. Additional doses will be provided to the Subject for self-administration or administration by a caregiver in the home setting as directed by the investigator or study staff.

Subjects will be seen in the clinic on Day 0, 1, 3* and 7 and will receive phone calls on Days 2, 4, 5, 6 and 17 where the study staff will assess subject's signs and/or symptoms of congestion. These visits should all be conducted as early in the day as possible to accommodate the 5-hour infusion. 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.

After the Day 7 clinic visit, subjects will be instructed to continue utilize provided equipment to weigh themselves and record their blood pressure and heart rate approximately same time each morning. If their symptoms worsen after they are transitioned to their oral maintenance diuretic regimen, they will be instructed to contact the investigator. Site staff will determine

based on the presence congestion symptoms (e.g. dyspnea, edema, and/or excess weight gain) if Subjects diuretic regimen should be modified, including additional doses of Furoscix in the treatment group or oral diuretics for the treatment as usual control group. 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.

The Follow-up Phase will consist of a one-day visit on Day 30 ± 5 days post randomization (in-clinic visit).

6.2.1. Screening (Day 0)

The initial Screening assessment will be conducted the same day as the start of the Treatment Phase.

The following procedures/assessments will be performed at Screening:

- Informed consent (must be done prior to **any** of the following procedures)
- Eligibility review
- Medical history and Subject demographics (date of birth, gender, ethnic origin and race)
- Limited Physical Exam including NYHA Classification
- Composite Congestion Score (CCS)
- 5-point Current Dyspnea Score (using the script - Appendix 7)
- Weight and height (Calculate BMI)
- Vital Signs
- % Lung Fluid Measurement (ReDS)
- Venous blood for clinical chemistries, hematology (run locally for eligibility), NT-proBNP (run locally for eligibility; 2nd sample sent to a centralized laboratory for subjects who qualify to participate)
- Urine pregnancy test on females of childbearing potential
- Administer the Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
- Administer the patient global assessment visual analog scale (VAS)
- Administer Six Minute Walk Test (6MWT)
- Assess for adverse events
- Record concomitant medications (all medications taken within 48 hours)
- Schedule next study visit (Day 1).

6.2.2. Treatment Phase (Day 0)

After the screening activities have been completed and laboratory analyses reviewed to confirm eligibility, the patient may be randomized (2:1) to receive either Furoscix or continued medical therapy with oral diuretics. Subjects randomized to continued medical therapy will follow the same schedule of assessments, excluding study product administration.

The initial dose of the study product should be administered after randomization. If randomized to Furoscix, product training with subject and/or caregiver will be conducted. The initial dose of the study product may be administered in the clinic or at home on the day of enrollment. Study staff will dispense additional doses of Furoscix. Subjects will be provided a Subject Diary in which to record any observed device issues and self-assessments that will be completed at home.

The Subject will be reminded to use the provided equipment to weigh themselves and record their blood pressure and heart rate and complete the patient global assessment VAS upon returning home and first thing in the morning on Day 1. They will also be reminded to bring their study product (device) and Subject Diary back to the clinic on Day 1.

6.2.3. Day 1 (In-Clinic Visit)

Subjects will have been instructed to use the provided equipment to weigh themselves (scale) and record their blood pressure and heart rate and complete the patient global assessment VAS at home prior to presenting to the clinic. The clinic visit should occur early in the day (morning if possible) and have the following assessments completed or recorded:

- Limited physical exam including NYHA Classification
- CCS (Composite Congestion Score)
- 5-point Current Dyspnea Score (using the script - Appendix 7)
- 7-point Dyspnea Score (using the script – Appendix 7)
- Weight
- Vital Signs
- % Lung Fluid Measurement (ReDS)
- Labs drawn for safety analyses
- Patient global assessment VAS (should be done at home at approximately the time of weight is done)
- 6MWT
- Review Subject Diary for completeness and any recorded device issues
- Review any changes to concomitant medications since last visit
- Assess for adverse events
- Evaluate the clinical response to diuretic therapy and adjust as needed. Assess for transition back to oral maintenance diuretic therapy. For Furoscix subjects, additional doses may be prescribed and dispensed. For subjects receiving continued medical therapy, investigators will determine whether any modifications are needed.
- Schedule the next study visit (Day 2 – via phone call; preferably in the AM)

6.2.4. Day 2 (Phone Call)

Site staff will contact the study subject guided by the telephone script in the morning and review/monitor the following:

- Ensure the subject has completed the Subject Diary and recorded device issues and used the provided equipment and recorded their weight and blood pressure and heart rate.
- Ensure the subject has completed the patient global assessment VAS
- Using the script (Appendix 7), perform the 5-point Current Dyspnea Score questionnaire with the subject
- Using the script (Appendix 7), perform the 7-point Dyspnea Score questionnaire with the subject
- Any changes to concomitant medications since last visit are recorded
- Any adverse events are reported/documented
- The investigator will evaluate the clinical response to diuretic therapy and adjust as needed, including transition back to oral maintenance diuretic therapy. For Furoscix subjects, additional doses may be prescribed. For subjects receiving continued medical therapy, investigators will determine whether any modifications are needed.
- Schedule the next visit (Day 3 - in-clinic visit). *Remind the subject to use the provided equipment to weigh themselves and record their blood pressure and heart rate and complete the patient global assessment VAS in the morning. In addition, they should bring back the used study product well as the Subject Diary to the clinic visit.*

6.2.5. Day 3* (In-Clinic visit)

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.

Subjects will have been instructed to use the provided equipment to weigh themselves (scale), record their blood pressure and heart rate and complete the patient global assessment VAS at home prior to presenting to the clinic. The clinic visit should occur early in the day (morning if possible) and have the following assessments completed:

- Limited physical exam including NYHA Classification
- CCS (Composite Congestion Score)
- 5-point Current Dyspnea Score (using the script - Appendix 7)
- 7-point Dyspnea Score (using the script – Appendix 7)
- Weight
- Vital Signs
- % Lung Fluid Measurement (ReDS)
- Labs drawn for safety analyses (local lab) and NT-proBNP (send to centralized lab)
- Patient global assessment VAS (should be done at home at approximately the time of weight/blood pressure monitoring is done)
- Review Subject Diary for completeness and any recorded device issues
- Review any changes to concomitant medications since last visit
- Assess for adverse events

- Evaluate the clinical response to diuretic therapy and adjust as needed. Assess for transition back to oral maintenance diuretic therapy. For Furoscix subjects, additional doses may be prescribed. For subjects receiving continued medical therapy, investigators will determine whether any modifications are needed.
- Dispense study product for Days 4, 5 and 6 (if applicable)
- Schedule the next study visits (Days 4, 5, and 6 – via phone call)

6.2.6. Days 4, 5, and 6 (Phone Calls)

Site staff will contact the study subject in the morning guided by the telephone script and review/monitor the following:

- Ensure the subject has completed the Subject Diary and recorded device issues and used the provided equipment and recorded their weight and blood pressure and heart rate.
- Ensure the subject has completed the patient global assessment VAS
- Using the script (Appendix 7), perform the 5-point Current Dyspnea Score questionnaire with the subject
- Using the script (Appendix 7), perform the 7-point Dyspnea Score questionnaire with the subject
- Record any changes to concomitant medications since last visit
- Assess for any adverse events
- Evaluate the clinical response to diuretic therapy and adjust treatment as needed. Assess for transition back to oral maintenance diuretic therapy. For Furoscix subjects, additional doses may be prescribed. For subjects receiving continued medical therapy, investigators will determine whether any modifications are needed.
- Schedule the next visits (on Days 4 and 5 – via phone call). On Day 6 remind the Subject the Day 7 visit will be an in-clinic visit and they should *use the provided equipment to weigh themselves and complete the patient global assessment VAS in the morning and to bring back all study product (device and cartridges, used and unused) as well as Subject Diary to the clinic visit.*

6.2.7. Day 7 (In-Clinic Visit)

Subjects will have been instructed to use the provided equipment to weigh themselves (scale) and record their blood pressure and heart rate and complete the patient global assessment VAS at home prior to presenting to the clinic. The clinic visit should occur early in the day (morning if possible) and have the following assessments completed or recorded:

- Limited physical exam including NYHA Classification
- CCS (Composite Congestion Score)
- 5-point Current Dyspnea Score (using the script - Appendix 7)
- 7-point Dyspnea Score (using the script – Appendix 7)
- Weight
- Vital Signs

- % Lung Fluid Measurement (ReDS)
- Labs drawn for safety analyses (local lab) and NT-proBNP (send to centralized lab)
- KCCQ-12
- Patient global assessment VAS (should be done at home at approximately the time weight is measured)
- 6MWT
- Review Subject Diary for completeness and any recorded device issues
- Review any changes to concomitant medications since last visit
- Assess for adverse events
- Schedule the next study visits (Day 17 phone call and Day 30 clinic visit)
- Subjects should be reminded to continue to complete the Study Diary and use the provided equipment to weigh themselves and record their blood pressure and heart rate at home each morning through the Day 30 visit. The subject should also be reminded to complete the patient global assessment VAS the morning of Day 17 and Day 30. The equipment should be returned at the Day 30 visit.
- Subjects should be instructed to call the study site if they have any worsening heart failure symptoms due to congestion, go to the Emergency Department or are admitted to the hospital.

6.2.8. Day 17 ± 3 (Telephone Call Follow-Up)

A telephone call follow-up guided by the telephone script will be conducted on Day 17 ± 3 days. The primary purpose of this call is to assess Subject's congestion symptoms to determine if a change in diuretic management is needed and assess whether the Subject has experienced or is experiencing a study related adverse event. The following assessments will be performed:

- Ensure the subject has completed the Subject Diary and recorded device issues and used the provided equipment and recorded their weight and blood pressure and heart rate.
- Ensure the subject has completed the patient global assessment VAS (should be done at home at approximately the time of weight is done)
- Using the script (Appendix 7), perform the 5-point Current Dyspnea Score questionnaire with the subject
- Using the script (Appendix 7), perform the 7-point Dyspnea Score questionnaire with the subject
- Record any changes to concomitant medications since last visit
- Assess for any adverse events
- Evaluate the clinical response to diuretic therapy and adjust treatment as needed. For Furoscix subjects, additional doses may be prescribed (after an in-clinic evaluation). More than 7 doses of Furoscix in the 30-day study period require approval by the medical monitor. For subjects receiving continued medical therapy with oral diuretics, investigators will determine whether any modifications are needed.

- Determination if an unscheduled in-clinic visit or an unscheduled phone call is indicated and schedule as appropriate.

6.2.9. Day 30 ± 5 (In-Clinic Visit)

Subjects will be instructed to use the provided equipment to weigh themselves (scale) and record their blood pressure and heart rate and complete the patient global assessment VAS at home prior to presenting to the clinic. They should return the equipment to the clinic at this visit. The following assessments will be completed or recorded:

- Limited physical exam including NYHA Classification
- CCS (Composite Congestion Score)
- 5-point Current Dyspnea Score (using the script - Appendix 7)
- 7-point Dyspnea Score (using the script – Appendix 7)
- Weight
- Vital Signs
- % Lung Fluid Measurement (ReDS)
- Labs drawn for safety analyses (local lab) and NT-proBNP (send to centralized lab)
- KCCQ-12
- Patient global assessment visual analog scale (should be done at home at approximately the time of weight is done)
- 6MWT
- Review Subject Diary for completeness and any recorded device issues
- Review any changes to concomitant medications since last visit
- Assess for adverse events
- Collect any used and unused study product since the last in-clinic visit

6.2.10. Unscheduled Visit (In-Clinic Visit)

If subjects experience worsening signs and symptoms they can be seen in the clinic as an unscheduled visit. For subjects presenting for an unscheduled visit the following assessments may be performed:

- Limited physical exam including NYHA Classification
- CCS (Composite Congestion Score)
- 5-point Current Dyspnea Score (using the script - Appendix 7)
- 7-point Dyspnea Score (using the script – Appendix 7)
- Weight
- Vital Signs
- % Lung Fluid Measurement (ReDS)
- Labs drawn for safety analyses (local laboratory) and NT-proBNP (send to centralized laboratory)

- Review Subject Diary for completeness and any recorded device issues
- Review any changes to concomitant medications since last visit
- Assess for adverse events
- Evaluate the clinical response to diuretic therapy and adjust as needed. For Furoscix subjects, additional doses may be prescribed. More than 7 doses of Furoscix in the 30-day study period require approval by the medical monitor. For subjects receiving continued medical therapy with oral diuretics, investigators will determine whether any modifications are needed. If diuretic modifications are made after Subjects' are transitioned to their oral maintenance diuretic regimen, including additional doses of Furoscix in the treatment group or oral diuretics for the treatment as usual control group, the Subjects' follow-up assessments and timing of those assessments will be based on the investigator's clinical judgement. Additional unscheduled clinic and phone visits can be conducted as needed.

6.2.11. Unscheduled Phone Visit

At the discretion of the investigator, or if subjects experience worsening signs and symptoms, they can speak to the research staff via phone as an Unscheduled Phone Visit. For an Unscheduled Phone Visit the following assessments may be performed:

- Ensure the subject has completed the Subject Diary and recorded device issues and used the provided equipment and recorded their weight and blood pressure and heart rate.
- Using the script (Appendix 7), perform the 5-point Current Dyspnea Score questionnaire with the subject
- Using the script (Appendix 7), perform the 7-point Dyspnea Score questionnaire with the subject
- Record any changes to concomitant medications since last visit
- Assess for any adverse events
- Discuss with investigator if Subject requires modifications to their oral maintenance diuretic regimen based on the presence of congestion symptoms (e.g. dyspnea, edema, and/or excess weight gain), including additional doses of Furoscix in the treatment group or oral diuretics for the treatment as usual control group and if the Subject should come in for an unscheduled in-clinic evaluation.
- If an unscheduled in-clinic visit is indicated, schedule as appropriate.

6.2.12. NT-proBNP Assessments

Blood samples will be obtained by direct venipuncture at screening on Day 0, Day 3, Day 7, Day 30 and on unscheduled in-clinic visit (first unscheduled in-clinic visit only).

A total of 3.5 mL of blood will be collected in pre-labeled tubes. Blood samples will be processed and stored in appropriately labeled cryotubes at minus 70˚C or colder until shipped to the bioanalytical laboratory as described in the Laboratory Manual. Day 0 NT-proBNP must

be done locally to determine eligibility but a 2nd sample will be sent to the centralized laboratory and that result is the one that will be used in the analysis.

6.2.13. Clinical Laboratory Tests

All routine samples will be analyzed by a local licensed clinical laboratory. The clinical laboratory tests are as follows:

- **Blood Clinical Chemistry**: blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, bicarbonate, magnesium
- **Urine pregnancy test**: βhCG test.

The Investigator is responsible for determining if out-of-range laboratory values are clinically significant or not. All clinically significant values will be followed until stabilization, resolution, or loss to follow-up or until no further improvement is expected.

6.2.14. Physical Examinations

A limited physical examination will be performed consisting of assessments of the following: skin of abdominal area, lungs/chest, heart, abdomen and periphery.

6.2.15. Heart Failure Symptom Scoring

The New York Heart Association (NYHA) Functional Classification will be used in this study.

New York Heart Association (NYHA) Functional Classification	
NYHA Class	Symptoms
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

6.2.16. Composite Congestion Score (CCS)

CCS is a 4-point grading scale ranging from 0 to 3 for investigator-assessed signs and symptoms of congestion (dyspnoea, orthopnoea, fatigue, rales, pedal oedema, and JVD) (Appendix 4). This assessment will be done and documented on Days 0, 1, 3, 7, 30 and during any unscheduled in-clinic visit.

6.2.17. Vital Signs

Vital signs will be conducted during screening (Day 0). Vital signs will include respiratory rate (respirations per minute), blood pressure (mmHg) and heart rate (beats per minute [bpm]). Vital signs will be obtained after the Subject has been resting in sitting position for 5 minutes.

Height and weight will be collected for BMI. Height collected Day 0 only.

On Days 1-30 weight, heart rate and blood pressure will be obtained by the Subject at home using the equipment supplied at screening and recorded daily in the Subject Diary. These will be collected at home in the morning even for those days where visits to the clinic are required.

Vital signs (respiratory rate, blood pressure, heart rate) will also be collected at each in-clinic visit. Weight will also be collected at each in-clinic visit.

6.2.18. % Lung Fluid Measurement (ReDS)

The ReDS System is a non-invasive diagnostic device consisting of a Bedside Console connected to a wearable Sensor Unit that is used for the measurement of lung fluid. The system is FDA cleared for use by qualified healthcare practitioners, under the direction of a physician, in hospitals, hospital-type facilities and home environments, for the non-invasive monitoring and management of patients with fluid management problems in a variety of medically accepted clinical applications.

The ReDS System is indicated for patients:

- With fluid management problems
- Taking diuretic medications
- Living with heart failure
- Recovering from a coronary artery disease-related event

The Sensor Unit consists of two sensors and a positioner. One sensor is placed on the patient's upper right chest through light clothing and another on the upper-right part of the patient's back. The Sensor Unit is connected by a non-detachable cable to the Bedside Console. Low power electromagnetic (EM) signals are emitted and pass through the thorax and software in the console calculates an average dielectric coefficient that reflects the percentage of lung tissue fluid content.

The system provides an on-screen reading within 45 seconds. Measurements are recorded in units of percent (%), representing the percent of lung tissue volume that is occupied by fluid. The normal value of lung fluid volume ranges between 20% and 35%. The full range of lung fluid volume provided by the ReDS system spans from 15% to 60%.

Study Staff will be trained on the use of the ReDS system.

6.2.19. Patient Global Assessment Visual Analog Scale

The patient global assessment visual analog scale is a patient reported assessment of how good or bad a patient feels their health is that day. It is reported on a visual scale of 0-100 with 100 being the best health they can imagine and 0 being the worst health they can imagine. The EQ-VAS tool will be utilized for this assessment. This patient reported assessment will be obtained on Days 0-7, Day 17 and Day 30. This assessment should be done in the morning at approximately the same time as weight is being measured.

6.2.20. 5-Point Current Dyspnea Score

The 5-Point Current Dyspnea Questionnaire is a single-item, self-administered instrument that quantifies current symptoms of dyspnea (see Appendix 5). This will be administered after a verbatim script is read by study staff (see Appendix 7). This assessment will be done on Days 1, 2, 3, 4, 5, 6, 7, 17 and 30 and during an unscheduled in-clinic or phone visit.

6.2.21. 7-Point Dyspnea Score

The 7-Point Dyspnea Questionnaire is a single-item, self-administered instrument that quantifies changes in dyspnea symptoms since initiation of study product (see Appendix 6). This will be administered after a verbatim script is read by study staff (see Appendix 7). This assessment will be done on Days 1, 2, 3, 4, 5, 6, 7, 17 and 30 and during an unscheduled in-clinic or phone visit.

6.2.22. Kansas City Cardiomyopathy Questionnaire – 12 (KCCQ-12)

The KCCQ-12 is a shortened version of the original KCCQ with 23 questions. This questionnaire is a patient reported assessment designed to capture symptom frequency, physical and social limitations, and quality of life impairment as a result of heart failure, as well as an overall summary score. This assessment will be done on Days 0, 7 and 30.

6.2.23. Six Minute Walk Test (6MWT)

The 6MWT is a test to measure the distance a subject can walk over a total of six minutes. The Subject is instructed to walk as far as possible in 6 minutes on a hard, flat surface. If needed, the Subject may rest and pace themselves during this time as they move back and forth along a marked path. This assessment is done on Days 0, 1, 7 and 30.

6.2.24. Subject Diary

During the study period and for all treatment days, these data will be recorded in the Subject Diary by the Subject and reported to the study staff during phone contacts:

- Infusor Kit serial number (Furoscix treatment group)
- Infusor start and stop dates/times for each dose (Furoscix treatment group)
- Oral diuretic use in addition to the study drug (name, dose, date, time)
- Adverse events and/or device issues should be noted in the comments/issues section of the diary.
    - See section 7.1 for the definition of an adverse event.
    - A device issue is defined as anything the user states occurred that resulted in the device not functioning as expected.

6.2.25. Study Product Training

Study Staff will be trained on the use of the study product, subject/caregiver considerations, and methods for training subjects and/or their caregivers who are enrolled into the study. The study staff and enrolled subjects will be trained using the Instructions for Use.

7. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. AEs will be assessed continuously

through the last study visit unless the nature of the AE or SAE requires continued monitoring. All AEs are recorded as mild, moderate or severe, and as Not Related, Possibly Related, Probably Related, or Definitely Related to the Investigational Product.

7.1. Definition of an Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence associated with the use of an Investigational Product (IP) in humans, whether considered related to the IP. An adverse event (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an Investigational Product (IP) and does not imply any judgment about causality. An adverse event can arise with any use of the IP (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

A “pre-existing” condition is one that is present prior to IP administration and is reported as part of the Subject’s medical history. Pre-existing conditions should be reported as AEs only if the frequency, intensity, or character of the pre-existing condition worsens during the study.

Laboratory or functional test abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms or require medical intervention. A laboratory abnormality (e.g. a clinically significant change detected on clinical chemistry, hematology, urinalysis) or functional test abnormality (e.g. a clinically significant change detected on ECG, pulse oximetry, or spirometry) that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to IP interruption or discontinuation, must be considered an AE.

All AEs judged to be clinically significant, including clinically significant laboratory results, ECG and functional test abnormalities, will be followed until resolution or return to baseline or until no further improvement is expected.

An AE **does** include any:

- Exacerbation of a pre-existing illness.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study product placement and/or drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

An AE **does not** include a/an:

- Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions).

- Overdose of either study drug or concurrent medication without any signs or symptoms.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE.

7.2. Definition of a Serious Adverse Event (SAE)

An SAE is any AE occurring at any dose that results in any of the following outcomes:

a. Death.

b. A life-threatening AE.

- *NOTE: Life-threatening means that the Subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that, had it occurred in a more severe form, might have caused death.*

c. Inpatient hospitalization or prolongation of existing hospitalization.

- *NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.*
- *NOTE: "Inpatient" hospitalization means the Subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a "casualty" or emergency room.*

d. A disability/incapacity.

- *NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.*

e. A congenital anomaly in the offspring of a Subject who received drug.

f. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in Subject hospitalization, or the development of drug dependency or drug abuse.

- Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

7.3. Definition of an Adverse Event of Special Interest (AESI)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsors program, for which ongoing monitoring and rapid

communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

7.4. Severity of AEs/SAEs

Severity (mild, moderate, or severe) of each AE/SAE must be assessed by the Investigator or designee. The following criteria should be considered when assessing severity:

- Mild — The symptom is barely noticeable to the Subject and does not influence performance or functioning.
- Moderate — The symptom is of sufficient severity to make the Subject uncomfortable, and performance of daily activities is influenced. Treatment for the symptom may be needed.
- Severe — The symptom causes severe discomfort. Treatment for the symptom may be necessary.

7.5. Outcome of AE/SAEs

- Not Recovered/Not Resolved: One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated.
- Recovered/Resolved: One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated.
- Recovered/Resolved with Sequelae: One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.
- Recovering/Resolving: One of the possible results of an adverse event outcome that indicates that the event is improving.
- Unknown: Not known, not observed, not recorded, or refused.
- Fatal: The termination of life as a result of an adverse event

7.6. Assessment of Relatedness to Study Product

The Investigator will assess each AE and SAE for causality based on their best medical judgment, the observed symptoms associated with the event, and the available information on the Investigational Product (IP). The relatedness guidance provided below can be used to assist in determining the relationship of the IP to the AE or SAE. However, it is ultimately the investigator's responsibility to determine the relationship based on their best medical judgment, knowledge, and experience.

- **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.

7.7. Method, Frequency, and Time Period for Detecting Adverse Events and Serious Adverse Events

At appropriate intervals, Subjects should be assessed for AEs and SAEs as in Section 6.2.

7.7.1. Timeframes for Reporting SAEs

Prompt notification of the sponsor regarding SAEs is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. The Investigator must report SAEs according to the following time frames:

- Initial notification of all SAEs based on the available information must be provided to the sponsor or designee **within 24 hours** of the investigational site learning of the event. **(Initial notification within 24 hours of Death and life-threatening events is extremely important).**
    - Follow-up information when available must be sent to the sponsor or designee **within 48 hours** of receipt of the information by the investigational site.

7.7.2. SAE Information to Report

At a minimum, SAE reports must contain the Subject ID, the serious adverse event term, onset date, relationship to study product, and a brief narrative of the event. Please note that **relationship to study product/causality is very important** and must be included in the initial report as it may impact expedited regulatory reporting requirements for the event.

Copies of medical records will be requested. **However, it is not acceptable for the Investigator to send photocopies of the Subject's medical records in lieu of completion of the appropriate AE/SAE pages**. For medical records submitted, all Subject personal identifiers must be completely and thoroughly redacted prior to submission.

7.7.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

The Investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., vital signs) that are judged by the Investigator as clinically

significant must be recorded as AEs or SAEs if they meet the definition of an adverse event. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected after study product administration or that are present before study product administration but worsen after study product administration should be assessed for AE criteria.

7.7.4. Documenting AEs and SAEs

All adverse events, including SAEs that occur after dosing of study product must be documented in the Subject's medical records and on the CRF.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE term.

7.7.5. Regulatory/Ethics reporting requirement

The Investigator must comply with the applicable local regulatory requirements related to the reporting of SAEs to the IRB.

7.7.6. Follow-up of AEs and SAEs

All AEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts. AEs and SAEs will be followed until the last study visit unless the nature of the AE or SAE requires continued monitoring. If a Subject dies during participation in the study or during a recognized follow-up period, a copy of any post-mortem findings, including histopathology, should be obtained, if available, and forwarded to scPharmaceuticals or designee. New or updated information will be recorded on the originally completed SAE Report Form with all changes electronically signed/dated by the Investigator or designee.

7.7.7. Post-study AEs and SAEs

Should the Investigator learn of an AE or SAE occurring within 30 days after a Subject completes the study, the event should be reported if it is considered related to study product.

7.7.8. Medical Monitor

SAEs and other medical matters can be discussed with the Medical Monitor.

8. STATISTICS

8.1. General Statistical Issues

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

Unless otherwise specified, all safety data, effectiveness data, demographic data, and other baseline clinical characteristics will be summarized by treatment group. 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 compared to baseline values.

Statistical analysis tests will be performed at a two-sided alpha level of 0.05, unless otherwise specified. Between-group analyses of baseline characteristics will employ descriptive statistics as described in the SAP. Mortality and morbidity events will be assessed using appropriate statistical tests as described in the SAP. The primary endpoint will be measured using the Finkelstein-Schoenfeld Method, comparing components of the composite endpoint hierarchically, as described in the SAP. There will be no imputation of missing data.

8.2. Analysis Populations

- Intent-to-Treat (ITT): All randomized subjects.
- Safety: All randomized subjects who received at least one dose of the Investigational Product.
- Per-Protocol (PP): All randomized subjects who received at least one dose of the Investigational Product AND completed the Day 30 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 as further defined in the SAP. Safety analyses will be performed on the safety population.

8.3. Baseline Characteristics and Subject Disposition

Subject disposition (e.g., the number of Subjects enrolled, completed, and discontinued overall and by reason) will be summarized using the categorical descriptive statistics described in §8.1 above. Overall baseline clinical and demographic data will be summarized using descriptive statistics and compared between treatments using appropriate statistical tests as defined in the SAP.

8.4. Effectiveness Analyses

The following endpoints will be assessed.

8.4.1. Primary Endpoints

The primary analysis compares the components of the primary composite endpoint hierarchically using the Finkelstein-Schoenfeld Method. Each patient is compared to all other patients with respect to each of the following endpoints at 30 days:

- CV death
- HF hospitalization
- Urgent ED/Clinic visit for worsening heart failure (defined as IV diuretics, augmentation of or new administration of metolazone)
- Change in NT-proBNP from baseline at Day 7.

Each endpoint will be descriptively presented as well.

Incidence of Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events will be described in each group.

8.4.2. Secondary Endpoints

Descriptive and statistical comparisons of treatment vs. control group will be conducted for each secondary endpoint at a two-sided 0.05 level of significance. The following secondary endpoints will be compared between treatment groups on the ITT and Per-Protocol populations as described in SAP:

- Days alive and heart failure event-free (hospitalization for heart failure or ED visits for heart failure) over 30 days.
- Changes from baseline in patient global assessment via visual analog scale (VAS) across follow-up timepoints.
- Changes from baseline in composite congestion score across follow-up timepoints.
- Changes from baseline in 5-point Current Dyspnea Score across follow-up timepoints.
- 7-point Dyspnea Score across follow-up timepoints.
- Changes from baseline in health-related quality of life measured by the KCCQ-12 Short Form Summary Score across follow-up timepoints.
- Changes from baseline in serum creatinine across follow-up timepoints.
- Changes from baseline in ambulatory body weight across follow-up timepoints.
- Changes from baseline in Six-Minute Walk Test (6MWT) across follow-up timepoints.
- Changes from baseline in the ReDS Lung Fluid Measurement across follow-up time points.

8.5. Interim Analysis

There will be no formal interim analysis.

8.6. Safety Analyses

Safety analysis will be performed on the safety population. No imputation will be performed for missing data. The incidence (number and percentage of subjects) of adverse events will be presented overall and by MedDRA System Organ Class (SOC) and Preferred Term (PT) for each treatment group. This analysis will be repeated for serious adverse events, for treatment-related adverse events, adverse events of special interest and for adverse events leading to premature study withdrawal.

Descriptive statistics at each time point will be presented for laboratory variables, vital signs, and body weight, stratified by treatment group.

8.7. Subgroup Analysis

The primary endpoint will be compared between treatment groups within pre-specified subgroups defined in the SAP. There will be no formal treatment comparisons within subgroups. The purpose of the analysis within subgroups is not to show statistical significance between treatments within subgroups, but to assess the consistency of treatment effect across subgroups.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study Subject. For studies conducted under a United States IND, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Approval

This protocol and any accompanying material to be provided to the Subject (such as advertisements, Subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted, by the Investigator, to an IRB [or] EC. Approval from the IRB/EC must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

Any modifications or amendment to the protocol must also be submitted to the IRB/EC for approval prior to implementation.

9.1.3. Informed Consent

It is the responsibility of the Investigator or designee to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. The Investigator or designee must utilize an IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the Subject and the person obtaining consent. A copy of the signed consent form will be provided to the Subject.

9.1.4. Confidentiality

All information about the nature of the proposed investigation provided by the Sponsor or study monitor to the Principal Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the Subject, or the appropriate regulatory authority) must be kept in confidence by the Principal Investigator.

The Investigator must assure that Subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only Subject initials and an identification code (i.e., not names) should be recorded on any form submitted to the Sponsor and IRB. The Investigator must keep a Subject log showing codes and, names, for all enrolled in the trial.

9.1.5. Compensation, Insurance, and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

9.1.6. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories including (although not limited to) the following: (1) Investigator's study file, and (2) Subject clinical source documents.

The Investigator's study file will contain the protocol/amendments, IRB/EC approval, informed consent, drug accountability records, staff curriculum vitae, medical licenses as applicable, financial disclosure forms, local laboratory documentation, screening and enrollment log, and other appropriate documents and correspondence.

Subject clinical source documents would include (although is not limited to) the following: Subject hospital/clinic records, physician's and nurse's notes, laboratory reports, worksheets, consultant letters, etc.

All clinical study documents must be retained by the Investigator until at least two years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, until two years after the IND is discontinued and regulatory authorities have been notified. The Investigator must notify scPharmaceuticals prior to destroying any clinical study records.

Should the Investigator wish to move study records to another location, arrangements must be made to store these in sealed containers so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the Subject, appropriate copies should be made for storage outside of the site.

9.1.7. Case Report Forms

For each Subject who signs informed consent, a CRF must be completed and signed (or electronically signed if eCRF) by the principal Investigator or sub-Investigator within a reasonable time period after data collection. This also applies to records for those Subjects who fail to complete the study. If a Subject withdraws from the study, the reason must be noted on the CRF. If a Subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

9.1.8. Protocol Deviations

Neither the Investigator nor the Sponsor is permitted to intentionally deviate from the protocol without proper notification to the FDA or to other relevant regulatory authorities in the form of a protocol amendment. Protocol deviations that occur during the study must be documented.

The Investigator will not alter this study protocol without obtaining the written agreement from the sponsor. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol and will require re-approval of the Institutional Review Board (IRB/Independent Ethics Committee (IEC).

9.1.9. Disclosure of Data

The Principal Investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the name of the Principal Investigator, their addresses, qualifications and extent of involvement. It is understood that the Principal Investigator is required to provide scPharmaceuticals with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the US FDA and other regulatory authorities, by scPharmaceuticals and its designees, and the IRB as appropriate. At a Subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during this study is confidential and disclosure to third parties other than those noted above is prohibited.

9.1.10. Financial Disclosure

The US FDA Financial Disclosure by Clinical Investigators (21 CFR 54) regulations require Sponsors to obtain certain financial information from Investigators participating in covered clinical studies; each Principal Investigator and Sub-investigator is required to provide the required financial information and to promptly update scPharmaceuticals with any relevant changes to their financial information throughout the course of the clinical study and for up to 1 year after its completion. This rule applies to all Principal Investigators and Sub-investigators participating in covered clinical studies to be submitted to the FDA in support of an application for market approval.

9.1.11. Drug and Device Product Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) and Subject dispensing records and returned study product. Dispensing records will document quantities received and quantities dispensed to Subjects, including lot number, date dispensed, Subject identifier number, Subject initials, and the initials of the person dispensing the medication. All used study product will be returned from the subject to the site for accountability as well and should be documented as the dispensation is.

At the end of the study, following final product reconciliation by the monitor, the Sponsor will instruct the study site how to handle the handling of all used and unused study product and materials.

9.1.12. Inspections

The Investigator will provide access to source documents and all study records for this trial to appropriately qualified personnel from scPharmaceuticals or its representatives, and to regulatory authority inspectors.

9.2. Sponsor Responsibilities

9.2.1. Study Materials and Instructions

It is the Sponsor's responsibility to ensure that the Investigator is provided with the documents and other study materials necessary to conduct the study. Examples of those materials include, but are not limited to protocol, Investigator's Brochure, study product, CRF, logs, etc. The Sponsor or designee will also provide training and oversight through site and medical monitoring.

9.2.2. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study Subjects, will be made by Sponsor-initiated amendment. IRB approval must be obtained before changes can be implemented.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Access to Information for Monitoring

In accordance with International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered. The monitor should have access to any Subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

9.3.2. Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs and IECs. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the Subjects' interests.

10. REFERENCES

Agarwal, S. K., Wruck, L., Quibrera, M., Matsushita, K., Loehr, L. R., Chang, P. P., . . . Coresh, J. (2016). Temporal Trends in Hospitalization for Acute Decompensated Heart Failure in the United States, 1998-2011. *Am J Epidemiol, 183*(5), 462-470. doi:10.1093/aje/kwv455

Ambrosy, A. P., Pang, P. S., Khan, S., Konstam, M. A., Fonarow, G. C., Traver, B., . . . Gheorghiade, M. (2013). Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J, 34*(11), 835-843. doi:10.1093/eurheartj/ehs444

Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., . . . Muntner, P. (2018). Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation, 137*(12), e67-e492. doi:10.1161/cir.0000000000000558

Costanzo, M. R., Johannes, R. S., Pine, M., Gupta, V., Saltzberg, M., Hay, J., . . . Fonarow, G. C. (2007). The safety of intravenous diuretics alone versus diuretics plus parenteral vasoactive therapies in hospitalized patients with acutely decompensated heart failure: a propensity score and instrumental variable analysis using the Acutely Decompensated Heart Failure National Registry (ADHERE) database. *Am Heart J, 154*(2), 267-277. doi:10.1016/j.ahj.2007.04.033

Ellison, D. H., & Felker, G. M. (2017). Diuretic Treatment in Heart Failure. *New England Journal of Medicine, 377*(20), 1964-1975. doi:10.1056/NEJMra1703100

Fonarow, G. C., Adams, K. F., Jr., Abraham, W. T., Yancy, C. W., & Boscardin, W. J. (2005). Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *Jama, 293*(5), 572-580. doi:10.1001/jama.293.5.572

Greene, S. J., Mentz, R. J., & Felker, G. M. (2018). Outpatient Worsening Heart Failure as a Target for Therapy: A Review. *JAMA Cardiol, 3*(3), 252-259.doi:10.1001/jamacardio.2017.5250

Mullens, W., Damman, K., Harjola, V. P., Mebazaa, A., Brunner-La Rocca, H. P., Martens, P., . . . Coats, A. J. (2019). The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. doi:10.1002/ejhf.1369

Neuenschwander, J. F., 2nd, & Baliga, R. R. (2007). Acute decompensated heart failure. *Crit Care Clin, 23*(4), 737-758, vi. doi:10.1016/j.ccc.2007.08.003

Schiff, G. D., Fung, S., Speroff, T., & McNutt, R. A. (2003). Decompensated heart failure: symptoms, patterns of onset, and contributing factors. *Am J Med, 114*(8), 625-630.

Sica, D. A., Muntendam, P., Myers, R. L., Ter Maaten, J. M., Sale, M. E., de Boer, R. A., & Pitt, B. (2018). Subcutaneous Furosemide in Heart Failure: Pharmacokinetic Characteristics of a Newly Buffered Solution. *JACC Basic Transl Sci, 3*(1), 25-34. doi:10.1016/j.jacbts.2017.10.001

Vasko, M. R., Cartwright, D. B., Knochel, J. P., Nixon, J. V., & Brater, D. C. (1985). Furosemide absorption altered in decompensated congestive heart failure. *Ann Intern Med, 102*(3), 314-318.

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Jr., Drazner, M. H., . . . Wilkoff, B. L. (2013). 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol, 62*(16), e147-239. doi:10.1016/j.jacc.2013.05.019

11. APPENDICES

11.1. Appendix 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.

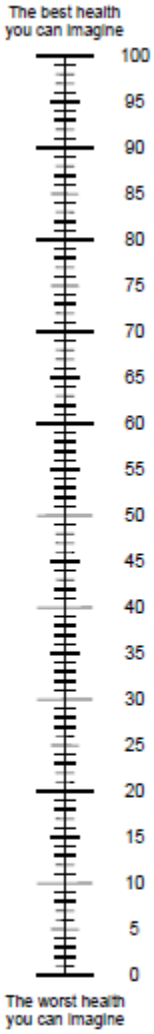
[8]If Subject receives unscheduled at-home phone call, the staff should perform assessments in the Unscheduled Phone Visit column.

[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.

11.2. Appendix 2. Patient Global Assessment Visual Analog Scale (EQ-VAS)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

11.3. Appendix 3. Kansas City Cardiomyopathy Questionnaire – 12

Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Activity	**Extremely** Limited	**Quite a bit** Limited	**Moderately** Limited	**Slightly** Limited	**Not at all** Limited	Limited for other reasons or did not do the activity
a. Showering/bathing	O	O	O	O	O	O
b. Walking 1 block on level ground	O	O	O	O	O	O
c. Hurrying or jogging (as if to catch a bus)	O	O	O	O	O	O
	1	2	3	4	5	6

2. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

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

3. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

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

4. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

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

5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

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

Rev. 2012-04-11

6. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
O	O	O	O	O
1	2	3	4	5

7. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
O	O	O	O	O
1	2	3	4	5

8. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Activity	**Severely** Limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
a. Hobbies, recreational activities	O	O	O	O	O	O
b. Working or doing household chores	O	O	O	O	O	O
c. Visiting family or friends out of your home	O	O	O	O	O	O
	1	2	3	4	5	6

11.4. Appendix 4: Composite Congestion Score

Table 1 Grading scale for investigator-assessed signs and symptoms of congestion

Signs/ symptoms	0	1	2	3
Dyspnoea	None	Seldom	Frequent	Continuous
Orthopnoea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
JVD (cm H_2O)	≤6	6–9	10–15	≥15
Rales	None	Bases	To <50%	To >50%
Oedema	Absent/ trace	Slight	Moderate	Marked

JVD, jugular venous distension.

Source: Ambrosy et al. (2013)

11.5. Appendix 5: Current Dyspnea Status - 5-Point Likert Scale

CURRENT DYSPNEA STATUS

How much difficulty are you having in breathing now?

not short of breath	mildly short of breath	moderately short of breath	severely short of breath	very severely short of breath
☐	☐	☐	☐	☐

11.6. Appendix 6: Dyspnea Status - 7-Point Likert Scale

Patient-Assessed Dyspnea Status

Compared to how much difficulty you were having with your breathing just before starting in the study, how is your breathing now?

Markedly better	Moderately better	Minimally better	No change	Minimally worse	Moderately worse	Markedly worse
☐	☐	☐	☐	☐	☐	☐

11.7. Appendix 7: Instructions for study staff administering Current Dyspnea Status Questionnaire (5-Point Likert Scale) and Dyspnea Status Questionnaire (7-Point Likert Scale)

Please administer the Current Dyspnea Status Questionnaire (5-point Likert scale) first. Make the following statement to the Subject:

"You have been provided a 5-point questionnaire about how you feel".

"I want you to think about the last day and how limited you have been in doing the tasks you normally do; for example: going to the bathroom, eating, moving from the bed to a chair, walking, etc."

Then ask the Subject to look at the Current Dyspnea Status Questionnaire (5-point Likert scale) and say ***"please indicate the box that reflects the shortness of breath you have felt over the last day."***

After the Current Dyspnea Status Questionnaire (5-point Likert scale) is completed say

"Again, I want you to think about the last day and how limited you have been in doing the tasks you normally; do for example: going to the bathroom, eating, moving from the bed to a chair, walking, etc. Now, mark down how limited you have felt during this recent time frame, compared with how you felt before you started in the study."

Then ask the Subject to look at the Patient-Assessed Dyspnea Status Questionnaire (7-point Likert scale) and say ***"please indicate the box that reflects how your breathing is now compared to before starting in the study."***